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Factors Affecting The Prevalence Of Herpes Simplex Virus Type 2 Antibody: A Seroepidemiologic Survey

Joanne Chiavetta

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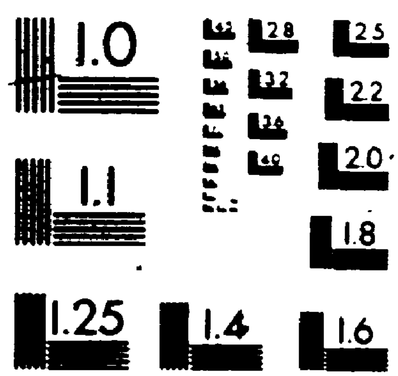

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FACTORS AFFECTING THE PREVALENCE OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY

A SEROEPIDEMIOLOGIC SURVEY

by
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Submitted in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
University of Western Ontario
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ABSTRACT

A cross-sectional seroepidemiologic survey of socioeconomic, contraceptive and sexual factors and HSV-2 antibody was carried out in Toronto, Canada between 1978 and 1980. The objective of this survey was to identify the contraceptive, sexual and socioeconomic factors associated with antibody evidence of HSV-2 infection. A stratified random sampling method was used to obtain men and women from diverse socioeconomic areas of the city. A door-to-door survey was carried out in which eligible candidates were invited to participate, and then interviewed in their homes. Following the interview a blood sample was drawn by the interviewer. The sera were analyzed using a radioimmuno-assay method for HSV type-specific and crossreacting antibodies.

Men and women between the ages of 35 and 50 were eligible for the study. Of 1,220 persons invited to participate, 957 (78.4%) completed interviews. Seven hundred and forty-eight serum samples were retrieved from 320 men and 428 women. Herpes simplex virus antibody was found in 587 (78.5%) of those tested. HSV-2 specific antibody was found in the sera of 116 (15.5%) participants consisting of 41 (12.8%) men and 75 (17.5%) women. The data were analyzed using summary statistics, Chi square univariate analysis and multiple logistic regression. Both men and women with HSV-2 antibody had begun intercourse at an earlier age, had had more sexual partners, and were more likely to rent their homes than those without antibody. Men with HSV-2 antibody more frequently reported living in their homes for a shorter period of time, had more sexual partners in the year preceding the interview, and more frequently reported genital infections than did men without antibody. Men

with and without antibody were similar with regard to all dimensions of socioeconomic status. Women with HSV-2 antibody were more often previously married, had a lower educational level and lower household income, reported fewer years of condom use by their partners, had more years of oral contraceptive use, more frequently reported intercourse prior to marriage, more frequently reported having had a hysterectomy and having had cervical cancer, and were more likely to have received a blood transfusion than women without antibody. When the sexual and contraceptive variables as well as other socioeconomic and lifestyle variables of interest were examined using logistic regression, men who began intercourse by age 17, who reported at least 10 sexual partners, who rented their home, and lived in an apartment, were more likely to show HSV-2 antibody even when adjustment was made for present age, condom use, education, marital status and other factors. Women who began intercourse by age 19, reported at least 2 sexual partners in their life, reported condom use by their partners for fewer years, who had used an oral contraceptive for at least ten years, rented their home, and had undergone a hysterectomy, were more likely to have HSV-2 antibody, even when adjustment was made for present age, education, marital status and other factors.

It is not known whether or not the unexpected association of rental status is a spurious one or whether it reflects an aspect of sexual behaviour or lifestyle which would greatly increase HSV-2 exposure. Further studies are required to resolve this issue. The results indicate that multiple sexual partners, early first intercourse and rental status for both men and women, and oral contraceptive use and having undergone a hysterectomy for women, are associated with

HSV-2 antibody and that statistically significant associations for socioeconomic status or other lifestyle factors could not be demonstrated by the present data.

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et al., 1981).

In the 1970s there was a marked increase in medical and public attention to genital herpes. This may have been due to the association of HSV-2 with cervical carcinoma, improved methods of detection, popularized presentation of the incurable nature of the infection and possibly some real elevation in the occurrence of genital herpes. In addition, Meltzer (1979) as well as other authors suggest that there has been more sexual freedom over the last decade and, with this, an increase in the frequency of genital herpes. Although there are no studies which validate this hypothesis, it is evident that genital herpes now affects, and perhaps always has affected a substantial number of people and, when symptoms do occur, cause a great deal of suffering. A survey of herpes victims done by the American Social Health Association (1981) revealed that those with symptoms experience extreme personal and physical discomfort.

From information in previous investigations, it is evident that venereal transmission of HSV-2 is possible and that women who are sexually active and who represent lower socioeconomic groups are more likely to show evidence of HSV-2 infection than others. In addition, both men and women with genital herpes infections are more likely to have other venereal diseases than are those without genital herpes.

There have been few studies which have examined the individual association between age at first intercourse, number of sexual partners, contraceptive practices, socioeconomic and lifestyle factors and HSV-2 infection. There have been no studies which examine the separate effects of any of these factors while taking into account the effect of the other interrelated factors. Therefore information about

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CHAPTER 1

INTRODUCTION

Clinical descriptions of herpes genitalis were recorded by Jean Astruc in France as early as 1736 (Hutfield, 1966). With modern laboratory techniques, herpes simplex viruses were later isolated and identified (Wildy, 1973). Among the five herpes viruses infecting man, herpes simplex type 1 (HSV-1) was identified as causing localized infections of the mouth, oral cavity and areas above the waist, while herpes simplex type 2 (HSV-2), the topic of this study, was found to infect the genital area and other sites below the waist (Pauls and Dowdle, 1967; Nahmias and Dowdle, 1968).

When symptoms of genital herpes infection occur, symtoms include: painful blisters occur and last from one day to several weeks, often accompanied by pain and swelling in the infected area and lymph nodes as well as fever.

HSV-2 infections are often asymptomatic and clinically difficult to detect. Viral shedding can occur during asymptomatic as well as symptomatic episodes and up to one month following an episode. Therefore the infected individual is capable of unknowingly infecting others through physical contact. Once infection occurs the virus remains in the neural ganglia indefinitely, most frequently in a latent state, but capable of reactivation during periods of stress or illness. The infected individual may as a result experience repeated episodes throughout life (Rawls, 1973). Although a number of agents which can curtail the episodes as well as a preventive vaccine are under investigation, no effective cure for genital herpes currently exists.

The prevalence of HSV-2 infections is difficult to establish because of the asymptomatic nature of many herpes infections and because until recently in most parts of the world, including Canada, genital herpes was not a reportable disease. The Centers for Disease Control in the United States estimates that approximately 300,000 new cases of genital herpes occur each year in the U.S. (U.S. Centers for Disease Control, 1980). An estimate of the prevalence of HSV-2 infections can be obtained from serologic surveys of HSV-2 antibody. In Canada information on the occurrence of HSV-2 antibody is available from two household surveys. Using a microneutralization test McDonald et al. (1974a) reported that 19 percent of 430 women in Montreal showed HSV-2 antibody. Similarly, Rawls et al. (1980) used a radioimmunoassay (RIA) technique and found HSV-2 antibody in the sera of 22 percent of 255 women residing in Toronto.

One of the most serious consequences of HSV-2 infection is transmission to the newborn from the birth canal of the mother during delivery. Neonatal herpes is reported to occur in from 1 in 30,000 to 1 in 1,000 deliveries (Nahmias and Starr, 1977). The American Academy of Pediatrics (1980) has estimated that approximately 60 percent of newborns infected with HSV-2 die and 50 percent of those who survive suffer serious ocular or neurologic consequences.

In addition to the direct health effects of this virus, HSV-2 has been implicated in the etiology or promotion of cervical cancer. Numerous investigators have reported that HSV-2 antibody is more frequently found in women with cervical cancer than in women of similar ages who do not have cervical cancer (Kessler, 1974a). Recently, this virus has also been investigated in relation to prostatic cancer (Baker et al., 1981).

In the 1970s there was a marked increase in medical and public attention to genital herpes. This may have been due to the association of HSV-2 with cervical carcinoma, improved methods of detection, popularized presentation of the incurable nature of the infection and possibly some real elevation in the occurrence of genital herpes. In addition, Meltzer (1979) as well as other authors suggest that there has been more sexual freedom over the last decade and, with this, an increase in the frequency of genital herpes. Although there are no studies which validate this hypothesis, it is evident that genital herpes now affects, and perhaps always has affected a substantial number of people and, when symptoms do occur, cause a great deal of suffering. A survey of herpes victims done by the American Social Health Association (1981) revealed that those with symptoms experience extreme personal and physical discomfort.

From information in previous investigations, it is evident that venereal transmission of HSV-2 is possible and that women who are sexually active and who represent lower socioeconomic groups are more likely to show evidence of HSV-2 infection than others. In addition, both men and women with genital herpes infections are more likely to have other venereal diseases than are those without genital herpes.

There have been few studies which have examined the individual association between age at first intercourse, number of sexual partners, contraceptive practices, socioeconomic and lifestyle factors and HSV-2 infection. There have been no studies which examine the separate effects of any of these factors while taking into account the effect of the other interrelated factors. Therefore information about the relative impact of each of these factors on the acquisition of HSV-2 was not available in the literature.

The present investigation was designed to obtain sexual, contraceptive and other relevant information from a wide range of socioeconomic groups, within essentially one culture, with the purpose of examining the separate and possibly confounding effects of these factors on the occurrence of HSV-2 antibody.

The primary aim of this investigation was to simultaneously examine biologically plausible factors which could directly affect exposure to HSV-2 infection in order to identify special conditions of risk of HSV-2 infection within the context of sociologic and behavioural factors which could affect such exposure.

CHAPTER 2

REVIEW OF THE LITERATURE

INTRODUCTION

The topics covered in the review of the literature have been selected to provide sufficient information about herpes simplex virus and the factors reported to be associated with HSV-2 infection to place the current investigation in scientific and historic context.

The first section of this review provides information about the biological and biochemical characteristics of herpes simplex virus which are of special importance to the survival and subsequent transmission of this virus.

Section 2 covers some of the clinical manifestations, health consequences and treatment of HSV infection.

Section 3 provides an overview of the methods of detection of genital herpes infections with an emphasis on the methods and problems of serologic confirmation of past type 2 infection.

A brief historical review is presented in Section 4.

The general prevalence of herpes simplex infection is reviewed in Section 5. Seroepidemiologic studies of type 2 antibody are reviewed, including only those studies which differentiate between HSV-1 and HSV-2.

In Section 6, the factors reported to be associated with herpes virus type 2 infection are discussed. Information from seroepidemiologic studies as well as clinical studies of HSV-2 infections is utilized.

In the summary and conclusion of the literature review, the factors reported to be associated with HSV-2 infection are summarized and the questions regarding the risk of HSV-2 infection which remain unanswered by information from the published literature are discussed in terms of the objectives of the present investigation.

Only seroepidemiologic studies of HSV-2 antibody have been reviewed in this chapter in detail. Not all seroepidemiologic cancer studies have been included, because some report only antibody differences between cancer cases and control groups without complete information about risk factors unrelated to cancer. Only those cancer studies which represent various parts of the world and provide some information on specific risk factors have been included.

2.1 HERPESVIRUS

The family herpesviridae encompasses over 70 viruses which affect at least 30 different species (Nahmias and Norrild, 1979).

This group of viruses is primarily identified by the structure of their virion (Fenner et al., 1974). Herpesviruses are relatively large, morphologically distinct enveloped viruses, 150 to 200 nanometers in diameter, containing a double-stranded DNA core of approximately 100 million daltons in molecular weight, contained in a protein icosahedral capsid of 162 subunits (Fenner et al., 1974; Nahmias et al., 1976b).

Five herpesviruses are known to infect humans. These viruses are cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2(HSV-2) (Fenner et al., 1974; Nahmias and Norrild, 1979).

2.1.1 Herpes Simplex Virus

Type Differentiation

Two biochemically and antigenically distinct serotypes of herpes simplex virus, HSV-1 and HSV-2, have been identified (Pauls and Dowdle, 1967; Nahmias and Dowdle, 1968; Rawls, Tompkins and Melnick, 1969).

Although strain differences within each subtype have been identified, most clinical methods of detection do not go beyond characterization of the virus as type 1 or 2.

HSV-1 and HSV-2 share common antigens which produce crossreacting antibodies. This cross-reactivity makes serologic detection of type-specific antibody particularly difficult. Serologic standards and methods to deal with this problem are discussed in Section 2.3 of this chapter.

Although both HSV-1 and HSV-2 are capable of infecting most body sites, HSV-1 generally produces infection on the lips, face and other areas above the waist. HSV-2 causes genital lesions and infections of other body sites below the waist, although some reports estimate that nearly half of the isolates found in the genital area are type 1 (Barton et al., 1982; Ishiguro et al., 1982; Ozaki et al., 1980). However, from a number of larger studies, it is estimated that at least 85 percent of viral isolates from genital lesions have been found to be type 2, and more than 70 percent of isolates from herpetic lesions above the waist were found to be type 1 (Kaufman et al., 1973; Rawls et al., 1971; Tantivanich and Tharavanij, 1980; Wolontis and Jeansson, 1977).

2.2 Clinical Manifestations

Although the site and systemic consequences of infection due to HSV-1 and HSV-2 differ, the pathogenic effects of each virus on the host cell are similar. Both types of viruses share the characteristic of persistence through latency in the infected individual and, although antibodies are produced, an absolute immunity through exposure to either type of virus is not acquired.

Unless otherwise specified, the clinical descriptions that follow have been taken from a review of herpes simplex infections by Rawls (1973).

Herpetic lesions often occur in tissues derived from embryonic ectoderm. These include the skin, oral cavity, vagina, conjunctiva and nervous system.

Herpes simplex viruses are cytolytic, causing cell necrosis and inflammation of the surrounding area (Rawls, 1973; Fenner et al., 1974). Systemic infections such as encephalitis can result in coagulation necrosis of vital organs. Actual cell changes have been observed through histologic examination of exfoliated cervical cells. A "ground glass" appearance is seen in which the nucleus is structureless and swollen. Numerous multinucleated cells are seen and intranuclear inclusion bodies are apparent (Nahmias and Norrild, 1979; Rawls, 1973).

Clinical manifestations of type 1 infection include acute herpetic gingivostomatitis, herpes labialis, skin lesions, eczema varicelliform, herpecticum kaposi, traumatic herpes, follicular conjunctivitis, herpetic encephalitis and herpes hepatitis. Because of the particular focus on the above factors associated with the acquisition of HSV-2, this review will focus on the clinical manifestations and sequellae of type 2 virus.

HSV-2 infections usually affect the genital area, hips or thighs.

Lymph nodes in the area may become swollen and pain in the legs or buttocks may develop during an episode. Individuals with symptoms often experience initial tingling and then painful burning and itching in the affected area. Pain or burning during urination or pain during intercourse and, in women, a burning vaginal discharge can occur. Genital herpes infections often cannot be detected upon physical examination. When detectable upon physical examination, genital herpes sores consist of fluid-filled vesicles with a thick cornium.

Herpetic lesions are more readily detectable in men than in women (Rawls et al., 1971). An examination of 59 men from whom HSV-2 was isolated from the urethral area revealed that in 18 (31%), herpes lesions could not be detected. Similarly, of 52 women in which HSV-2 was isolated from the cervix, 23 (44%) showed no evidence of genital herpes lesions (Jeansson and Molin, 1975).

Confirmation of infection through viral isolation is often not possible. Sumaya, Marx and Ullis (1980) isolated HSV in 13 (68.4%) of 19 specimens examined, taken from patients with clinical evidence of genital herpes, while Smith, Peutherer and Robertson (1973) isolated HSV in only 30 (38.5%) of 78 women and 35 (38.5%) of 91 men diagnosed as having genital herpes.

Many genital herpes infections are asymptomatic. When viral isolation from genital secretions is possible, this usually indicates a subclinical infection. Jeansson and Molin (1975) carried out a study to assess the occurrence of subclinical genital herpes. They examined 2,506 men and women attending a venereal disease clinic in Stockholm, Sweden. Isolates were taken from the urethra in men and from the cervix in women and the specimens were typed using an immunoelectroosmophoresis test. HSV-2 was isolated from 59 (4.3%) of 1,377 men 52 (4.6%) of 1,129 women without clinically apparent genital herpes. Tantivanich and Tharavanij (1980) reported that HSV-2 was isolated from the genital tract of 14 (8.9%) of 157 women who had no symptoms of infection. Adam et al. (1979) reported that HSV-2 was isolated from 5 (10%) of 50 women without symptoms of herpes genitalis.

Viral shedding can occur during periods of reinfection and up to 30 days following the infection (Guinan et al., 1980; Rawls, 1973). Because viral shedding from those infected is the method of transmission to a receptive host, the fact that viral shedding can occur in the absence of symptoms of infection is a particularly important characteristic of this virus.

2.2.1 Latency

Endogenous and exogenous factors which are capable of reactivating the latent virus are factors which affect the host such as exposure to sunlight, fever, menstruation and emotional stress.

There is evidence that, after infection, the HSV-2 virus travels to the neuroganglia, remains with the individual in a latent stage and can be reactivated through physical or even emotional stress, or through renewed exposure to the virus itself from an exogenous source. This can result in a recurrence of infection (Nahmias and Roizman, 1973b; Rawls, 1973).

Latency has been confirmed in a number of ways. Studies of inoculated and sacrificed mice revealed evidence of infection (Rawls, 1973). Human autopsy studies have shown that HSV-1 can be isolated from the trigeminal nerves in individuals showing antibody evidence in their blood and that HSV-2 can be isolated from the sacral ganglia with correlated antibody evidence of type 2 in their sera (Forghani, Klassen and Baringer, 1977). In addition, it has been shown that persons with antibody to the virus can have repeated active episodes of localized infection (Nahmias and Roizman, 1973a).

Primary infections are those that are found in persons without herpes simplex virus antibody to that same viral type. It is possible to have a primary infection with type 2 and still have antibodies to type 1. When symptoms occur, initial (primary) genital herpes infections are usually more severe and last longer than recurrent episodes. Herpetic sores usually develop between 3 and 7 days after initial infection and can last up to 33 days. Recurrent infections are infections that occur in a person who already has antibodies to the virus of that type. Recurrent infections can last from one to 14 days (Rawls, 1973; Guinan et al., 1980).

2.2.2 Neonatal Infection

Herpesvirus infection in the neonate is usually due to contact with the virus in the mother's birth canal upon delivery, and can result in serious neurologic damage, blindness, chorioretinitis and sometimes death (Nahmias and Starr, 1977; Rawls, 1973). Nahmias et al. (1971) reported that 140 (1.02%) of 13,766 asymptomatic pregnant women examined showed cytologic evidence of HSV-2. Maternal HSV-2 genital infection at the time of delivery is estimated to be as high as one in 1,000 to one in 30,000 deliveries. Neonatal herpetic infection is reported to occur in one of every 7,500 births (Nahmias et al., 1971). Nahmias et al. (1971) reported the occurrence of pregnancy complications in women with genital herpes infection in comparison with the rates in general obstetric hospital statistics. In 37 women whose genital infection was detected up to 20 weeks' gestation, spontaneous abortions occurred in 12 (33%). This proportion was three times that of the hospital rate of 696 in 6,536 (10.6%) pregnancies.

Of 148 neonates born to mothers with genital herpes infections, 105 (71%) died during infancy and of those who survived 22 (15%) suffered neurologic or ocular sequelae (Nanmias, Alford and Korones, 1970a). Amstey (1975) reported that of 12 babies born to mothers with genital herpes infection more than 4 hours after the membrane had ruptured, either through vaginal delivery or by Caesarian section, five (42%) died and three (25%) suffered serious consequences.

In order to prevent neonatal infection, the American Academy of Pediatrics Committee on the Fetus and Newborn (1980) recommended that cytologic and virologic studies be done at least twice during the last six weeks of pregnancy. Because the risk of infection to the newborn is greatest once the membrane is ruptured, delivery should occur within four hours of rupture. Caesarian section is recommended only if the membrane has been ruptured for less than 12 hours.

2.2.3 Transmission

Transmission of herpes simplex virus occurs through direct contact with viral particles shed from secretions of those infected during or following herpetic episodes. Autoinoculation is also possible, in which virus shed from lesions on one body site can be spread to other areas (Nahmias and Dowdle, 1968).

HSV-1 is generally spread through the oral-respiratory route. Nosocomial infections in which an adult-to-child and child-to-child spread of HSV among patients, their families and hospital staff occurs, have been reported (Buddingh et al., 1953; Hatherley, Hayes and Jack, 1980a, Hatherley, Hayes and Jack, 1980b; Hatherley et al., 1980c). Selling and Kubrick (1964) described herpes gladiatorum in which HSV is spread through the physical contact of wrestling. They reported an outbreak of HSV infection among five members of a 30-member wrestling team during a 10-month period.

HSV-2 is most frequently spread through contact with infected genital areas. Maternal to neonate transmission of HSV-2 can occur either by the newborn's contact with the mother's infected birth canal during delivery or through ascending spread of the virus to the fetus prior to delivery once the membrane is ruptured (Nahmias and Visintine, 1976a). Transplacental transmission of HSV-2 is relatively rare (Amstey, 1975; Nahmias and Norrild, 1979).

Although HSV-1 and 2 are both capable of infecting all body sites, venereal transmission of HSV-2 is a primary route. Venereal transmission of HSV-2 has been established through the examination of the sexual contacts of persons with herpes genitalis. Nahmias et al. (1969) reported that 7 of 8 women who had recent sexual contact with men diagnosed as having genital herpes showed evidence of HSV-2 within one week of contact. In order to assess the possibility of venereal transmission of HSV, 30 women who were sexual contacts of these 30 men were examined by Rawls et al. (1971) for genital herpes. HSV was isolated in 10 (33%) of these women compared with the isolation of HSV from the genital secretions of 4 (1.8%) of 222 control women. In addition to this evidence of venereal transmission of HSV-2, other factors suggest that HSV-2 is primarily spread through sexual contact. Individuals who have other venereal diseases such as gonorrhea are more likely to show evidence of HSV-2 infection than are those without other venereal disease (Adelusi, Fabiyi and Osunkoy, 1978; Duenas et al., 1972; Montefiore, Sogbetun and Anong, 1980; Jeansson and Molin, 1975).

Women who are sexually active, and especially prostitutes, more frequently show serologic evidence of HSV-2 infection than those not sexually active (Adelusi, Fabiyi and Osunkoy, 1978; Tantivanich and Tharavanij, 1980; Menczer et al., 1975; Rawls, Tompkins and Melnick, 1969).

Further evidence of the venereal transmission of HSV-2 is the fact that the virus is rarely found in children and generally does not appear in most populations until the age at which sexual activity begins (Adam et al., 1973b; McDonald et al., 1974a; Ory et al., 1975; Strizóva et al., 1976).

Given that the viral particle is present, the precise conditions for transmission are not well understood. Montefiore, Sogbetun and Anong (1980) suggested that transmission via fomites may be possible as HSV-2 inoculum was able to survive under experimental conditions of heat and moisture, on cotton swabs. Once drying of the swabs began, the HSV titer diminished considerably within three hours. Roome, Montefiore and Waller (1975) suggested that HSV-2 may be acquired from towels and other materials shared in institutional settings because the proportion of persons with HSV-2 antibody in prisons was higher than that found in non-institutionalized persons.

2.2.4 Antibody and Immunity

Antibody to the virus following an initial infection usually appears within one week of infection and reaches maximum titer approximately four weeks later. As noted earlier, absolute immunity to herpes simplex virus does not generally occur as the result of exposure. Antibody does not indicate resistance to lesion development. Although there are no genetic or racial differences in the response to the virus, not all individuals are equally susceptible to infection. Persons with prior exposure to HSV-1 experience less severe initial episodes of HSV-2 infection. Persons who are on immunosup- pressive medication, suffering from other illnesses and, possibly, those who have other genital problems are more susceptible to HSV-2 infection (Nahmias and Norrild, 1979).

After infection, antibody remains for life. Evidence that antibody persists for life comes from studies of repeated sampling of the same individuals over time, and indirectly from the fact that the proportion of the population with antibody increases with age.

2.2.5 Associated Diseases

Cervical Cancer

Over the last 15 years, well over 30 serologic surveys of cervical cancer patients and comparison groups have been carried out. Nearly all of these investigations have revealed that women with squamous cell cancer of the cervix more frequently show antibody evidence of HSV-2 infection than do women of similar age, race and social class.[1]

Because women with cervical cancer are also more likely to have other venereal diseases, represent lower socioeconomic groups and are relatively more sexually active than comparison groups, it is not clear whether the association of cervical cancer and HSV-2 is one of covariability. That is, women who are more likely to be at risk of cervical cancer for unknown socioeconomic or sexual reasons may also be at greater risk of HSV-2 infection. The investigations indicate that the association between cervical cancer and HSV-2 antibody is not merely one of covariability (Adam et al., 1972; Graham et al., 1982; Rawls et al., 1976). In a comparison of sexual behaviour and HSV-2 antibody among women with cervical neoplasia and control women, Graham et al. (1982) reported that the percentage of women with HSV-2 antibody as measured by RIA rose with the severity of cervical abnormality even when adjustment was made for the number of sexual partners. However, in another study Vonka et al., 1984b, reported that when cancer cases and control patients were matched for sexual behaviour and other factors, no difference in the proportion of women with HSV-2 antibody was found between the case and control groups. Further studies are required to resolve this question. In addition, the association between HSV-2 and cervical cancer includes the possibility that the neoplastic condition increases the vulnerability of the genital area to infectious agents such as this virus.

1 Adam et al., 1974; Adam et al., 1973b: Adam et al., 1972; Aurelian, Davis and Julian, 1973; Graham et al., 1979; Janda et al., 1973; Kessler et al., 1974b; McDonald et al., 1974b; Menczer et al., 1975; Nahmias et al., 1970b; Ory et al,, 1975; Ozaki et al., 1978; Pacsa et al., 1975; Pridan and Lilienfeld, 1971; Rawls et al., 1980; Rawls et al., 1970; Rawls, Tompkins and Melnick, 1969; Royston and Aurelian, 1970; Vonka et al., 1984a; Vonka et al., 1984b.

A number of factors strengthen the possibility that HSV-2 may be involved in the genesis of cervical cancer. Although the actual proportion of women with HSV-2 antibody varies considerably with geographic area, the association between the virus and cervical cancer is relatively consistent around the world (Rawls, Adam and Melnick, 1972). Furthermore, Rapp (1978) reported that neoplastic conditions can be induced in laboratory hamsters by herpes inoculation (Rapp and Reed, 1976). The analogy of the association of Epstein-Barr virus and Burkitt's Lymphoma suggests that a herpesvirus can be involved in oncogenesis (Rafferty, 1973). More recently, a resolution of the question of association and causation may be achieved through histologic studies which attempt to isolate HSV-2 virus particles from scrapings of neoplastic cells (Goldberg and Gravell, 1976; Nahmias, 1980). Rawls et al. (1980) examined the correlation between cervical cancer rates and HSV-2 antibody from a number of studies from different parts of the world. When the proportion of control samples with HSV-2 antibody was correlated with cervical cancer incidence in the same area, it was noted that HSV-2 could only account for a portion of cervical cancer cases. Rawls et al. (1980) estimated that approximately 7-8 cases of cervical cancer per 100,000 would occur in most populations in the absence of HSV-2, and that for every 10% of the population with HSV-2 an additional 4.9 cases per 100,000 would occur.

Although the association of serologic evidence of HSV-2 with cervical cancer is well established, it is also clear that many women with cervical cancer (approximately 70 to 90 percent in some studies) do not show antibody evidence of herpes simplex infection (McDonald et al., 1974b: Menczer et al., 1975; Ozaki et al., 1978; Vonka et al., 1984b). This suggests that infection with HSV-2 may be a sufficient but not a necessary condition in the development of cervical cancer.

Complete reviews of cervical cancer in herpes simplex virus are available in Kessler (1976); Rawls et al. (1980); Josey, Nahmias and Zaib (1976).

Prostatic Cancer

Serological surveys of HSV-2 antibody in patients with prostatic cancer and comparison groups have been carried out (Baker et al., 1981; Schuman et al., 1977). Baker et al. (1981) reported a study of a serologic comparison between 50 men with prostatic cancer and 159 men with benign prostatic hypertrophy. The average age of both groups was 69. According to the authors, both groups were highly sexually active, judging by their reports of venereal disease, use of prostitutes and number of sexual partners. However, no standard was used to determine this assessment. Social-sexual variables were not reported in relation to antibody. Using an hemagglutination-inhibition test, 68 percent of those with prostatic cancer showed type 2 antibody as compared with 51 percent of the benigh prostatic hypertrophy group. This result is reported to show a statistically significant ($P \leq 0.05$) difference between the groups.

It is evident that the social-sexual profile of men with prostatic neoplastic conditions suggests that their chance of HSV-2 as well as other venereal diseases may be greater than others less sexually active. As in the case of cervical cancer, further studies are needed to determine whether HSV-2 may be associated with prostatic cancer as a mere covariate of sexual behaviour.

Other Chronic Disease and Neoplastic Conditions

Herpes simplex virus has been investigated in association with nasopharyngeal cancer, Hodgkin's Disease, Parkinson's Disease, Multiple Sclerosis and neural tube defects. No association between HSV-2 and any of these conditions was reported in the limited number of investigations of these illnesses (Martin, 1981; Marttila et al., 1981; McDonald, Williams and West, 1974c; Nahmias and Norrild, 1979; Rawls, Tompkins and Melnick, 1969).

2.2.6 Treatment and Prevention

The evidence currently available on HSV infections indicates that although the virus, once acquired, cannot be completely eradicated from its host, episodes of active infection can apparently be controlled in some individuals by avoiding precipitating events such as physical or emotional stress and exposure to sunlight.

There are a number of preparations which will limit the episode somewhat and reduce the immediate discomfort. These include drying agents such as alcohol, dye-light therapy, analgesics and warm baths (U.S. Centers for Disease Control, 1980; Felman and Nikitas, 1979; Nahmias, 1980). Trials of vaccines such as BCG and influenza vaccine, and of immune stimulants such as interferon have been carried out with essentially negative results. Other treatments attempted include vitamin therapy, steroid creams, silver suphadiazine and some contraceptive foams (U.S. Centers for Disease Control, 1980; Nahmias, 1980).

Of the antiviral agents that have been investigated, the most promising results have been with the use of acycloguanosine

(ACYCLOVIR), a topical cream which inhibits HSV replication by acting on the necessary enzyme thymidine kinase (U.S. Centers for Disease Control, 1980); Nahmias, 1980; Saral et al., 1981). Although this agent cannot cure the infection, it could play a major role in reducing transmission as it has been found to reduce viral shedding (Corey et al., 1982b).

Prevention of primary HSV infection essentially involves avoiding contact with others known to have active infections. This presents a serious problem because, as noted earlier, a large proportion of infections are asymptomatic and often invisible. Although the effectiveness of occlusive birth control methods in preventing herpes infections has not be established, the use of such methods is encouraged (Corey, 1982a; U.S. Centers for Disease Control, 1980).

2.3. Laboratory Detection

Infection due to herpes simplex virus is confirmed through the use of laboratory methods. Morphologic description of herpes simplex is possible through the use of cytologic methods such as Tzanck and Papanicolaou smears, as well as through histologic and electron microscopic examination (Nahmias and Norrild, 1979).

Detection of HSV as an active virus and type specification can be accomplished through tissue culture and inoculation of chorioallantoic membranes, rabbit cornea and laboratory animals. Viral antigens can be detected through the use of immunofluroescent techniques (Nahmias et al., 1970c; Riott, 1977).

2.3.1. Immunologic Methods

Infections by HSV-1 and HSV-2 are associated with the production of antibodies which have been measured by a number of techniques. At the time of a primary HSV infection antibodies to the virus cannot be detected in the acute phase serum. Antibodies become detectable about one week into the convalescent period and may not peak earlier than one month following primary infection. The proportion of individuals with antibodies may vary in relation to the ability of the assay to detect small quantities of antibodies (Subramanian and Rawls, 1977). However, a number of studies have shown that not only does the proportion of persons showing HSV antibody in the populations studied increase with age, but that upon repeated sampling of the same individuals over time, antibody is sustained (Cesario et al., 1969; Glezen, Fernold and Lohr, 1975; Forghani, Klassen and Baringer, 1977). Thus, the presence of detectable antibodies to HSV in serum appears to reflect past exposure to the viruses.

Differentiating antibody responses to HSV-2 from those to HSV-1 represents a special problem since these two virus types share common antigens. Primary infections with HSV-1 are associated with the production of antibodies to shared as well as specific antigens of HSV-1. The same is true for primary infections with HSV-2. However, HSV-2 infections in individuals who had previously been infected with HSV-1 may not result in the appearance of large quantities of HSV-2 specific antibodies (McClung, Seth and Rawls, 1976; Smith et al 1972). Thus, most serologic assays for HSV-2 infections have been based on the simultaneous quantification of antibodies to both virus types and the relative titers used to interpret the results (Plummer, 1973). Alternatively, antibodies to shared antigens have been removed from the sera by adsorption with heterologous virus and the remaining type-specific antibodies measured by one of several detection systems (Forghani et al., 1975).

The validity of the assays can be estimated by comparing the relationship between assay results and virus isolation from patients with clinical disease. This relationship can be expressed using standard terms of validity including sensitivity and specificity, and reliability including percent agreement. The methods of calculating validity are presented in Appendix I. Also, convergence of results among assays, can be examined. In reviewing the literature special attention will be paid to the comparison of the radioimmunoassay (RIA) used in the present investigation and the microneutralization (MN) test because this method has been used in numerous studies around the world. Published reports indicate results from sera analyzed by MN of approximately 3,000 persons. (Adam et al., 1972; Duenas et al., 1972; Kessler et al., 1974b; Mann et al., 1984; McDonald et al., 1974a; Nahmias et al., 1970b; Ozaki et al., 1978; Pridan and Lilienfeld, 1971; Rawls et al., 1970; Roome, Montefiore and Waller, 1975 and Strizova et al., 1975). A summary of studies reporting results of these assays applied to sera from patients with clinical HSV-2 infections is shown in Table 1. Two reports on the RIA indicate that all patients from which HSV-2 virus was isolated were positive by RIA while HSV-2 antibodies were also detected in 16 to 25 percent of patients from which the virus was not isolated (Forghani et al., 1975; Forghani, Klassen and Baringer, 1977). By microneutralization, 82.4 to 95.2 percent of patients from which virus was isolated were considered positive for HSV-2 antibodies while antibodies were detected in 6.7 to 32.8 percent of women from which the virus was not isolated (Rawls et al., 1970; 1971). These observations suggest that both assays are quite sensitive, but may lack

TABLE 1

Relationship Between Setologic Detection of HSV-2 Antibody and Clinical Evidence of HSV-2 Infection

SAMPLE	N	PERCENT SENSITIVITY	PERCENT SPECIFICITY	PERCENT FALSE NEGATIVE	PERCENT FALSE POSITIVE	PERCENT AGREEMENT	REFERENCE
RIA vs Viral Isolation from genital tract of persons with genital herpes	33	100	75.0	0	25.0	78.8	Forghani et al., 1975
RIA vs Viral Isolation from Neuralganglia	40	100	83.9	0	16.1	87.5	Forghani, Klassen and Baringer, 1977
MN vs Clinically diagnosed genital genital herpes	36	95.2	93.3	4.8	6.7	94.4	Rawls et al., 1970
MN vs Recurrent genital herpes							Rawls et al., 1970
HIGH SOCIOECONOMIC GROUP	106	82.4	93.1	17.6	6.9	91.8	
LOW SOCIOECONOMIC GROUP	96	85.7	67.2	14.3	32.8	74.0	

specificity.

There appear to be several limitations in drawing conclusions from these reports. Only a small number of individuals were studied. Secondly, antibody positive persons in whom virus could not be isolated may represent distant infection with the virus rather than infection at the time viral isolation was attempted. If this were the case, the specificity would be greater than suggested by the data shown. Finally, it is not known if conclusions drawn from studies of patients with clinical evidence of infection can be generalized to those with subclinical infections.

A second method of evaluating the assays is to compare the results obtained by different techniques. Table 2 illustrates data comparing radioimmunoassays with the MN test which was used as the "gold standard". The percent agreement of positive results between assays corresponds to "sensitivity" and percent agreement of negative results to "specificity: if one assay is used as a standard. Agreement of approximately 78 percent was observed in two studies. When compared with MN, RIA showed a percent agreement of positive results of 73.2 to 76.2 and percent agreement of negative results of 80.4 to 88.2. These values were observed from case-control studies of cervical cancer (Rawls et al., 1981) and from a selected sample of adult women in Prague Czechoslovakia (Suchankova et al., 1984). In another study (not shown on Table 2), HSV-2 antibody was detected in the sera of 57 (22%) of 255 women by RIA. When the sera of 251 of these same women were tested using the MN method 88 (35%) showed HSV-2 antibody (Rawls et al., 1980). However, positive and negative agreement of the RIA compared with the MN using data from this study could not be calculated

TABLE 2

Relationship between the Radioimmunoassay and the Microneutralization in the Detection of HSV-2 Antibody

SAMPLE	N	PERCENT POSITIVE AGREEMENT	PERCENT NEGATIVE AGREEMENT	PERCENT AGREEMENT	REFERENCE
RIA VS MN	133	73.2	88.2	78.9	Rawls, 1981*
RIA VS MN	282	76.2	80.4	79.4	Suchankova et al., 1984

* Same Laboratory as in the present study.

as those positive by the RIA and negative by MN were not reported in the 1980 study.

The validity of serological assays for HSV-2 antibodies is also suggested by data from studies correlating HSV-2 antibody with sexual activity. Antibodies to HSV-2 are not found until the age of adolescence in most populations studied (McDonald et al., 1974a; Rawls, Tompkins and Melnick, 1969; Strizova et al., 1975). Using an RIA, Patterson, Rawls and Smith (1978) detected HSV-2 antibody in sera from 10 (55%) of 18 prostitutes, while HSV-2 antibody was not detected in any of the sera from 18 Catholic nuns. When type-specific antibody was examined from 230 women in relation to number of sexual partners, Suchankova et al. (1984) showed that a greater proportion (30%) of women with multiple (>2) sexual partners showed HSV-2 antibody compared with 10 percent for women with only one sexual partner. Of 4 women who had never had intercourse, none showed HSV-2 antibody. However, in this same group of women no variation with regard to the proportion with HSV-1 antibody was observed. Approximately 86 percent of all women showed HSV-1 type-specific antibody regardless of their number of sexual partners.

While the MN and RIA methods appear to be reasonably sensitive but somewhat less specific in the detection of antibodies in patients with clinical HSV-2 infections, the true validity of these assay methods for the detection of antibody in the general population is unknown. From the limited information that is available, when the RIA is compared with the MN in a healthy population, slightly more individuals are identified as HSV-2 positive by MN than by RIA. Both methods are considered to be reasonably accurate in the detection of past subclinical infections. (Forghani et al. 1975; Forghani, Klassen and Baringer, 1977; Patterson, Rawls and Smith 1978; Rawls, 1978; Rawls, 1981). Compared with the MN the RIA is recommended for use in large scale studies because of its relative simplicity of application and low cost. Thus, the RIA was selected for the method of analysis in the present study.

2.4 Historical Aspects

The term "herpes" is said to have been derived from the Greek verb "to creep" ([illegible]) initially used to describe spreading skin lesions, and was applied to the present description of herpes lesions by Daniel Turner in 1714 (Beswick, 1962).

Hutfield (1966) reports that herpes febriles was first described by Herodotus in Rome in 100 A.D. Herpes-like skin lesions were often described in association with fever and ulcerative conditions. On occasion the term "herpes" was used to identify what may have been actual herpes conditions such as shingles and mouth sores in children (Beswick, 1962).

During the 18th century, venereal diseases, particularly syphilis, began to receive much attention in France. The French physician Jean Astruc is credited with the first clinical description of herpes genitalis in a treatise on venereal disease, _De morbis venereis_, published in 1736 (Hutfield, 1966). From that time onward there are records of herpes genitalis and its association with other venereal diseases, particularly among prostitutes and the "lower class". A variety of treatments, from cleansing rituals to arsenic preparations, was recommended (Hutfield, 1966).

Toward the end of the 19th century attempts were made to isolate the cause of herpetic infections and Wildy (1973) reports that herpes simplex virus was first successfully inoculated on to rabbit cornea in 1911 by Gruber and filtered in 1921 by Luger.

Serologic investigations of undifferentiated herpes simplex were begun by Andrewes and Carmichael in 1930, who noted infection in the presence of antibody. According to Burnet and Williams (1939), R. Doerr suggested in 1938 that this virus was essentially endemic in man. They refuted this conclusion when a serologic study of children showed evidence of both primary and recurrent infection apparently due to exogenous factors.. During the late 1950s, the morphologic characteristics of herpes virus were described (Wildy, 1973). The serologic similarity among herpesviruses as a group was first noted by Sabin in 1934 and contributions to the description of the subtypes of this virus were made by a number of investigators including Watkins, Watson and Wildy, Roizman and Halliburton (Wildy, 1973). A complete review of the development of the concept of herpes viruses and their subdivisions is provided by Wildy (1973).

The observation that oral and genital herpes lesions may be caused by different types of herpes simplex virus was made by Lipshutz in 1921 (Nahmias and Dowdle, 1968) and later confirmed using laboratory methods by Schneweis and Brandis (1961), Plummer (1964), Pauls and Dowdle (1967), Nahmias and Dowdle (1968) and Rawls et al. (1968).

The health consequences of HSV infections were noted especially with regard to neonatal infection (Nahmias and Roizman, 1973b). The association of HSV-2 with cervical cancer, first reported in the late 1960s, gave rise to many serologic investigations of cervical cancer patients and comparison groups (Naib, Nahmias and Josey, 1969; Nahmias and Roizman, 1973b; Rawls, Tompkins and Melnick, 1969).

Since the 1970s research has focused on the search for effective therapeutic and preventive methods, studies of general HSV-2 prevalence and attempts to quantify the undetected morbidity (Nahmias, 1980).

2.5 Disease Frequency

The prevalence of HSV-2 infections is difficult to establish for a number of reasons. In Canada, as in most parts of the world, genital herpes was not a reportable disease. Therefore incidence estimates must be extrapolated from clinical studies of genital herpes antibody surveys and reports of other venereal diseases.

Because of the asymptomatic, clinically elusive nature of many genital herpes infections, they are often not known to the host and not recorded in physicians' records. In addition, herpes infections may be misdiagnosed as other venereal diseases and elude clinical diagnosis because they co-exist with more easily diagnosable diseases (Judson, 1976).

Furthermore, as the antibodies to serotypes HSV-1 and HSV-2 cross-react, information about the distribution of HSV-2 from serologic surveys may affect the estimates of the prevalence of HSV-2 infection because of the specific population's prior exposure to HSV-1.

In addition, the variation in the criteria as to HSV-2-specific antibody across all the serologic methods as well as variation in the application of any one method may further obscure an accurate account of the distribution of this virus in any population.

With these difficulties in mind, an estimate of the overall prevalence of HSV-2 is available from a variety of sources. These include:

- Clinical studies of primary and recurrent genital herpes infections
- Clinical studies of venereal disease clinic attendees
- Surveillance studies of women attending prenatal and antenatal clinics
- Cross-sectional seroepidemiologic surveys
- Serologic surveys of diverse population groups, including occupational groups, students, prisoners and blood donors
- Seroepidemiologic surveys comparing cervical and prostatic cancer patients with control groups
- Reported occurrence of genital herpes infection from questionnaire surveys.

Although information from all of these sources will be utilized in this review, only seroepidemiologic investigations which measure past HSV-2 infection have been reviewed in detail in this chapter.

2.5.1 Reported Occurrence and Clinical Detection

Because the detection of HSV-2 can be affected by the individual's exposure to HSV-1, the general prevalence of undifferentiated HSV and, within this, HSV-1 antibody must be taken into account.

Herpes Labialis

The reported occurrence of herpes labialis (cold sores) provides estimates of possible HSV-1 infection. Estimates of reported cold sores range from 28 percent to 49 percent of individuals questioned (Rawls, Moses and Rotkin, 1975; Grout and Barber, 1976). Embil, Stephens and Manuel (1975) found that of 10,532 persons who replied, 33 percent of men and 28 percent of women had experienced two or more episodes of herpes labialis in their lifetimes. The highest proportion of persons who reported having had recurrent herpes labialis was found in North America (40%) and the lowest was in Asia (18%).

Herpes Genitalis

In a student population, Delva and McSherry (1984) reported that genital herpes was clinically diagnosed in 39 (0.6%) of 6,651 patients seen in the student health service of Queen's University in Kingston, Ontario, over a 9 month period.

Ishiguro et al. (1982) reported the rates of detection of HSV in two outpatient clinics. Although the overall rate was relatively low in both groups of patients, the rates were higher in women seen in the obstetrics and gynecology clinic, 0.24 percent of 13,788 patients, than those seen in a cancer screening clinic, 0.01 percent of 16,143.

It is estimated that from 0.8 to 9 percent of patients seen in venereal disease clinics in Great Britain and the U.S. are diagnosed as having genital herpes (Beilby et al., 1968; Chang, Fiumara and Weinstein, 1974; Nahmias et al., 1969; U.S. Department of Health and Social Security, 1980).

Reported clinical evidence of HSV-2 infections when compared to other venereal diseases indicates that herpes genitalis is less commonplace than gonorrhea but more frequently diagnosed than syphilis. The U.S. Centers for Disease Control (1980) reported that, based upon information from a sampling of clinics, there is approximately one case of genital herpes for every 10 cases of gonorrhea. They further state that the estimated number of new cases of genital herpes is approxmately 300,000 per year compared to approximately 2.7 million total cases of gonorrhea. The 1971 Annual Report of the Chief Medical Officer of England recorded 121.26 cases of gonorrhea, 7.96 cases of genital herpes and 5.94 cases of early syphilis per 100,000 men and women. This information was based upon the records of hospital clinics in England between 1967 and 1971 (U.K. Department of Health and Social Security, 1973).

A similar distribution of genital herpes and other venereal diseases has been reported by other investigators (Judson, 1976; Felman, 1980).

2.5.2 Evidence of Asymptomatic HSV

Because viral shedding is the primary source of HSV infection, the rate at which shedding occurs, particularly in the absence of symptoms, is of interest. Studies of undifferentiated HSV indicate that HSV can be isolated from the saliva of children and adults without symptoms of infection. Buddingh et al. (1953) isolated HSV from the saliva of 13 percent of 271 children between the ages of 7 months and 14 years. Cesario et al. (1969) studied the occurrence of HSV in a children's home over the six year period, 1961 to 1967. Of 143 children 32 percent excreted HSV in the saliva at least once during this time. HSV was isolated from the saliva of 10 percent of 340 hospital staff members (Hatherley, Hayes and Jack, 1980a).

In order to estimate the frequency of viral shedding from the genital tracts of persons without symptoms of genital herpes, a number of investigators have screened specific groups of people in an attempt to isolate the virus from genital secretions or exfoliated cells.

Pacsa et al. (1977) examined the exfoliated cervical cells of women by indirect immunofluorescence and found that HSV was identified in 9 percent of 710 sexually active women and was not found at all in 106 women who had never had sexual intercourse. Of 43,331 women examined by Wolinska and Melamed (1970), HSV was found in the cytologic specimens of 37 women.

Knox et al. (1979) attempted to isolate HSV-2 from the genital tracts of women in Birmingham, Alabama. HSV was isolated in 9 (1.4%) of 659 women.

Of particular interest with regard to risk to the newborn is the role of HSV isolation in antepartum and postpartum women. Nahmias et al. (1971) found that HSV could be isolated in 1.02 percent of 13,766 antepartum women and in 0.58 percent of 7,357 postpartum women. Unusually high rates of detection in pregnant women were reported in two studies. When Jacob et al. (1984) examined 215 pregnant women, seen in upper income private practices in Baltimore, Maryland, HSV was detected in 10 (4.6%) of cervicovaginal specimens. The risk of HSV-2 infection from latent maternal genital herpes to the newborn was assessed by Yeager (1984) in which asymptomatic viral excretion occurred in 2.4 percent of 338 pregnant women. Similarly, Scher et al. (1982) reported the detection of HSV in specimens of 4 percent of 488 pregnant women without symptoms of infection.

HSV was isolated from four (1.8%) smegma specimens from 198 patients attending a venereal disease clinic in Houston, Texas (Rawls et al., 1968). A rather high rate of HSV was reported by Centifanto et al. (1971). When 190 male patients who had no history of genital herpes infections were examined, HSV-2 was found in fluid from the prostatic urethra in 27 (14.2%). Viral detection is generally much higher in patients with symptomatic infections. Lawee et al., (1983) reported that HSV was cultured in specimens of 58 percent of 31 patients with symptomatic genital infections and only 0.5 percent of 179 asymptomatic patients with clinically diagnosed genital herpes.

The relatively low detection of HSV in genital specimens may be due in part to difficulty in the isolation technique, as HSV can be isolated in only a portion of even those persons with symptomatic HSV infections.

2.5.3 Relative Prevalence

The prevalence of serologic evidence of undifferentiated herpes simplex virus relative to other viruses infecting humans has been reported by a number of investigators, indicating that herpes simplex virus is less frequently found than Epstein-Barr virus, occurs with about the same frequency as Varicella-Zoster virus, and is less often found than cytomegalovirus, rubella, parainfluenza virus and influenza virus A (Cabau et al., 1980; Mufson et al., 1967; Porter, Wimberly and Benyesh-Melnick, 1969; Sohier et al., 1974; Wentworth and Alexander, 1971).

The prevalence of HSV-2 antibody relative to other viruses has been examined. HSV-2 antibody is usually found to be less prevalent than antibody to Epstein-Barr or cytomegalovirus, (Black et al., 1974; Timbury and Edmond, 1979).

2.5.4 Evidence of Past HSV Infection

Undifferentiated HSV Antibody

Early studies of undifferentiated herpes simplex virus indicated HSV antibody was found in a substantial proportion (40% to 90%) of adults and that the proportion of persons with antibody rose with age (Andrewes and Carmichael, 1930; Burnet and Williams, 1939b; Anderson and Hamilton, 1949). Similar results were reported in later studies (Yoshino et al., 1962; Wentworth and Alexander, 1971; Rawls, Moses and Rotkin, 1975; Hatherley, Hayes and Jack, 1980a).

HSV-1 and HSV-2 Antibody

HSV-2 is generally found to occur approximately one-third as frequently as intermediate antibody and HSV-1. The distribution of HSV-1 and HSV-2 antibody is shown in Appendix I.

Strizova et al. (1975) examined the sera of 246 randomly selected townspeople obtained through a door-to-door survey. Using a standard microneutralization test, HSV-1 antibody was found in 25 percent of children under the age of 10. No HSV-2 was found in this age group. HSV-1 was found in 63 percent of young persons between the age of 10 and 19 and HSV-2 occurred in 11 percent of persons in this age group. Among adults aged 20 and over HSV-1 antibody occurred in 69 percent compared to 21 percent of adults who showed HSV-2 antibody. In another household survey of 564 children and women in Montreal carried out by McDonald et al. (1974a), 35 percent of children between the ages of 2 and 15 showed HSV antibody when their sera were measured by microneutralization. Approximately 48 percent of the women were found to have HSV-1 specific antibody response, and 19 percent showed HSV-2 antibody. If the intermediate and HSV-1 responders are combined, it is evident that HSV-2 antibody occurs at slightly over 1/3 the rate of HSV-1 and intermediate response.

HSV-2 Antibody

A summary of HSV-2 antibody prevalence appears in Appendix I. The studies are listed by type of sample and, within this, by assay method. It is evident that there is a wide range in the proportion of persons with HSV-2 antibody using any one assay method both within and between studies. These household surveys include those done by McDonald et al., 1974a; Strizova et al., 1975; Black et al., 1974; Niederman, Horstmann and Opton, 1960; and Rawls et al., 1980. Both McDonald et al. (1974a) and Strizova et al. (1975) stated that their samples were "randomly selected" but no information about just how representative the participants were of the populations examined was given. Both used a standard microneutralization test. McDonald et al. (1974a) found that 18 percent of 430 women between the ages of 16 and 55 showed HSV-2 antibody. Strizova (1975) did not report the antibody prevalence by gender but stated that both men and women were included. Twenty percent of 181 persons between the ages of 15 and 55 showed evidence of HSV-2 antibody.

Black et al. (1974) reported the results of a study that compared sera from members of Indian tribes in the Amazon Basin in Brazil to the sera of persons in cities in Connecticut gathered some years earlier (Niederman, Horstmann and Opton, 1960). The study surveyed both groups for a variety of viruses including influenza, measles and poliovirus. Of 141 tribesmen tested, 116 (82%) were antibody positive to type 2 antigen. Of 91 townspeople tested, 39 (43%) were antibody positive to type 2 antigen.

In Toronto a comparison group of cervical cancer cases was obtained using a door-to-door household survey method. Of 255 control women 57 (22%) showed HSV-2 antibody when their sera were analyzed by the radioimmunoassay method used in this study (Rawls et al., 1980).

The variation in antibody prevalence relative to social class and other factors will be discussed in Section 2.6.

2.5.5 Trends

Over the last decade, there has been increased attention to herpes infections in the media, which may have made people more likely to consult their doctors about genital infections. Improvements in laboratory diagnostic methods may have resulted in better differential diagnosis of herpes from other genital infections.

In addition, the increase in publications in the medical literature regarding genital herpes in particular in relation to cervical cancer may have resulted in an increased attention on the part of physicians to the diagnosis of genital herpes problems.

The rates of new cases of genital herpes seen in hospital clinics in England between 1971 and 1975 and reported in the 1975 Annual Report of the Chief Medical Officer indicated that for men the rates per 100,000 dropped from 22.22 in 1971 to 14.71 in 1973. For women the rates increased from 3.95 in 1971 to 6.48 in 1973. Statistics for only the first half of 1974 and 1975 were available and indicate 8.69/100,000 for men in 1975 and 3.90 for women (U.K. Department of Health and Social Security, 1977).

Information was collected on trends in genital herpes in the United States from 1966 to 1979 by the National Disease and Therapeutic Index, which is a national survey from a stratified random sample of patients seen by physicians in the U.S. This sample includes all consultations for genital herpes between patients and physicians but does not include clinical confirmation of the diagnosis. It is reported that consultations for genital herpes rose from 29,560 in 1966 to 260,890 in 1979. This increase was from 3.4/100,000 physician consultations in 1966 to 29.2/100,000 consultations in 1979, and represents a ninefold increase in genital herpes consultation over this time period (U.S. Centers for Disease Control, 1980).

Tobias and Hermon (1983) reported a trend in the occurrence of diagnosed genital herpes infections through specimens submitted to the National Health Institute in Wellington, New Zealand, during 1971-1973 and 1981-1982. The authors note that while the overall proportion of HSV infection for both types of virus was similar for these time periods, a shift in the virus type with regard to site was evident. During the 1971-1973 period, 4 percent of genital isolates were HSV-1, whereas in 1981 this rose to 11 percent, and oral isolates rose from 6 percent of HSV-2 to 24 percent in 1981-82.

A number of authors suggest that genital herpes infections might well be on the increase because of other evidence that venereal diseases in general have increased over the last decade (Felman, 1980; Morton, Horton and Baker, 1979). There has also been increased use of non-occlusive contraceptive methods such as the birth control pill. There is, as well, considerable speculation in the social sciences literature on changes in sexual mores, permitting greater access to numerous sexual partners and therefore an increase in the likelihood of contracting a venereally transmitted disease (Morton, Horton and Baker, 1979).

2.6 Factors Associated with HSV-2

HSV-2 antibody studies are summarized in Appendix I. A list of factors investigated with regard to HSV-2 infection is presented in Table 3 in this section. Only studies that reported results in terms of the proportion of persons with HSV-2 antibody are included in this table. In addition, selected information from viral isolation studies is included, when these studies report sexual, socioeconomic and contraceptive factors.

Statistical analysis of the relationship of the factors involved in HSV-2 infection was rarely available in the reported investigations. Chi squares for independence were applied to the data in some instances and are specified in the text. An additional limitation of the available information is that the representativeness of the study participants in terms of their population was not reported in most studies. Because of the great variation not only among assay methods but within the same method used at different times, some caution must be exercised when interpreting differences between one study and another. Comparisons of groups within each study provide the most useful information. In general, the groups compared within each study were similar in age. The factors discussed most often represent "single factor" associations and potential confounding factors that could be associated with both the attributes and HSV-2 antibody were generally not taken into account by the investigators.

Information on the estimated distribution of past type 2-specific infections in a number of populations is available from three major types of published investigations. These include household surveys, surveys of specific population groups and studies of cancer cases and controls.

Household Surveys

These are cross-sectional surveys which utilize a residential sampling method to obtain willing participants who have not been otherwise identified through a specific organization, institution or health care facility. Included in this group of studies are those which use comparison subjects sought from neighbourhoods where cancer cases reside.

Surveys of Specific Population Groups

These studies include surveys of specific groups of persons within a population expected to vary in sexual experience. Populations included venereal disease clinic attendees, school children, and Catholic nuns.

Antibody Comparison Studies of Cancer Cases and Controls

A number of seroepidemiologic surveys carried out over the last 15 years have compared the frequency of type 2-specific antibody in women with and without cervical cancer. Most often information is gathered through personal interview with both the cancer case and control participants. Sera are usually obtained before treatment and chemotherapy have begun. The use of information from cervical cancer studies in describing specific factors and HSV-2 is limited in two ways. Usually control women are matched not only for age and race with their appropriate case, but for socioeconomic status as well. Although this careful matching is useful in the case-control comparison, unfortunately potential HSV-2 risk factors which may be socioeconomically determined as well, such as sexual behaviour, cannot be directly examined. A second limitation is that comparison groups are usually taken from the hospital or clinic groups which may not reflect the traits or viral experience of their original population. Antibody comparisons between men with prostatic cancer and control groups have been reported as well, providing information about HSV-2 antibody in men.

Although there are many characteristics associated with evidence of HSV-2 infection, it may be possible to reduce these to a few factors which may directly increase the chance of exposure to HSV-2, such as numerous sexual partners; or indirectly encourage infection through hygienic or other lifestyle factors. Factors investigated in association with HSV-2 infection are reviewed in the sections that follow.

2.6.1 Age

Around the world, HSV-2 antibody is rarely found in persons under the age of 15. The proportion of the population with antibody evidence of HSV-2 increases rapidly in the early twenties and stabilizes some-what after the age of 40. This finding is consistent with the theory of venereal transmission in that antibody does not appear until sexual

activity has begun.

McDonald et al. (1974a) examined HSV antibody in a group of 564 female residents of Montreal between the ages of 2 and 55. This study indicated that the percentage of persons with HSV-2 antibody rose from 6 percent of children between the ages of 2 and 15 to 18 percent of persons between the ages of 26 and 35 to 24 percent of persons between the ages of 46 and 55. A household seroepidemiologic survey was carried out by Strizova et al. (1975) in Ostrava and Prague, Czechoslovakia, to assess age distribution and prevalence of HSV-1 and HSV-2 in this population. Sera from 246 randomly selected persons were examined using a microneutralization technique. The age of the study sample ranged from infancy to 60 years. No type 2 antibody was found in children under nine years of age. The proportion of persons with type 2 specific antibody rose from 4 percent in those aged 10-14 years, to 17 percent in those aged 15-19 years, to 18 percent in those aged 20-34 years, and finally to 23 percent in those aged 35 years and over.

The age distribution of HSV-2 antibody in a group of persons primarily made up of Negroes attending low income medical care facilities in Houston, Texas was reported by Rawls, Tompkins and Melnick (1969). The 266 persons examined were between the ages of 1 month and 61 years. HSV-2 antibody, as measured by kinetics of neutralization, was not found in children under the age of 12. Nine percent of children between the ages of 13 and 16 showed HSV-2 antibody, increasing to 17 percent in persons aged 17 to 25, 20 percent in those aged 26 to 40 and 22 percent in those over age 40. A similar age trend was reported by numerous other investigators.

2.6.2 Race

In a review of geographic variation in HSV-2 antibody, Rawls, Adam and Melnick (1972) reported a difference between Negro and non-Negro cervical cancer patients in the proportion of women with HSV-2 antibody. The authors stated that from 68 percent to 96 percent of Negro patients showed antibody compared to lower proportions of 27 percent to 60 percent of non-Negro women, but that these differences did not take socioeconomic or cultural factors into account. In three other studies no racial differences in the proportion of women with HSV-2 antibody were found (Duenas et al., 1972; Adam et al., 1973b; and Rawls et al., 1980). Of particular interest is the study by Duenas et al. (1972) in which two groups of women with similar degrees of promiscuity were compared. The authors reported the occurrence of HSV-2 antibody in two racial groups of prostitutes. A similar proportion of HSV-2 antibody was found in both racial groups: of the 196 Mestizo Indian women, 123 (63%) showed HSV-2 antibody and 91 (62%) of 147 Negro women were HSV-2 positive. The authors concluded that if differences in the occurrence of HSV-2 antibody were found in different racial groups these may reflect differences in exposure to the virus due to behavioural factors rather than any difference in the immunologic responses to the virus between races.

2.6.3 Tribe

When women of all ages were combined, Adam et al. (1972) did not find a difference in the proportion of women with HSV-2 antibody between Ganda and non-Ganda tribes in Kampala, Uganda.

2.6.4. Religion

Differences in HSV-2 prevalence with religion may indicate differences in sexual exposure to the virus because of religious customs. However, no differences between Jewish and non-Jewish women in the occurrence of HSV-2 antibody were found by McDonald et al. (1974b). Similarly, Kessler et al. (1974c) did not find a difference in the proportion of Moslem and non-Moslem women with HSV-2 antibody.

2.6.5 Urbanization

Although HSV-2 antibody was more frequently found at an earlier age in rural than in urban areas of the Delhi region in India, Seth et al. (1981) did not find an urban-rural difference in the proportion of men and women with HSV-2 antibody. Rawls, Adam and Melnick (1972) reported that a greater proportion of Negro women living in rural areas outside Houston, Texas showed HSV-2 antibody than those living in the city.

2.6.6 Circumstance

Roome, Montefiore and Waller (1975) compared the occurrence of HSV-2 antibody in 111 male blood donors living in various towns in England with prison inmates of similar ages (average age 32). Fourteen (13%) of the 111 free-living men showed HSV-2 antibody, compared to 87 (42%) of 206 prison inmates. A higher proportion of men in long term prisons showed antibody than those in short-term prisons. Of 111 men from two long-term prisons, 61 (55%) showed HSV-2 antibody and of 95 men in short-term prisons, 26 (27%) had antibody. The authors suggested that HSV-2 transmission may be more likely to occur in institutional settings due to possible homosexual contact or non-sexual contact via fomites on non-living material such as towels.

2.6.7. Pregnancy

In most investigations little difference in the proportion of women with and without HSV-2 antibody was found with regard to age at first pregnancy, number of pregnancies or number of live births (Adam et al., 1972; Adam et al., 1973a; Adam et al., 1974; Duenas et al., 1972). Duenas et al. (1972) reported that among a group of prostitutes, those who had been pregnant were more likely to show HSV-2 antibody than those who had not. Twelve (67%) of 18 women who had been pregnant showed HSV-2 antibody compared to 14 (36%) of women who had not. Ory et al. (1975) reported that a greater proportion of women who had had at least two pregnancies showed HSV-2 antibody than those with no more than one.

2.6.8. Marriage

In a serologic survey of 507 men and women in Delhi, India, Seth et al. (1981) found that HSV-2 antibody was more frequently found in married than in unmarried men and women. No significant difference in the occurrence of HSV-2 antibody according to marital status, age at first marriage and number of marriages was reported by other authors (Adam et al., 1973a; Adam et al., 1974; Ishiguro and Ozaki, 1978).

2.6.9 Age at First Intercourse

Age at first intercourse in relation to HSV-2 antibody was examined by a number of investigators. Ishiguro and Ozaki (1978) carried out a study to look at sexual behaviour and HSV-2 antibody in 171 gynecology patients in Osaka, Japan and found little difference in the distribution of the age at first intercourse and HSV-2 antibody. In one study of cancer patients and controls no association between age at first intercourse and HSV-2 antibody was found in a Ganda tribe examined (Adam et al., 1972). In the non-Ganda tribe in this same study as well as in two other studies, HSV-2 antibody was associated with an early first intercourse (Adam et al., 1972; Adam et al., 1974; Adam et al., 1973b).

2.6.10. Number of Sexual Partners

A statistically significant difference in the proportion with HSV-2 antibody was observed between Japanese women who reported 1 sexual partner and those who reported 2 or more. Women who reported at least 2 sexual partners in a lifetime more frequently showed antibody (Ishiguro and Ozaki, 1978). Suchonova et al (1984) also found that HSV-2 antibody was more frequently found in women with many sexual partners than those with few.

Graham et al. (1982) carried out an investigation of the relationship between number of sexual partners and HSV-2 antibody among women with cervical neoplasia and a comparison group of patients in Los Angeles County. Among 128 control patients, a greater proportion of women who reported 2 or more sexual partners showed HSV-2 antibody compared to those who reported 1 partner.

In two studies conducted in Houston, Texas, no significant difference in the proportion of women with HSV-2 antibody was found between women reported few or those who reported many sexual partners (Adam et al., 1973b; Adam et al., 1974).

Donovan (1984) reported the clinically diagnosed genital herpes infection in a group of prostitutes in Sydney, Australia. The group of 70 women studied reported exposure to an average of 80 different sexual partners each week. In the women examined over a six month period, 12 (17%) showed evidence of genital herpes and experienced an average of 2 episodes of infection each during this period. When the unusually high number of partners is taken into account, the high rate of diagnosed genital herpes is not surprising. These results provide one documented example of the rate of genital herpes in a group of women with what might be close to a maximum number of conceivable sexual exposures.

2.6.11 Sexual Activity and Venereal Disease

Ishiguro and Ozaki (1978) reported that of 17 women who had not had sexual intercourse, none showed HSV-2 antibody, compared to 16 (12%) of 137 women of similar ages who had experienced sexual intercourse. In an investigation done by Pacsa et al. (1977) in Hungary, an indirect immunofluorescence technique was used to identify HSV in cervical specimens of 816 women. HSV was not isolated in any of the specimens of women who had not had intercourse compared to 9 percent of 710 women who had begun sexual activity.

When Menczer et al. (1975) examined the sera of 202 women from several groups for HSV-2 antibody, 10 percent of imprisoned prostitutes showed antibody compared to 2 percent of individuals described as "healthy" participants, but they were not significantly different from a group of gynecology and cervical cancer patients. Among several groups examined by Adelusi, Fabiyi and Osunkoy (1978), both prostitutes (46%) and venereal disease clinic patients (47%) were similar in the proportion with HSV-2 antibody, and both of these groups had a higher proportion with antibody than other patients examined. In gynecology patients and family planning clinic attendees 25 and 29 percent showed antibody. Tantivanich and Tharavanij (1980) reported that 40 percent of 157 women working as hospitality girls, bar girls and masseuses showed HSV-2 antibody compared to 11 percent of 101 pregnant women and health care workers. When 51 healthy patients were compared with 43 "promiscuous women and prostitutes" with regard to HSV-2 antibody, Rawls, Tompkins and Melnick (1969) reported that a significantly higher proportion (57%) of the promiscuous women and prostitutes showed HSV-2 antibody of the healthy patients (22%) examined. Similarly, Patterson, Rawls and Smith (1978) reported that HSV-2 antibody was not found in any serum samples from 18 Catholic nuns, but was present in 10 percent of the sera of 18 prostitutes.

Additional information regarding sexual behaviour is available within the reported investigations. In a study of 343 prostitutes, Duenas et al. (1972) found that the occurrence of HSV-2 antibody increased with the duration of prostitution even when age was taken into account. Jimenez et al. (1979) examined HSV-2 antibody using a neutralization test in 20 women living in Costa Rica and without adjustment for number of sexual partners, reported that significantly higher antibody titers were evident for women with more years of sexual experience. Judson et al. (1980) monitored the attendees of a Denver Health Clinic for an 18-month period and reported that in 12,201 visits by homosexual men and 5,342 visits by heterosexual men, genital herpes was diagnosed at a lower rate (0.93%) in homosexuals than in heterosexuals (3.65%) and this difference was statistically significant even when adjusted for age and race. These authors suggest that HSV-2 may more frequently be harboured by women than by men and thus more readily acquired by heterosexual men. Different conclusions with regard to sexual preference were reached by Melbye et al. (1983). These authors reported a study of homosexual men in Denmark. Two hundred and fifty-nine participants were obtained through the membership of a regional homosexual organization. In addition, 100 men from the same communities, who were reportedly heterosexual, were included. Overall HSV-2 antibody was much more prevalent in the sera of the 259 (71%) homosexual men, than in the 100 (22%) heterosexual group. Furthermore, among homosexual men, HSV-2 antibody was associated with a greater number of sexual partners, and more years of homosexual activity.

A study of the prevalence of HSV infections among male homosexuals was conducted in a sexually transmitted disease clinic in Seattle, Washington by Mann et al., 1984. Using a microneutralization test, HSV-2-specific antibody was found in the sera of 38 (44%) and intermediate antibody in 13 (15%) of 86 men. An association between multiple sexual partners and HSV-2 antibody was noted within this group of homosexual men. The authors report that men with HSV-2 antibody reported a greater number of sexual partners ($\bar{X}$=12.1) during the preceding twelve month period than those without antibody ($\bar{X}$=8.9).

2.6.12. Venereal Disease

It is evident that HSV-2 infection is more frequently found in those attending venereal disease clinics than in patients seen in other types of health care facilities (Montefiore, Sogbetun and Anong, 1980; Adelusi, Fabiyi and Osunkoy, 1978; Tantivanich and Tharavanij, 1980). Furthermore, persons with evidence of HSV-2 more frequently have had other venereal diseases such as trichomonas and gonorrhea than have persons without HSV-2 infection (Felman, 1980; Felman and Nikitas, 1979; Jeansson and Molin, 1975; Kaufman et al., 1973; Knox et al., 1979; McCormack et al., 1981; Rawls et al., 1971).

2.6.13. Circumcision

Parker and Banatvala (1967) reported that of 21 men in whom HSV could be isolated from genital lesions, 18 (86%) were uncircumcised.

Through a review of information from medical records of male patients attending the Whitechapel clinic in London, England, Taylor and Rodin (1975) found that of 214 male patients with genital herpes 162 (75.7%) were uncircumcised compared with 263 (64.1%) of 410 patients without genital herpes. The authors concluded that men who were not circumcised had an increased risk of genital herpes. Even when this comparison was controlled for social class as measured by occupation, men who were not circumcised were still more likely to have genital herpes. Condom use was not taken into account.

One thousand, three hundred and fifty men attending a public health clinic in Perth, Australia were examined with regard to circumcision and HSV-2 infection by Parker et al. (1983). Fewer men with genital herpes were circumcised than men without genital herpes. Of 104 men with genital herpes 58 percent were uncircumcised, compared to (37%) of men without genital herpes. The authors correctly speculate that part of this difference may be due to the possibility that uncircumcised men are more likely to have symptoms during an active HSV-2 episode than are circumcised men and therefore to seek medical care.

2.6.14. Contraception

Few studies report HSV-2 infection in relation to contraception. Wolinska and Melamed (1970) examined 43,318 women attending Planned Parenthood Centres of New York City. Of 21 women with cytologically confirmed genital herpes for whom information on contraceptive use was available, 13 (62%) used oral contraceptives and 6 (26%) did not use any form of contraception, and 2 (10%) used the diaphragm or the IUD for at least one year prior to the diagnosis. When the rates of genital herpes were examined against the number of women using each method of contraception, 0.09 percent (13) of women who reported using oral contraceptives for one year or more were found to have genital herpes. The lowest rate of genital herpes was among diaphragm users (0.03%), while the highest rate was found among those women who reported using no contraception at all (0.3%). Wolinska and Melamed (1970) reported that women who did not use any type of contraceptive method at all had higher rates of genital herpes than those using oral contraceptives.

A laboratory study of the protective effect of condoms done by Conant et al. (1984) provides indirect evidence of protection from HSV-2. In this experiment, concentrations of HSV-2 kept in latex condoms for 8 hours or more did not migrate across the barrier; however, as the authors point out, the condom would only protect the area of direct contact during intercourse and not surrounding tissue.

When contraceptive practices among men were considered, genital herpes appeared to have occurred less frequently among condom users than those who did not use condoms. Barlow (1977) examined 3,543 men attending the Department of Genito-Urinary Medicine at St. Thomas' Hospital in London, England. Over a six-month period it was found that 2 (3%) of 59 patients with genital herpes reported frequent condom use.

Taylor and Rodin (1975) in a study reported earlier, found that of 155 men with genital herpes 14 (9%) reported condom use compared with 47 (15%) men without genital herpes. The authors report that the association between genital herpes and lack of condom use was statistically significant at $P \leq 0.02$.

2.6.15. Socioeconomic Status

A variety of measurements of socioeconomic status have been used in the published investigations. These range from indirect indicators such as the socioeconomic allocation of the participants' census area of residence to more direct measures such as income.

In a household serologic survey of 564 women and children in Montreal, McDonald et al. (1974a) used the socioeconomic allocation of the census tract of residents as the measure of social class. Both HSV type 1 and type 2 antibodies were more frequently found in persons from lower income areas. Of 206 persons between the ages of 36 and 55, a similar proportion of persons from the low and middle income census areas showed antibody. However, the proportion was smaller among persons from the high income area. Approximately 20 percent of individuals from the low and middle income areas showed HSV-2 antibody compared to 12 percent of those from high income areas.

A gradual decrease in the proportion of persons with HSV-2 antibody in relation to increased social class as measured by area of residence in Baltimore, Maryland was reported by Royston and Aurelian (1970). The authors reported that the proportion of persons with HSV-2 antibody was highest in the lowest social class areas: 61 percent of 70 patients showed HSV-2 antibody and this proportion dropped to 54 percent of 26 patients in the middle income group to 41 percent of 22 patients from the highest income areas.

Based upon the reported per-capita income of 507 patients in Delhi, India, Seth et al. (1981) found no evidence of a socioeconomic gradient. The study found that the proportion of persons with HSV-2 antibody was slightly higher in the middle income group than in the high and low groups. Thirty-two percent of 176 men and women in the low income group showed HSV-2 antibody, as compared with 40 percent of 192 persons in the middle income group, and 28 percent of 39 persons in the high income group.

In addition to antibody studies of social class, antigen and clinical studies have been reported. Using a micro-quantitative complement fixation test, Aurelian, Davis and Julian (1973) examined levels of AG-4, a tumour-specific type-2-induced antigen, by social class group based upon income. Sixty-seven percent of 42 cervical cancer cases from lower income groups were AG-4 positive. The percentages of AG-4 positive in the middle and upper class groups were 75 percent and 67 percent respectively. The authors concluded that there was no significant social class difference in the prevalence of AG-4 antigen.

Wolinska and Melamed (1970), in studying the income distribution of women with cytologic evidence of genital herpes seen in a planned parenthood clinic in New York City, reported that of 43,331 women seen in the clinic 37 were diagnosed as having genital herpes. Twenty-five of these women were in a low income group and 12 were in a higher income group.

The inverse relationship between socioeconomic level and the frequency of disease is not unique to HSV-2 infections or venereal disease. HSV-1, cytomegalovirus and other viruses and microbial infections generally occur more often in lower than in higher social class strata of the populations studied (Cabau et al., 1980); McDonald et al., 1974a; Porter, Wimberley, and Benyesh-Melnick, 1969).

Although the contribution of type 2-specific virus to the overall herpes response cannot be assessed in these studies, all serologic surveys of undifferentiated HSV which looked at social class show that HSV occurs more frequently in those from the lowest social strata (Anderson and Hamilton, 1949; Andrewes and Carmichael, 1930; Burnet and Williams, 1939b; Glezen, Fernald and Lohr, 1975; Hatherley, Hayes and Jack, 1980a; Hatherley, Hayes and Jack, 1980b; Hondo, 1974). The role of social class with regard to the occurrence of HSV-2 infection is not well understood. In extremely poor environments it is possible that poor hygiene or family crowding in the home increases exposure, particularly to type 1 virus. Hygiene surrounding sexual intercourse, use of occlusive contraceptives and even differences in sexual practices may vary enough with social class in some settings to permit great variation in exposure to this virus.

2.7 Summary and Conclusions from Previous Investigations - Biological and Clinical Evidence

The characteristics of herpes simplex virus type 2 which substantially promote its survival and propagation through man include the following:

- Once infected, the host becomes a long-term carrier because the virus remains latent in the neural ganglia and is capable of causing recurrent episodes of disease.

- As viral isolation is not possible in a large portion of persons with detectable lesions, even if those with suspected herpes lesions are examined, the absence of virus in the isolate does not rule out infectivity.

- Individuals who have never noticed a herpetic episode are capable of shedding virus. Furthermore, viral shedding can occur not only in the absence of symptoms during episodes, but for a long period after an episode.

- As many herpetic infections cannot be clinically detected, individuals capable of infecting others may not be identified.

- The available serologic methods for differentiating between type 1 and type 2 antibodies have some margin of misclassification due to the cross-reacting antibodies between the two types of herpes simplex virus. It is therefore difficult to identify the factors which may increase the risk of infection with type 2 alone.

- There is no cure for herpes simplex infection.

Epidemiologic Evidence

When the information about factors found to be associated with HSV-2 is combined from the diverse sources of information currently available, the following conclusions can be reached:

- Herpes simplex virus type 2 is rarely acquired before puberty and population rates generally stabilize past the third decade of life.

- Those who are sexually active and who have multiple sexual partners are at greater risk of HSV-2 infection.

- HSV-2 is most often transmitted by the genital route. The analogies of other venereal diseases can be applied to herpes genitalis.

- Herpes genitalis is frequently found in association with other venereal diseases.

- The prevalence of herpes simplex virus type 2 antibody and the frequency of genital herpes appear to be inversely related to socio-economic level in some of the studies reported.

- Men with prostatic cancer and women with cervical cancer more frequently show antibodies to herpes simplex virus type 2 antigen than do those in comparison groups.

Non-Independence of Sexual Patterns, Contraception, Socioeconomic Status, Lifestyle, and HSV-2 Infection

Among the numerous investigations of HSV-2 infections and factors which may increase the chance of infection, a possible intercorrelation among the factors involved has not been taken into account.

There is evidence that other venereal diseases are more prevalent in persons of lower socioeconomic status. Contraceptive practices vary with social class, as do sexual behaviour and venereal disease (Darrow, 1979; Swan and Brown, 1981). Sexual precocity has been associated with lower income or educational levels (Zelnick and Kantner, 1977). Also, the number of sexual partners is not independent of the age at first intercourse. Women who began intercourse earlier in life more frequently report multiple sexual partners than do women who began intercourse at a later age (Rawls et al., 1976). Furthermore, the role of socioeconomic status with regard to sexual or other behaviour is not well understood. By its strictest definition, socioeconomic status is merely a way which allows us to stratify a population into subgroups with different access to economic and social resources (Curtis and Scott, 1979; Mausner and Bahn, 1974). How these subgroups may differ with regard to their awareness of illness, use of medical care, lifestyle and environment, factors which could affect the acquisition of an infectious disease, is not clear.

In the scientific literature, most of the information that is available on sexual patterns and HSV-2 infection is taken from studies of cervical cancer patients and compares groups generally matched for social class level. Because cervical cancer appears to be more prevalent in women from lower socioeconomic groups, little information is available on the sexual patterns of adults from other social class levels. In addition, some information on sexual patterns is available from reports from venereal disease clinics and family planning centres. Unfortunately, the social class level of these groups is often not reported and studies which do not report social level often represent only lower socioeconomic groups. Without adequate information on sexual patterns and contraceptive practices across all social levels, it is difficult to separate the possible effect of a particular sexual/contraceptive pattern on the risk of disease from its socioeconomic setting. Simultaneous investigation of many of the individual factors associated with HSV-2 infection has not been reported. Therefore, because of the fact that each of the attributes examined in previous investigations may be associated with one another as well as HSV-2 antibody, it is not known whether or not the chance of HSV-2 infection:

- Is only due to sexual exposure at an early age,
- Is singularly related to the number of sexual partners, and
- Can be affected by contraceptive practices, and/or
- Requires certain socioeconomic/hygienic circumstances.

It is therefore necessary to consider several possible factors at once in order to asses's the relative impact of these factors on the acquisi- tion of HSV-2.

This investigation is designed to examine the combined and separate effects of sexual behaviour, contraceptive practice and socioeconomic factors on the risk of HSV-2 infection.

Table 3

Factors Investigated: HSV-2 Antibody

Antibody Studies Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Age			McDonald et al. 1974a (Montreal)
(n=564)			
2-15	134	6 *	
16-25	101	12	
26-35	123	18	
36-45	115	22	
46-55	91	24	
* % approximate			
(n=246)			Strizová et al. 1975 (Ostrava and Prague, Czechoslovakia)
0-9	43	0	
10-14	22	4	
15-19	35	17	
29-34	46	18	
35-60	100	23	
(n=266)			Rawls, Tompkins & Melnick, 1969 (Houston, Texas)
1 mo - 12 yrs	138	0	
13-16	24	9	
17-25	39	17	
26-40	43	20	
41-61	22	22	

Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Race			
Negro	68	96 *	Rawls, Tompkins & Melnick 1969 (Houston, Texas)
Caucasian	27	60	
Negro (prostitutes)	147	62	Duenas et al. 1972 (Cali, Columbia)
Mestizo Indians (prostitutes)	196	63	
Negro	241	40	Adam et al. 1973b (Houston, Texas)
Caucasian	53	35	
Negro	33	39	Rawls et al. 1980 (Los Angeles, California)
Chicano Americans	66	38	
Tribe			
Ganda (cancer cases and controls)	89	81 *	Adam et al. 1972 (Kampala, Uganda)
Non-Ganda (cancer cases and controls)	30	71	
Religion			
Jewish	43	19	McDonald et al. 1974b (Montreal)
Non-Jewish	43	19	
Moslem	150	23	Kessler et al. 1974c (Yugoslavia)
Non-Moslem	200	25	

*P ≤ 0.05

Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Urbanization			
Urban	411	34	Seth et al. 1981 (Delhi, India)
Rural	96	34	
Urban	257	49	Rawls, Adam and Melnick, 1972 (Houston, Texas)
Rural	28	82	
Circumstance			
Non-institutionalized men	111	13*	Roome, Montefiore and Waller, 1975 (England)
Short Stay Prison Inmates	95	28	
Long Stay Prison Inmates	111	55	
Pregnancy			
Age 1st Pregnancy			
≤ 14	8	63 *	Adam et al. 1972 (Kampala, Uganda)
15-16	19	74	
≥ 17	22	73	
≤ 16	78	46	Adam et al. 1973a (Houston, Texas)
≥ 17	146	40	
≤ 16	63	52	Adam et al. 1974 (Houston, Texas)
≥ 17	112	40	

*P ≤0.05

Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Pregnancies (continued)			
Never pregnant	14	36 *	Duenas et al. 1972 (Cali, Columbia)
Ever pregnant	18	67	
Live births			Adam et al. 1973b (Houston, Texas)
1, 2	63	43	
≥ 3	120	35	
Women between ages 15–24 pregnant			Ory et al. 1975 (Atlanta, Georgia)
0, 1	93	9 *	
≥ 2	57	23	
Marriage			
Marital Status			Seth et al. 1981 (Delhi, India)
Married	236	44 *	
Unmarried	78	19	
Married	124	11	Ishiguro & Ozaki, 1978 (Osaka, Japan)
Unmarried	13	15	
Age at First Marriage			Adam et al. 1973a (Houston, Texas)
≤ 16	62	45	
≥ 17	151	38	

*P ≤0.05

Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Marriage (continued)			
Age at First Marriage (continued)			
≤ 16	52	50	Adam et al. 1974 (Houston, Texas)
≥ 17	120	44	
Number of Marriages			Adam et al. 1974 (Houston, Texas)
1	93	43	
≥ 2	78	49	
Age at First Intercourse			
Early (≤ 20)	40	18	Ishiguro and Ozaki, 1978 (Osaka, Japan)
Late (≥ 21)	114	11	
Ganda Tribe			
Early (≤ 15)	31	71	Adam et al. 1972 (Kampala, Uganda)
Late (≥ 16)	21	71	
Non-Ganda Tribe			
Early (≤ 15)	10	60 *	
Late (≥ 16)	7	14	
Early (≤ 15)	67	52	Adam et al. 1974 (Houston, Texas)
Late (≥ 16)	116	41	
Early (≤ 16)	16	50 *	Adam et al. 1973b (Houston, Texas)
Late (≥ 17)	35	31	

*P ≤0.05

Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Number of Sexual Partners			
Few	119	8 *	Ishiguro & Ozaki, 1978 (Osaka, Japan)
Many	35	26	
Controls			
Few (1)	63	36 *	Graham et al. 1982 (Los Angeles County, California)
Many (≥2)	65	64	
Controls			
Few (1-3)	74	43	Adam et al. 1974 (Houston, Texas)
Many (≥ 4)	105	46	
Controls			
Negro Women			
Few (1-3)	96	36	Adam et al. 1973b (Houston, Texas)
Many (≥ 4)	135	42	
Caucasian			
Few (1-2)	32	31	
Many (≥ 3)	19	47	
0	4	0 *	Suchanova et al. 1984 (Prague, Czechoslovakia)
2	88	10	
2-10	78	27	
11-50	60	33	
Sexual Activity & Venereal Disease			
Virgins	17	0	Ishiguro & Ozaki, 1978 (Osaka, Japan)
Non-Virgins	137	12	

*P ≤0.05

Factor	Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Sexual Activity & Venereal Disease (continued)			
Gynecology Patients & Cervical Cancer Cases	78	12	Menczer et al. 1975 (Tel Hashomer, Isreal)
"Healthy"[1] Participants	94	2	
Imprisoned Prostitutes	30	10	
Gynecology Patients	101	29	Adelusi, Fabiyi & Osunkoy, 1978 (Ibadan, Nigeria)
Pregnant Women	102	25	
Family Planning Clinic Attendees	101	27	
Venereal Disease Clinic Patients	30	47	
Prostitutes	55	46	
Catholic Nuns	18	0	Patterson, Rawls and Smith, 1980 (San Antonio, Texas)
Prostitutes	18	10	
Hospitality Girls (Venereal Disease Clinic Attendees)	157	40*	Tantivanich & Tharavanij 1980 (Bangkok, Thailand)
Pregnant Women & Health Care Workers	101	11	
"Healthy"* Patients	51	22*	Rawls, Thompkins and Melnick, 1969 (Houston, Texas)
Promiscuous Women & Prostitutes	43	57	
Sexual Preference			
Homosexual Men	259	71*	Melbye et al., 1983 (Denmark)
Non-Homosexual Men	100	22	

[1] Described by the authors as "healthy" participants with no further information about their origin.

Factor		Number Tested	Percent HSV-2 Antibody Positive	Reference (Location)
Socioeconomic Status	Census Area n=206			
	High	specific numbers	12	McDonald et al. 1974a (Montreal, Quebec)
	Low, Middle	not available	20	
	Census Area			
	High	22	41	Royston & Aurelian 1970 (Baltimore, Maryland)
	Middle	26	54	
	Low	70	61	
	Reported Income			Seth et al. 1981 (Delhi, India)
	High	39	28	
	Middle	192	40	
	Low	176	32	

CHAPTER 3

MATERIALS AND METHODS

3.1 Study Design and Method

3.1.1 Design

A cross-sectional seroepidemiologic survey of sexual and socio-economic factors and HSV-2 antibodies was carried out in a residential sample of the population. This survey was designed to allow access to a presumably healthy sample of men and women, in that they were not identified through a hospital or clinic.

A door-to-door survey method was used to find willing subjects who were interviewed at their convenience in their homes. Information about sexual patterns, contraception, health and socioeconomic status was obtained. Following the interview a blood sample was requested by the interviewer.

3.1.2 Study Site and Population

The survey was carried out in Toronto, Ontario and the sample was drawn from the 440 Census Tracts which make up this city's central downtown area. This field site was selected in the hope of obtaining a wide range of socioeconomic and sexual patterns that might exist in an urban centre. The study was administered and the data processed through the Department of Epidemiology and Biostatistics at the University of Western Ontario in London, Ontario, where the grants for research were awarded. A local centre for interviewer training and temporary blood storage was located at the University of Toronto. Blood samples were shipped to McMaster University in Hamilton, Ontario

- Other factors such as smoking history, vitamin intake and family size
- Circumstantial factors which could affect the quality of the interview such as the privacy of the interview and the interviewer's impressions

3.4.4 Interview Procedure

The study was introduced to the prospective participants as one of viruses and health, rather than of herpes to avoid undue concern or distress caused by the heavy media coverage this virus had at the time of the study.

The interview consisted of two parts:

1. An interviewer-administered part, in which all but the questions directly related to the participant's sexual history were asked.
2. A self-administered section of eight questions about the age at first coitus and number of sexual partners. In the middle of the interview the participant was asked to complete this form, seal it in the envelope provided and give it to the interviewer. This was done during the interview, following the contraceptive questions, but preceding questions on marital status.

At the close of the interview, a 10 cc blood sample was drawn from a superficial vein according to the standard medical procedure. This sample was taken by the interviewer who was certified in the procedure.

3.4.5. Data Processing

The completed questionnaires and blood samples were submitted to the Toronto centre where the dates and codes were checked by the reduced the chance of misunderstanding sensitive questions related to sexual behaviour.

Race

Because the question of variation in herpes simplex virus prevalence among races has not been resolved, the sample was confined to Caucasians, proportionately the largest English-speaking group in the city of Toronto. The inclusion of all racial groups would have greatly increased the sample size requirements and extended the field work beyond practical limits.

3.3 Sampling Method

A multistage, stratified, random sampling method was used in order to obtain a socioeconomically diverse study sample made up of approximately equal proportions of high, middle, and low social class groups.

3.3.1 Primary Sampling Unit: Enumeration areas

The sampling procedure began with the random selection of primary sampling units drawn from a list of socioeconomically ordered enumeration areas. This list was prepared by the York University Survey Research Unit. Based upon 1971 census data, all enumeration areas in the city of Toronto were ordered into three social class strata using a composite score of education, income and occupation (Patel, 1978; Blishen and McRoberts, 1976). Within each stratum the areas were listed in random rather than numeric order through a computerized random allocation program (Patel, 1978).

An equal number of enumeration areas was initially selected from each socioeconomic stratum. A total of 175 enumeration areas were selected. They were used consecutively from each list until the required sample size was achieved. Ninety-seven enumeration areas in all were used in the study.

3.3.2 Secondary Sampling Unit. Household

The blocks in each enumeration area were numbered and using a random number list a block and a house were selected. This household was used as the starting point for a door-to-door search for eligible male and female subjects. The field procedure is described in Appendix III. The residents of the households were not enumerated. Rather the first willing and eligible person within the household was interviewed. The interviewer was instructed to interview up to five men and five women from each area, and to attempt to balance the sample of men and women.

3.3.3 Subject Search Procedure

Apartment blocks, row houses, private homes and all other types of dwelling were included. Commercial establishments were not included. The specified search procedure is presented in Appendix III. A fieldwork record of all subject searching outcomes was maintained by the interviewer. Participant searches were carried out between 5:00 p.m. and 8:00 p.m. weekdays and 1:00 p.m. and 8:00 p.m. weekends.

3.3.4 Sample Size Requirements

A sample size requirement of a total of 744 participants was originally estimated, based upon the differences between the expected proportions of persons with HSV-2 antibody and specific sexual patterns at an α of 0.05 and β of 0.20. The information for the expected proportions was estimated from information in an article by Adam et al. (1973b). The sample size formula for differences between proportions by Schlesselman (1974) was used to calculate the sample size. The sample size calculations and estimates of the adequacy of the sample obtained appear in Appendix VII.

3.4 Data Collection Procedures

All introductions, statements and procedures were specified in detail in the field protocol and interviewer's manual. This included a specific script for the introduction to the study, as well as the steps of the venipuncture procedure. This protocol was used for staff training and subsequent monitoring of field procedures. A copy of the field record and interviewer's manual can be found in Appendix III.

3.4.1 Introduction

The study was introduced to the prospective participant as one of viruses and health, rather than of herpes simplex virus specifically. At the participant's door the age criteria were stated and the participant's interest and eligibility determined.

If appropriate, an interview was arranged either by appointment or immediately, at the convenience of the participant. If the participant was not eligible, the interviewer asked if any other member of the household might meet the criteria.

3.4.2. Informed Consent

Prior to the interview, a consent form specifying the intimate nature of the questions and our pledge of confidentiality was signed by the participant. No interview took place unless this form was signed.

The consent for blood sample stated the amount of blood to be taken as well as the risk of the procedure. As with the interview consent, no blood sample was taken unless the consent form was signed.

3.4.3 The Interview

The interviews were carried out in as private a setting as possible in the participant's home. The questionnaire covered the following topics:

- Demographic attributes including age, marital status, and ethnicity
- Socioeconomic factors including years of education and training, occupation and income
- Contraceptive history
- Sexual attributes of:

  Age of first intercourse

  Number of sexual partners reported in specified time periods (i.e., number of sexual partners during each decade of life)

  Number of sexual partners during the year preceding the interview and total number of sexual partners
- Reproductive history and menstruation (women)
- Circumcision status (men)
- Reported history of selected illnesses and conditions including cold sores, genital sores or blisters, venereal disease, colds and flu

- Other factors such as smoking history, vitamin intake and family size
- Circumstantial factors which could affect the quality of the interview such as the privacy of the interview and the interviewer's impressions

3.4.4 Interview Procedure

The study was introduced to the prospective participants as one of viruses and health, rather than of herpes to avoid undue concern or distress caused by the heavy media coverage this virus had at the time of the study.

The interview consisted of two parts:

1. An interviewer-administered part, in which all but the questions directly related to the participant's sexual history were asked.
2. A self-administered section of eight questions about the age at first coitus and number of sexual partners. In the middle of the interview the participant was asked to complete this form, seal it in the envelope provided and give it to the interviewer. This was done during the interview, following the contraceptive questions, but preceding questions on marital status.

At the close of the interview, a 10 cc blood sample was drawn from a superficial vein according to the standard medical procedure. This sample was taken by the interviewer who was certified in the procedure.

3.4.5. Data Processing

The completed questionnaires and blood samples were submitted to the Toronto centre where the dates and codes were checked by the project director. The questionnaires were forwarded to London where they were stored in locked cabinets, with the signed consent forms stored in a separate locked cabinet. In London, the questionnaires were coded by two coders. Eight-five percent of the data was coded by one coder and a cross-check of coding decisions on approximately 100 questionnaires revealed no discrepancies between the two coders. The coded information was key punched onto cards and read onto magnetic tape for analysis. Before the statistical analysis began, computer checks for the accuracy and consistency of the coded information were carried out.

Once the blood was drawn into a pre-labelled sterile vacuum tube, the date was added and the subject code checked against the code on the completed interview. The sample was refrigerated within two hours and transported to the University of Toronto within 36 hours after collection. Here the samples were logged in and processed by the project director or laboratory assistant who noted the condition of the specimen, the identification number and date of collection. The samples were then centrifuged and the sera drawn under sterile conditions, using a flame, sterile pipettes and specimen bottles. Each sample was split and labelled and then frozen.

Periodically the samples were packed in dry ice and transported to the Laboratory at McMaster Medical Centre where they remained frozen until analysis.

When the radioimmunoassay results were submitted, the identifying code and date of specimen collection were checked against the questionnaire and date of interview by the coder in London.

3.4.6 Field Staff

Eleven women between the ages of 25 and 39 carried out the interviews. All but two of the women had some nursing or laboratory training. The two women without paramedical training (including the project director) had previous experience in medical interviewing. Women of this age group were hired because of evidence from the pretest experience and literature that both men and women respondents of all ages accept interviews most readily with women of this generation (Cartwright, 1974).

The interviewers were trained to carry out the introduction and interviews in as uniform a manner as possible. An interviewer's manual was provided which specifically outlined the field protocol, methods of recording, issues of attitude and approach, and venipuncture procedures. Specific scripts for the introduction to the study and other matters were used rather than allowing extemporaneous remarks by the interviewer.

Training consisted of group sessions with the project director followed by individual field experience during which the interviewer observed and was observed knocking on doors and interviewing. During group sessions interviewers became acquainted with the venipuncture procedure and were then trained and certified by the Paramed Company.

To avoid drawing special attention to sexual factors, the research question was generalized in its presentation to the interviewers, as being one of viruses and health, with herpes as a major interest. The interviewers' training emphasized the importance of not reacting to apparent variations of social class or other factors in the participants. To reduce the chance of differential response to social class by the interviewers, each interviewer was assigned an equal number of high, medium and low enumeration areas.

3.4.7 Quality Control

A number of measures were taken to gather and process the information in as accurate and consistent a way as possible. The questions asked, in general, were not open-ended and required as narrow a range of interpretation as possible for both the interviewer and the participant. A number of "control" questions were asked, such as whether or not an individual had ever donated blood, participated in a previous survey or smoked cigarettes. These factors are not known to differ between persons with and persons without HSV-2 exposure, and were used to assess the comparability of the HSV-2 positive and negative groups with regard to background and response differences.

Internal consistency checks were made, including subtracting the participant's birthdate from the year of interview and comparing it with reported age, comparing the number of marriages with the number of sexual partners, and comparing certain other sexual and social variables.

A specifically outlined coding manual with specific criteria was used to code all questionnaires.

Throughout the study ongoing interviewer training sessions were held to review fieldwork progress and to solve special problems such as high venipuncture refusal rates. Individual interviews were periodically observed by the project director to assure continued adherence to the field protocol.

In order to ascertain whether or not the interviews actually occurred, a small sample of participants was contacted by telephone by the project director. Only 18 subjects over the term of the study were contacted as, in truth, a breach of the agreement of confidentiality was commited by this practice. Of the respondents contacted, all had actually been interviewed and all but one actually appeared to be pleased with the interview.

3.4.8 Ethics, Confidentiality and Risk

The methods of data gathering were reviewed and approved by a Research Ethics Committee of the University of Western Ontario before the fieldwork began. An essential objective in the participant acquisition and data gathering process was the protection of the participant from distress or physical harm.

The assurance and maintenance of confidentiality was of primary concern in the selection and training of the interviewers and the management of the data. The participant's name appeared only on the consent forms, and beyond noting that it had been signed, was never linked or stored with the questionnaire information. The answers to the sexual questions, though linked by a code to the questionnaire data, were not seen by the interviewer, except in some few instances where the participant requested interviewer assistance with the sexual questionnaire. The participant was made to feel free to refuse to answer any questions or to discontinue the interview at any time. The interviewers were trained to watch for signs of discomfort or distress in the participant and to lose an interview rather than risk upsetting the participant in any way. This necessary concern for the participant was especially important in taking blood. During the interviewer training, particular attention was paid to the interviewer's competence in drawing blood as painlessly as possible. There was no known benefit to the respondent for participating in this study, with the exception of some marginal satisfaction of having contributed to a research project.

3.5 Serologic Method

The sera were examined for cross-reacting and type-specific antibodies to HSV using a radioimmunoassay method. This assay was used because it has been found to correlate reasonably well with clinical evidence of HSV-2 infection and showed good specificity when compared with the microneutralization method as well as with other serologic methods, (Forghani, Klassen and Baringer, 1977; Patterson, Rawls and Smith, 1978; Rawls et al., 1980; Rawls, 1981; Smith, Gehle and McCracken, 1974). A particular advantage of this assay was that it could be efficiently carried out on a large number of sera at a relatively low cost (Patterson, Rawls and Smith, 1978). A complete discussion of the relative merits of the available serologic methods and the validity of the radioimmunoassay is presented in Section 2.3.1 of Chapter 2.

3.5.1 Assay Technique

A complete description of the radioimmunoassay used is given in Appendix IV of this document. A brief description of the general strategy was to prepare antigens to be used for the assay and antigens for adsorption in Vero cells. Polycarbonate treated cadmium coated beads were used as antigen adsorbants. The beads were sensitized with the prepared HSV-2 antigen or control cell antigen and then washed with phosphate buffered saline containing BSA (PBS-BSA), then incubated with sera. Excess antibody was removed by washing and the bound antibody was detected by adding goat anti-human IgG labelled with ^{125} Iodine. Following 4 hours' incubation at room temperature, the beads were again washed three times and then counted in a gamma counter.

Since both cross-reacting and type 2-specific antibodies would react with beads sensitized with HSV-2 antigen, it was assumed that sera not yielding counts significantly different from control antigen coated beads did not contain antibodies to either virus subtype. These sera were excluded from further analysis for HSV-2 type-specific antibodies. Analysis of variations in counts obtained with control antigen yielded a cut-off of 300 CPM at a 1:20 level of probability. Sera with values of less than 300 CPM were found to be negative for neutralizing antibodies.

Sera with values greater than 300 CPM were adsorbed with HSV-1 antigen and then tested against beads sensitized with HSV-1 or HSV-2 antigens. The amount of antibody bound to the beads was detected with goat anti-human IgG labelled with ^{125} Iodine as described above. The CPM yielded by beads sensitized with HSV-2 antigen (with control CPM subtracted) minus CPM yielded by beads sensitized with HSV-1 (with control CPM subtracted) were considered those attributable to type 2-specific antibody. Analysis of variations indicated that CPM above 150 were significant and sera yielding these values were considered positive for HSV-2.

Sera without HSV antibodies were tested for the presence of IgG by immunoprecipitation. This was done to ensure that negatives for HSV antibodies were not due to destruction of antibodies by bacterial contamination. All but one of these sera contained normal levels of IgG.

3.6 Statistical Methods

3.6.1 Categorization of Variables

In the analysis, non-numeric variables were usually divided into sociologically homogeneous categories. For example individuals in similar types of occupations were grouped together into an occupational category. Continuous variables were used in categorized forms in most of the analysis in order to be able to assess the possibility of non-linear associations between levels of the exposure variables and HSV-2 antibody. Furthermore, the odds ratios calculated using categories rather than continuous variables can be easily interpreted. Categorization of the independent variables was based upon an approximately equal division of the participants with serological information across the range of the variable. These categories were determined by first examining the sex-specific distribution of the participants for the variable of interest. Then categories were selected based upon as equal a distribution of the participants as possible into each category. For example, the age distribution of women was examined. Then, if three age categories were desired the sample was allocated approximately into thirds without taking into account their distribution with regard to antibody status. In a number of instances exactly equal division of the participants for some variables was not possible because of an uneven distribution for such variables (e.g. see Table H, Appendix VI, Number of sexual partners in the thirties). Because of differing distributions of many variables between men and women, the sex-specific categories were often different. For example, as women tended to report fewer sexual partners than did men an approximately 50:50 division for total number of sexual partners for women fell at 1 partner vs $\geq$ 2 partners, while a 50:50 division of men resulted in a cut-off of $\leq$9 partners vs. $\geq$10. In the analysis, men and women were not compared with one another.

3.6.2 Procedures

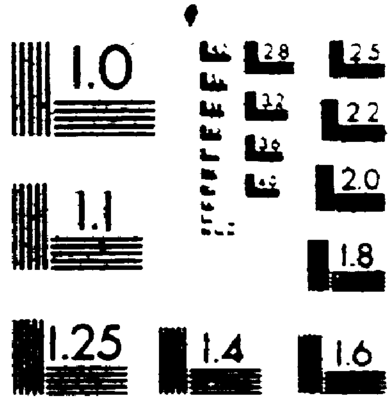
Two computer packages were utilized in the analysis. Descriptive statistics and univariate methods available in the Statistical Package for the Social Sciences were used (Nie, 1975). Multivariate analysis was carried out using the SAS Institute procedure LOGIST, a logistic regression programme based upon a regression model by Walker and Duncan (1967) and adapted for the SAS package by F. E. Harrell (SAS Institute, 1980).

3.6.3 Methods

Initially, frequency distributions and Pearson correlation coefficients were used to examine the characteristics of the sample and the simple relationships between variables.

Simple relationships between the antibody titer and individual variables were evaluated using Chi square statistics, including a Chi square for trend for multiple category variables. Odds ratios as

2



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

measurements of associations were calculated (Fleiss, 1973). Confidence intervals for the odds ratios were calculated using the method described by Woolf (1955).

Multivariate analysis was carried out in which the dependent variable of HSV-2 infection was expressed as present or absent according to the antibody positive or negative criterion of the assay method. Multiple logistic regression was used to examine the relationship of a number of independent variables to the presence of HSV-2 antibody. The SAS LOGIST procedure allowed the development of models to identify variables which best discriminated between the antibody positive and negative groups. The SAS programme computes maximum-likelihood estimates using the Newton-Raphson method. Beta coefficients for each variable were calculated, the antilog of which is an odds ratio indicating the risk of antibody at levels of the independent variable. The standard errors of the Beta coefficients were used to calculate confidence intervals for the odds ratios. The ratio of the Beta to its Standard Error, squared was used to evaluate the statistical significance of the individual coefficients.

CHAPTER 4

DEFINITION OF VARIABLES

4.1 Definition of the Primary Variables

Only variables that were not self-evident and those that were used in the final analysis are described here.

4.2 Antibody Groups

Based upon the assay criteria (Rawls, 1981), the antibody positive (seropositive) and antibody negative (seronegative) groups were classified as follows:

4.2.1 HSV Positive/Negative

Persons with a count per minute (CPM) of 300 or less were considered to be seronegative to both types of HSV. Because of the method of calculating HSV-2 positives it was not possible for an individual to be classified as HSV-2 positive but negative to HSV-1. Those with a CPM of 301 or greater were considered to be seropositive to HSV.

4.2.2 HSV-1 Positive/Negative

Sera with 300 CPM or greater antigen prior to adsorption but 150 CPM or less HSV-2 antigen after adsorption were considered to be HSV-1 positive only.

4.2.3 HSV-2 Positive/Negative

Those sera with a count of 151 or greater to HSV-2 after adsorption were considered to be HSV-2 positive; those below 151 were HSV-2 negative.

4.3 Demographic Factors

4.3.1 Marital Status

The categories of never married, presently married and common-law, divorced, separated, and widowed were combined into three categories: presently married or living common-law, previously married and never married. Persons presently married and living common-law were categorized together because both circumstances implied current sexual stability.

4.3.2 Socioeconomic

Dimensions of social class that were covered in the interview were: years of primary and secondary education, post-secondary education or training, type of further training, total number of years of education or training, occupation, household annual income, spouse's education and occupation, and parental occupation. These variables were highly correlated with one another.

Education

Total years of education and training were used as the primary measurement of socioeconomic status because:

- Among all three measurements of socioeconomic status: education, occupation and income, years of education was the most complete for all participants.
- Years of education were highly correlated with type of education and income, as well as occupation.

- In men and women age 35 and over, as in this study sample, education could be expected to be a complete or fixed factor, in contrast to income or occupation.
- In previous investigations, education rather than income was found to best represent the socioeconomic factor most related to health, lifestyle and venereal disease (Darrow, 1979; Syme and Berkman, 1976).

Years of primary and secondary education, further training and university were combined to equal the participant's total years of education and training. When night courses or part-time education were reported, the participant's estimate of the full-time equivalent of these courses was used to calculate the contribution of this to the total years of education. On-the-job training, if full-time and constituting a specific apprenticeship, was included in the years of education or training. Types of further education or training were taken to include apprenticeships and all other education or schooling, both university and non-university.

Household Annual Income

The participant was asked to classify his/her household's annual income from all members of the household into general financial categories based upon income before taxes.

Household annual income was not available for 40 (4%) participants in the sample. As reported in this study, household income represented a wide range of economic circumstances because of different family size and number of employed household members.

Occupation

Occupational categories were based upon the Blishen scale for residents of Canada (Blishen and McRoberts, 1976). The participant's occupation was not used as a major social class variable in most of the analyses, as the participant was frequently not employed at the time of interview. Although previous occupation was recorded, the circumstances for current unemployment ranged from inability to find work to independent wealth. Therefore simply "unemployed" as an "occupation" could not be used, and past occupation was not actually appropriate to the present point in time. This attribute was therefore less representative of social level than were income or education.

4.3.3 Residence

Questions involving home ownership, the length of present residence, total years of residence in Toronto, and type of dwelling were included to allow an indirect assessment of mobility as a part of life-style which might be related to health as well as social class. Household crowding was assessed by asking the participant to state the number of rooms, not including the kitchen, bathrooms, or permanent storage areas that the household contained, as well as the number of persons currently living in the household. The index of household crowding (a ratio of persons and rooms) calculated was one used in other studies assessing the risk of venereal disease (Morton, Horton and Baker, 1979).

4.3.4 Contraception and Sexual Factors

Contraception information included: whether any method was ever used, age at first use, years of use and consistency of use. For women, this involved use of a diaphragm, intrauterine device and oral contraceptives and use of condoms by sexual partners. For men, only condom use was asked.

In addition to the number of years of use of any one method, the consistency of use was asked in order to classify the participants into those who never, occasionally and consistently used each method. For women, concurrent use of more than one method was examined. Because of wide variation in the consistency of use of any one method for any participant over time, the consistency of contraceptive use was not utilized in the final analysis.

Number of Sexual Partners during Life Periods

The instructions for the sexual questionnaire specified that the number of different sexual partners during each decade of life should be reported. Therefore, a lifetime spouse would be reported several times, but counted once when the total number of sexual partners was recorded. A comparison of the number of sexual partners during specific life periods with the total number of sexual partners for those participants who recorded one sexual partner in their lifetimes indicated that this instruction was generally understood.

Total number of Sexual Partners

The participants were asked to note on the sexual questionnaire the total number of different persons with whom they had had sexual intercourse thus far in their lifetimes.

Number of Sexual Partners in the Last Year

The participants were asked to note how many different sexual partners (including those already reported) they had had during the twelve month period preceding the interview.

Categorization of the Number of Sexual Partners

As noted before, the absolute number of sexual partners was not used in the analysis. Rather, categories were used to divide the sample into roughly equal parts. For example, a cut-off of two or more sexual partners, as opposed to only one partner, was used to divide female participants into approximately equal size groups.

The use of categories of partner numbers rather than absolute numbers allowed for the possibility of imprecise reporting by some members of the sample, with the assumption that general rather than precise differences in the number of sexual partners may affect the risk of HSV-2 infection.

Assumption of Heterosexuality

In the questionnaire, sexual preference was not asked. Unless otherwise specified by the participant, all sexual activity reported was assumed to be heterosexual.

Sexual Intercourse Outside Marriage

Whether or not a participant had had intercourse outside marriage was not directly asked. The categories for this variable were divided into those participants who reported intercourse but had never been married, those who reported the age of first intercourse as preceding age at first marriage and those who reported intercourse only after marriage.

Unmarried Pregnancy

Whether or not a woman had had a pregnancy outside marriage was not directly asked. Instead, women were divided into groups:(1) those who reported a pregnancy but had never been married, or whose age at first pregnancy preceded their age at first marriage and (2) women whose stated age at first pregnancy followed that of first marriage.

4.3.5 Health Factors and Illnesses

The participant was asked about his/her history of cold sores, genital blisters or sores and other genital problems. Because these problems are often ill-defined and very much dependent upon the participant's own perception, the specific number of episodes was not used in the analysis.

Furthermore, genital blisters, sores and problems were examined as a group, as well as individually, to accommodate the possibility of different definitions of each of these conditions.

Questions regarding general illnesses and symptoms of infection were asked in order to get a picture of the participant's reported susceptibility to infection.

4.3.6 Lifestyle and General Factors

Smoking, vitamin use and blood donation were included in the analysis as indirect indicators of health awareness.

4.4 Specific Categories of the Variables Used

The categories of the variables used in the multivariate analysis are specified in Section 3.3 of Chapter 5.

CHAPTER 5

RESULTS

5.1 Outcome of Field Search

5.1.1 Participant Acquisition

The outcome of the field search for participants is outlined on the following page. In 13,940 households approached, 1,220 eligible subjects were found. Of the 1,220 persons invited to participate in the study, 957 (79%) completed interviews. Individuals who elected not to particpate stated that they did not have time for the interview.

Age was the primary reason for ineligibility. Of the 6,521 persons designated as ineligible, 4,656 (71%) were outside the required age range, divided almost equally between those too young and those too old. Other reasons for ineligibility included language and race.

5.1.2 Blood Sample Acquisition

Of the 957 persons who were interviewed, 805 were willing to have a blood sample taken by the interviewer. Venipuncture could not be successfully accomplished in 45 of these participants due to the health problems of the respondent or due to the difficulty of the interviewer in drawing blood. When venipuncture proved difficult, this was attempted only twice in order to protect the respondent from excessive discomfort.

Eight samples of whole blood were mailed in vacutainer tubes and did not reach the laboratory centre in Hamilton. This method of transporting samples through the mail was immediately discontinued. One blood sample was lost in freezer storage due to a breakdown of the freezer. One sample was found to be unsuitable for analysis and the

Table 4

OUTCOME OF THE FIELD SEARCH

13,940
number of households approached

6,199
no response

1,220
eligible

6,521
ineligible

263
refused interview

TOTAL
STUDY
SAMPLE

957 (391 men, 566 women)
accepted interview

152 (57 men, 95 women)
refused blood sample

805 (334 men, 471 women)
agreed to blood sample

45
venipuncture could
not be accomplished

8
blood sample
lost in transit

1
blood sample
lost in storage

3
blood sample
unsuitable for analysis

STUDY SAMPLE
WITH ANTIBODY
INFORMATION

748 (320 men, 428 women)
suitable
blood samples
analyzed

results of two other samples were considered to be unreliable as the measurements fell outside reasonable limits. Blood samples from 748 persons (320 men, 428 women) were found suitable for analysis and made up the final study sample.

5.1.3 Quality of the Data

Annual income or sexual patterns were not reported by a number of participants. Twenty subjects (6 men, 14 women) stated that they did not know their approximate household annual income. Another 20 persons (8 men, 12 women), or 2 percent of the 957 persons interviewed, refused to report household income.

Seven men and 7 women who did not deny coitus elected not to complete the sexual questionnaire. Of those who accepted the sexual questionnaire, three men and one woman did not report their age at first intercourse. The total number of sexual partners was not given by 35 men and 25 women. Although sexual partner totals were not given, these participants reported their number of sexual partners during certain life periods.

Beyond an initial description of the antibody groups, the spouse's occupation and education, and parental occupation were not used in the analysis, because these attributes were often not available for many of the participants.

Internal consistency checks of the questionnaire data such as comparisons of birthdate, date of interview with reported age, number of marriages not in excess of total number of sexual partners revealed no discrepancies. It was not expected that the participants would be able to remember precisely how many episodes of fever blisters or even the number of sexual partners they had had. This information was analyzed only in categorized form which emphasized general rather than precise differences among participants. The data were scanned for extreme values that might indicate severe recall problems or even fabrication.

5.2 Antibody Results

5.2.1 HSV Antibody

The antibody results of the participants were presented in Table 5. Of the 748 participants with serologic information, 587 (78.5%) showed antibody evidence of one or both types of herpes simplex virus. Four hundred and seventy-one (63.0%) participants showed antibody evidence of HSV-1 alone and 116 (15.5%) participants showed HSV-2 type specific antibody. The analysis presented in this document focuses upon the comparison of those participants who were positive and negative to HSV-2 type specific antigen.

5.2.2 HSV-2 Antibody

Of 320 men, 41 (12.8%) showed HSV-2 antibody compared to 279 (87.2%) who were found to be HSV-2 negative. Seventy-five women (17.5%) were HSV-2 positive and 353 (82.5%) were without HSV-2 antibody.

5.3 Statistical Analyses

In the statistical analysis, participants without serologic information were compared with the HSV-2 antibody groups. Unadjusted odds ratios and 95% confidence intervals reflecting the differences

Table 5

ANTIBODY EVIDENCE OF HERPES SIMPLEX VIRUS

	Number Tested	WITHOUT ANTIBODY #	WITHOUT ANTIBODY %*	TYPE 1 ONLY #	TYPE 1 ONLY %	TYPE 2 SPECIFIC #	TYPE 2 SPECIFIC %	TYPE 1 OR TYPE 2 #	TYPE 1 OR TYPE 2 %
Men	320	74	23.1	205	64.1	41	12.8	246	76.9
Women	428	87	20.3	266	62.1	75	17.5	341	79.7
Total	748	161	21.5	471	63.0	116	15.5	587	78.5

* Indicates the percent of those tested

between participants with and without HSV-2 antibody were then examined.

In the multivariate analysis, multiple logistic regression models were developed in which the relationship between independent variables and HSV-2 antibody was examined for separate and combined associations. Among the variables included in the analysis were those which could directly affect exposure to HSV-2 infection. Additional variables included were those which have been found to be associated with this virus in previous investigations, other variables which were statistically significant in the univariate analysis, and those which might be associated with HSV-2 antibody and other variables of interest. Interactions among the primary variables of interest were examined. In addition, the association between HSV-2 antibody and number of sexual partners was further examined by including the number of sexual partners during specific life periods in the analysis.

5.3.1 Comparison of Participants without Serologic Information with the HSV-2 Antibody Groups

The distribution of variables among participants with HSV-2 antibody, without HSV-2 antibody and participants without serologic information is presented in Tables E and F in Appendix VI. Serologic information was unavailable for 71 (18%) of 391 men and 138 (24%) of 566 women. The possible effects of the lack of antibody information on the study results will be discussed in Chapter 6.

Men

Men without serologic information were similar to men with serum samples with regard to age at interview and birthplace. Those without serum samples less frequently reported English as their first language, more frequently were married, less often reported having had further education or training, had fewer years of education, a higher income, less often reported condom use, having been circumcised, having donated blood or having participated in a previous survey than men with serologic information.

Men without serum samples were similar to men without HSV-2 antibody in that both less frequently reported renting their homes, living in an apartment, having fewer sexual partners in their lifetimes and in the year preceding the interview and less frequently reported smoking cigarettes.

Both those without serum samples and those with HSV-2 antibody reported having begun intercourse at an earlier age than those without antibody.

Women

Women without serum samples were similar to women with serum samples with regard to birthplace, first language, pregnancy, contraception, number of sexual partners in the year preceding the interview, cigarette smoking and having participated in a previous survey.

Women without serum samples differed from both the HSV-2 positive and negative groups with regard to years of education and residential status. Those without serum samples more frequently reported a lower level of education than women with HSV-2 antibody. Women without serum samples more often reported renting their home than those without HSV-2 antibody, but less often than those with antibody.

Women without serum samples were similar to those without HSV-2 antibody in that both groups were somewhat older, less frequently previously married, reported higher incomes, less often lived in apartment buildings, began intercourse at an earlier age and reported fewer sexual partners than women with HSV-2 antibody.

Women without serum samples resembled those with HSV-2 antibody in that they less frequently reported further education or training and were less likely to have donated blood.

5.3.2 Comparison of the HSV-2 Seropositive and Seronegative Groups: Individual Variables

Odds ratios and 95% confidence intervals are presented in Tables 6 and 7. The P values noted on these tables indicate the probability level of the associated Chi square statistic. For variables divided into more than ~~two categories~~, the P value represents the significance of a Chi square test for trend.

In order to assess the possibility of a "dose response" relationship between some attributes and HSV-2 antibody, variables such as number of sexual partners were categorized into multiple levels. Because ~~of~~ the relatively small numbers, the categorization into four levels occasionally resulted in wide confidence intervals for some of these variables. In the multivariate analysis, the levels chosen were collapsed into two categories, maintaining the same middle cut-off point as those in the univariate analysis. The numbers and percentages that were used in the calculations are contained in Tables G & H of Appendix VI.

Men

Demographic Factors

Descriptive

Men with HSV-2 antibody and those without HSV-2 antibody were similar in the distribution of age at interview, birthplace, paternal birthplace, first language, marital status, number of marriages, age at first marriage, and age at which the marriage ended.

Socioeconomic

Men with HSV-2 antibody and those without HSV-2 antibody were not significantly different with regard to the highest grade of school, further education or training, type of further education or training, total number of years of education, household annual income, and occupation.

Residence

Men with HSV-2 antibody and men without antibody were similar with regard to length of residence in Toronto and length of residence in their current home, and were similar with regard to household crowding in their current or in their childhood households.

Men who were HSV-2 positive were more likely to have rented rather than owned their own homes than were men who were HSV-2 negative (O.R. = 3.21, 95% Confidence Interval 1.64, 6.26). A greater number of men with HSV-2 antibody lived in apartment buildings than in single family houses (O.R. = 4.40, C.I. 1.82, 10.69).

Contraception and Sexual Factors

Contraception

The difference between men with HSV-2 antibody and men without HSV-2 antibody was not statistically significant with regard to the use of contraception, specifically condoms, years of condom use and consistency of condom use.

Sexual Variables

Men with HSV-2 antibody and men without HSV-2 antibody were similar with regard to circumcision and whether or not sexual intercourse preceded or occurred without marriage.

More men with HSV-2 antibody reported that they had begun sexual intercourse by age 15 than men without HSV-2 antibody (O.R. = 3.87, C.I. 1.35, 11.04). HSV-2 antibody was also associated with a greater number of sexual partners. The association between sexual partners and

HSV-2 antibody rose with increasing numbers of partners in a lifetime from 1.23 (0.32, 4.79) for men who reported 4-9 partners over those who reported no more than 3 partners to 3.88 (1.23, 12.23) for men who reported at least 25 sexual partners. When asked about the number of sexual partners in the one year preceding the interview, again the association between number of sexual partners and HSV-2 antibody rose from 2.07 (0.71, 6.05) for those men reporting 2 partners over those reporting no more than 1 partner to 4.41 (1.77, 10.99) for men who reported at least 5 sexual partners.

The inquiry about the number of sexual partners during specific life periods revealed that significantly more men with HSV-2 antibody reported more sexual partners during each life period than did men without HSV-2 antibody. For number of sexual partners during the teenage years, the estimate rose from 3.09 (1.01, 9.40) for men who reported 2 partners over those who reported no more than 1 partner to 4.55 (1.92, 10.75) for men who reported 5 or more partners. A similar increase in the odds ratios from no more than one partner to many was evident for the number of sexual partners in the twenties, thirties and forties. Since sexual preference was not asked in the interview, the possibility of a correlation with HSV-2 antibody could not be assessed. Three men with HSV-2 antibody and 1 man without antibody volunteered the information that they were bisexual or homosexual.

Health Factors and Illnesses

Men with HSV-2 antibody and those without HSV-2 antibody were similar in the distribution of hernia operations, cancer, tuberculosis, measles, mumps, chicken pox, whooping cough, scarlet fever, infectious mononucleosis, viral meningitis, shingles, pneumonia, other viral illness, the number of colds or flu each year, sore throat, swollen glands, mouth sores, cold sores, frequency of cold sores in a lifetime, genital blisters, and non-specific genital problems.

Liver disease, including hepatitis, was more frequently reported in men with HSV-2 antibody than men without (O.R. = 3.76, C.I. 1.63, 8.65). Although the numbers were really too small to consider the results valid, more men with HSV-2 antibody reported having had genital sores than did men without antibody (O.R. = 4.70, C.I. 1.46, 15.16). When all men reporting any type of genital problem (including blisters, sores, or lesions) were combined, significantly more men with HSV-2 antibody reported at least 2 genital problems than did men without HSV-2 antibody (O.R. = 2.70, C.I. 1.17, 6.52).

Lifestyle and General Factors

Men with HSV-2 antibody and those without HSV-2 antibody were not significantly different with regard to cigarette smoking, vitamin use, whether or not they had ever received a blood transfusion, had ever donated blood, or had ever participated in a previous study.

Women

Demographic Factors

Descriptive

Women with HSV-2 antibody and those without HSV-2 antibody were similar in the distribution of age at interview, paternal birthplace, age of first marriage, and the age at which marriage ended.

Women with HSV-2 antibody were more likely to have been born in Canada than were women without HSV-2 antibody (O.R. = 1.73, C.I. 1.01,

Table 6

Unadjusted Odds Ratios for HSV-2 Seropositive and Seronegative Groups

MEN

(n=320)

Variable	Odds Ratio	95% Confidence Interval
Demographic Factors		
Descriptive		
Age at Interview		
39–43 vs. ≤38	1.13	(0.53, 2.41)
≥44 vs. ≤38	0.69	(0.30, 1.60)
Birthplace		
Canada vs. Other	1.23	(0.64, 2.36)
Paternal Birthplace		
Canada vs. Other	0.89	(0.46, 1.74)
First Language as a Child		
French vs. English	0.71	(0.09, 5.79)
Other vs. English	1.26	(0.61, 2.62)
Marital Status		
Previously Married vs. Married, Common-law	1.39	(0.54, 3.26)
Never married vs. Married, Common-law	1.49	(0.88, 4.45)

* $P \leq 0.05$
** $P \leq 0.01$

Variable	Odds Ratio	95% Confidence Interval
Descriptive continued		
Number of Marriages		
None vs. 1	2.17	(0.95, 4.95)
≥2 vs. 1	1.75	(0.44, 3.95)
Age at First Marriage		
≤24 vs. ≥25	0.96	(0.44, 2.09)
Age Marriage Ended		
≤29 vs. ≥30	0.26	(0.06, 1.10)
Socioeconomic Factors		
Highest Grade of School		
≤12 vs. ≥13	1.23	(0.62, 2.44)
Further Education or Training		
No vs. Yes	0.86	(0.40, 1.83)
Type of Further Education or Training		
Non-University Education Post Secondary vs. University	0.93	(0.40, 1.89)
Non-University Education or Training Post Primary vs. University	1.40	(0.37, 5.33)
No Further Education or Training vs. University	0.84	(0.37, 2.18)

Variable	Odds Ratio	95% Confidence Interval
Socioeconomic continued		
Total Number of Years of Education		
16-18 vs. ≥19	2.24	(0.76, 6.63)
12-15 vs. ≥19	2.17	(0.71, 6.54)
≤11 vs. ≥19	1.73	(0.57, 5.23)
Household Annual Income		
\$30,000-\$39,000 vs. ≥\$40,000	2.34	(0.76, 7.23)
\$25,000-\$29,999 vs. ≥\$40,000	2.06	(0.70, 6.06)
≤\$16,000 vs. ≥\$40,000	2.18	(0.76, 7.23)
Occupation		
Professional vs. Administrative Professional	0.86	(0.31, 2.39)
White Collar vs. Administrative Professional	0.47	(0.15, 1.50)
Blue Collar vs. Administrative Professional	0.63	(0.27, 1.49)
Unemployed vs. Administrative Professional	0.96	(0.21, 3.21)
Residence		
Residence Status		
Rent vs. Own	3.21**	(1.64, 6.26)
Duration of Residence		
≤10 years vs. ≥11 years	2.87	(0.99, 8.34)

Variable	Odds Ratio	95% Confidence Interval
Residence continued		
Duration in Toronto		
≤10 years vs. ≥11 years	1.81	(0.90, 3.67)
Type of Dwelling		
Multiple Family House vs. Single Family House	1.34	(0.60, 2.96)
Apartment Building vs. Single Family House	4.40**	(1.82, 10.69)
Household Crowding		
Ratio of Rooms/Person in Current Household		
≤4.5 vs. ≥4.6	0.76	(0.40, 1.48)
Ratio of Rooms/Persons in Childhood Household		
≤3.5 vs. ≥3.6	1.41	(0.73, 2.71)
Contraception		
Ever Used Contraception (Condom)		
No vs. Yes	0.84	(0.39, 1.81)
Years of Condom Use		
6-9 vs. ≥10	1.13	(0.35, 3.61)
1-5 vs. ≥10	1.01	(0.40, 2.55)
None vs. ≥10	0.83	(0.37, 1.87)

Variable	Odds Ratio	95% Confidence Interval
Contraception continued		
Consistency of Condom Use		
Never vs. consistently	0.91	(0.37, 2.26)
Occasionally vs. consistently	1.18	(0.53, 2.59)
Sexual Factors		
Circumcised		
No vs. Yes	0.58	(0.30, 1.14)
Ever Had Sexual Intercourse		
Yes vs. No	∞	
Age at First Intercourse		
18-20 vs. $\geq$21	1.00	(0.30, 3.29)
16-17 vs. $\geq$21	1.66	(0.54, 5.13)
$\leq$15 vs. $\geq$21	3.87**	(1.35, 11.04)
Total Number of Sexual Partners in a Lifetime		
4-9 vs. $\leq$3	1.23	(0.32, 4.79)
10-24 vs. $\leq$3	2.44	(0.71, 8.35)
$\geq$25 vs. $\leq$3	3.88**	(1.23, 12.23)

Variable	Odds Ratio	95% Confidence Interval
Sexual Factors continued		
Number of Sexual Partners in the Year Preceding the Interview		
1 vs. 0	2.07	(0.71, 6.05)
2 vs. 0	1.47	(0.40, 5.39)
≥3 vs. 0	4.41**	(1.77, 10.99)
Number of Sexual Partners in Teenage Years		
1 vs. 0	3.09	(1.01, 9.40)
2 vs. 0	1.54	(0.55, 4.34)
≥3 vs. 0	4.55**	(1.92, 10.75)
Number of Sexual Partners during Twenties		
2 vs. ≤1	2.11	(0.54, 7.84)
3 vs. ≤1	3.69	(1.16, 11.75)
≥4 vs. ≤1	5.15**	(1.64, 16.23)
Number of Sexual Partners during Thirties		
2 vs. ≤1	1.14	(0.38, 3.42)
3,4 vs. ≤1	1.65	(0.49, 5.53)
≥5 vs. ≤1	3.22**	(1.46, 7.12)

Variable	Odds Ratio	95% Confidence Interval
Sexual Factors continued		
Number of Sexual Partners during Forties		
2 vs. ≤1	2.92	(0.87, 9.81)
3,4 vs ≤1	2.72	(0.50, 14.80)
5 vs. ≤1	4.08*	(1.27, 13.18)
Sexual Intercourse Preceded or Occurred without Marriage		
Yes vs. No	2.31	(0.53, 10.08)
Health Factors and Illnesses		
Hernia Operation		
Yes vs. No	0.57	(0.17, 1.94)
Ever had Cancer		
Yes vs. No	0	
Illnesses		
Ever had Tuberculosis		
Yes vs. No	0	
Measles		
Yes vs. No	1.04	(0.45, 2.39)
Mumps		
Yes vs. No	0.64	(0.33, 1.27)

Variable	Odds Ratio	95% Confidence Interval
Health and Illnesses continued		
Illnesses		
Chicken Pox		
Yes vs. No	0.87	(0.44, 1.71)
Whooping Cough		
Yes vs. No	1.94	(0.95, 3.96)
Scarlet Fever		
Yes vs. No	0.63	(0.18, 2.18)
Infectious mononucleosis		
Yes vs. No	2.99	(0.89, 10.03)
Viral Meningitis		
Yes vs. No	4.71	(0.76, 29.02)
Shingles		
Yes vs. No	2.12	(0.56, 8.06)
Pneumonia		
Yes vs. No	0.61	(0.26, 1.45)
Other Viral Illness		
Yes vs. No	1.37	(0.29, 6.48)
Liver Disease (including hepatitis)		
Yes vs. No	3.76**	(1.63, 8.65)

Variable	Odds Ratio	95% Confidence Interval
Health and Illnesses continued		
Illnesses		
Colds and Influenza		
Number of Colds or Flu Each Year: Current		
≥ 2 vs. ≤ 1	1.00	(0.52, 1.94)
Number of Colds or Flu Each Year: Teens		
≥ 2 vs. ≤ 1	0.72	(0.36, 1.46)
Number of Colds or Flu Each Year: Twenties		
≥ 2 vs. ≤ 1	0.76	(0.39, 1.51)
Symptoms of Infection		
Sore Throat		
Yes vs. No	0.77	(0.21, 2.77)
Swollen Glands		
Yes vs. No	0.79	(0.41, 1.53)
Mouth Sores		
Yes vs. No	0.90	(0.47, 1.74)
Cold Sores		
Yes vs. No	1.11	(0.57, 2.14)

Variable	Odds Ratio	95% Confidence Interval
Health and Illnesses continued Symptoms of Infection Frequency of Cold Sores in a Lifetime		
1,2 vs. none	1.79	(0.82, 3.92)
≥3 vs. none	0.74	(0.33, 1.69)
Symptoms of Infection Genital Blisters		
Yes vs. No	2.17	(0.92, 5.16)
Genital Sores		
Yes vs. No	4.70**	(1.46, 15.16)
Other Genital Problems		
Yes vs. No	0.22	(0.03, 1.69)
Total Number of Genital Problems		
≥2 vs. ≤1	2.70*	(1.17, 6.52)
Lifestyle and General Factors Ever Smoked Cigarettes		
Yes vs. No	2.37	(0.90, 6.29)
Ever taken Vitamins as an Adult		
Yes vs. No	1.16	(0.58, 2.34)
Received Blood Transfusion		
Yes vs. No	1.45	(0.56, 3.76)

Variable	Odds Ratio	95% Confidence Interval
Lifestyle and General Factors continued		
Ever Donated Blood		
Yes vs. No	0.92	(0.47, 1.80)
Ever Participated in a Previous Survey		
Yes vs. No	1.23	(0.64, 2.37)

2.95). Women with HSV-2 antibody were also more likely to have reported French rather than English as their first language (O.R. = 3.64, C.I. 1.39, 9.50). When considering any factors such as birthplace or language, it should be kept in mind that this study was restricted to English-speaking persons.

HSV-2 antibody was more frequently found in women who had been previously married, including those separated, divorced and widowed, than in women who were presently married, living common-law or never married (O.R. = 2.47, C.I. 1.43, 4.29). Women who were HSV-2 antibody positive were more likely to report at least 2 marriages than were women without HSV-2 antibody (O.R. = 2.99, C.I. 1.65, 5.42).

Reproductive Factors

The distribution of the age at menarche, number of pregnancies and number of live births was similar in both HSV-2 antibody positive and HSV-2 antibody negative groups of women.

More women with HSV-2 antibody had ceased menstruating than those women without antibody (O.R. = 2.09, C.I. 1.20, 3.64).

Socipeconomic

No statistically significant difference between women with HSV-2 antibody and those without HSV-2 antibody was found in the distribution of type of further education or training and occupation.

A lower level of education was associated with HSV-2 antibody in women. More women with HSV-2 antibody reported having completed no more than 11 grades of school (O.R. = 2.38, C.I. 1.42, 3.98), and fewer reported further education or training (O.R. = 1.76, C.I. 1.07, 2.91) than did women without antibody. When the total number of years of education or training was combined, women with HSV-2 antibody were more likely to have no more than 16 years of education than were women without HSV-2 antibody (O.R. = 2.21, C.I. 1.12, 4.36).

Women with HSV-2 antibody more frequently reported a lower household annual income than those without antibody (O.R. = 6.47, C.I. 2.78, 15.10).

Residence

Women with HSV-2 antibody were not significantly different from women without antibody with regard to the duration in their present residence or length of residence in Toronto. There were no difference between women with or without HSV-2 antibody with regard to household crowding as a child.

Women with HSV-2 antibody were more likely to have rented rather than owned their homes than were women without HSV-2 antibody. This difference was highly significant with an odds ratio of 4.85 (C.I. 2.87, 8.19). There was a similarly strong association between HSV-2 antibody in women and the type of dwelling that they occupied. Women with HSV-2 antibody were more likely to have resided in a multiple family house or in an apartment building, as opposed to a single family home, than were women without HSV-2 antibody (O.R. = 5.93, C.I. 2.89, 12.18). Women with HSV-2 antibody currently lived in more crowded circumstances in their home than women without antibody (O.R. = 2.34, C.I. 1.37, 3.97).

Contraception and Sexual Factors

Contraception

Women with HSV-2 antibody and those without antibody were similar with regard to the use of contraception in general, consistency of condom use, years of diaphragm use, and years of IUD use.

Although the association fell short of statistical significance, women with HSV-2 antibody were more likely to report condom use by their sexual partner(s) for less than 10 years of their lives than were women without HSV-2 antibody (O.R. = 2.25, C.I. 1.00, 5.04). Women with HSV-2 antibody more frequently report oral contraceptive use for at least 10 years than those without antibody (O.R. = 2.23, C.I. 1.13, 4.41).

Sexual Variables

Women with HSV-2 antibody were not found to differ significantly from women without antibody with regard to the number of sexual partners in the year preceding the interview, the number of sexual partners during their forties, and whether or not there was an unmarried pregnancy.

The proportion of women with HSV-2 antibody was inversely related to the age at which they began sexual intercourse. The estimate rose from 0.79 (0.33, 1.89) for women who reported beginning intercourse at 18 or 19 years of age over those who began intercourse by age 17 and rose to 2.53 (1.18, 5.40) for women who began intercourse at age 23 or oldet. The association between lifetime number of sexual partners and HSV-2 antibody increased from an odds ratio of 2.48 (1.17, 5.25) for women who reported 2 or 3 partners over those who reported 1 partner to 3.73 (1.85, 7.53) for women who reported at least 7 sexual partners. An examination of the number of sexual partners during specific life periods indicated that women with HSV-2 antibody were more likely to report multiple sexual partners during each decade than were women without HSV-2 antibody. The estimate for number of sexual partners during the teenage years rose from 0.76 (0.97, 3.20) for women who reported 1 partner over those who reported no sexual partners during this time period to 13.60 (6.29, 29.41) for women who reported at least 3 partners. A similar increase in the estimates with number of sexual partners was evident for the number of partners in the twenties and thirties. Seropositive women more frequently reported that they had had intercourse but were never married or had a reported age of first intercourse which preceded their age at first marriage (O.R. = 1.77, C.I. 1.04, 3.00).

Health Factors and Illnesses

No statistically significant difference between women with HSV-2 antibody and those without HSV-2 antibody was found in the distribution of tuberculosis, measles, mumps, chicken pox, whooping cough, scarlet fever, viral meningitis, shingles, other viral diseases, liver disease (including hepatitis), number of colds or flu each year, sore throat, swollen glands, mouth sores, cold sores, frequency of cold sores in a lifetime, genital blisters, genital sores, other genital problems and total number of genital problems.

Women with HSV-2 antibody were more likely to have reported having had a hysterectomy than were women without HSV-2 antibody (O.R. = 2.73, C.I. 1.47, 5.07). Women with HSV-2 antibody were also more likely to have reported having had cancer than women who did not (O.R. 3.53, C.I. 1.30, 9.60). In particular, of 7 women with cervical

Table 7

Unadjusted Odds Ratios for HSV-2 Seropositive and Seronegative Groups

WOMEN
(n=428)

Variable	Odds Ratio	95% Confidence Interval
Demographic Factors		
Descriptive		
Age at Interview		
39-44 vs. ≤38	1.10	(0.61, 1.99)
≥45 vs. ≤38	0.85	(0.44, 1.62)
Birthplace		
Canada vs. Other	1.73*	(1.01, 2.95)
Paternal Birthplace		
Canada vs. Other	0.62	(0.37, 1.04)
First Language as a Child		
French vs. English	3.64*	(1.39, 9.50)
Other vs. English	0.92	(0.51, 1.68)

* $P < 0.05$
** $P \leq 0.01$

Variable	Odds Ratio	95% Confidence Interval
Descriptive continued		
Marital Status		
Previously Married vs. Married, Common-law	2.47**	(1.43, 4.29)
Never married vs. Married, Common-law	1.39	(0.50, 3.86)
Number of Marriages		
None vs. 1	1.35	(0.48, 3.73)
≥2 vs. 1	2.99**	(1.65, 5.42)
Age at First Marriage		
≤21 vs. ≥22	1.68	(0.99, 2.85)
Age Marriage Ended		
≤29 vs. ≥30	0.97	(0.28, 3.40)
Reproductive Factors		
Age at Menarche		
≤12 vs. ≥13	0.80	(0.48, 1.32)
Menopause Status		
Ceased Menstruating vs. Still Menstruating	2.09**	(1.20, 3.64)
Ever Pregnant		
Yes vs. No	0.75	(0.38, 1.50)

Variable	Odds Ratio	95% Confidence Interval
Reproductive Factors continued		
Total Number of Pregnancies		
1,2 vs. None	0.68	(0.31, 1.46)
≥3 vs. None	0.84	(0.41, 1.73)
Number of Live Births		
1 vs. None	2.33	(0.47, 11.40)
≥2 vs. None	1.28	(0.28, 5.82)
Socioeconomic Factors		
Highest Grade of School		
≤11 vs. ≥12	2.38**	(1.42, 3.98)
Further Education or Training		
No vs. Yes	1.76*	(1.07, 2.91)
Type of Further Education or Training		
Non-University Education Post-Secondary vs. University	0.90	(0.44, 1.84)
Non-University Education or Training Post-Primary vs. University	1.44	(0.28, 7.40)
No Further Education or Training vs. University	1.67	(0.88, 3.17)

Variable	Odds Ratio	95% Confidence Interval
Socioeconomic continued		
Total Number of Years of Education		
13-15 vs. ≥16	0.68	(0.30, 1.54)
10-12 vs. ≥16	1.54	(0.79, 3.00)
≤9 vs. ≥16	2.21 *	(1.12, 4.36)
Household Annual Income		
$25,000-$34,999 vs. ≥$35,000	0.74	(0.25, 2.17)
$9,000-$24,999 vs. ≥$35,000	1.77	(0.80, 3.93)
≤$8,999 vs. ≥$35,000	6.47**	(2.78, 15.10)
Occupation		
Professional vs Administrative Professional	0.58	(0.20, 1.69)
White Collar vs. Administrative Professional	1.02	(0.37, 2.84)
Blue Collar vs. Administrative Professional	1.13	(0.46, 2.79)
Unemployed vs. Administrative Professional	1.18	(0.52, 2.65)
Residence		
Residence Status		
Rent vs. Own	4.85**	(2.87, 8.19)
Duration of Residence		
≤10 years vs. ≥11 years	1.43	(0.82, 2.47)

Variable	Odds Ratio	95% Confidence Interval
Residence continued		
Duration in Toronto		
≤10 years vs. ≥11 years	0.81	(0.42, 1.57)
Type of Dwelling		
Multiple Family House vs. Single Family House	3.52**	(1.84, 6.72)
Apartment Building vs. Single Family House	5.93**	(2.89, 12.18)
Household Crowding		
Ratio of Rooms/Person in Current Household		
≤4.5 vs. ≥4.6	2.34**	(1.37, 3.97)
Ratio of Rooms/Persons in Childhood Household		
≤3.5 vs. ≥3.6	0.99	(0.60, 1.64)
Contraception		
Ever Used Contraception		
No vs. Yes	1.21	(0.67, 2.18)
Years of Condom Use		
6-9 vs. ≥10	2.20	(0.73, 6.63
1-5 vs. ≥10	2.25	(0.92, 5.50)
None vs. ≥10	2.25*	(1.00, 5.04)

Variable	Odds Ratio	95% Confidence Interval
Contraception continued		
Consistency of Condom Use		
Never vs. Consistently	1.45	(0.72, 2.92)
Occasionally vs. Consistently	1.28	(0.60, 2.754)
Years of Diaphragm Use		
6-9 vs. $\geq$10	1.60	(0.21, 12.28)
1-5 vs. $\geq$10	3.84	(0.81, 18.30)
None vs. $\geq$10	3.84	(0.89, 16.47)
Years of IUD Use		
6-9 vs. $\geq$10	1.10	(0.54, 2.26)
1-5 vs. $\geq$10	0.54	(0.12, 2.41)
None vs. $\geq$10	1.54	(0.30, 7.81)
Years of Oral Contraceptive Use		
6-9 vs. $\geq$10	0.88	(0.47, 2.23)
1-5 vs. $\geq$10	0.59	(0.24, 1.13)
None vs. $\geq$10	2.23*	(1.13, 4.41)
Sexual Factors		
Ever Had Sexual Intercourse		
Yes vs. No	∞	

Variable	Odds Ratio	95% Confidence Interval
Sexual Factors continued		
Age at First Intercourse		
20-22 vs. ≥23	0.79	(0.33, 1.89)
18-19 vs. ≥23	2.63**	(1.25, 5.53)
≤17 vs. ≥23	2.53**	(1.18, 5.40)
Total Number of Sexual Partners in a Lifetime		
2,3 vs. 1	2.48**	(1.17, 5.25)
4-6 vs. 1	3.21**	(1.48, 6.98)
≥7 vs. 1	3.73**	(1.85, 7.53)
Number of Sexual Partners in the Year Preceding the Interview		
1 vs. 0	0.36	(0.17, 0.77)
2 vs. 0	0.70	(0.23, 2.11)
≥3 vs. 0	0.55	(0.13, 2.33)
Number of Sexual Partners in Teenage Years		
1 vs. 0	0.76	(0.97, 3.20)
2 vs. 0	2.34	(0.96, 5.72)
≥3 vs. 0	13.60**	(6.29, 29.41)

Variable	Odds Ratio	95% Confidence Interval
Sexual Factors continued		
Number of Sexual Partners during Twenties		
2 vs. ≤1	2.07	(0.99, 4.33)
3 vs. ≤1	1.83	(0.78, 4.30)
≥4 vs. ≤1	2.86**	(1.47, 5.57)
Number of Sexual Partners during Thirties		
2 vs. ≤1	1.91	(0.87, 4.18)
3,4 vs. ≤1	1.49	(0.61, 3.62)
≥5 vs. ≤1	2.25*	(1.05, 4.84)
Number of Sexual Partners during Forties		
2 vs. ≤1	0.54	(0.15, 1.92)
3,4 vs. ≤1	0.72	(0.15, 3.44)
≥5 vs. ≤1	0.90	(0.18, 4.43)
Sexual Intercourse Preceded or Occurred without Marriage		
Yes vs. No	1.77*	(1.04, 3.00)
Unmarried Pregnancy		
Yes vs. No	1.27	(0.56, 2.91)

Variable	Odds Ratio	95% Confidence Interval
Health Factors and Illnesses		
Hysterectomy		
Yes vs. No	2.73**	(1.47, 5.07)
Ever had Cancer		
Yes vs. No	3.53**	(1.30, 9.60)
Illnesses		
Ever had Tuberculosis		
Yes vs. No	0.72	(0.16, 3.27)
Measles		
Yes vs. No	1.05	(0.48, 2.25)
Mumps		
Yes vs. No	0.99	(0.59, 1.67)
Chicken Pox		
Yes vs. No	1.37	(0.76, 2.47)
Whooping Cough		
Yes vs. No	1.25	(0.73, 2.14)
Scarlet Fever		
Yes vs. No	1.68	(0.83, 3.40)
Infectious mononucleosis		
Yes vs. No	2.24*	(1.02, 4.92)

Variable	Odds Ratio	95% Confidence Interval
Health and Illnesses continued		
Illnesses		
Viral Meningitis		
Yes vs. No	3.19	(0.52, 19.41)
Shingles		
Yes vs. No	0.89	(0.25, 3.14)
Pneumonia		
Yes vs. No	1.77*	(1.03, 3.03)
Other Viral Illness		
Yes vs. No	3.20	(0.88, 11.64)
Liver Disease (including hepatitis)		
Yes vs. No	1.72	(0.83, 3.59)
Colds and Influenza		
Number of Colds or Flu Each Year: Current		
≤ 2 vs. ≥ 1	1.21	(0.73, 2.00)
Number of Colds or Flu Each Year: Teens		
≤ 2 vs. ≥ 1	0.64	(0.38, 1.08)

Variable	Odds Ratio	95% Confidence Interval
Health and Illnesses continued		
Colds and Influenza		
Number of Colds or Flu Each Year: Twenties		
≥2 vs. ≤1	0.78	(0.47, 1.29)
Symptoms of Infection		
Sore Throat		
Yes vs. No	1.94	(0.24, 15.52)
Swollen Glands		
Yes vs. No	1.09	(0.66, 1.83)
Mouth Sores		
Yes vs. No	0.78	(0.47, 1.29)
Cold Sores*		
Yes vs. No	1.04	(0.63, 1.71)
Frequency of Cold Sores in a Lifetime		
1,2 vs. None	0.87	(0.43, 1.78)
≥3 vs. None	1.14	(0.66, 1.98)
Genital Blisters		
Yes vs. No	2.02	(0.93, 4.40)
Genital Sores		
Yes vs. No	1.30	(0.35, 4.76)

Variable	Odds Ratio	95% Confidence Interval
Health and Illnesses continued		
Other Genital Problems		
Yes vs. No	0.95	(0.48, 1.86)
Total Number of Genital Problems		
≥2 vs. ≤1	0.61	(0.32, 1.17)
Lifestyle and General Factors		
Ever Smoked Cigarettes		
Yes vs. No	1.26	(0.73, 2.18)
Ever taken Vitamins as an Adult		
Yes vs. No	1.47	(0.89, 2.43)
Received Blood Transfusion		
Yes vs. No	2.13**	(1.26, 3.60)
Ever Donated Blood		
Yes vs. No	1.77*	(1.02, 3.06)
Ever Participated in a Previous Survey		
Yes vs. No	0.72	(0.44, 1.19)

cancer, 6 had HSV-2 antibody. Infectious mononucleosis (O.R. = 2.24, C.I. 1.02, 4.92) and pneumonia (O.R. = 1.77, C.I. 1.03, 3.02) were more frequently reported by women with HSV-2 antibody than those without antibody.

Lifestyle and General Factors

Women with HSV-2 antibody and those without HSV-2 antibody were similar with regard to cigarette smoking, vitamin use, and participation in a previous study. Women with HSV-2 antibody more frequently reported having received a blood transfusion than women without antibody (O.R. = 2.13, C.I. 1.26, 3.60). Fewer women with HSV-2 antibody reported that they had ever donated blood than did women without antibody (O.R. = 1.77, C.I. 1.02, 3.06).

5.3.3 Multivariate Analysis

Introduction

The general purpose of the multivariate analysis was to evaluate the relative importance of the single factor associations with HSV-2 antibody and, in particular, to examine the separate effects of "biologically plausible" factors which may directly affect the chance of HSV-2 exposure, such as number of sexual partners, or contraceptive behaviour and the impact of socioeconomic or lifestyle factors.

Multiple Logistic Regression Procedure

HSV-2 antibody level, dichotomized into positive and negative categories, coded as 1 and 0 respectively, was entered as the dependent variable into a number of logistic regression models. The independent variables consisted of those factors of interest in assessing the relationship between antibody status and sexual, contraceptive, socio-economic, and lifestyle factors. With the exception of age at interview, which consisted of three levels, all independent variables were dichotomized into approximately equal size groups based upon the median for each variable in the regression analysis.

Objectives

The primary objectives of the logistic regression analysis were to:

1. Evaluate the independent and combined effects of the biologically plausible variables, that is those that could directly affect exposure to HSV-2 antibody. These included: age at first intercourse, total number of sexual partners, condom use and oral contraceptive use for women.
2. Assess the possible confounding effect of additional socioeconomic and lifestyle factors on the associations between the biologically plausible variables and HSV-2 antibody.
3. Examine the independent associations of the socioeconomic or lifestyle factors with HSV-2 antibody.

With these objectives in mind, a number of logistic regression models were developed. Age at interview was included in all of the regression models. The associations between basic biological variables and HSV-2 antibody were examined. The estimates of the odds ratios in this basic model were then compared to a full model containing all additional socioeconomic and lifestyle factors. The change in magnitude and direction of the odds ratios for the primary variables in the basic model with those in the full model was assessed. The impact of the additional variables on the associations of the primary variables and

HSV-2 antibody was examined. To identify the individual effect of the additional variables on the primary variables, separate models were examined including the basic biological variables plus one socio-economic or lifestyle variable at a time. Any shift in the original odds ratios of the basic (biologically plausible) variables was observed and in addition the magnitude of the odds ratio of each additional variable was assessed in terms of its own association with the outcome.

Statistical Inference

In the logistic regression procedure the role played by chance in any of the individual associations observed can be evaluated by any one of three approximately equivalent methods. All of these methods assess the statistical significance of the contribution of the individual variable to the overall model with all other variables in the model taken into account. These include the Score Statistic which tests the difference among the Maximum Likelihood Estimates for different models. In addition, the G statistic represents the difference between the -2 Log Likelihood X^2 between models with and without each additional variable. These two methods give approximately the same result as the square of a Z statistic which is the ratio of the Beta Coefficient to its standard error. These statistics all follow an approximate X^2 distribution. In the description that follows, statistical significance will be described using this last method.

Variables Considered in the Regression Models

In addition to the primary variables of interest, for which a prior hypothesis existed about the association with HSV-2 antibody, a number of additional variables were included, either because of their individual association with HSV-2 antibody at P ≤ 0.05, or to assess their possible impact, however minor, on the association between the primary variables of interest and the outcome. In addition, it was of interest to investigate the possible individual association of these variables and HSV-2 antibody. The variables examined in the logistic models are noted in Table 8 that follows. Part a) indicates variables maintained in the analysis and part b) includes additional variables that were examined in the logistic models but not maintained in the main models. Their exclusion in the main model was not only due to their high correlation with certain other variables in the models, but because in some instances such as type of dwelling and residence status closely represented the same individual. For example, of 40 men who lived in an apartment, 90% rented this home. Theoretically in these instances each variable could essentially serve as a substitute for the other.

In order to assess the possible combined effect of specific factors, interaction terms made up of sets of two variables at a time, of variables already in the models, were examined. None of these interaction terms resulted in a statistically significant contribution to any of the models assessed.

For the purpose of discussion, the primary or basic variables are considered to be those factors which for biological reasons could directly affect exposure to HSV-2 infection. These include number of sexual partners, age at first intercourse, years of condom use for men, reported years of partner(s)' condom use for women, and years of oral contraceptive use for women.

Independent variables were first examined for intercorrelations

TABLE 8

List of Variables used in the Development of the

Logistic Regression Models

Men and Women

(a) Variables Maintained in the Logistic Models

Biological and Sexual
- Age at Interview
- Age at First Intercourse
- Total Number of Sexual Partners

Contraceptive
- Condom Use
- Oral Contraceptive Use (women only)

Socioeconomic
- Total Years of Education or Training

Descriptive
- Marital Status
- Household Crowding
- Hysterectomy Status (women only)
- Birthplace (women only)
- Receipt of a Blood Transfusion (women only)

Lifestyle and Mobility
- Residence Status
- Duration in Current Residence
- Duration in Toronto

(b) Additional Variables Examined in the Logistic Models
- Type of Education or Training
- Household Annual Income
- Type of Dwelling

before their concurrent use in any one model. Correlation matrices are presented in Appendix VI, Tables A-D. High correlation between certain variables noted above may have warranted restriction of the simultaneous inclusion of these variables in the same models. This concern occurred for residence status with type of dwelling, for years of education with income, and for years of education with type of education. In each case, separate models were examined, in which type of dwelling was substituted for residence status and income, or type of education was substituted for years of education. In addition, both correlated variables were examined in the same models. These are presented in Tables P-R in Appendix VI for men and S-U for women. Related to these concerns in the development of the logistic model, the issue of an appropriate measure of socioeconomic status must be noted. In Section 4.3.2, the dimensions of socioeconomic status were discussed, in particular the preference of educational level over income as the indicator of socioeconomic status in this study. To reiterate part of the rationale for this decision, this variable was the most complete of the socioeconomic variables for all participants. Education was also highly correlated with both income and occupation, and there is evidence that educational level reflects socioeconomic factors which may be related to the acquisition of illness in general and of venereal disease in particular (Darrow, 1979; Syme & Berkman, 1976). However, as noted earlier, income was examined in some of the models.

Because the logistic regression procedure requires that all variables for all persons in the models be complete, the total number of persons was somewhat reduced. Therefore, to examine the relationship between the outcome and the variables, unadjusted odds ratios, 95 percent confidence limits were calculated on these reduced numbers. These are presented in Tables 9 for men and 12 for women.

Although the absolute odds ratio and 95 percent confidence intervals were altered slightly in the univariate analyses when the overall numbers were reduced from 321 to 282 for men and 428 to 393 in some of the models for women, the associations between each factor and HSV-2 antibody were similar to those found in the analyses of the total sample.

Initially, separate models were developed for men and for women. In further analysis, in which factors common to both sexes were assessed, men and women were combined.

Multiple Logistic Regression Results

Men

A comparison of the unadjusted odds ratios and adjusted odds ratios in the basic model and in the full model are presented in Table 10.

When the estimates of the adjusted odds ratios for the primary variables of number of sexual partners, age at first intercourse and years of condom use were first compared with the unadjusted odds ratio, it was evident that the unadjusted odds ratio for multiple sexual partners was reduced from 3.20 to 2.63 and early age at first intercourse from 2.72 to 2.08, with only a minimal change in the odds ratio for years of condom use in the basic model. These shifts could be accounted for from the interrelationship among the sexual variables in the basic model. When the odds ratios for the sexual and contraception variables were compared to those in the full model, the odds ratio in the basic model for multiple sexual partners dropped from 2.63 to 2.09

Table 9

Unadjusted Odds Ratios for Participants with Complete Information for All Variables

Men

Variable	Odds Ratio	95% Confidence Interval
a) Variables Maintained in the Logistic Models		
Age at Interview		
39-44 vs. ≤38	0.82	(0.35, 1.92)
≥45 vs. ≤38	0.98	(0.46, 2.05)
Total Number of Sexual Partners in a Lifetime		
≥10 vs. ≤9	3.20**	(1.39, 7.37)
Age at First Intercourse		
≤17 vs. ≥18	2.72**	(1.25, 5.95)
Years of Condom Use ≤ 9 vs. ≥10	0.75	(0.36, 1.56)
Total Number of Years of Education		
≤15 vs. ≥16	0.89	(0.43, 1.84)
Residence Status		
Rent vs. Own	2.95**	(1.41, 6.15)
Marital Status		
Unmarried vs. Married	2.44*	(1.37, 4.36)

* P<0.05.
** P≤0.01

Table 9 continued

Variable	Odds Ratio	95% Confidence Interval
Duration of Residence		
≤10 years vs. ≥11 years	2.15	(0.73, 6.38)
Duration in Toronto		
≤10 years vs. ≥11 years	1.46	(0.66, 3.25)
Household Crowding		
≤4.5 Rooms/Person vs. ≥4.6	1.08	(0.52, 2.23)
b) Additional Variables		
Type of Education or Training		
Non-University vs University	0.91	(0.44, 1.88)
Household Annual Income		
≤$29,000 vs. ≥$30,000	1.16	(0.55, 2.45)
Type of Dwelling		
Apartment vs. House	3.27*	(1.37, 7.81)

Table 10

Comparison of Unadjusted Odds Ratios and Adjusted Odds Ratios: Basic Model and Full Model

Men (n=282)

Variable[1]	Unadjusted Odds Ratio	Adjusted Odds Ratio Basic Model	Adjusted Odds Ratio Full Model
Total Number of Sexual Partners in a Lifetime			
≥ 10	3.20**	2.63*	2.09
Age at First Intercourse			
≤ 17	2.72**	2.08	2.24
Years of Condom Use			
≤ 9	0.75	0.90	0.76
Total Number of Years of Education			
≤ 15	0.89		0.58
Residence Status			
Rent	2.95**		2.32
Marital Status			
Unmarried	2.44**		1.61
Duration of Residence			
≤ 10 years	2.15		1.11

[1] Age at Interview included in all logistic models

* P ≤ 0.05
**P ≤ 0.01
P value for variables in the logistic models indicates the statistical significance of the association of the variable with HSV-2 antibody, with all other variables taken into account.

Table 10 continued

Variable[1]	Unadjusted Odds Ratio	Adjusted Odds Ratio Basic Model	Adjusted Odds Ratio Full Model
Duration in Toronto			
$\leq$ 10 years	1.46		1.33
Household Crowding			
$\leq$ 4.5 Rooms/Person	1.08		0.99

in the full model and rose from 2.08 to 2.24 for early age at first intercourse. In the full model these estimates fell below statistical significance. Minimal change was evident for condom use. The additional variables in the full model included years of education, Residence status, marital status, duration in the current residence and in Toronto, and household crowding. In order to identify the individual impact of each of the additional variables on the primary variables, several models were examined, which include the entry of only one of the additiodal variables in each model (Appendix VI, Table K).

A slight reduction in the odds ratio for multiple sexual partners was evident in most models, with the greatest reduction from the basic model in the model containing marital status. The odds ratio for age at first intercourse in the basic model was elevated somewhat in most models but greatly reduced in the model containing residence status. With the exception of a reduction from 0.90 to 0.78 in the model containing residence status, the odds ratio for condom use remained relatively stable regardless of which additional variable was included.

Table L in Appendix VI provides complete details of the basic model. It is evident that multiple sexual partners, and early age at first intercourse are each associated with HSV-2 antibody, when each as well as condom use is taken into account. Condom use does appear to affect the chance of HSV-2 antibody as measured in this analysis.

Complete information for the full model is presented in Table 11. It is clear that the association between multiple sexual partners, early first intercourse and HSV-2 antibody is sustained, but falls short of statistical significance, when all other factors including residence status and marital status are taken into account. It also

Table 11

Logistic Regression Results Full Model:

Men
(n=282)

Variable[1]	Beta	$S.E._\beta$	$\left(\frac{\beta}{S.E._\beta}\right)^2$	Odds Ratio	95% Confidence Interval	P Value
Number of Sexual Partners in a Lifetime ≥ 10	0.7399	0.4771	2.41	2.09	(0.82, 5.34)	0.1208
Age at First Intercourse ≤ 17	0.8085	0.4496	3.23	2.24	(0.93, 5.41)	0.0722
Years of Condom Use ≤ 9	-0.2737	0.4075	0.45	0.76	(0.34, 1.69)	0.5016
Total Number of Years of Education ≤ 15	-0.5453	0.4656	1.37	0.58	(0.23, 1.44)	0.2415
Residence Status Rent	0.8427	0.4477	3.54	2.32	(0.99, 5.46)	0.0598
Marital Status Unmarried	0.4777	0.4228	1.28	1.61	(0.70, 3.69)	0.2585
Duration of Residence ≤ 10 years	0.1067	0.6385	0.03	1.11	(0.32,3.88)	0.8672
Duration in Toronto ≤ 10 years	0.2851	0.4612	0.38	1.33	(0.54, 3.28)	0.5365
Household Crowding ≤ 4.5 Rooms/Person	-0.0036	0.4216	0.00	0.99	(0.44, 2.28)	0.9932

1 Age at interview included

appears that there is a non-significant association between rental status and HSV-2 antibody with all other variables present, and that the association between marital status and antibody did not sustain statistical significance when all other factors were included in the model.

In summary, it is clear that multiple sexual partners, early age at first intercourse, and renting one's home, each show a non-significant association with HSV-2 antibody, even when all other potentially confounding or interrelated factors have been taken into account.

Women

As for men, the unadjusted odds ratios and adjusted odds ratios for variables in the basic model and those in the full model were compared. This comparison is presented in Table 13. It is evident that the adjusted odds ratios for the primary variables in the basic model including number of sexual partners, age at first intercourse, partner's condom use and oral contraceptive use differed somewhat when compared to the unadjusted estimates. The odds ratio for multiple sexual partners dropped from 3.38 to 2.43 in the basic model, early first intercourse dropped from 3.14 to 2.43 and long term contraceptive use dropped only slightly from 2.58 to 2.31. The unadjusted odds ratio for sexual partner(s)' short term condom use rose slightly from 2.89 to 2.99 in the basic model.

A comparison of the estimates for the primary variables in the basic model and the full logistic model revealed an elevation from 2.43 to 2.52 for multiple sexual partners, a reduction from 2.43 to 1.80 for

Table 12

Unadjusted Odds Ratios for Participants with Complete Information for All Variables

Women

Variable	Odds Ratio	95% Confidence Interval
a) Variables Maintained in the Logistic Models		
Age at Interview		
39-44 vs. ≤ 38	0.83	(0.44, 1.55)
≥ 45 vs. ≤ 38	1.15	(0.58, 2.28)
Total Number of Sexual Partners in a Lifetime		
≥ 2 vs. ≤ 1	3.38**	(1.84, 6.24)
Age at First Intercourse		
≤ 19 vs. ≥ 20	3.14**	(1.79, 5.52)
Years of Condom Use ≤ 9 vs. ≥ 10	2.89*	(1.21, 6.95)
Years of Oral Contraceptive Use		
≥ 10 vs. ≤ 9	2.58**	(1.37, 4.85)
Total Number of Years of Education		
≤ 12 vs. ≥ 13	2.09**	(1.23, 3.57)
Residence Status		
Rent vs. Own	5.16**	(2.99, 8.93)

* $P<0.05$
** $P\leq 0.01$

Table 12 continued

Variable	Odds Ratio	95% Confidence Interval
Marital Status		
Unmarried vs. Married	2.46**	(1.44, 4.18)
Duration of Residence		
≤10 years vs. ≥11 years	1.57	(0.88, 2.78)
Duration in Toronto		
≤10 years vs. ≥11 years	0.72	(0.35, 1.48)
Household Crowding		
≤4.5 Rooms/Person vs. ≥4.6	2.52**	(1.45, 4.40)
Hysterectomy		
Yes vs. No	3.04**	(1.63, 5.72)
Received Blood Transfusion		
Yes vs. No	2.02**	(1.17, 3.46)
Birthplace		
Other vs. Canada	1.65	(0.95, 2.89)
b) Additional Variables		
Type of Education or Training		
Non-University vs University	1.44	(0.59, 3.50)
Household Annual Income		
≤$24,999 vs. ≥$25,000	3.16**	(1.68, 5.93)
Type of Dwelling		
Apartment vs. House	3.22**	(1.76, 5.88)

early first intercourse, and from 2.99 to 2.40 for partner(s)' condom use. The estimate for long term contraceptive use rose from 2.31 in the basic to 3.44 in the full model.

The individual effects of the additional variables on the association between the primary variables and HSV-2 antibody appear in Table M in Appendix VI. An increase in the estimate for multiple sexual partners was evident from that in the basic model to those found in the separate models with the greatest elevation for the model containing years of education. The estimate for multiple sexual partners was reduced from that in the basic model in a number of models, with the greatest reduction for the model including marital status, followed by the model containing residence status. The estimate for early first intercourse was elevated in some of the models, with the greatest increase for the model containing duration in residence. The odds ratio was reduced in other models, with the greatest reduction for the model containing years of education. With the exception of the model containing household crowding, the odds ratio in the basic model for partner(s)' condom use was reduced in the additional models with the greatest reduction in the model containing residence status.

An elevation in the estimate for long term oral contraceptive use was evident in a number of models, with the greatest elevation for the model containing hysterectomy status.

The bivariate relationships among the independent variables verify that many factors not strictly defined as socioeconomic could affect the association between educational level and the outcome, with the sexual and contraceptive factors taken into account. In order to assess this issue, further models were examined in which sexual and

Table 13

Comparison of Unadjusted Odds Ratios and Adjusted Odds Ratios: Basic Model and Full Model

Women
(n=393)

Variable[1]	Unadjusted Odds Ratio	Adjusted Odds Ratio Basic Model	Adjusted Odds Ratio Full Model
Total Number of Sexual Partners in a Lifetime			
≥ 2	3.38**	2.43**	2.56*
Age at First Intercourse			
≤ 19	3.14**	2.43**	1.80
Years of Condom Use			
≤ 9	2.89*	2.99*	2.40
Years of Oral Contraceptive Use			
≥ 10	2.58**	2.31*	3.44**
Total Number of Years of Education			
≤ 12	2.09**		1.68
Residence Status			
Rent	5.16**		3.38**
Marital Status			
Unmarried	2.46**		0.99
Duration of Residence			
≤ 10 years	1.57		1.26

[1]Age at Interview was included in all logistic models
* $P \leq 0.05$
** $P \leq 0.01$

Table 13 continued

Variable	Unadjusted Odds Ratio	Adjusted Odds Ratio Basic Model	Adjusted Odds Ratio Full Model
Duration in Toronto			
≤ 10 years	0.72		0.65
Household Crowding			
≤ 4.5 Rooms/Person	2.52**		1.16
Hysterectomy			
Yes	3.04**		2.93**
Received Blood Transfusion			
Yes	2.02**		1.20
Birthplace			
Canada	1.65		0.94

contraceptive factors along with years of education were examined and one additional variable included alone in each model. The results of this analysis are presented in Table N in Appendix VI. The greatest reduction in the estimate for education occurred in the model containing residence status (from 2.23 to 1.85) followed by the model containing marital status (to 1.89). With the exception of that for duration in Toronto the estimates of all other variables in each model remained highly elevated. It is apparent that educational level as a socioeconomic indicator is affected by other factors, and the other factors themselves together are associated with antibody.

Complete details of the logistic regression results for the basic model are presented in Table O in Appendix VI.

It is evident that the elevated odds ratio for all variables in the model are statistically significant at P $\leq$0.05, even when all of these factors were simultaneously examined. Details of the full model are presented in Table 14. It is apparent that, of the primary variables, multiple sexual partners and long term oral contraceptive use, each shows a statistically significant association with HSV-2 antibody and the estimates for an early age at first intercourse and short term condom use of sexual partner(s) fall just short of statistical significance, even when socioeconomic and lifestyle factors have been taken into account. In addition, renting one's home and having had a hysterectomy were independently associated with antibody when adjustment for biologically plausible and all other factors had been made. Although an elevated odds ratio of 1.68 was apparent for low educational level, the association did not reach statistical significance.

Table 14

Logistic Regression Results Full Model:

Women
(n=393)

Variable[1]	Beta	S.E.$_\beta$	$\left(\frac{\beta}{S.E._\beta}\right)^2$	Odds Ratio	95% Confidence Interval	P Value
Number of Sexual Partners in a Lifetime ≥ 2	0.9396	0.3893	5.83	2.56	(1.19, 5.49)	0.0158
Age at First Intercourse ≤ 19	0.5849	0.3435	2.90	1.80	(0.92, 3.51)	0.0886
Years of Condom Use ≤ 9	0.8736	0.4846	3.25	2.40	(0.93, 6.19)	0.0714
Years of Oral Contraceptive Use ≥ 10	1.2344	0.3764	10.76	3.44	(1.64, 7.18)	0.0010
Total Number of Years of Education ≤ 12	0.5168	0.3567	2.10	1.68	(0.83, 3.37)	0.1475
Residence Status Rent	1.2188	0.3959	9.48	3.38	(1.56, 7.35)	0.0021
Marital Status Unmarried	-0.0038	0.3565	0.00	0.99	(0.49, 2.00)	0.9915

[1] Age at interview included

Table 14 continued

Variable	Beta	S.E.$_\beta$	$\left(\frac{\beta}{S.E._\beta}\right)^2$	Odds Ratio	95% Confidence Interval	P Value
Duration of Residence						
≤ 10 years	0.2334	0.3735	0.39	1.26	(0.61, 2.63)	0.5320
Duration in Toronto						
≤ 10 years	-0.4269	0.4430	0.93	0.65	(0.27, 1.55)	0.3351
Household Crowding						
≤ 4.5 Rooms/Person	0.1507	0.3982	0.14	1.16	(0.53, 2.53)	0.7050
Hysterectomy						
Yes	1.0756	0.4070	6.99	2.93	(1.32, 6.51)	0.0082
Received Blood Transfusion						
Yes	0.1853	0.3418	6.29	1.20	(0.62, 2.35)	0.5877
Birthplace						
Canada	-0.0583	0.3411	0.03	0.94	(0.48, 1.84)	0.8644

Additional Variables

Men

As noted earlier, although additional variables were considered for the logistic models, because of the correlation and overlap between certain variables, these were examined in separate models. It will be seen that when both variables were included, occasionally estimates for each were diluted.

Type of Education and Years of Education

Theoretically the type of education may be as important as a sociologic indicator of health behaviour as years of education. The models presented in Table P indicate that in the model in which type of education is substituted for years of education the estimate for age at first intercourse is slightly elevated from 2.24 to 2.37. For men, it was evident that education, as any other measure of socioeconomic status, was not associated with HSV-2 antibody, and moreover did not appear to affect the relationship between other attributes and antibody.

Household Annual Income and Years of Education

As indicated by the information in Table Q, only minor shifts in the estimates occur with the greatest change for number of sexual partners in the original from 2.25 to 1.87, and for age at first intercourse from 2.07 to 1.98 with income substituted for years of education.

Type of Dwelling and Residence Status

Table R illustrates the results of the models containing type of dwelling. It is evident that the estimate for number of sexual partners and age at first intercourse in the original model is somewhat reduced in the model containing type of dwelling. The estimate for type of dwelling, although elevated (2.38), did not reach statistical significance. In the model containing both dwelling and residence status, the estimates for each were somewhat reduced.

Women

Type of Education and Years of Education (Table S)

With the exception that the estimate for age at first intercourse reached statistical significance in the model in which type of education was substituted for years of education, little difference in the association between the variable and HSV-2 antibody was apparent from those in the original model. The estimate for type of education in any of the models did not reach unity.

Household Annual Income and Years of Education

As indicated in Table T, there was a slight shift in the estimate for age at first intercourse upward which reached statistical significance in the models containing income. However, little difference between these models and the original final model was evident. The estimate for income was elevated (2.13) but did not reach statistical significance.

Type of Dwelling and Residence Status (Table U)

When type of dwelling was substituted for residence in the original full model, the estimates for age at first intercourse and years of condom use rose slightly and achieved statistical significance. With these exceptions the estimates for model variables were essentially unaltered from those in the original model. The estimate for type of dwelling was elevated (2.00) but did not reach statistical significance.

Number of Sexual Partners During Specific Life Periods

The univariate analysis of the number of sexual partners during each decade of life and during the year preceding the interview revealed that HSV-2 antibody was generally more frequently found in men and women with multiple sexual partners during specified life periods. This information could be of interest in assessing (1) whether or not exposure to multiple sexual partners at a particular time of life would increase the chance of HSV-2 acquisition and (2) whether or not recent exposure as indicated by the number of sexual partners during the twelve months before the interview had an effect on the detection of HSV-2 antibody. In order to further refine the relationship between HSV-2 antibody and number of sexual partners, the number of sexual partners during a specific life period was added to the full logistic models for men and women.

The analysis of the impact of the number of sexual partners during a specific time period presented somewhat of a problem in that the association between the number of partners during each decade and HSV-2 antibody could not effectively be separated from the impact of the lifetime total of sexual partners. Further difficulties existed because of the high correlation among the number of partners reported during each life period, particularly between those in the twenties and thirties. To take this problem into account, the entry of the number of partners during specific time periods was examined in sets with relatively lower correlation in the same model.

A compromise was devised in which the number of sexual partners during certain life periods, though highly correlated with one another, but still not preventing convergence of the model, were entered. The strength of the association between the variables entered and HSV-2 antibody was then compared 1) with the overall model containing total number of sexual partners in a lifetime, 2) with each model and 3) between models. In each case the full model was run. That is, age at interview, number of sexual partners as appropriate, age at first intercourse, condom use, oral contraceptive use for women, years of education, all residence variables, household crowding, hysterectomy status, blood transfusion and birthplace for women. The results of these models are presented in Table 15 for men and in Table 16 for women. The estimates of the odds ratios and the P value indicating the statistical significance of the contribution of each model to the total model for only the biologically related variables are presented. Although all other variables in the full model were included, as the results were similar to those in the original model containing total number of sexual partners, these additional variables are not illustrated.

It is important to note that the number of sexual partners during the forties was not examined because this variable was not available for a large number of participants who were not yet into their forties. Furthermore, although adjustment for the number of sexual partners

Table 15

Logistic Regression Results: Full Model
Comparison of Adjusted Odds Ratios
for Number of Sexual Partners During Life Periods
and Total Number of Sexual Partners
in a Lifetime

Men
(n=282)

Variables[1]	Model 1 Total Number of Sexual Partners	Model 2 Number of Partners 20s	Model 3 Number of Partners 30s	Model 4 Number of Partners 20s, 30s
Age at First Intercourse ≤ 17	2.24	2.04	2.02	2.17
Years of Condom Use ≤ 9	0.76	0.73	0.66	
Total Number of Partners ≥ 10	2.09	-	-	-
Number of Partners in Teens ≥ 2	-	0.80	0.89	0.71
Number of Partners in Twenties ≥ 2	-	1.83	-	2.00
Number of Partners in Thirties ≥ 2	-	-	0.91	0.81
Number of Partners in Year Preceding Interview ≥ 2	-	1.86	2.04	1.93

1 Age at Interview and all other variables in the Full Model have been included but are not shown here.

Table 16

Logistic Regression Results: Full Model
Comparison of Adjusted Odds Ratios
for Number of Sexual Partners During Life Periods
and Total Number of Sexual Partners
in a Lifetime

Women
(n=393)

Variables[1]	Model 1 Total Number of Sexual Partners	Model 2 Number of Partners 20s	Model 3 Number of Partners 30s	Model 4 Number of Partners 20s, 30s
Age at First Intercourse $\leq$ 19	1.80	1.45	1.53	1.48
Years of Condom Use $\leq$ 9	2.40	2.03	2.03	2.03
Years of Oral Contraceptive Use $\geq$10	3.44**	3.45**	3.70**	3.76**
Total Number of Partners $\geq$ 2	2.56*	-	-	-
Number of Partners in Teens $\geq$ 2	-	1.68	1.87	1.63
Number of Partners in Twenties $\geq$ 2	-	2.30*	-	2.03
Number of Partners in Thirties $\geq$ 2	-	-	1.27	1.06
Number of Partners in Year Preceding Interview $\geq$ 2	-	0.91	0.95	0.93

1 Age at interview and all other variables in the Full Model have been included but are not shown here.

* $P \leq 0.05$
** $P \leq 0.01$

during certain time periods has been made in each model, as these variables were not independent of one another, the total number of sexual partners has not been taken into account.

For men, the model containing the number of sexual partners in the teens, twenties and thirties and partners in the last year, an odds ratio of 1.93, though not statistically significant, indicated an association between multiple sexual partners during the year preceding the interview, even when the number of sexual partners during the teenage years, twenties and thirties were taken into account. Similarly, a non-significant estimate of 2.00 indicated an association between number of partners in the twenties and HSV-2 antibody. It should be noted that for both men and women the number of sexual partners in the twenties was highly correlated (r=0.8580) with the total number of sexual partners, suggesting that this life period contributes greatly to the overall total.

For women, elevated but not statistically significant odds ratios indicated an association between multiple sexual partners during the teenage years, with a statistically significant association between multiple partners in the twenties and HSV-2 antibody evident.

Therefore it appears that early sexual exposures for women may enhance the acquisition of HSV-2 infection, with some suggestion that exposure in the twenties as well as recent exposure affects infection for men.

Summary and Conclusions

Table 17 illustrates the logistic regression results for both men and women combined in which the associations between variables common

Table 17

Logistic Regression Results: Men and Women

Combined: Full Model

Variable[1]	Beta	$S.E._\beta$	$\left(\frac{\beta}{S.E._\beta}\right)^2$	Odds Ratio	95% Confidence Interval	P Value
Gender						
Women	0.8639	0.2771	9.72	2.37	(1.38, 4.08)	0.0018
Total Number of Sexual Partners in a Lifetime						
≥ 4	0.6436	0.2909	4.89	1.90	(1.08, 3.37)	0.0270
Age at First Intercourse						
≤ 18	0.5940	0.2550	5.42	1.81	(1.09, 2.99)	0.0198
Years of Condom Use						
≤ 9	0.2320	0.2781	0.70	1.26	(0.73, 2.18)	0.4040
Total Number of Years of Education						
≤ 13	0.0721	0.2669	0.07	1.07	(0.63, 1.81)	0.7870
Residence Status						
Rent	1.0996	0.2734	16.17	3.00	(1.76, 5.13)	0.0001
Marital Status						
Unmarried	0.3039	0.2615	1.35	1.36	(0.81, 2.26)	0.2452
Duration of Residence						
$\leq$ 10 years	0.1622	0.3064	0.28	1.18	(0.65, 2.14)	0.5965
Duration in Toronto						
$\leq$ 10 years	-0.2074	0.3095	0.45	0.81	(0.44, 1.49)	0.5028
Household Crowding						
$\leq$ 4.5 Rooms/Person	0.0123	0.2642	0.15	1.11	(0.66, 1.86)	0.6994

[1] Includes Age at Interview

to both sexes and HSV-2 antibody were examined. With the exception of age at interview, which was included in all three categories, all other continuous variables were dichotomized, based upon the median value for both sexes together. It is evident that, for both men and women, multiple sexual partners and early first intercourse each make a statistically significant contribution to the model. In addition, the association for rental status was highly significant when age at interview, years of education, marital status, duration in the current residence and in Toronto, household crowding and gender were taken into account. Interaction terms made up of gender and each variable of interest did not indicate any significant effects.

With regard to possible effect of multiple sexual partners during specific times of life on HSV-2 acquisition, the somewhat limited analysis of this issue indicated that multiple partners early in life, particularly in the twenties, increased the chance of HSV-2 infection for women. For men, there was a non-significant association between multiple partners in the twenties and during the year preceding the interview and HSV-2 antibody.

From both the logistic analysis stratified by gender as well as the combined analysis, we can conclude that multiple sexual partners, early first intercourse and rental status are associated with HSV-2 antibody for both men and women. In addition to these factors, for women it is apparent that long-term use of oral contraceptives, low condom use by sexual partners and having undergone a hysterectomy are associated with HSV-2 antibody.

For women, it is of particular interest to note that the estimates for number of sexual partners, oral contraceptive use and hysterectomy status remained relatively stable regardless of the other combinations of variables included in various models. Further, the inclusion of each of these factors in the models did not greatly affect the estimates of the other variables. This would suggest that these are "real" and essentially independent associations with HSV-2 antibody.

Because of the potential interdependence of sexual and contraceptive behaviour and socioeconomic status, as well as the possible independent association of low socioeconomic status with HSV-2 antibody, it is of interest to note that no socioeconomic effect was observed for men, and the association between low socioeconomic status as measured by education or income and antibody for women fell short of statistical significance when all other factors were taken into account. It may be that educational level does not alone indicate "socioeconomic status" in the practical sense. This possibility was partially demonstrated by the reduction that residence and lifestyle factors had upon the strength of the association between education and antibody. Furthermore, because the sample size achieved did not permit sufficient power to detect relatively small differences, these negative results must be interpreted with caution. That is, based upon this study sample, we could not demonstrate an association between socioeconomic status and HSV-2 antibody.

CHAPTER 6

DISCUSSION

6.1 Introduction

The objective of this investigation was to assess simultaneously a number of interrelated factors which could affect exposure to HSV-2 infection. In order to evaluate the study results in terms of this objective, a number of issues must be addressed. These issues include the assay method, sample size, non-response and loss of information, study ~~methods~~, comparability of the results with other studies and regression analysis. Recommendations for extensions of the present investigation and future studies must also be considered.

6.2 Radioimmunoassay Method

A comparison of the radioimmunoassay and microneutralization methods with clinical detection of disease (Table 1, Chapter 2) suggested that the radioimmunoassay was more sensitive but less specific than the microneutralization method when compared with clinically evident HSV-2 infection. When the sera of apparently healthy individuals were tested using both assay methods, a greater proportion of those tested were classified as HSV-2 positive by microneutralization than by the radioimmunoassay. A discussion of the relationship between the radioimmunoassay and microneutralization methods appears in Section 2.3.1 of Chapter 2. Tables and calculations related to this discussion are contained in Appendix I. When 133 serum samples were tested by both methods, using the microneutralization as the standard, the percentage of false positives by radioimmunoassay was

11.8. In this comparison persons without known genital herpes infection, the radioimmunoassay was found to show a lower rate of positive agreement, but a higher rate of negative agreement.

The possible effects of misclassification of antibody status must be considered. It has been suggested by a number of authors that random (non-differential) misclassification of the outcome, will tend to reduce the association found (Bross, 1954; Kleinman, Kupper and Morgenstern, 1982; MacMahon and Pugh, 1978). If individuals had been randomly misclassified according to antibody status unrelated to exposure, then the odds ratios calculated could have underestimated the associations found. Non-random misclassification could also occur which would either inflate or reduce the associations. In the present study, the possibility of non-random (differential misclassification) could occur. For example, because the detection of HSV-2 type specific antibody is affected by prior infection with HSV-1, false-negatives to HSV-2 may have occurred more frequently among individuals possibly exposed to HSV-1 (such as those of lower socioeconomic status) than those without prior HSV-1 infection.

As noted in Section 2.3.1. "sensitivity" corresponds to the agreement of positive results when two assay methods are compared with one another. To illustrate the potential effects of unequal "sensitivity" of the radioimmunoassay at different levels of the exposure variable, an estimate using the exposure variable years of education was recalculated using data from another study, carried out in the same city as the present investigation. In this latter study, participants' sera were tested using both the radioimmunoassay and microneutralization (Rawls et al., 1980). It was found that the radioimmunoassay identified 22 percent of 255 women as HSV-2 positive, compared to 35 percent identified as positive by the microneutralization test (Rawls et al., 1980). Thus 1/3 fewer persons were identified as HSV-2 positive when the radioimmunoassay rather than microneutralization test was used. Although the sera for all but 4 persons in the study were tested by both assay methods, the number of those positive by the radioimmunoassay but not the microneutralization were not reported in the publication, and therefore cannot be taken into account in the comparison with the present data.

If all persons found to be HSV-2 positive by microneutralization but not by radioimmunoassay were allocated to the HSV-2 positive category in the low educational group (See Appendix IX), the estimate of association was elevated from 2.10 to 5.92 suggesting that the study estimates could have been underestimated. Conversely, if all HSV-2 positive by microneutralization but not radioimmunoassay were allocated to the high educational HSV-2 positive category, the odds ratio would have been reduced to 1.17, and the original estimate overestimated.

It is important to keep in mind that all these recalculations of the present data based upon comparisons with other data represent speculation. Frozen sera for all participants in the present investigation remains available. It would be ideal to analyze this sera using the microneutralization or other assay method.

6.3 Adequacy of the Sample Size and Power Estimates

Sample Size

The original sample size for the study was calculated from the formula of Schlesselman (1974). This was based on an assumed prevalence of 34 percent for HSV-2 antibody in the population without exposure to the trait, as suggested by the study of Adam et al. (1973b). An exposure prevalence of 44 percent for multiple sexual partners, the primary risk factor of interest, was assumed in the population, together with a relative risk of 1.51 (Adam et al., 1973b). This resulted in a total required sample size of 744, which also gave reasonable power for various other combinations of exposure prevalence and relative risk as illustrated in Table 19.

Using the variable of age at interview, power was calculated for varying levels of population "exposure" (P_o), in this case, an older age, as indicated by the estimated risk ratios (Schlesselman, 1982).

For example, for men, a risk ratio of a minimum of 3.0 would have been necessary to achieve at least an 80% chance of detecting an odds ratio that would differ significantly from 1.0 at $\alpha = 0.05$.

It should be noted that this sample size and power calculation is application to risk factors which applied to the whole sample both in terms of exposure prevalence and relative risk. Therefore, for exposure factors which apply to gender, such as oral contraceptive use, or which differ between the genders, the power of the study is somewhat reduced. However, as the required sample size was obtained within the resources of the study, and as it provided reasonable power for main effects, this sample size was established as the objective.

Table 18

Power for the Detection of Various Levels of Risk Based upon the Study Sample Age at Interview

(α = 0.05 2-tailed test)

	P_o Exposure in The Population	Risk Ratio	Power $(1-\beta)$
Men			
	0.6095	1.5	0.2177
	0.6750	2.0	0.5039
	0.7225	2.5	0.7323
	0.7570	3.0	0.8577
Women	0.5903	1.5	0.3483
	0.6570	2.0	0.7549
	0.7051	2.5	0.9406
	0.7421	3.0	0.9871

Interpretation of Negative Results

The original sample size and power calculations were based on the assumption that the prevalence of the antibody in the population would be 34 percent. As reported, in practice the prevalence in the study group turned out to be much lower (15%) and thus of course the power of the study was reduced. The interpretation of negative results, i.e., those which failed to show a statistically significant association between exposure and HSV-2 antibody, is most appropriately based on the confidence interval estimates for those exposures as obtained in the study. Nevertheless the power estimates earlier were recalculated using the observed prevalence of HSV-2 antibody in this study. This is shown below in Table 19. This resulted in much lower powers than those computed for the study. This factor could explain the failure to obtain statistically significant results from some of the exposure factors which a-priori might have been expected to show association with HSV-2 antibody, though as stated in interpretation of specific negative results should be based upon the 95 percent confidence interval estimates obtained which show the reasonable lower and upper bounds for the magnitude for any possible effect.

As would be expected, for a variable that was found to differ between persons with and without HSV-2 antibody, such as number of sexual partners, there was at least an 80 percent chance of detecting this difference. For men, an odds ratio of 2.86 (C.I. 1.32, 6.19) indicated an association between multiple sexual partners and HSV-2

Table 19
Power for the Detection of the Relative Risk Based Upon the Prevalence of HSV-2 Antibody in the Study Sample Based Upon Age at Interview

	Exposure in the Study Sample	Risk Ratio	Power $(1-\beta)$
Men	0.4330	0.736	0.1587
Women	0.4061	0.723	0.2611

antibody with at least an 82 percent chance of being detected. For women, an odds ratio of 2.94 (C.I. 1.64, 5.26) also indicated an association between multiple sexual partners and HSV-2 antibody and had at least a 97 percent chance of being detected in this study sample.

Cluster sampling

The use of a cluster as opposed to a random sample reduces the estimation of standard errors (Moser and Kalton, 1972). There is no direct way to take this into account using the multiple logistic regression model, but work by Stavrsky et al. (1983) using the present data indicated that the standard errors will have been underestimated by less than 10 percent and that this should not make any observed statistically significant results non-significant at the level 0.05 used (Kish and Frankel, 1974).

6.4 Loss of Information: Non-Response

6.4.1. Refusal of Interview

Of the 1220 persons who were eligible to participate in the study, 957 (79%) completed interviews.

There is limited information available concerning the characteristics of the 263 persons (21%) who chose not to participate. Information that is available was based upon the socioeconomic (SES) designation of the census area that was used in the sampling process. Appendix V illustrates the SES distribution of households approached, refusals for interview, and interviews obtained. It is evident that the refusal rate was inversely related to SES area with 42 percent refusals in low SES areas, 37 percent in middle areas, and 21 percent in high SES areas.

These results suggest that higher refusal rates by persons from low and middle SES areas biased the socioeconomic census composition of the study sample. However, to bias the study findings, non-participants would have to vary from participants both in terms of the risk factor and HSV-2 antibody status, and the exposure and antibody would have to be related to one another. Theoretically this circumstance would have been unlikely because, when invited to participate, individuals were not aware that it was a study of HSV-2. Furthermore, there is no reason to expect that the respondents would be aware of their own HSV-2 antibody status or that this would affect their willingness to participate in the study.

6.4.2 Refusal of Blood Sample

The objective of considering various conditions regarding those without serologic information is to estimate how the study findings may have differed had the antibody status for all of those interviewed been known.

Because the distribution of the exposure variables is known for those without serum samples, one needs only to speculate about their antibody status. In order to assess the possible effect of loss of serologic information on the study results, a worst case analysis was used (Schlesselman, 1982). Odds ratios were calculated for total number of sexual partners, a variable that was significantly associated with HSV-2 antibody. For illustrative purposes, a number of examples of the effect of this on the calculated odds ratios are presented in Appendix IX.

For most attributes, men and women without serologic information resembled the exposure distributions of the HSV-2 negative group. Because of this similarity, if they all were allocated to the seronegative group, the magnitude of the estimate for most variables would remain unchanged. However, if they were added to the seropositive group the estimates would be reduced.

If allocated proportionately to the actual data, as only a small portion of either group are HSV-2 positive the results remain unchanged. Of particular importance is whether those who elected not to provide a blood sample were more likely to possess characteristics which would affect their chance of HSV-2 antibody. For example, if participants had been aware of our interest in HSV-2, the individuals own knowledge of their sexual exposures (i.e. many sexual partners) may have made them more likely to refuse a blood sample than those with fewer sexual partners. In this example, it is possible that a larger proportion without serologic information might have had many sexual partners <u>and</u> HSV-2 antibody. This circumstance would have resulted in an underestimate of the odds ratio in the present investigation. Clearly the converse of this circumstance could have occurred if those who refused were more likely to be HSV-2 positive with few sexual partners. Overall the estimates would have varied if the choice not to provide a blood sample related to exposures which could affect antibody status.

In order to illustrate these various possibilities, a number of examples of the effects on the measure of association (odds ratios) are presented in Table B in Appendix IX. The relationship between total number of sexual partners and HSV-2 antibody for men has been used as the example.

It is evident that the estimates remain relatively stable when those without serum samples are independently allocated to antibody groups <u>or</u> to the exposure groups. However, when antibody status and exposure level are interrelated, and those without serologic informaton are allocated to antibody groups at specific levels of the exposure the estimates are reduced or elevated depending upon the group allocation. For example, as indicated in Table B, Appendix IX, the estimate is elevated to 9.63 if it is assumed that all those without serum samples would have been HSV-2 positive and had many sexual partners.

In reality the distribution of the number of sexual partners as well as other exposure variables for those who elected not to provide a blood sample is known. As those without serologic information generally resembled the HSV-2 negative group in terms of these exposure variables, it is likely that the direction and even the strength of the associations found in this study would have remained had serologic information been available for all study participants.

Under the extreme conditions of allocating all of those without serologic information to the antibody positive group, the odds ratio was reduced from that found in the study. However, there is no evidence that all who did not provide a blood sample would be antibody positive. In reality, the participants' antibody status cannot be determined by their willingness to provide a blood sample.

6.5 Study Methods

6.5.1. Quality of the Reported Information

Although every attempt was made to encourage candid responses during the interview, the validity of the participants' responses cannot be assured. Problems of memory and protection of personal privacy would have contributed to the number of incorrect responses. Furthermore, it cannot be assured that inaccurate responses would have been randomly distributed throughout the sample. For example, there may have been variation in the reporting of sexual or contraceptive practices among social class groups due to conventions, or even understanding of the questions. The questionnaires showed good internal consistency with regard to concrete items such as birthdate and age.

6.5.2 Contraception and Sexual Patterns

In the areas of contraception and sexual patterns, some information was not gathered because the inquiries would have been particularly intrusive, or would have required speculation or especially good recall on the part of the respondent. These issues included such questions as to how carefully condoms were used during intercourse, whether or not the number of sexual partners represented a number of semi-monogamous relationships or casual encounters, and the frequency of intercourse. The fact that a similar odds ratio with regard to multiple sexual partners was apparent but represents a wide difference in absolute numbers of partners (10 or more for men and 2 or more for women) is of interest. This could easily represent different reporting patterns between men and women or even the effect of the participant's partner's unknown number of sexual partners. Other than speculation about the "double standard" regarding sexual behaviour, a study by Carns (1967) of 1,177 university students reported that women were more reluctant to acknowledge sexual intercourse to their peers and parents than were men. It does not seem reasonable that the chance of HSV-2 exposure would be greatly increased by 2-3 sexual partners as evident for women (O.R. 2.48 for 2,3 vs. 1 partner). Another suggestion for an increased female receptivity to the virus is that Judson et al. (1980) reported that rates of genital herpes were higher in heterosexual than homosexual men seen in a venereal disease clinic. However, contrary to this finding, Melbye et al. (1983) reported lower rates of HSV-2 infection in heterosexual over homosexual men.

Further information about all non-occlusive contraceptive methods, such as tubal ligations, vasectomies in the partners, and the use of contraceptive foam or gel, would have been useful, particularly in understanding the association between long term contraceptive use and HSV-2 antibody. It is not clear whether the association between non-occlusive methods represents an increased vulnerability of the genital area to many infectious agents due to the hormonal effect of the pill, a difference in sexual behaviour not identified in this studyor other unidentified sexual or health factors associated with oral contraceptive use.

6.5.3 Lifestyle and Housing

In addition to information about socioeconomic status it might have been useful to obtain standard information about health behaviour such as preventive medical and dental care, automobile seat belt use and alcohol consumption. The association between rental status and HSV-2 antibody might have been explained by additional information such as a residence history including the duration of time in different areas, and types of residences.

6.6 Comparison of the Results with Previous Investigations

When findings from previous studies are compared with those from this investigation, it is important to keep in mind that in previous studies only single factor associations were considered.

When the proportion of persons in this investigation with HSV-2 antibody was compared with that of other studies, using a similar radioimmunoassay method, it was apparent that a lower proportion of men and women showed HSV-2 antibody (17.5%) in the present investigation than in that of Graham et al. (1982). The authors reported that 44 percent of 130 women tested showed HSV-2 antibody in Los Angeles County, California. However, when Rawls et al. (1980) examined 255 women who were used as a comparison group for cervical cancer patients in a residential sample in Toronto, they reported only a slightly higher proportion than in the present investigation: 22 percent of 255 women showed HSV-2 antibody.

With regard to present age, the results of this investigation were in keeping with evidence from previous studies. Although the present investigation was restricted to men and women between the ages of 35 and 50, no age trend was evident. Information from previous investigations indicated that the proportion of persons with antibody evidence of past HSV-2 infection stabilized by the fourth decade (McDonald et al., 1974a; Rawls, Tompkins and Melnick, 1969; Strizova et al., 1975).

The results of this study indicated that, without adjustment for other factors, an early age at first intercourse was associated with HSV-2 antibody for both men and women. Information available on women only from published investigations indicated an association between early first intercourse and HSV-2 antibody in most of the groups investigated (Adam et al., 1972; Adam et al., 1973b; Adam et al., 1974; Ishiguro and Ozaki, 1978).

Several investigators reported that women who had had multiple sexual partners more frequently showed HSV-2 antibody than did women who reported only one partner (Ishiguro and Ozaki, 1978; Graham et al., 1982). The findings of this study are in keeping with these results. Women who reported at least two sexual partners more frequently showed HSV-2 antibody than women with one partner, even when adjustment was made for age at first intercourse and other factors. Suchankova et al. (1984) reported an association between multiple sexual partners and HSV-2 antibody but noted that the relationships between number of partners and the proportion with antibody was not linear. The proportion with antibody (27%) did not increase significantly for those who reported 2 partners over those who reported 11 or more. Information about HSV-2 infections and number of sexual partners for men was not available from previous investigations; however, as for women in this study, men who reported multiple (at least 10) partners were more likely to show antibody.

Information on HSV-2 antibody and condom use was not available from previous studies. However, in studies of patients attending venereal disease clinics, men with genital herpes were less likely to report condom use than were men without herpes infection (Bar'ow, 1977; Taylor and Rodin, 1975). An association between low condom use and HSV-2 infection was not evident for men in the present investigation.

The finding that long term oral contraceptive use was associated with HSV-2 antibody even when adjustment was made for other factors could not be supported by other information in the literature. Wolinska and Melamed (1970) reported that among women attending a family planning clinic, the higher rates of genital herpes were found in women who reported using no contraception whatever over those taking the oral contraceptive. Of women who reported using no contraceptive 0.3 percent showed genital herpes compared to 0.09 percent who reported oral contraceptive use within the last year. Although genital herpes was not reported, Schachter, Avram and Gorodeski (1983) reported a correlation between cervical inflammation and oral contraceptive use. Theoretically, this finding suggests that oral contraceptive users may be more susceptible to secondary infection.

One explanation of the association between oral contraceptive use and HSV-2 is that when the pill is used alternative protective occlusive methods of contraception such as the diaphragm and the condom are not used. However, this could not be illustrated from data in this investigation. Another might be that oral contraceptive use was correlated with multiple sexual partners. However, the association between oral contraceptive use and HSV-2 antibody was sustained even when the number of sexual partners and condom use were included in the regression model. It is possible that there is some aspect of sexual behaviour that has not been measured in this investigation which might reflect not only the number of sexual partners but the type of relationships, such as casual vs. sustained relationships, which some women taking the oral contraceptive may experience.

A number of previous investigations suggested an inverse relationship between low socioeconomic status and HSV-2 infection. When the socioeconomic classification of the areas was used as the measure of social class, a greater proportion of persons with HSV-2 antibody lived in lower economic areas (McDonald et al., 1974a; Royston and Aurelian, 1970). Seth et al. (1981) reported low income in association with HSV-2 antibody for men and women examined in Delhi, India; however, it is not possible to assess the role of different hygienic and environmental conditions and income in this different country. No association between any measure of socioeconomic status and HSV-2 antibody was found in the present investigation for men. It may be possible that men of higher educational level and income are more likely to have multiple sexual partners (thereby a greater chance of HSV-2 exposure). Beyond the moral issues in a culture which appears to encourage monogamy, it might be speculated that the choice to have multiple sexual partners for men is, in part, dependent upon options which may increase with social status. Contrary to this, for women the "choice" to have multiple sexual partners may tend toward the acceptance rather than the initiation of sexual relationships. Although this may seem like an outdated theory, we do not know whether or not it may be relevant, particularly in the age group of these study participants.

For women, a lower socioeconomic status as measured by educational level and income was associated with HSV-2 antibody when other factors such as sexual behaviour and contraception were not taken into account. In the multivariate analysis, however, when sexual Behaviour, contraception, and socioeconomic status were simultaneously examined, the association between low socioeconomic status and HSV-2 antibody for women fell below statistical significance.

The difference between the findings of this study and previous studies with regard to social class may in part be due to the fact that sexual and contraceptive behaviour were not taken into account in the previous investigations. Furthermore, other studies used different measures of social class, such as socioeconomic area of residence, from those used in this study. It might be speculated, also, that greater socioeconomic diversity existed in the other areas studied than in the city of Toronto used in the present study. It is possible that this culture is relatively homogeneous in terms of health care and lifestyle when compared to other areas, and that a socioeconomic gradient that would affect health, i.e., the chance of infection, is too subtle to be measured by current methods.

6.7 Statistical Analysis and Interpretation

In the logistic regression analysis the relationships between the biologically relevant factors of age at first intercourse, number of sexual partners and contraceptive practice and HSV-2 antibody were explored while taking into account other, potentially confounding or interdependent socioeconomic and lifestyle factors. The individual association between these factors and antibody was evaluated as well. In this analysis associations were quantified via Beta coefficients (odds ratios) and, through the associated significance levels, the role played by chance in these associations was assessed. It should be emphasized that in this analysis associations, not causal pathways, were assessed (Schlesselman, 1982). Therefore factors such as hysterectomy status were included in the models.

In keeping with the aim of the study, socioeconomic, descriptive and lifestyle factors were maintained in the full models, with the purpose of illustrating their effect on the primary biological variables, as well as to evaluate their own association with the outcome. These models were not "efficient" in terms of the prediction of the outcome with a minimum number of parameters, but did explore the relationships of interest.

In interpreting the results of the present study the fact that a number of comparisons have been made on the same data and the impact of this on the significance levels and confidence interval estimates must be kept in mind. This problem is common to many studies which include a number of exposure variables. Armitage (1971) suggests that it is appropriate to accept the significance levels for the variables considered a-priori to constitute the main hypothesis, and to give a somewhat more cautious interpretation to the positive results for other exposure factors which did not have a strong prior hypothesis, particularly when the significance level for these other variables is close to the rejection region, i.e., $P \leq 0.05$. Therefore there is a greater acceptance of the significance levels for the primary variables of number of sexual partners, age at first intercourse and contraceptive use than for the many socioeconomic or lifestyle factors examined.

6.8 Recommendations for Future Studies

As noted earlier, it would be of interest to analyze sera for the present investigation using another assay method. Furthermore, a review of the data using HSV-1 as the outcome might shed light on the common and different factors associated with each type of virus in this study sample.

It might be of interest to carry out a study of a similar design and purpose as the present investigation outside Canada. It is possible that socioeconomic or sexual factors in relation to HSV-2 infection may differ in areas such as the Southern United States or in less affluent countries. For example, based upon the present investigation, socioeconomic status does not appear to play a major role in HSV-2 acquisition, thereby indirectly suggesting that biological rather than sociological factors are operative. In a relatively homogeneous population in Toronto, perhaps a socioeconomic effect would have been detected using a larger sample. However, the purpose of carrying out this investigation elsewhere would be to assess the impact of extreme variation, particularly with regard to hygiene or perhaps even non-sexual transmission of the virus. This would be best done in regions with great variation in health awareness and practice.

In addition, similar studies of younger age groups than those in the survey might provide a closer look at the time of initial infection and the contraceptive or sexual patterns which precede infections. Such a study might even be done through the involvement of secondary schools.

In addition, this investigation and the information on sexual behaviour and HSV-2 antibody might be utilized in conjunction with similar information from women with cervical cancer drawn from new cases in Toronto. The primary question in the comparison of this study's results with cervical cancer studies is to assess whether cervical cancer cases are similar to HSV-2 antibody positive or negative groups in terms of the factors investigated. In conjunction with this the inclusion of a large group of gynecology patients could be utilized to further investigate the possibility of common circumstances leading to both HSV-2 infection and gynecological problems resulting in hysterectomy. In particular, as women with cervical cancer were less likely to have regular Pap smears (Clark and Anderson, 1979), it might be of interest to include Pap smear histories in future HSV-2 studies.

Perhaps the most basic, but useful, study yet to be done is a true prevalence study of all age groups in which a representative sample of the population would provide regional baseline data for both men and women. This sort of study is of particular importance in terms of assisting us to evaluate suggested "epidemics" of this often silent condition.

6.9 Summary and Conclusions

The finding that an association between multiple sexual partners

and HSV-2 antibody for both men and women even with other factors taken into account is consistent with the etiology of other sexually transmitted diseases. However, it would appear that women are at equal risk of HSV-2 infection as are men but through exposure to far fewer sexual partners. As noted earlier, this difference between men and women with regard to the number of exposures likely to result in infection suggests that women are far more susceptible to HSV-2 infection than are men if exposed. For women, the finding that early exposure to multiple sexual partners, particularly in the teenage years, could suggest a particular susceptibility to the virus and other agents because of more rapid proliferation of the cervical epithelium during adolescence (Coppleson and Reid, 1968). It is possible that short term condom use and HSV-2 infection were not found to be associated for men either because condoms were not used consistently enough to prevent infection, or the information on condom use was not thoroughly obtained, or the sample size for men was inadequate.

The association between long-term oral contraceptive use and HSV-2 antibody for women even when the number of sexual partners and condom use were taken into account suggests that oral contraceptive use may be an indirect measure of sexual behaviour that is not sufficiently explored by the questions regarding the number of sexual partners. Alternatively, it is possible that oral contraceptive use affords some particular susceptibility of the cervix to viral infection.

The association between hysterectomy status and HSV-2 antibody may indicate that women who are sexually active are at greater risk of gynecologic problems which could lead to hysterectomy. It is also likely that women who are sexually active are more likely to undergo gynecological examination and therefore have an otherwise undiagnosed condition discovered which might result in a hysterectomy. Whether or not a woman has had a hysterectomy should not be considered a "risk factor" of HSV-2 in the strictest sense. It can be seen here as a descriptive factor, that is, as part of a profile of women who appear to have acquired HSV-2 in their lifetime. One might speculate that HSV-2 infection might be a risk factor of hysterectomy.

A major objective of this investigation was not only to differentiate among sexual and contraceptive factors and the risk of HSV-2 infection, but to evaluate the relative impact of socioeconomic status on HSV-2 exposure. It has been speculated that low socioeconomic status has been associated with poor hygiene, promiscuity, and low use of contraceptive methods (Darrow, 1979; Morton, Horton and Baker, 1979; Kinsey et al., 1953). Although the association between low socioeconomic status and HSV-2 antibody when sexual and contraceptive patterns were taken into account fell short of statistical significance, the elevated estimate does suggest an association between this factor and HSV-2 antibody. Therefore socioeconomic status in itself does not appear to be merely an indirect measure of sexual behaviour.

Rental status may be in part a socioeconomic and behavioural factor affecting HSV-2 acquisition. The association between rental status and HSV-2 antibody for both men and women has not been explained by other factors in this investigation. Among the possibilities investigated were household crowding, mobility, marital status, and income. It could be speculated that from a hygienic standpoint rental accommodations may be more likely to contain infectious agents because of a more frequent turnover of residents. However, with regard to the survival of HSV-2 on non-living media the only studies that have looked into this have indicated that under prime conditions of heat and moisture, the virus lived for no more than four hours. Therefore, it is unlikely that the physical environment of a household would transmit HSV infection. It is perhaps more likely that rental status does represent an indirect measure of sexual behaviour that has not been clarified through this investigation.

CHAPTER 7

SUMMARY AND CONCLUSIONS

7.1 Summary

7.1.1 Introduction

The objective of this investigation was to identify the sexual, contraceptive, socioeconomic and lifestyle factors associated with antibody evidence of HSV-2 infection. To this end, 957 men and women were interviewed regarding relevant information in a household seroepidemiologic survey. Sera were obtained from 748 participants and analyzed by radioimmunoassay for herpes simplex virus antibodies.

HSV-2 type-specific antibody was found in the sera of 41 (12.8%) of 320 men and 75 (17.5%) of 428 women. A summary of the findings of this investigation follows.

7.1.2 Univariate Results

Participants with and without HSV-2 antibody, both men and women were similar with regard to age at interview, paternal birth-place, age at first marriage, age at which the first marriage ended, type of further education or training, occupation, how long they had lived in Toronto, general contraceptive use, experience of general illnesses such as tuberculosis, measles, mumps and childhood illnesses, the frequency of colds or influenza, symptoms of infection including sore throats, cold sores, cigarette smoking, vitamin use, and whether or not they had participated in previous surveys.

Men with and without HSV-2 antibody were similar with regard to circumcision status, and to whether or not they had had a hernia operation. Women with and without antibody were similar with regard to pregnancy prior to marriage, age at menarche, pregnancy history, diaphragm use or use of an intrauterine device, and whether or not they had ever had genital infections.

Both men and women with HSV-2 antibody were more likely to rent their homes, have begun intercourse at an earlier age, have had more sexual partners during their teens, twenties, thirties and overall in their lifetime, than were those without HSV-2 antibody.

Men with HSV-2 antibody more frequently reported living in the current homes for a shorter period of time, having had more sexual partners in the year preceding the interview and during their forties, having had a liver disease and having had genital infections, than did men without HSV-2 antibody.

Compared to women without HSV-2 antibody, women with HSV-2 antibody were more frequently born in Canada than born outside Canada, more frequently reported French as their first language, were more often presently widowed, separated or divorced, more frequently reported at least two marriages, were pre-menopausal, having completed fewer grades of school and fewer years of education or training, less frequently had education or training beyond secondary school, reported a lower household annual income, currently lived in a more crowded household, reported fewer years of partners' condom use and more years of oral contraceptive use, more frequently had intercourse prior to marriage, reported having had a hysterectomy and having had cancer (particularly cervical cancer), infectious mononucleosis and pneumonia, having received a blood transfusion and having donated blood.

7.1.3 Multivariate Results

In the logistic regression analysis, variables which could directly affect exposure to HSV-2 infection, including age, age at first intercourse, number of sexual partners and contraceptive use were examined simultaneously. Factors which may be confounded with other variables such as socioeconomic status as measured by years of education residence status and other lifestyle factors, were examined both for their effect on the estimates for the primary biological factors as well as their own independent association with HSV-2 antibody. The individual association of each of these factors with the outcome was assessed by examining the magnitude estimate of the odds ratio and the statistical significance of the individual association with all other factors taken into account in the models evaluated.

Initially separate models were examined for men and women. It was evident that men who began intercourse by age 17, reported at least 10 sexual partners in their lifetime, and who currently rented their homes were more likely to show antibody evidence of HSV-2 infection even when age at interview, condom use, years and type of education, income, marital status, duration in the current home and in Toronto, household crowding and type of dwelling were taken into account. Women who began intercourse by age 19, reported at least 2 sexual partners in their lifetime, reported fewer years of condom use by their partners, at least 10 years of oral contraceptive use, who rented their home, and who had undergone a hysterectomy, more frequently showed HSV-2 antibody than did women without these traits, even when adjustment was made for age at interview, years and type of education, marital status, duration in the current residence and in Toronto, household crowding, type of dwelling, birthplace, and the receipt of a blood transfusion.

In an attempt to identify specific times of life in which exposure to multiple sexual partners might particularly enhance the chances of becoming infected with HSV-2 virus, the number of sexual partners during certain life periods was substituted for the total number of sexual partners in the logistic models. The results of these analyses indicate a non-significant association between multiple partners during the twenties, multiple sexual partners during the year preceding the interview and HSV-2 antibody for men. For women, a significant association evident between multiple sexual partners during the twenties, and a non-significant association between multiple sexual partners in the teenage years and HSV-2 antibody suggest that exposures early in life may increase the chance of infection.

When logistic analysis was carried out with men and women together in the same model, it was apparent that early first intercourse, multiple sexual partners, and rental status each were associated with HSV-2 antibody even when age at interview, condom use, years of education and other factors were taken into account.

7.2 Conclusions

The association of both an early first intercourse and multiple sexual partners with HSV-2 antibody for men and women is in keeping with a standard venereal disease profile. It is not surprising that the chance of acquisition of this infectious agent would increase with the number of possible exposures to different partners. As an early first intercourse sustained an association even when number of sexual partners was taken into account, it would appear that this is not merely a covariate of multiple sexual partners, and in itself increases the chance of infection. The association between long term oral contraceptive use and short term condom use of sexual partners for women indicates that non-occlusive birth control methods enhance the chance of HSV-2 exposure. The finding that women who have undergone a hysterectomy were more likely to possess HSV-2 antibody does indicate a relationship between genital infection and other gynecologic illness; however, a causal association in either direction cannot be assumed.

It is of interest to note that the association between socioeconomic status, as measured by educational level or income, fell short of statistical significance for women and that there was no association between any measure of socioeconomic status and HSV-2 antibody for men. It may be that the classic indicators of "socioeconomic status" such as education or income do not adequately reflect sociologic or behavioural factors which could affect health. Household crowding, mobility and other factors must be taken into account. For example, it is likely that the strong association between rental status and HSV-2 antibody represents an indirect measure of hygienic, social or sexual factors that cannot be identified through information in this study, and warrants further investigation. It appears that the specific contraceptive or sexual factors which might directly affect exposure to HSV-2 infection, namely non-occlusive contraception for women and early first intercourse and multiple sexual partners for both men and women, do increase the risk of infection.

APPENDIX I

ASSESSMENT OF SEROLOGIC METHODS
AND SUMMARY OF SEROEPIDEMIOLOGIC STUDIES
OF HERPES SIMPLEX VIRUS ANTIBODY PREVALENCE

APPENDIX I

Table

Figure

APPENDIX I

FIGURE 1

Validity of Serologic Methods: Calculations

		DISEASE (or standard) PRESENT	ABSENT
SEROLOGIC RESULTS	POSITIVE	TRUE POSITIVES	FALSE POSITIVES
	NEGATIVE	FALSE NEGATIVES	TRUE NEGATIVES

PERCENT SENSITIVITY= $\frac{TP}{TP+FN} \times 100$ = The ability of the method to correctly identify those persons who have been infected with HSV-2 as measured by type-specific antibody.

SPECIFICITY= $\frac{TN}{TN+FP} \times 100$ = The ability of the method to correctly identify those persons who have not been infected with HSV-2 as measured by type specific antibody.

PERCENT FALSE NEGATIVE= $\frac{FN}{TP+FN} \times 100$ = Those with HSV-2 antibody but were not infected according to the standard.

PERCENT FALSE POSITIVE= $\frac{FP}{TN+FP} \times 100$ = Those who do not have HSV-2 antibody but were incorrectly identified as having type 2 antibody by the method used.

PERCENT AGREEMENT= $\frac{TP+TN}{\text{TOTAL SPECIMENS TESTED}}$ = The ratio of those identified as HSV-2 positive and HSV-2 negative by both the "standard" and the serologic test method to the total sample of specimens tested.

APPENDIX I

TABLE A

RELATIONSHIP BETWEEN DETECTION OF HSV-2 ANTIBODY BY RIA AND VIRAL ISOLATION

HSV-2 GENITAL HERPES IDENTIFIED THROUGH VIRAL ISOLATION

		POSITIVE	NEGATIVE	
RIA	POSITIVE	5 TP	7 FP	12
	NEGATIVE	0 FN	21 TN	21
		5	28	33

FORGHANI ET AL 1975

$$\text{PERCENT SENSITIVITY} = \frac{TP}{TP+FN} \times 100 = \frac{5}{5} \times 100 = 100\%$$

$$\text{PERCENT SPECIFICITY} = \frac{TN}{TN+FP} \times 100 = \frac{21}{28} \times 100 = 75.0\%$$

$$\text{PERCENT FALSE NEGATIVES} = \frac{FN}{TP+FP} \times 100 = \frac{0}{7} \times 100 = 0$$

$$\text{PERCENT FALSE POSITIVES} = \frac{FP}{TN+FP} \times 100 = \frac{7}{28} \times 100 = 25.0\%$$

$$\text{PERCENT AGREEMENT} = \frac{TP+TN}{TOTAL} \times 100 = \frac{26}{33} \times 100 = 78.8\%$$

APPENDIX I

TABLE B

RELATIONSHIP BETWEEN RIA AND MN IN THE DETECTION OF HSV-2 ANTIBODY

		MICRONEUTRALIZATION		
		POSITIVE	NEGATIVE	
RIA	POSITIVE	60 TP	6 FP	66
	NEGATIVE	22 FN	45 TN	67
		82	51	133

RAWLS, 1981

$$\text{PERCENT POSITIVE AGREEMENT} = \frac{TP}{TP+FN} \times 100 = \frac{60}{82} \times 100 = 73.2\%$$

$$\text{PERCENT NEGATIVE AGREEMENT} = \frac{TN}{TN+FP} \times 100 = \frac{45}{51} \times 100 = 88.2\%$$

$$\text{PERCENT AGREEMENT} = \frac{TP+TN}{TOTAL} \times 100 = \frac{105}{133} \times 100 = 78.9\%$$

APPENDIX I

TABLE C

HSV-1 AND HSV-2 ANTIBODY PREVALENCE

AGE IN YEARS	NUMBER TESTED	HSV-1 PERCENT	HSV-2 PERCENT	REFERENCE
0-9	43	25	0	Strizova et al. 1975
10-19	57	63	12	
≥ 20	146	69	21	

AGE	NUMBER TESTED	HSV-1 PERCENT	INTERMEDIATE PERCENT	HSV-2 PERCENT	REFERENCE
2-15	134	35	11	4	McDonald et al. 1974a
16-55	430	48	14	19	

TABLE D

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2
ANTIBODY PREVALENCE

Serologic Methods: Abbreviations		Race: Abbreviations	
MN	Microneutralization	C	Caucasian
NT	Neutralization	N	Negro
RIA	Radioimmunoassay	O	Oriental
CF	Complement Fixation	-	Not Reported
IHA	Indirect Hemagglutination		
IPH	Inhibition Passive Hemagglutination		
NK	Neutralization Kinetics		
MI	Microimmunofluorescence		
ELISA	Enzyme-Linked Immunosorbent Assay		
MICRO-SPRIA	Micro-Solid Phase Radioimmunoassay		

APPENDIX I

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE[1]

Household Samples

Geographic Area	Type of Sample	Race	Age	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method*	Reference
Montreal, Quebec	Household	C	16-55	430	77	18	MN	McDonald et al., 1974a
Ostrava, Prague Czechoslovakia	Household	C	15-55	181	37	20	MN	Strizova et al., 1975
Amazon Basin, Brazil	Isolated Indian Tribes "Household" Survey	Carib & Kayabo Indian	1 month to 60 yrs.	141	161	82	NT	Black et al., 1974
New Haven, Connecticut	Household	C & N	1 month to 60 yrs.	91	39	43	NT	Black et al., 1974
Toronto, Ontario	Household (Comparison Group)[2]	C	20-69	255	57	22	RIA	Rawls et al., 1980

[1]Data has been summarized when necessary to facilitate comparisons between studies

[2]Neighbourhood Control Sample for cervical cancer cases

*See List of Assay Methods on previous page

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Diverse Population Groups

Geographic Area	Type of Sample	Race	Age (average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method	Reference
Bath, Bristol, Dursley, England	Blood Donors (male)	—	32	111	14	13	MN	Roome, Montefiore and Waller, 1975
	Blood Donors (female)	—	30	68	8	12		
	Prisoners (male)	—	30	206	87	42		
Cali, Columbia	Registerd Prostitutes	N	15	147	91	62	MN	Duenas et al., 1972
	Registered Prostitutes	Mestizo Indian	15	196	123	63		
Seattle Washington	VD Clinic Attendees Homosexual Men	—	30 (estimated)	96	38	40	MN	Mann et al., 1984
Ibadan, Nigeria	Blood Donors (male)	N	28	228	47	21	NT	Montefiore, Sogbetum and Anong, 1980

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Diverse Population Groups continued

Geographic Area	Type of Sample	Race	Age (average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method	Reference
Ibadan, Nigeria	Antenatal Clinic Patients (female)	N	Child-bearing age	283	79	28	NT	Montefiore, Sogbetun and Anong, 1980
	Family Planning Clinic Patients	N	"	159	44	28		
	VD Clinic Patients	N	28	167	57	34		
Osaka, Japan	Patients	O	39	171	19	11		Ishiguro and Ozaki, 1978
Ibadan, Nigeria	School Children	N	-	100	3	3	CP	Adelusi, Fabiyi and Osunkoy, 1978
	Gynecology Outpatients	N	-	101	30	30		
	Pregnant Women Antenatal Clinic	N	-	102	26	25		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Diverse Population Groups continued

Geographic Area	Type of Sample	Race	Age (average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method	Reference
	Professional Prostitutes	N	-	55	25	45		Adelusi, Fabiyi and Osunkoy, 1978 continued
	Venereal Disease Clinic Patients	N	-	30	14	47		
	Family Planning Clinic Attendees	N	-	101	27	27		
Bangkok Thailand	Hospitality Girls (Venereal Disease Clinic Attendees)	-	16-57	157	62	39	IHA	Tantivanich and Tharavanij 1980
	Pregnant Women Antenatal Clinic Attendees and Health Workers	-	-	101	11	11		
Delhi, India	Men	0	1 month - ≥ 40 years	279	93	33	IHA	Seth et al., 1981
	Women	0		228	81	36		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Diverse Population Groups continued

Geographic Area	Type of Sample	Race	Age (average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	%	Method	Reference
Philadelphia, Pennsylvania	Asymptomatic Pregnant Outpatients	N,C,O	44	985	352	36	IHA	Bolognese et al., 1976
Copenhagen, Aarhus, Denmark	Homosexual Men Residing in Copenhagen	-	32	170	108	63	ELISA	Melbye et al., 1983
	Residing in Aarhus	-	27	89	69	78		
	Control Group (assumed to be heterosexual)	-	30	100	22	22		
Baku, The Gambia	Antanatal Clinic Attendees	N	25	100	53	53	MI	Mabey et al., 1984
Prague, Czechoslovakia	Screening Clinic Attendees	C	25-35	50	13	26	MICRO-SPRIA	Suchankova et al., 1984
			36-45	52	12	23		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence: Number Tested	Positive Number	Positive %	Method	Reference
Montreal, Quebec	Dysplasia	C	31	39	15	38	MN	McDonald et al., 1974b
	C.I.S.	C	40	50	16	32		
	Invasive Cancer	C	53	57	12	21		
	Cervical Neoplasia Cases:							
	Dysplasia	C	31	39	12	31		
	C.I.S.	C	40	50	20	40		
	Invasive Cancer	C	54	57	20	35		
	Hospital Gynecology Controls Patients:							
	Jewish	C	54	43	8	19		
	Non-Jewish	C	54	43	8	19		
Croatia, Slovenia, and other areas in Yugoslavia	Cervical Cancer Cases:							Kessler et al., 1974b
	Moslem	C	46	150	53	35	MN	
	Hospital Controls	C	46	150	35	23		
	Cervical Cancer Cases:							
	Non-Moslem	C	46	200		40		
	Hospital Controls	C	46	200		25		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence: Number Tested	Positive Number	Positive %	Method	Reference
Kampala, Uganda	Ganda Tribes: Cervical Cancer Cases:	N	44	41	37	90	MN	Adam et al., 1972
	Outpatient Clinic Controls	N	45	52	37	71		
	Non-Ganda Tribes: Cervical Cancer Cases:	N	44	24	16	67		
	Outpatient Clinic Controls:	N	45	19	14	74		
Osaka, Japan	Cervical Cancer Patients:	O	45	69	19	28	MN	Ozaki et al., 1978
	Gynecology Clinic Patients	O	45	112	17	15		
Atlanta, Georgia	Cervical Neoplasia Cases: Atypia	N	25	32	3	9	MN	Nahmias et al., 1970b
	Hospital Out-patients Control	N	30	45	4	9		
	C.I.S.	N	32	38	11	30		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence: Number Tested	Positive Number	Positive %	Method	Reference
Atlanta, Georgia continued								
	Control Patients	N	32	38	5	13		Nahmias et al., 1970b continued
	Cervical Neoplasia & Genital Herpes:	N	-	14	4	29		
	Prior Genital Herpes	N	-	54	25	46		
Auckland, New Zealand	Cervical Neoplasia Cases:							Rawls et al., 1970
	C.I.S.	C	39	44	14	32	MN	
	Invasive Cancer	C	54	52	16	31		
	Gynecology Out-patients Controls:	C	42	53	12	23		
Tel Aviv, Haifa, Israel	Cervical Cancer Cases	C	-	78	30	38	MN	Pridan and Lilienfeld, 1971
	Gynecology Controls	C	-	33	17	52		
	General Population	C	-	39	5	13		
Tel Hashomer, Israel	Cervical Cancer Cases:	C	≥40	39	6	15	NT	Menczer et al., 1975

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method	Reference
Tel Hashomer, Israel continued								
	Gynecology Patients:	C	$\geq$ 40	39	3	8		Menczer et al., 1975 continued
	Imprisoned Prostitutes	C	17-24	30	3	10		
	"Health" Subjects (source not reported)	-	17-81	94	2	2		
Houston, Texas	Cervical Cancer Cases:	N	25-66	60	39	65	NT	Adam et al., 1973b
	Hospital Controls	N	"	241	96	40		
	Cervical Cancer Cases:	C	"	25	16	64		
	Controls	C	"	53	19	36		
Houston, Texas	Breast Cancer	N	30 -$\geq$ 60	43	18	42	NT	Adam et al., 1974
	Cervical Cancer	N	"	50	32	64		
	Control Patients	N	"	186	84	45		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method	Reference
Baltimore, Maryland	Cervical Atypia	N	30	36	34	94	NT	Royston and Aurelian, 1970
	Controls for Atypia	N	30	36	16	44		
	C.I.S.	N	35	32	32	100		
	Hospital Controls	N	32	32	17	53		
	Invasive Cancer	N	53	42	42	100		
	Hospital Controls	N	50	42	28	67		
	Cancer of Other Sites	N	-	20	10	50		
Prague, Czechoslovakia	Cervical Cancer Cases (all stages)	C	42	79	39	49	NT	Janda et al., 1973
	Control Patients	C	42	75	14	19		
Houston, Texas	Cervical Neoplasia Cases:							Rawls, Tompkins, and Melnick, 1969
	Dysplasia	N	25	21	5	24	KN	
	C.I.S.	N	37	23	8	35		
	Invasive Cancer	N	52	65	47	72		
	Hospital Controls	N	40	51	11	22		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence: Number Tested	Positive Number	Positive %	Method	Reference
Houston, Texas continued								
	Male Cancer Patients	C	-	20	2	10		Rawls, Tompkins, and Melnick, 1969 continued
	Promiscuous Women and Prostitutes	N	25	43	23	54		
	"Well Controls"	N	40	51	11	22		
Atlanta, Georgia	Attendees of a Cervical Screening Program							Ory et al., 1975
	Dysplasia	N	15-44	36	16	44	IPH	
	Without Dysplasia	N	15-44	329	90	27		
Kansas City, Kansas	Prostatic Neoplasia Cases:							Baker et al., 1981
	Benign Hypertropy	N,C	70	50	34	68	IHA	
	Prostatic Catc.	N,C	68	159	81	51		

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence: Number Tested	Positive Number	Positive %	Method	Reference
Baltimore, Maryland	Cervical Neoplasia Cases: Atypia	-	34	20	19	95	CF	Aurelian, Davis and Julian, 1973
	Hospital Controls	-	31	20	10	50		
	C.I.S.	-	39	22	22	100		Aurelian, Davis and Julian, 1973 continued
	Hospital Controls	-	35	22	12	55		
	Invasive Cancer	-	49	27	27	100		
	Controls	-	48	27	17	63		
Toronto, Ontario	Household Controls*	C	20-69	255	57	22	RIA	Rawls et al., 1980
	Cervical Cancer Cases:	C	20-69	112	37	33		

* Included under Household Samples as well

SEROEPIDEMIOLOGIC STUDIES OF HERPES SIMPLEX VIRUS TYPE 2 ANTIBODY PREVALENCE

Cancer Cases and Controls continued

Geographic Area	Type of Sample	Race	Age (Average)	HSV-2 Antibody-Evidence Number Tested	Positive Number	Positive %	Method	Reference
Los Angeles, California	Cervical Neoplasia Cases:						RIA	Rawls et al., 1980
	C.I.S.	N	-	12	8	67		
	Invasive Cancer	N	-	7	4	57		
	Control Patients	N	-	33	13	39		
	C.I.S.	Chicano Americans	-	63	32	51		
	Invasive Cancer	"	-	37	27	73		
	Control Patients	"	-	66	25	38		
Los Angeles, California	Severe Dysplasia	Multiple Racial Groups	-	47	21	45	RIA	Graham et al., 1982
	Carcinoma in Situ			83	46	55		
	Cervical Cancer			51	37	73		
	Control Patients			130	56	43		
Prague, Czechoslovakia	Carcinoma in Situ Stage II	C	25-45	145	19	13	RIA	Vonka et al., 1984b
	Carcinoma in Situ Stage III	C	"	76	14	18		
	Control Patients	C	"	267	31	12		
	Invasive Carcinoma	C	"	21	2	10		
	Control Patients	C	"	205	30	15		

APPENDIX II

SUMMARY OF STUDY ROUTINES

APPENDIX II

SUMMARY OF STUDY ROUTINES

FLOW DIAGRAM

INTERVIEWER TRAINING
FOR INTERVIEW AND VENIPUNCTURE

FIELD ASSIGNMENTS

SUBJECT SEARCH
AND
INTERVIEW

QUESTIONNAIRE/SPECIMEN
DELIVERED TO TORONTO CENTRE

QUESTIONNAIRE/SPECIMEN
CHECKED

SPECIMEN SPUN,
SPLIT, FROZEN

SPECIMENS
SENT TO
HAMILTON

SPECIMENS
ANALYZED
FOR
ANTIBODY

RESULTS
SENT TO LONDON

CODED, KEYPUNCHED

QUESTIONNAIRES
FORWARDED
TO LONDON

CODING, KEYPUNCHING
OF INFORMATION

STATISTICAL ANALYSIS

APPENDIX III

INTERVIEW MANUAL AND

SUBJECT SEARCH PROCEDURE

TORONTO HEALTH SURVEY

INTERVIEWER'S MANUAL

INTRODUCTION

Objective

The purpose of this investig on is to determine the prevalence of Herpesvirus Type II in the Toronto population and to observe this prevalence in relation to socioeconomic factors and coital patterns.

There is evidence in the literature that in order to understand the effect that this virus has on health we must examine its frequency in context of other conditions which may affect health, such as living circumstances and lifestyle factors.

Herpesvirus Type II is of current research interest not only because in itself it causes discomfort and pain, but because it is one of several viruses causing colds, influenza, encephalitis and meningitis and is implicated in the development of cervical cancer.

The study is presented to the general population as one of VIRUSES AND HEALTH rather than specifically of Herpesvirus for two reasons:

- We hope to avoid a biased response due to educational or disease experience factors,

  e.g. Many people have never heard of herpesvirus.
- In the truth, we ARE interested in general susceptibility to a variety of viruses and viral illness.

ADMINISTRATION

The study is administered through the Department of Epidemiology and Preventive Medicine at the University of Western Ontario in London, Ontario, by Dr. K.M. Stavraky.

STUDY TERM

The study term begins on April 1, 1979 and the data gathering process should end by August.

DATA GATHERING

The data gathering process is the key component of this investigation. No question or procedure has been included that is not vital to the investigation.

The subject interview should be seen as a measuring instrument in which an infinite variety of individuals and attributes can be accurately measured. With this in mind every effort must be made to achieve uniformity, consistency, accuracy, and objectivity through all aspects of the subject ascertainment, interview and record keeping procedures.

So that this might be accomplished some basic guidelines are specified in this manual. This is an attempt to standardize the data gathering procedure, as much as "humanly possible".

STUDY SAMPLE

In order to obtain our sample we are using a stratified random sampling method in which Enumeration Areas throughout Toronto have been selected. Within these Enumeration Areas, again using a random method, a household number is selected. Your subject search begins at this household number.
(see map, next page)

Subject Ascertainment

(Please see the attached map as an example.)

You begin your subject search at the household number and street assignment on your map. You search in this Enumeration Area according to the map instruction until <u>one</u> of several possibilities:

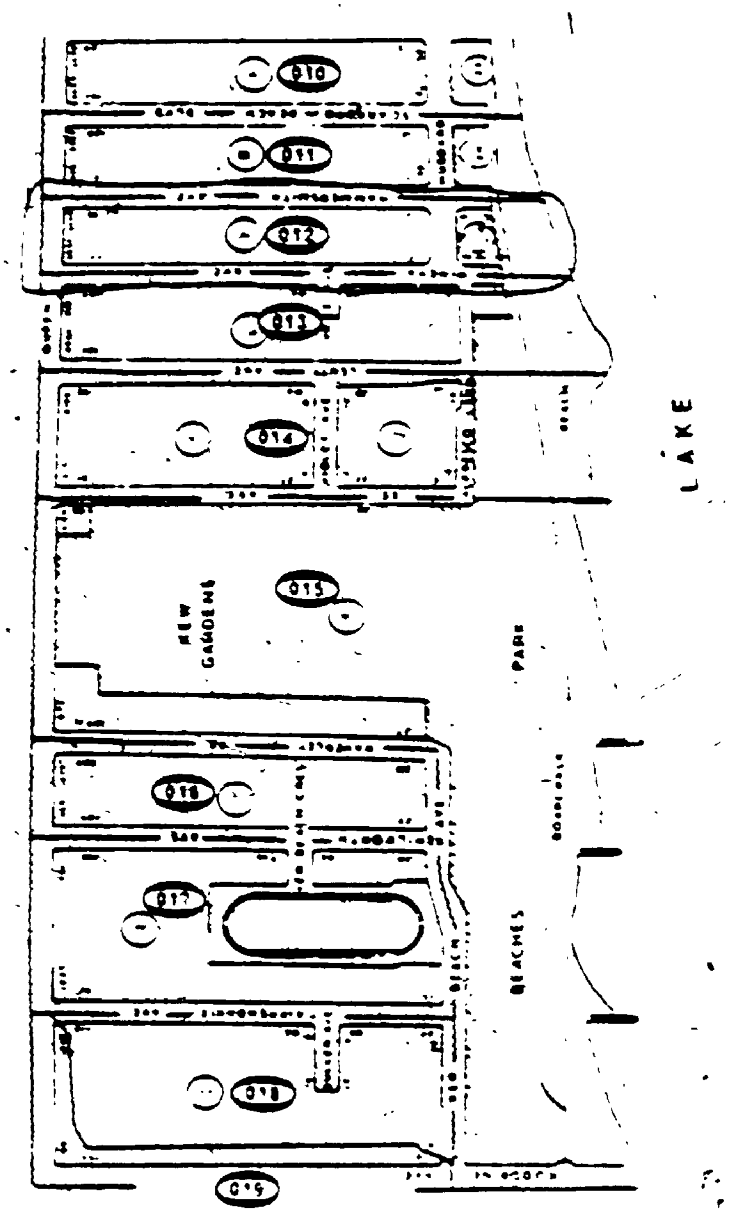
- 5 subjects have been interviewed

or

- 10 appointment cards have been given out

or

- 100 households have been approached in the evening or



TORONTO

1971

CT 21

ED 515

weekends yielding no suitable respondents.

Ideally 10 subjects per Enumeration Area should be interviewed (5 male 5 female)

SUBJECTS

Criteria: A person is eligible for interview if he she is:

- Between the ages of 35-50 inclusive (That is persons who are age 35 or are age 50 are eligible)
- residents of that household
- English speaking.

Only one person/household may be interviewed

INTRODUCTION

"Hello, I'm (name). I am doing a survey about the health of men and women between the ages of 35 and 50"

(WAIT FOR RESPONSE)

(IF MISUNDERSTOOD, REPEAT THE ABOVE STATEMENT)

"If you are between the ages of 35 and 50 (inclusive) would you have time to talk with me for about twenty minutes at some time."

(WAIT FOR RESPONSE)

"The survey is about colds and flu in the Toronto population. The questions are about colds, flu, other illnesses and factors which may make us susceptible to illness."

(ONLY IF THE RESPONDENT ASKS):

"The study is being done by the Department of Preventive Medicine at the University of Western Ontario."

WHEN AN APPOINTMENT IS BEING MADE

Take out the appointment card.

Tear off the half with your name on it and give it to the respondent. THEN ask them for their address and phone number. Attempt to make an appointment. Be sure to write the appointment time and date on BOTH halves of the appointment cards.

PHONE CALL FOR APPOINTMENT

Ask for the lady or gentlemen of the house. State that you are calling about the "Health Survey". Be sure that you are talking to the right person. State that you have left your card (and when).

If necessary, repeat the Study introduction that was done at the door.

Be sure that you are being understood about who you are, how you happen to have their number and why you are calling.

Response

Several outcomes to this initial inquiry are possible:

1. Ineligibility obvious

   The respondent is of the wrong age or sex:

   If someone of the opposite (wrong) sex answers, ask if anyone in the household who is presently at home would be interested in participating.

   An appointment card must be left. The phone number is taken. If the phone number is refused, return to this household at another time.

   If they are not at home at present, continue on to the next dwelling.

2. Language problem

   If the person who answers the door does not speak English, ask if someone is at home who does.

   If an appointment card is left, be sure that the 'eligible' respondent does speak English well enough to be interviewed.

3. Refusal

Accept this. Ask why. The reason for refusal should be ascertained and recorded.

4. Ineligible, but not stated

It may become apparent DURING the interview that the respondent is of the wrong age. If so, the interview will be taken to a certain point, indicated by the questionnaire, and politely terminated.

A blood sample will not be taken with the explanation that this is required only by alternate members of the sample.

A letter of appreciation will be left with each respondent who participates in any part of the interview.

5. Eligible

(a) Interview Occurs.
OR
(b) An appointment is made.

TYPES OF DWELLINGS

Different types of dwellings may present special problems. The search procedure and method of access for each type is as follows:

(The term 'dwelling' refers to the building, and 'household' refers to the family unit.)

1). Houses

- Single households

  Approach each door (including rowhouses)

- Multiple households, e.g. Shared living accommodations for more than one family.

  Inquire about anyone eligible in any one household. Only ONE PERSON is to be interviewed in the whole dwelling.

- Multiple households, Separate accommodations (includes Rooming Houses), e.g. Apartments within a large house.

  Inquire at each household.

  Only ONE PERSON may be interviewed in the whole dwelling.

2). Apartment Buildings

- Inquire at each household

- Small (≤ 20 units)

Only ONE PERSON may be interviewed in the whole dwelling.

- Medium (20-50 units)

Only TWO PERSONS may be interviewed.

- Large (> 50 units)

Up to FIVE PERSONS may be interviewed.

3). Commercial Buildings

Business establishments must be excluded. Be sure to INCLUDE households that may be overhead, e.g. Apartments over stores, etc.

4). Institutions

Nursing Homes, Schools, Hospitals must be excluded. Halfway houses should be INCLUDED.

5). Hotels or Tourist Housing

Excluded.

SUBJECT SEARCHES AND TIMES

Times

Subject searching (door-knocking) should NOT be done:

Before 10:00 a.m. weekdays and Saturdays

Before 1:00 p.m. Sundays

After 8:00 p.m. any evening.

The times when people are most often at home are:

Evenings. . .5:00 p.m. - 8:00 p.m.

Saturday. . .10:00 a.m. - 8:00 p.m.

Sunday. . . .1:00 p.m. - 3:00 p.m.

Day time subject searching during the week may also be done, however an Enumeration Area cannot be eliminated on the basis of only a weekday (Monday-Friday) daytime subject search.

The "Search Run"

One Search Run consists of 100 households.

Elimination of an Area

An Enumeration Area might be eliminated if any of the following things happen:

- After approaching at least 100 households during evenings or weekends, no suitable subjects are found.

- Apartment Buildings: The superintendent will not allow you access.

- Imminent danger (e.g. you are threatened or witness a crime).

- The area is apparently non-residential (e.g. less than 10 households).

INTERVIEW

Privacy

The interview should be done in complete privacy. If there are other people around, please state that privacy is necessary. Suggest coming back at another time. If the respondent wishes to carry on without privacy, continue and RECORD the circumstance on the questionnaire.

If PARTS of the interview were done in privacy, indicate this on questionnaire itself.

(e.g. Write beside MARITAL STATUS: "No one else in the room at this time".)

Procedure

Prior to the interview, a consent form for interview will be signed. At the close of the interview the consent for blood is signed. The following issues must be made clear to the respondent:

a). We are studying viruses and health and the ways in which viruses are transmitted.

b). All information gathered will be held in the strictest confidence. We are, by law, not permitted to divulge any of the information obtained.

INTERVIEWER CODE

		COMMENTS	CODE
Search (Indicate initial 1st return, 2nd return)			
Address: Search Begun			
Day: (Monday - Sunday)	DATE Day Month Year		
Time: Begun	A.M. P.M.		
Ended	A.M. P.M.		
Total Hours/Minutes	hours minutes		
OUTCOME. # Immediate Interviews			
Appointment Cards Left: with respondent			
with other household member			
# Ineligibles Due to: Age: Too Old			
Too Young			
RACE			
LANGUAGE			
GENDER			
OTHER			
# NO ANSWER			
# REFUSALS *			
OTHER			
Address. Search Ended			
Total # Households Approached			

* List reasons for refusals

In response to direct questions about the personal health implications of the blood sample findings, the following points will be made:

a). The fact that though there may be evidence of viral infection in the blood of some persons, this rarely indicates any health problem in them, but may reflect a distant episode of infection. The fact that many well persons carry evidence of past viral infections in their blood without any health danger will be emphasized.

b). Viral evidence in the blood will be explained as evidence that the body's defense mechanisms once fought off a virus (antibody explanation) and NOT that there are viruses in the blood.

NOTE: All of the above remarks will be made only <u>if</u> the respondent expresses fear or concern about the study and their own health.

It is, of course, best to avoid all explanation of viruses, etc. if possible.

FIELDWORK STEPS

The following checklist describes the fieldwork process:

- Enumeration Area Assignment
- Subject Search is carried out
  - Interviews, appointments are made
- Fieldwork Record is completed
- Appointments are followed up
- Interview occurs
- Questionnaire is reviewed, 'coded'
  - subject code number on each page
  - times, dates
  - comments
- Blood Sample Questionnaire is delivered to centre
- Interview, blood sample is recorded in log
- Expense and work sheet is completed

THE INTERVIEW (Checklist)

The Interview and blood sample should be done as follows:

- Introduction to the Study
- Consent for interview signed
- Interview
- Consent for blood sample must be signed
- Blood Sample drawn
  - code blood sample
- Conclusion of interview
- Leave taking

INTERVIEW KIT

Each Interview Kit should be made up of the following. Coded:

- Consent for Interview
- Cover Sheet (with address)
- Consent for Blood Sample
- Questionnaire
- Coital Questionnaire
- Envelope
- Letter of Appreciation

VENIPUNCTURE KIT

You will need:

- Extra Needles
- Extra vacutainers
- Vacutainer holder
- Tournequet
- Extra alcohol swabs
- Extra cotton balls
- Extra band-aids
- Kleenex
- Extra labels
- Waterproof pen

For EACH subject the individual blood taking kit contained in a small plastic bag should include:

- Labelled Vacutainer Tube
- Needle
- 3 cotton balls
- 2 alcohol swabs
- 1 band-aid

VENIPUNCTURE PROTOCOL

THE CONSENT MUST BE SIGNED.

The subject must be comfortably positioned.

There should be sufficient light in the room.

The procedure is as follows:

Cleanse your own hands with alcohol swab and kleenex.

Draw the blood.

Ask subject to hold the cotton swab over the area for a few minutes.

BE SURE BLEEDING HAS STOPPED COMPLETELY BEFORE APPLYING THE BAND-AID.

Apply the band-aid.

Do not leave the subject's home until you are sure that they have suffered no ill effects of the venipuncture procedure.

THE SUBJECT'S SIGNATURE

The respondent must sign the consent for interview BEFORE the interview begins, and accordingly the consent for blood sample must be signed BEFORE the blood sample is drawn.

If the subject requests that their NAME not appear on the consent form an alternative is provided.

The subject may be instructed to write, IN THEIR OWN HANDWRITING, the following statement:

"I have read this consent form and agree to the interview."

Date: ____________________

OR AS APPROPRIATE

"I have read this consent form and agree to the blood sample."

Date: ____________________

This alternative is to be used SPARINGLY, and ONLY if the respondent wishes to be intervimed but refuses the signature.

THE INTERVIEW/BLOOD SAMPLE MUST NOT OCCUR UNLESS THE APPROPRIATE CONSENT FORMS HAVE BEEN SIGNED OR THE ABOVE DECLARATION HAS BEEN WRITTEN.

SAFETY PRECAUTIONS:

NEVER INTERVIEW IN A SITUATION IN WHICH YOU ARE FRIGHTENED.

Do not enter a home in which the respondent is apparently inebriated or hostile.

POLITELY and QUICKLY discontinue an interview at the slightest hint of danger.

UNPLEASANT AREAS OF THE CITY:

In these areas, NEVER "door-knock" after dark.

If you feel uneasy at other times, you may, with the approval of the Project Director, share the area with another interviewer.

If you feel uneasy about an interview appointment, you may bring another interviewer along.

CONFIDENTIALITY

The Study

The contents of the questionnaire and all other details about the Study should be kept as confidential. ONLY MEMBERS OF THE STUDY STAFF SHOULD HAVE ACCESS TO COPIES OF THE QUESTIONNAIRE, CONSENT FORMS, OR DETAILED INFORMATION ABOUT THE STUDY ITSELF, EVEN AFTER THE STUDY IS OVER.

The Participants

Those persons who help us in the Study are volunteers whose complete privacy must be respected beyond the interview encounter. Therefore any information gathered as well as even the fact of their participation in the study must be kept in the strictest confidence.

Comments

It is extremely important not to give advice, even by implication only, about any health or social problem. ALWAYS AVOID comment. Direct the person to their physician. Do not debate or discuss any social issues with the respondent or members of the family.

Strive to be as accepting, and non-judgemental as possible. We must keep in mind that the respondent is a "volunteer" who has given up time to help us. Try to take the point of view of the respondent in your assessment of his/her comments. Write out all impressions or unusual events.

Allow time at the close of the encounter AFTER the blood has been taken for the respondent to ask you questions, or express concerns or doubts about the study.

We must be sure to leave the respondent in AT LEAST a comfortable state as when we found him!!!

METHODS OF RECORDING

The abbreviations of MORE than, LESS than may be used as follows.

> = greater than, or more than

< = less than

$\geq$ = greater than or equal to

$\leq$ = less than or equal to

EXAMPLES.

ANSWER. "I was over 10 when I had that."
RECORD. > 10

ANSWER: "I was at least 10 when I had that."
RECORD: $\geq$ 10

ANSWER: " I was younger than 10 when I had that."
RECORD: < 10

ANSWER: "I was age 10 or younger when I had that."
RECORD: $\leq$ 10

METHODS OF RECORDING cont'd

Use both columns when recording numbers
The dashes denote the space between two digits of the same number.

EXAMPLE

ANSWER: "I had polio when I was nineteen years old. This was the only episode of this illness."

	a	b		c		d	
	Ever had	Age at first episode		Frequency		Age at most recent episode	
12. Polio	yes	1	9	0	1	1	9

Always use the spaces from right to left.

EXAMPLE.

Length of Interview (Forty minutes

		4	0

VIRAL SYMPTOMS

So that we might assess the lifetime pattern of symptoms such as sore throats, swollen glands, etc,.

We will ESTIMATE the frequency as follows (The respondent first had a sore throat at age 5. Has a sore throat right now at 37)

INTERVIEWER: "Up until the age of 10, how frequently did you have a sore throat?"

RESPONDENT: "I don't remember."

INTERVIEWER. "During this time period would you say that you had a sore throat as much as ONCE EACH YEAR?"

RESPONDENT: "At least as much as that."

INTERVIEWER: "Would you say this was as much as TWICE EACH YEAR?"

RESPONDENT: "NO. MORE THAN THAT."

INTERVIEWER. "Would you say that you had a sore throat THREE TIMES EACH YEAR?"

RESPONDENT. "NO. NOT AS MUCH AS THAT."

INTERVIEWER: "Would you say you had a sore throat MORE than TWICE EACH YEAR, but NOT AS MUCH AS THREE TIMES EACH YEAR?"

RESPONDENT: "Yes thats about right."

ESTIMATE OF FREQUENCY

RECORD

	a	b	c	d					e	f
				Frequency During Ages:						
	Ever had	Age 1st ep.	Age last ep.	i 1-10	ii 11-19	iii 20-29	iv 30-39	v 40+	Tot. ep.	Co.
Sore throat	yes	5	37	>2 yr						

Continue through all age categories.

FREQUENCY OF ILLNESSES, SYMPTOMS

Be sure to clarify whether the frequency of an illness reported is the lifetime total or annual total.

EXAMPLE

INTERVIEWER: "During the last 3 or 4 years how often have you had a cold?"

RESPONSE: "3 times."

INTERVIEWER: "Is that every year or three times in all, in the last three years?"

ADDITIONAL RESPONSES

The respondent may occassionally report an illness that has not been asked.

Using the respondent's own words, identify the illness and take down the information in the "Other" category. Be sure to note which question or disease triggered the response.

EXAMPLE.

INTERVIEWER: "Have you ever had pneumonia?"

RESPONSE: "I have had bronchitis, once when I was sixteen years old."

	a	b		c		d	
	Ever had	Age at first episode		Frequency (incl. 1st episode)		Age at most recent episode	
13. Other Bronchitis	yes	1	6	0	1	1	6

Then repeat: "Have you ever had pneumonia?"

Take down the appropriate information.

ANSWER INAPPROPRIATE

The respondent may volunteer information that it is not asked. E.g. a description of stomach surgery when questions about stomach flu are asked.

Note this information in brief form, but guide the conversation back to the question at hand.

REFUSAL TO ANSWER

Accept this for all questions.

Assure the subject of his/her right to do so, but do NOT encourage this in subsequent questions.

Always gently ask why the respondent has refused.

If the respondent expresses concern about the question explain the purpose of the question, reinforce confidentiality, but ACCEPT the REFUSAL WITHOUT **PRESSING the ISSUE FURTHER**.

BLOOD-TAKING PROCEDURE

Place the subject in a COMFORTABLE SEATED POSITION WITH ARM SUPPORT.

Select arm

Cleanse your own hands with an alcohol swab

Dry hands with Kleenex

Prepare the needle

- Break seal on needle (Be sure it is a NEW needle.
- Remove white plastic part
- Screw the RED end of the needle into the VACUTAINER HOLDER

Put TOURNIQUET ON ARM

- Check for comfort and fit
- Ask subject to extend arm and to make a fist

TEST VEIN

Vein should be palpable, but not <u>necessarily</u> visable.

Wipe the area with a new alcohol swab

Dry the area with cotton

Place the vacutainer into the vacutainer holder BUT NOT on the needle.

Remove cap from the needle

Check to see that the BEVEL is UPWARD

Pull skin TAUT across the VEIN

Tell the subject that there will be a slight pin prick

QUICKLY insert the needle

Press vacutainer ONTO the needle, TAKING CARE <u>NOT</u> TO PUSH THE NEEDLE AS WELL

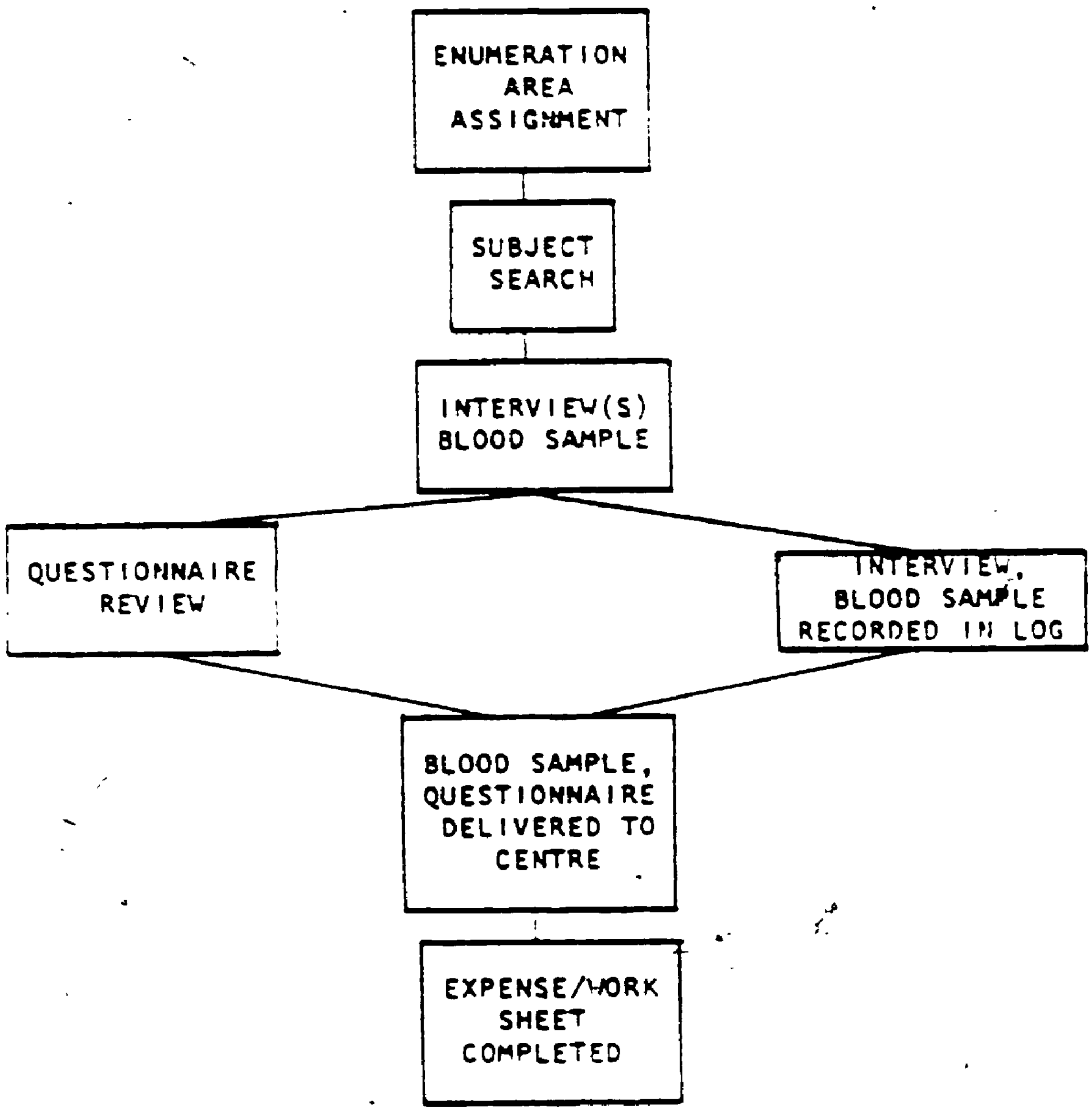
Draw blood

WHEN the vacutainer is 2/3 full

Tell subject to relax hand

Remove tourniquet

FIELDWORK
FLOW CHART



SUBJECT LOG

INTERVIEWER CODE

Date Record Began ____________

Subject Code	Date Interview Completed	Blood Sample				
		Drawn		Date Drawn	Date Delivered to Centre	Comments
		No	Yes			

FIELDWORK
RECORD

Sampling	Schedule	Assignment	Dwelling Number	Interviewer Code
ED	CT	E.A.		

TARGET ADDRESS

____

____

____

How would you describe this area?

AREA CLASSIFICATION

- [ ] Primarily houses (single family dwelling)
- [ ] Houses (single-multiple dwellings)
- [ ] Apartment Blocks
    - Old
    - New
    - Mixed
- [ ] Mixed dwellings (apartments and houses)
- [ ] Other (specify) ____________________

Immediate area around the TARGET DWELLING

- [ ] Residential (mostly apartments)
- [ ] Semi-residential (homes, some commercial buildings)
- [ ] Commercial (mostly stores, a few houses)
- [ ] Strictly commercial
- [ ] Other (specify) ____________________

INTERVIEWER CODE

		COMMENTS	CODE
Search (Indicate initial 1st return, 2nd return)			
Address: Search Begun			
Day (Monday - Sunday)	DATE Day Month Year		
Time: Begun	A.M. P.M.		
Ended	A.M. P.M.		
Total Hours/Minutes	hours minutes		
OUTCOME. # Immediate Interviews			
Appointment Cards Left: with respondent			
with other household member			
# Ineligibles Due to: Age: Too Old			
Too Young			
RACE			
LANGUAGE			
GENDER			
OTHER			
# NO ANSWER			
# REFUSALS *			
OTHER			
Address: Search Ended			
Total # Households Approached			

* List reasons for refusals

ETHNICITY

How would you describe the ethnicity of this area ?

☐ Primarily English Speaking Canadians
(with some few non-English speaking persons)

☐ Other Please specify
Below

Ethnic groups which predominate

1st ______________________

2nd ______________________

3rd ______________________

Comments

Please comment on any special conditions

or problems in this area

____

____

____

AREA SUMMARY

Please list the address, interview date, gender and subject Code Number of all completed interviews in this area

ADDRESS	DATE OF INTERVIEW	GENDER	SUBJECT CODE
1)			
2)			
3)			
4)			
5)			
6)			
7)			
8)			
9)			
10)			
11)			
12)			

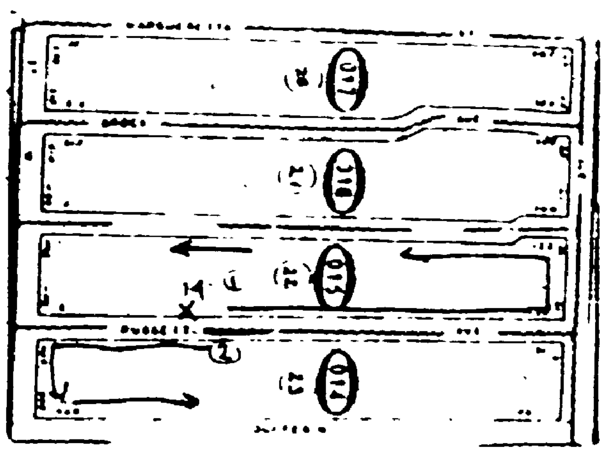
APPENDIX III

SUBJECT SEARCH PROCEDURE

Apartment blocks, row houses, primate homes and all other types of dwellings were included.

Each search-run consisted of approaches to approximately 50 households. An example of a street search follows:

Dwelling number 14 on Russett Avenue may be the start point. From that point, the search for a study candidate begins and proceeds according to the search protocol. The interviewer, having inquired at dwelling number 14, proceeds to the dwelling directly to the right (when facing that dwelling) down the block until the corner is reached, around the corner as illustrated:



In the event that no suitable candidate is found after completing two call backs to that block (one initial search run, plus two return visits at the time of day assigned to that area), the interviewer was instructed to cross the street, and begin at the house directly across from the original starting point (number 14) proceeding in a similar manner until a suitable candidate was found. The interviewer abandons this target and returns for another random assignment only after one initial search run plus two call backs have been completed without success.

Apartment Blocks

Each search run consisted of approaches to approximately 50 apartment doors. In apartment dwellings, the interviewer began at the apartment assigned by the sampling schedule and continued around that floor from right to left in a circular manner until a suitable candidate was found. As indicated in the street search protocol, one initial visit plus two call backs to that floor were permitted. Failing this, the interviewer proceeded to one more floor in that apartment block. This floor is designated to be either higher or lower than the original assigment depending upon the results of a coin toss. In the event that the bottom or top floor was the initial assignment, the next available level was chosen. If one initial search run and two return visits to this second assignment did not yield a subject, the interviewer returned to the sampling schedule for a new assignment.

APPENDIX IV

RADIOIMMUNOASSAY METHOD

APPENDIX IV

RADIOIMMUNOASSAY METHOD

Preparation of Reagents

(1) Treatment of Beads (Crossman B.B. shot, 0.33 mm)

The beads were cadmium coated to ensure a smooth surface (X-pert Metal Finishing, Burlington). They were then coated with polycarbonate by immersing the beads in a 5% (wt/vol) solution of polycarbonate dissolved in methylene chloride. The beads were drained and scattered on brown wrapping paper to allow the methylene chloride to evaporate, leaving a thin polycarbonate coating on the beads.

(2) Preparation of Antigens

Confluent 150 cm^2 flasks of Vero cells are inoculated with 1 plaque forming unit (PFU) of HSV-1, or 1 PFU HSV-2, or left uninfected (mock). The flasks were then incubated for 24 hours at 37°C and harvested by scraping cells into medium. The cells are pelleted by centrifugation, washed 2X with PBS and then resuspended in 10 ml PBS/150 cm^2 flask. The cell suspensions were frozen and thawed 2X and sonicated for 30 seconds prior to use.

(3) Preparation of Tagged Antibody (I^{125})

Goat anti-human IgG was purchased from Cappel Laboratories and labelled with I^{125} using the chloramine T method. The reaction mixture was passed through on a Sephadex G-25 column to separate the labelled antibody from the remaining free iodine. Each preparation of labelled antibody was titred against a known positive antigen to ensure an equal amount of reactivity between experiments.

Conducting the Assay

(1) Sensitizing Beads

Ten ml of the desired antigen (HSV-1, HSV-2 or mock infected cells (control)) was thawed and incubated with beads at room temperature for 1 hour. Excess antigen was removed from the beads and 10 ml of 1% BSA in PBS was added to the beads, after which they were incubated for 1 hour at room temperature. The incubation with the BSA solution reduced the background counts by preventing non-specific binding of the antibody to the beads.

(2) Incubation with Serum

The sera were diluted 1:50 in 1% BSA in PBS, and 0.2 ml of each serum was placed in four wells of a plexiglass plate. Two wells receive beads sensitized with HSV-2, and two wells receive beads sensitized with control antigen. The beads and sera were incubated for 16 hours at $4^{o}C$.

(3) Incubation with I^{125} Labelled Goat anti-human IgG

After incubation with sera, the beads were washed twelve times in tap water; by lifting them out of the plexiglass wells with a magnetic holder and dipping them in two basins of tap water, six times each.

The washed beads were dropped into wells of a plexiglass plate containing 0.2 ml of I^{125} labelled goat anti-human IgG, and incubated for 4 hours at room temperature. The washing procedure was then repeated, as above, and the beads were dropped into 12 x 75 mm test tubes and counted for 1 minute each in the gamma counter.

By initially testing the sera against HSV-2 antigen and control antigen, the obvious negative sera could be identified and removed from further analysis. From the rest of the sera, a 0.1 ml sample was set aside for adsorption with HSV-1 infected cell lysate.

(4) Adsorption

Confluent flasks of Vero cells were infected with HSV-1 virus for 24 hours at 37°C. When virus cytopathic effect was observed in 90% of the cells, the cells were scraped into the medium and spun down at 1,000 rpm for 10 minutes. The cell pellet was washed twice with PBS and then frozen and thawed twice. To each serum sample (0.1 ml) was added 0.1 ml of cell lysate and 0.8 ml of PBS, and this was shaken at 4°C overnight. The adsorbed sera were then centrifuged, and the supernatants were collected and tested as described below.

(5) Testing Adsorbed Sera

Each serum (0.05 ml) was placed in four wells of a plexiglass plate which already contained 0.15 ml of HSV-1 cell lysate. (This acted as a second adsorption.) Two wells then received beads sensitized with HSV-1 antigen and two wells received beads sensitized with HSV-2 antigen. To establish how much non-specific binding was occurring, ten random samples of sera were pooled together and tested against beads sensitized to control antigen. The incubations and washing were performed as described above.

Calculations

The counts for the duplicate beads for each serum to HSV-1 and HSV-2 were first averaged and recorded. The counts for the pooled sera run against control antigen were averaged and subtracted from the HSV-1 or HSV-2 counts for each serum. The specific counts for HSV-2 for each serum was determined by subtracting the HSV-1 counts for that particular serum.

APPENDIX V

FIELDWORK OUTCOME

APPENDIX V

FIELD OUTCOME

Record of all subject searching outcomes for each was maintained by the interviewers. The outcomes of these searches are summarized on the following table:

Results of Field Searches*
All Areas Combined

Numbers of Enumeration Districts	14
Census Tracts	69
Enumeration Areas	97

Fieldwork Outcomes

Households Approaches	13,940
Interviews	957
Refusals	263
Ineligible Because	
Too Old	2,459
Too Young	2,197
Race	921
Language	665
Gender	136
Other Outcomes	153
Not at home	6,199

*One fieldwork record was incomplete, resulting in missing information.

	Percent
Interviewers Area Description:	
Type of Area:	
Residential (homes only, no commercial establishments)	51.6
Semi-Residential (homes, some commercial establishments)	45.3
Primarily Commercial (Areas with some homes)	2.8
	99.7
Type of Dwellings	
Primarily Single Family Houses	41.1
Houses containing multiple households	32.9
Old and New Apartment buildings, unit housing including rooming houses	26.0
	100.0
Ethnicity of Area	
Primarily English-Speaking	73.6
Canadian + Ethnic	6.4
Italian	11.4
Portuguese, Oriental, Indian, African	8.6
	100.0

Socioeconomic Distribution of Households
Approached, Refusals for Interview,
and Interviews Obtained

Socionomic Area*	Households Approached		Refusals of Interview		Interviews Obtained	
	Number	%**	Number	%	Number	%
Low	5130	41.86	98	41.88	326	38.17
Middle	4160	33.95	87	37.17	296	34.66
High	2965	24.19	49	20.95	232	27.17
Total	12255		234		854	

* Based upon the socioeconomic designation of the Census Area.
** Column Percent

Note: SES Data unavailable for 1414 households, 24 refusals, 83 interviews.

APPENDIX VI

STATISTICAL TABLES

APPENDIX VI

O Logistic Regression Results, Basic Model:
Primary Variables: WOMEN

P Comparison of Adjusted Odds Ratios:
Original Full Model, Type of Education,
Years of Education: MEN

Q Comparison of Adjusted Odds Ratios:
Original Full Model, Household Annual
Income, Years of Education: MEN

R Comparison of Adjusted Odds Ratios:
Original Full Model, Type of Dwelling,
Residence Status: MEN

S Comparison of Adjusted Odds Ratios:
Original Full Model, Type of Education,
Years of Education: WOMEN

T Comparison of Adjusted Odds Ratios:
Original Full Model, Household Annual
Income, Years of Education: WOMEN

U Comparison of Adjusted Odds Ratios:
Original Full Model, Type of Dwelling,
Residence Status: WOMEN

CORRELATION MATRICES

Legend:

* Pearson Correlation Coefficient

** P value

*** n

Please note

The sign of the coefficients between dummy variables may differ from those for the continuous in some cases, because the dummy variables were coded 0, 1 with 1 often representing the level of the variable "associated" with the outcome. For example, the coefficient for number of sexual partners with age at first intercourse, because of an inverse relationship, would indicate a negative coefficient in their original form and a positive coefficient for the dummy variables (e.g. 1 = many partners, 0 = few; 1 = early intercourse, 0 = late).

TABLE A

MEN: Continuous Variables

	Age at Interview	Total Years of Education	Household Annual Income	Occupation Present	Occupation Past
Age at Interview	1.00000* 0.0000** 320***	-0.22583 0.0001 316	-0.16605 0.0034 309	-0.12294 0.0342 297	0.07741 0.7387 21
Total Years of Education	-0.22583 0.0001 316	1.00000 0.0000 316	0.58930 0.0001 305	0.72297 0.0001 294	0.72829 0.0002 21
Household Annual Income	-0.16605 0.0034 309	0.58930 0.0001 305	1.00000 0.0001 309	0.62708 0.0001 288	0.46250 0.0462 19
Occupation Present	-0.12294 0.0324 297	0.72297 0.0001 294	0.62708 0.0001 288	1.00000 0.0000 297	0
Deccupation Past	0.07741 0.7387 21	0.72829 0.0002 21	0.46250 0.0462 19	0	1.00000 0.0000 21
Years of Condom Use	0.18359 0.0010 317	0.20755 0.0002 313	0.20473 0.0003 306	0.09716 0.0964 294	0.20066 0.3831 21
Age at 1st Intercourse	0.05775 0.3093 312	0.20179 0.0004 308	0.10108 0.0795 302	0.29324 0.0001 240	0.15341 0.5184 20
No of Sexual Partners in Teenage Years	0.07965 0.1619 310	-0.05302 0.3554 306	-0.13442 0.0196 301	-0.11608 0.0487 299	0.23321 0.3366 19
No. of Sexual Partners in 20s	0.01064 0.8542 301	0.01563 0.7885 297	-0.07570 0.1971 292	0.03924 0.5132 280	0.19569 0.4220 19
No. of Sexual Partners in 30s	0.0220[illegible] 0.7033 301	0.04492 0.4406 297	-0.06593 0.2615 292	0.06342 0.2903 280	0.21822 0.3694 19
No. of Sexual Partners in 40s	-0.03772 0.6284 167	0.10537 0.1767 166	0.14457 0.0656 163	0.08550 0.2917 154	-0.40636 0.1692 13
Total No. of Sexual Partners in a Lifetime	-0.00687 0.9067 288	0.02294 0.7003 284	-0.05304 0.3757 281	0.04191 0.4949 270	-0.11245 0.6467 16
No. of Sexual Partners in Tear Preceding the Interview	-0.11058 0.0561 317	0.06482 0.2671 295	-0.03201 0.5872 290	0.06339 0.2922 278	-0.11245 0.6467 19

Table A continued

	Years of Condom Use	Age at 1st Intercourse	No. of Sexual Partners in Teens	No of Sexual Partners in 20s	No. of Sexual Partners in 30
Age at Interview	0.18359 0.0010 317	0.05775 0.3093 312	0.07965 0.1619 310	0.01064 0.8542 301	0.02254 0.7033 301
Total Years of Education	0.20755 0.0002 313	0.20179 0.0004 308	-0.05302 0.3554 306	0.01563 0.7885 297	0.04492 0.4406 297
Household Annual Income	0.20473 0.0003 306	0.10108 0.0795 302	-0.13442 0.0196 301	-0.07570 0.1971 292	-0.06593 0.2615 292
Occupation Present	0.09716 0.0964 294	0.29324 0.0001 290	-0.11608 0.0487 289	0.03924 0.5132 280	0.06342 0.2903 280
Occupation Past	0.20066 0.3831 21	0.15341 0.5[illegible]84 20	0.23321 0.3366 19	0.14569 0.4220 19	0.21822 0.3694 19
Years of Condom Use	1.00000 0.0000 317	-0.19901 0.0004 312	-0.03023 0.5959 310	-0.11170 0.0529 301	-0.11642 0.0436 301
Age at 1st Intercourse	-0.19901 0.0004 312	1.00000 0.0000 312	-0.24856 0.0001 307	-0.18014 0.0018 298	-0.13174 0.0227 299
No. of Sexual Partners in Teenage Years	-0.03023 0.5959 310	-0.24856 0.0001 307	1.00000 0.0000 310	0.68168 0.0001 301	0.58676 0.0001 293
No. of Sexual Partners in 20s	-0.11170 0.0529 301	-0.18014 0.0018 298	0.68168 0.0001 301	1.00000 0.0000 301	0.96045 0.0001 293
No. of Sexual Partners in 30s	-0.11642 0.0436 301	-0.13174 0.0227 299	0.58676 0.0001 293	0.96045 0.0001 293	1.00000 0.0000 301
No. of Sexual Partners in 40s	-0.02302 0.7678 167	-0.09060 0.2457 166	0.05733 0.4632 166	0.39540 0.0001 150	0.50886 0.0001 163
Total No. of Sexual Partners in a Lifetime	-0.09159 0.1209 288	-0.15728 0.0077 286	0.42708 0.0001 288	0.85808 0.0001 282	0.83929 0.0001 284
No. of Sexual Partners in Year Preceding the Interview	-0.08357 0.1480 299	-0.06945 0.2328 297	0.01637 0.7792 296	0.43464 0.0001 288	0.57245 0.0001 290

Table A continued

	No. of Sexual Partners in 40s	Total Number of Sexual Partners in a Lifetime	No. of Sexual Partners in Year Preceding the Interview
Age at Interview	-0.03772 0.6284 167	-0.00687 0.9076 288	-0.11058 0.0561 299
Total Years of Education	0.10537 0.1767 166	0.02294 0.7003 284	0.06482 0.2671 295
Household Annual Income	0.14457 0.0656 163	-0.05304 0.3757 281	0.03201 0.5872 290
Occupation Present	0.08550 0.2917 154	0.04191 0.4949 270	0.06339 0.2922 278
Occupation Past	-0.40636 0.1682 13	0.16375 0.5445 16	-0.11245 0.6467 19
Years of Condom Use	-0.02302 0.7678 167	-0.09159 0.1209 288	-0.08387 0.1480 299
Age at 1st Intercourse	-0.09060 0.2457 166	-0.15728 0.0077 286	-0.06945 0.2328 297
No. of Sexual Partners in Teenage Years	0.05733 0.4632 166	0.43708 0.0001 288	0.01637 0.7792 296
No. of Sexual Partners in 20s	0.39540 0.0001 160	0.35808 0.0001 282	0.43464 0.0001 288
No. of Sexual Partners in 30s	0.50886 0.0001 163	0.83929 0.0001 284	0.57245 0.0001 290
No. of Sexual Partners in 40s	1.00000 0.0000 167	0.22090 0.0053 158	0.75454 0.0001 163
Total No. of Sexual Partners in a Lifetime	0.22090 0.0053 158	1.00000 0.0000 288	0.25295 0.0001 283
No. of Sexual Partners in Year Preceding the Interview	0.75454 0.0001 163	0.25295 0.0001 283	1.00000 0.0000 299

TABLE B

WOMEN: Continuous Variables

	Age At Interview	Total No. of Pregnancies	Total Years of Education	Household Annual Income	Occupation Present	Occupation Past
Age at Interview	1.00000	0.19721	-0.19598	-0.21926	-0.13632	-0.32384
	0.0000	0.0001	0.0001	0.0001	0.0283	0.0001
	428	428	426	414	259	147
Total No. of Pregnancies	0.19721	1.00000	-0.36642	-0.28193	-0.27309	-0.38908
	0.0001	0.0000	0.0001	0.0001	0.0001	0.0001
	428	428	426	414	259	147
Total Years of Education	-0.19598	-0.36642	1.00000	0.58523	0.71263	0.71682
	0.0001	0.0001	0.0000	0.0001	0.0001	0.0001
	426	426	426	412	258	146
Household Annual Income	-0.21926	-0.28193	0.58523	1.00000	0.50485	0.51255
	0.0001	0.0001	0.0001	0.0000	0.0001	0.0001
	414	414	412	414	252	142
Occupation Present	-0.13632	-0.27309	0.71263	0.50485	1.00000	
	0.0283	0.0001	0.0001	0.0001	0.0001	
	259	259	258	252	259	0
Occupation Past	-0.32384	-0.38908	0.71682	0.51255		1.00000
	0.0001	0.0001	0.0001	0.0001		0.0000
	147	147	146	142	0	147
Years of Condom Use	0.06800	-0.12462	0.14968	0.10799	[illegible]	[illegible]
	0.1642	0.0106	0.0022	0.0296	[illegible]	[illegible]
	420	420	418	406	253	145
Years of Diaphragm Use	0.15325	-0.05338	0.22139	0.14157	0.13112	[illegible]
	0.0011	0.2734	0.0001	0.0022	0.0364	[illegible]
	423	423	421	409	255	146
Years of I.U.D. Use	-0.22538	0.01732	0.11030	0.04201	0.07055	-0.02139
	0.0001	0.7228	0.0236	0.3968	0.2616	0.7931
	423	423	421	409	255	146
Years of Oral Contraceptive Use	-0.21400	-0.06019	0.23272	0.19722	0.15485	0.24851
	0.0001	0.2167	0.0001	0.0001	0.0133	0.0025
	423	423	421	409	255	146
Age at 1st Intercourse	0.03254	-0.34066	0.32506	0.21226	0.16568	0.35932
	0.5060	0.0001	0.0001	0.0001	0.0083	0.0001
	420	420	418	406	253	145
No. of Sexual Partners in Teens	-0.07984	0.12664	-0.06314	-0.16712	-0.06143	-0.[illegible]653
	0.1031	0.0094	0.1934	0.0007	0.3305	0.0037
	420	420	418	406	253	145
No. of Sexual Partners in 20s	-0.23238	-0.13203	0.17560	0.0[illegible]93	0.20660	[illegible]
	0.0001	0.0067	0.0002	0.3734	0.0009	0.[illegible]846
	421	421	419	407	253	146
No. of Sexual Partners in 30s	-0.10561	-0.10434	0.19359	-0.03201	0.23433	0.08666
	0.0313	0.0334	0.0001	0.5222	0.0002	0.301[illegible]
	416	416	414	402	251	144
No. of Sexual Partners in 40s	0.02638	-0.00672	0.09981	-0.02629	0.04931	-0.3[illegible]
	0.6744	0.9148	0.1125	0.6816	0.54[illegible]3	0.0025
	256	256	255	246	156	96
Total No. of Sexual Partners in a Lifetime	-0.18293	-0.09348	0.19138	-0.06669	0.24505	0.02448
	0.0002	0.0599	0.0001	0.1870	0.0001	0.7733
	406	406	405	393	245	141
No. of Sexual Partners in Year Preceding Interview	-0.16495	-0.07696	0.13[illegible]	0.01138	0.13513	0.03533
	0.0007	0.1167	0.0061	0.8198	0.0317	0.6753
	417	417	415	403	253	143

Table B continued

	Years of Condom Use	Years of Diaphragm Use	Years of I.U.D. Use	Years of Oral Contra-ceptive Use	Age at 1st Intercourse	No. of Sex-ual Partners in Teens
Age at Interview	0.06800 0.1642 420	0.15825 0.0011 423	-0.22638 0.0001 423	-0.21900 0.0001 423	0.03254 0.5060 420	-0.07984 0.1031 420
Total No. of Pregnancies	-0.12462 0.0106 420	-0.05338 0.2734 423	0.01732 0.7224 423	-0.06019 0.2167 423	-0.18066 0.0001 420	0.12664 0.0094 420
Total Years of Education	0.14968 0.0022 418	0.22109 0.0001 421	0.11030 0.0236 421	0.23272 0.0001 421	0.32508 0.0001 418	-0.06376 0.1934 418
Household Annual Income	0.10799 0.0296 406	0.15070 0.0022 409	0.04201 0.3968 409	0.19722 0.0001 409	0.21226 0.0001 406	-0.16712 0.0007 406
Occupation Present	0.11056 0.0792 253	0.13112 0.0364 255	0.07095 0.2616 255	0.15485 0.0133 255	0.16568 0.0083 253	-0.06143 0.3305 253
Occupation Past	0.20431 0.0137 145	0.22592 0.0061 146	-0.02189 0.7931 146	0.24851 0.0025 146	0.35932 0.0001 145	-0.17553 0.0337 145
Years of Condom Use	1.00000 0.0000 420	0.12532 0.0101 420	-0.03506 0.4736 420	0.01390 0.7765 420	-0.05824 0.2354 417	-0.03043 0.5333 417
Years of Diaphragm Use	0.12532 0.0101 420	1.00000 0.0000 423	0.04413 0.3652 423	-0.02623 0.5932 423	-0.00849 0.3623 420	0.01242 0.7996 420
Years of I.U.D. Use	-0.03506 0.4736 420	0.04413 0.3652 423	1.00000 0.0000 423	0.05625 0.2482 423	-0.10317 0.0345 420	0.18574 0.0001 420
Years of Oral Contra-ceptive Use	0.01390 0.7765 420	-0.02623 0.5932 423	0.05626 0.2482 423	1.00000 0.0000 423	-0.07774 0.1117 420	-0.00727 0.3818 420
Age at 1st Intercourse	-0.05824 0.2354 417	-0.00849 0.8623 420	-0.10317 0.0345 420	-0.07774 0.1117 420	1.00000 0.0000 420	-0.19157 0.0001 420
No. of Sex-ual Partners in Teens	-0.03043 0.5333 417	0.01242 0.7996 420	0.18574 0.0001 420	-0.00727 0.8818 420	-0.19157 0.0001 420	1.00000 0.0000 420
No. of Sex-ual Partners in 20s	0.06205 0.2055 418	0.05079 0.2984 421	0.25242 0.0001 421	0.02943 0.5529 421	-0.14822 0.0023 420	0.31080 0.0001 420
No. of Sex-ual Partners in 30s	0.05316 0.2811 413	0.15492 0.0015 416	0.02181 0.6579 416	0.15321 0.0017 416	-0.07990 0.1041 415	0.03095 0.5295 415
No. of Sex-ual Partners in 40s	0.05[illegible] 0.3435 254	0.27562 0.0001 256	0.04584 0.4653 256	0.05117 0.4120 256	-0.09546 0.1286 255	0.10615 0.0893 255
Total No. of Sexual Partners in a Lifetime	0.05424 0.2773 403	0.15079 0.0023 406	0.28654 0.0001 406	0.14149 0.0043 406	-0.23698 0.0001 405	0.42217 0.0001 405
No. of Sexual Partners in Years Preceding Interview	0.07581 0.1235 414	0.06500 0.1853 417	0.12580 0.0101 417	0.13527 0.0057 417	-0.07364 0.1333 417	0.07182 0.1432 417

Table B continued

	No. of Sexual Partners in 20s	No. of Sexual Partners in 30s	No. of Sexual Partners in 40s	Total No. of Sexual Partners in a Lifetime	No. of Sexual Partners in Year Preceding Interview
Age at Interview	-0.23238 0.0001 421	-0.10561 0.0313 416	0.02638 0.6784 256	-0.18293 0.0002 406	-0.16495 0.0007 417
Total No. of Pregnancies	-0.13203 0.0067 421	-0.14434 0.0034 416	-0.00672 0.9148 256	-0.09348 0.0599 406	-0.07694 0.1167 417
Total Years of Education	0.17860 0.0002 419	0.19359 0.0001 414	0.09961 0.1126 255	0.19138 0.0001 405	0.13444 0.0061 415
Household Annual Income	0.00793 0.8734 407	-0.03201 0.5222 402	-0.02629 0.6816 246	-0.06669 0.1870 393	0.05138 0.3198 403
Occupation Present	0.20660 0.0009 253	0.23433 0.0002 251	0.04931 0.5410 156	0.24505 0.0001 245	0.13513 0.0317 253
Occupation Past	0.14322 0.0846 146	0.08666 0.3017 144	-0.01341 0.9025 86	0.02448 0.7733 141	0.05533 0.5153 143
Years of Condom Use	0.06205 0.2055 418	0.05316 0.2811 413	0.01284 0.8435 254	0.05424 0.2773 403	0.07581 0.1235 414
Years of Diaphragm Use	0.05079 0.2984 421	0.15492 0.0015 416	0.27562 0.0001 256	0.15079 0.0023 406	0.06500 0.1851 417
Years of I.U.D. Use	0.26242 0.0001 421	0.02181 0.6574 416	0.04584 0.4653 256	0.25854 0.0001 406	0.12580 0.0101 417
Years of Oral Contraceptive Use	0.09443 0.0529 421	0.15321 0.0017 416	0.05117 0.4120 256	0.14149 0.0043 406	0.13524 0.0057 417
Age at 1st Intercourse	-0.14822 0.0023 420	-0.07990 0.1041 415	-0.09540 0.1286 255	-0.23698 0.0001 405	-0.07364 0.1333 417
No. of Sexual Partners in Teens	0.31080 0.0001 420	0.03595 0.5296 415	0.10843 0.0899 255	0.42210 0.0001 405	0.07132 0.1432 417
No. of Sexual Partners in 20s	1.00000 0.0000 421	0.42251 0.0001 415	0.14367 0.0215 256	0.83353 0.0001 406	0.23686 0.0001 417
No. of Sexual Partners in 30s	0.42251 0.0001 416	1.00000 0.0000 416	0.21284 0.0007 253	0.76670 0.0001 408	0.28959 0.0001 414
No. of Sexual Partners in 40s	0.14367 0.0215 256	0.21284 0.0007 253	1.00000 0.0000 256	0.57712 0.0001 250	0.46231 0.0001 255
Total No. of Sexual Partners in a Lifetime	0.83353 0.0001 406	0.76670 0.0001 408	0.57712 0.0001 250	1.00000 0.0000 406	0.33820 0.0001 405
No. of Sexual Partners in Year Preceding Interview	0.23686 0.0001 417	0.28959 0.0001 414	0.46231 0.0001 255	0.33820 0.0001 405	1.00000 0.0000 417

TABLE C

AIDS: Dummy Variables

	Marital Status	Type of Education	Total Years of Education	Household Annual Income	Residence Status	Duration in Residence
1. Marital Status	1.00000	-0.00893	-0.04351	0.07853	0.32381	0.13248
	0.0000	0.8736	0.4408	0.1685	0.0001	0.0177
	320	320	316	309	320	320
2. Type of Education	-0.00893	1.00000	0.62004	0.42628	0.10836	-0.18673
	0.8736	0.0000	0.0001	0.0001	0.0528	0.0008
	320	320	316	309	320	320
3. Total Years of Education	-0.04351	0.62004	1.00000	0.47516	0.19088	-0.14755
	0.4408	0.0004	0.0000	0.0001	0.0006	0.0086
	316	316	316	305	316	316
4. Household Annual Income	0.07853	0.42628	0.47516	1.00000	0.23528	-0.13530
	0.1685	0.0001	0.0001	0.0000	0.0001	0.0173
	309	309	305	309	309	309
5. Residence Status	0.32381	0.10836	0.10988	0.23528	1.00000	0.23094
	0.0001	0.0528	0.0006	0.0001	0.0000	0.0001
	320	320	316	309	320	320
6. Duration in Residence	0.13248	-0.18673	-0.14750	-0.13530	0.23094	1.00000
	0.0177	0.0008	0.0086	0.0173	0.0001	0.0000
	320	320	316	309	320	320
7. Duration in Toronto	0.04622	-0.19254	-0.16958	-0.11038	0.06730	0.29532
	0.4100	0.0005	0.0025	0.0526	0.2299	0.0001
	320	320	316	309	320	320
8. Type of Dwelling	0.26934	0.02673	0.11128	0.14569	0.52112	0.13732
	0.0001	0.6397	0.0518	0.0118	0.0001	0.0157
	309	309	306	298	309	309
9. Household Crowding	0.11272	0.21859	0.25497	0.26146	0.23344	-0.05344
	0.0451	0.0001	0.0001	0.0001	0.0001	0.3407
	320	320	315	309	320	320
10. Years of Condom Use	0.06745	0.1[illegible]	0.11005	0.16130	0.08836	0.02807
	0.2311	0.0[illegible]	0.0518	0.0047	0.1164	0.6186
	317	[illegible]	313	306	317	317
11. Age at First Intercourse	0.03584	0.18554	0.24611	0.07923	0.17958	0.04575
	0.5282	0.0010	0.0001	0.1696	0.0014	0.4208
	312	312	308	302	312	312
12. Total Number of Sexual Partners	0.25974	-0.02411	-0.00060	-0.16225	0.14664	0.28529
	0.0001	0.6837	0.9920	0.0064	0.0127	0.0001
	288	288	284	282	288	288

TABLE C continued

	Duration in Toronto	Type of Dwelling	Household Crowding	Years of Condom Use	Age at First Intercourse	Total Number of Sexual Partners
1. Marital Status	0.04622	0.26934	0.11212	0.06745	0.03584	0.25974
	0.4100	0.0001	0.0451	0.2311	0.5282	0.0001
	320	309	320	317	312	288
2. Type of Education	-0.19257	0.02673	0.21859	0.13122	0.18954	-0.02411
	0.0005	0.6397	0.0001	0.0194	0.0001	0.6837
	320	309	320	317	312	288
3. Total Years of Education	-0.16958	0.11128	0.25497	0.11005	0.24614	-0.00060
	0.0025	0.0518	0.0001	0.0518	0.0001	0.9920
	316	306	316	313	308	284
4. Household Annual Income	-0.11038	0.14569	0.26146	0.16130	0.07923	-0.16225
	0.0526	0.0118	0.0001	0.0047	0.1696	0.0064
	309	298	309	306	302	281
5. Residence Status	0.06738	0.52112	0.23344	0.08836	0.14958	0.14665
	0.2299	0.0001	0.0001	0.1164	0.0014	0.0127
	320	309	320	317	312	288
6. Duration in Residence	0.29532	0.13732	-0.05344	0.03607	0.04573	0.29529
	0.0001	0.0157	0.3407	0.5186	0.4208	0.0001
	320	309	320	317	312	288
7. Duration in Toronto	1.00000	0.03830	0.06854	0.04384	0.00029	0.07501
	0.0000	0.5023	0.2214	0.4367	0.9960	0.2044
	320	309	320	317	312	288
8. Type of Dwelling	0.03830	1.00000	0.37413	0.06240	0.15529	0.12154
	0.5023	0.0000	0.0001	0.2765	0.0069	0.0420
	309	309	309	306	301	280
9. Household Crowding	0.06854	0.37413	1.00000	0.10691	0.06465	-0.07348
	0.2214	0.0001	0.0000	0.0572	0.2549	0.2137
	320	309	320	317	312	288
10. Years of Condom Use	0.04384	0.06240	0.10691	1.00000	-0.09053	-0.13359
	0.4367	0.2765	0.0572	0.0000	0.1105	0.0234
	317	306	317	317	312	288
11. Age at First Intercourse	0.00029	0.15529	0.06465	-0.09053	1.00000	0.25845
	0.9960	0.0069	0.2549	0.1105	0.0000	0.0001
	312	301	312	312	312	286
12. Total Number of Sexual Partners	0.07501	0.12154	-0.07348	-0.13359	0.25895	1.00000
	0.2044	0.0420	0.2137	0.0234	0.0001	0.0000
	288	280	288	288	286	288

TABLE D

WOMEN: Dummy Variables

	Birthplace	Marital Status	Type of Education	Years of Education	Household Annual Income
1. Birthplace	1.00000 0.0000 428	0.16241 0.0007 428	-0.00450 0.9261 428	0.09066 0.0616 426	-0.01390 0.7780 414
2. Marital Status	0.16241 0.0007 428	1.00000 0.0000 428	0.00367 0.9396 428	-0.01911 0.6941 426	0.29723 0.0001 414
3. Type of Education	-0.00450 0.9261 428	0.00367 0.9396 428	1.00000 0.0000 428	0.51546 0.0001 426	0.41242 0.0001 414
4. Years of Education	0.09066 0.0616 426	-0.01911 0.6941 426	0.51546 0.0001 425	1.00000 0.0000 428	0.49433 0.0001 4[illegible]
5. Household Annual Income	-0.01390 0.7780 414	0.29723 0.0001 414	0.41242 0.0001 414	0.49433 0.0001 412	1.00000 0.0000 414
6. Residence Status	0.1[illegible]25 0.0004 428	0.31161 0.0001 428	0.18086 0.0002 428	0.20823 0.0001 426	0.35616 0.0001 414
7. Duration in Residence	0.03551 0.4637 428	0.16602 0.0006 428	-0.28160 0.0001 428	-0.23790 0.0001 426	-0.18242 0.0002 414
8. Duration in Toronto	-0.14092 0.0035 428	0.03747 0.4394 428	-0.29258 0.0001 428	-0.22450 0.0001 426	-0.1[illegible]54 0.0[illegible]33 414
9. Type of Dwelling	-0.00037 0.9940	0.27911 0.0001 418	0.06662 0.1740 418	0.05027 0.3064 416	[illegible] 0.0001 404
10. Household Crowding	0.01003 0.8361 428	0.11456 0.0177 428	0.20728 0.0001 428	0.29808 0.0001 425	0.39675 0.0001 414
11. Years of Condom Use	-0.05282 0.3060 420	-0.00159 0.9741 420	-0.03394 0.4879 420	0.08002 0.1023 418	0.10244 0.0391 406
12. Years of Oral Contraceptive Use	0.01927 0.6927 423	0.07941 0.1029 423	-0.09325 0.0553 423	-0.10426 0.0325 421	-0.05612 0.2574 409
13. Age at First Intercourse	0.05202 0.2875 420	0.12151 0.0127 420	0.18356 0.0002 420	0.25630 0.0001 418	0.12225 0.0137 406
14. Total Number of Sexual Partners	0.10774 0.0300 406	0.42105 0.0001 406	-0.13869 0.0051 406	-0.13025 0.0087 405	0.05129 0.3042 393
15. Hysterectomy Status	0.06729 0.1646 428	0.09633 0.0464 428	0.07285 0.1324 428	0.[illegible] 0.0803 426	0.09633 0.0464 428
16. Receipt of a[illegible] Blood Transfusion	0.12439 0.0107 420	0.02187 0.6550 420	0.10812 0.0267 420	0.13802 0.0047 418	0.12512 0.0116 406

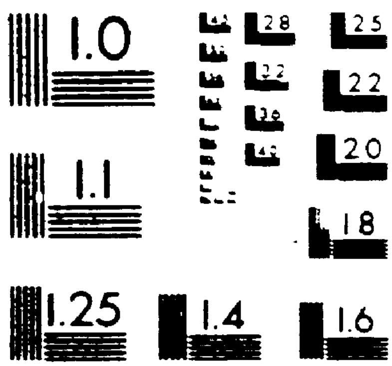
TABLE 9 Continued

	Residence Status	Duration in Residence	Duration in Toronto	Type of Dwelling	Household Crowding
1. Birthplace	0.17126 0.0004 428	0.03551 0.4637 428	-0.14092 0.0035 428	-0.00037 0.9940 418	0.01003 0.8361 428
2. Marital Status	0.31161 0.0001 428	0.16602 0.0006 428	0.03747 0.4394 428	0.27911 0.0001 418	0.11456 0.0177 428
3. Type of Education	0.18086 0.0002 428	-0.26160 0.0001 428	-0.29208 0.0001 428	0.06662 0.1740 418	0.20728 0.0001 428
4. Years of Education	0.20823 0.0001 426	-0.23790 0.0001 426	-0.22450 0.0001 426	0.05027 0.3064 416	0.29808 0.0001 426
5. Household Annual Income	0.35616 0.0001 414	-0.18242 0.0002 414	-0.11594 0.0183 414	0.21351 0.0001 404	0.29875 0.0001 414
6. Residence Status	1.00000 0.0000 428	0.19860 0.0001 428	0.09696 0.0450 428	0.60049 0.0001 418	0.48425 0.0001 428
7. Duration in Residence	0.19860 0.0001 428	1.00000 0.0000 428	0.34412 0.0001 428	0.11948 0.0145 418	0.05135 0.289 428
8. Duration in Toronto	0.09696 0.0450 428	0.34412 0.0001 428	1.00000 0.0000 428	0.15554 0.0014 418	0.05515 0.2550 428
9. Type of Dwelling	0.60049 0.0001 418	0.11948 0.0145 418	0.15554 0.0014 418	1.00000 0.0000 418	0.39683 0.0001 418
10. Household Crowding	0.48425 0.0001 428	0.05135 0.2891 428	0.05515 0.2550 428	0.39683 0.0001 418	1.00000 0.0000 418
11. Years of Condom Use	0.08998 0.0654 420	0.04870 0.3194 420	-0.04913 0.3152 420	0.02141 0.6656 410	0.03208 0.5120 420
12. Years of Oral Contraceptive Use	0.00823 0.8660 423	0.06712 0.1689 423	0.05405 0.2678 423	-0.00045 0.9929 413	-0.04932 0.3116 423
13. Age at First Intercourse	0.16804 0.0005 420	-0.05621 0.2504 420	-0.03511 0.4730 420	0.02918 0.5602 410	0.11544 0.0179 420
14. Total Number of Sexual Partners	0.11631 0.0190 406	0.14388 0.0037 406	0.06999 0.1592 406	0.10576 0.0352 397	-0.08625 0.0827 406
15. Hysterectomy Status	0.16191 0.0008 428	-0.04427 0.3609 428	-0.08280 0.0871 428	0.15105 0.0020 413	0.07258 0.1333 428
16. Receipt of a Blood Transfusion	0.17808 0.0002 420	-0.06671 0.1724 420	-0.08164 0.0947 420	0.07365 0.1365 410	0.10039 0.0397 420

TABLE D Continued

	Years of Condom Use	Years of Oral Contraceptive Use	Age at First Intercourse	Total Number of Sexual Partners	Hysterectomy Status	Receipt of a Blood Transfusion
1. Birthplace	-0.01202	0.01927	-0.05202	0.10768	0.06729	0.12639
	0.8060	0.6927	0.2875	0.0300	0.1656	0.0107
	420	423	420	406	428	420
2. Marital Status	-0.30159	0.07981	0.12151	0.32105	0.09883	0.02187
	0.3781	0.2029	0.0127	0.0001	0.0468	0.6550
	420	423	420	406	428	420
3. Type of Education	-0.03398	-0.09326	0.18396	-0.13869	0.07285	0.10812
	0.4679	0.0553	0.0002	0.0051	0.1328	0.0267
	420	423	420	406	428	420
4. Years of Education	0.08002	-0.10426	0.25630	-0.13025	0.08482	0.13862
	0.1023	0.0325	0.0001	0.0087	0.0803	0.0047
	418	421	418	405	426	418
5. Household Annual Income	0.10298	-0.06112	0.12225	0.01298	0.09833	0.12515
	0.0391	0.2178	0.0137	0.8042	0.0464	0.0115
	406	409	406	393	428	406
6. Residence Status	0.08998	0.50823	0.16804	0.12851	0.16191	0.17548
	0.0654	0.3660	0.0005	0.0109	0.0008	0.0002
	420	423	420	406	428	420
7. Duration in Residence	0.54870	-0.56772	-0.55625	0.14188	-0.54427	-0.5664
	0.3194	0.1682	0.2504	0.0037	0.3609	[illegible]
	420	423	420	406	428	420
8. Duration in Toronto	-0.54913	0.55405	-0.53511	0.56996	-0.58256	-0.58154
	0.3152	0.2578	0.4730	0.1592	0.2871	0.0987
	420	423	420	406	428	420
9. Type of Dwelling	0.52141	-0.56045	0.52176	0.10576	0.15165	0.54444
	0.5656	0.9928	0.6602	0.0352	0.0020	[illegible]
	410	413	410	397	413	410
10. Household Crowding	0.53256	-0.54932	0.11944	-0.06625	0.07268	[illegible]
	0.5120	0.3116	0.0179	0.1827	0.1333	[illegible]
	420	423	420	406	428	420
11. Years of Condom Use	1.00000	-0.55913	-0.60595	0.53916	-0.51426	[illegible]
	0.0000	0.2266	0.9133	0.4337	0.7710	[illegible]
	420	420	417	403	420	412
12. Years of Oral Contraceptive Use	-0.55913	1.00000	0.59924	0.13375	-0.14254	-0.15445
	0.2266	0.0000	0.0421	0.0070	0.0033	[illegible]
	420	423	420	406	423	415
13. Age at First Intercourse	-0.50535	0.59924	1.00000	0.29113	0.59354	[illegible]
	0.9133	0.0421	0.0000	0.0001	0.2554	0.0004
	417	420	420	405	420	412
14. Total Number of Sexual Partners	0.53916	0.13375	0.29113	1.00000	0.52234	-0.52491
	0.4337	0.0007	0.0001	0.0000	0.9536	0.5786
	403	406	405	406	406	398
15. Hysterectomy Status	-0.51426	-0.14237	0.59354	0.52234	1.00000	0.10624
	0.7710	0.0033	0.0954	0.9536	0.0000	0.0001
	420	423	420	406	428	420
16. Receipt of a Blood Transfusion	0.57731	-0.56564	0.17391	-0.52495	0.10624	1.00000
	0.1172	0.1861	0.0004	0.5786	0.0001	0.0000
	412	415	412	398	420	420

4



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

Table E

Percentage Distribution of Variables among HSV-2 Seropositive, Seronegative Participants and Participants without Serologic Information

MEN

Variable	HSV-2 Antibody Positive (n = 41)*		Negative (n = 279)*		No Sera (n = 71)*	
	Number	Percent**	Number	Percent	Number	Percent
Demographic Factors						
Descriptive						
Age at Interview						
≤ 40	23	56.10	135	48.39	34	47.89
≥ 41	18	43.90	144	51.61	37	52.11
Birthplace						
Canada	21	51.22	157	56.27	36	50.70
Other	20	48.78	122	43.73	35	49.30

* Numbers may vary throughout the table because of missing information for some of the variables.
** Indicates column percentage.

Table E continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent	No Sera (n = 71) Number	Percent
Descriptive continued						
First Language as a Child						
English	28	68.29	200	71.94	40	56.34
French	1	2.44	10	3.60	0	0.00
Other	12	29.27	68	24.46	31	43.66
Marital Status						
Married, Common Law	34	58.54	195	69.89	58	81.69
Previously Married	7	17.07	43	15.41	9	12.68
Never Married	10	24.39	41	14.70	4	5.63
Socioeconomic						
Further Education or Training						
Yes	31	75.61	202	72.66	39	54.93
No	10	24.39	76	27.34	32	45.07

Table E continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent	No Sera (n = 71) Number	Percent
Socioeconomic continued						
Total Number of Years of Education						
15	22	55.00	142	51.45	49	71.01
16	18	45.00	134	48.55	20	28.99
Household Annual Income						
$29,999	15	40.54	128	47.06	21	32.31
$30,000	22	59.46	144	52.94	44	67.69
Residence						
Residence Status						
Rent	22	53.66	74	26.52	20	28.17
Own	19	46.34	205	73.48	51	71.83
Type of Dwelling						
Single Family House	13	33.33	134	49.63	27	40.30
Multiple Family House	14	35.90	108	40.00	27	40.30
Apartment Building	12	30.77	28	10.37	13	19.40

Table E continued

Variable	HSV-2 Antibody Positive (n = 41)		Negative (n = 279)		No Sera (n = 71)	
	Number	Percent	Number	Percent	Number	Percent
Contraception						
Ever Used Contraception (Condom)						
Yes	31	75.61	199	72.63	32	47.06
No	10	24.39	76	27.37	36	52.94
Sexual Factors						
Circumcised						
Yes	22	55.00	115	41.67	19	27.14
No	18	45.00	161	58.33	51	72.86
Ever had Sexual Intercourse						
Yes	41	100.00	275	98.92	68	98.55
No	0	0.00	3	1.08	1	1.45
Age at First Intercourse						
17	29	70.73	129	47.60	42	64.62
18	12	29.27	142	52.40	23	35.38

Table E continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent	No Sera (n = 71) Number	Percent
Total Number of Sexual Partners in a Lifetime						
9	9	26.47	129	50.79	31	52.54
10	25	73.53	125	49.21	28	47.46
Number of Sexual Partners in the Year Preceding the Interview						
1	18	51.43	194	73.48	47	79.66
2	17	48.57	70	26.52	12	20.34
Sexual Preference						
Heterosexual	38	92.68	273	99.64	65	100.00
Bisexual	1	2.44	0	0.00	0	0.00
Homosexual	2	4.88	1	0.36	0	0.00

Table E continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent	No Sera (n = 71) Number	Percent
Lifestyle and General Factors						
Ever Smoked Cigarettes						
Yes	36	87.80	209	75.18	54	76.06
No	5	12.20	69	24.82	17	23.94
Ever Donated Blood						
Yes	25	60.98	164	58.99	26	36.62
No	16	39.02	114	41.01	45	63.38
Ever Participated in a Previous Survey						
Yes	20	48.78	120	43.48	22	31.43
No	21	51.22	155	56.16	48	68.57

Table F

Percentage Distribution of Variables among HSV-2 Seropositive, Seronegative Participants and Participants without Serologic Information

WOMEN

Variable	HSV-2 Antibody					
	Positive (n = 75)*		Negative (n = 353)*		No Sera (n = 138)*	
	Number	Percent**	Number	Percent	Number	Percent
Demographic Factors						
Descriptive						
Age at Interview						
≤ 41	43	57.33	174	49.29	61	44.20
≥ 42	32	42.67	179	50.71	77	55.80
Birthplace						
Canada	52	69.33	200	56.66	87	63.04
Other	23	30.67	153	43.34	51	36.96

* Numbers may vary throughout the table because of missing information for some of the variables.
** Indicates column percentage.

Table F continued

Variable	HSV-2 Antibody Positive (n = 75)		Negative (n = 353)		No Sera (n = 138)	
	Number	Percent	Number	Percent	Number	Percent
Descriptive continued						
First Language as a Child						
English	50	66.67	250	70.82	96	70.07
French	8	10.67	11	3.12	5	3.65
Other	17	22.66	92	26.06	36	26.28
Marital Status						
Married, Commonlaw	43	57.33	264	74.79	95	69.34
Previously Married	27	36.00	67	18.98	31	22.63
Never Married	5	6.67	22	6.23	11	8.03
Reproductive Factors						
Ever Pregnant						
Yes	63	84.00	308	87.50	123	89.13
No	12	16.00	44	12.50	15	10.87

Table F continued

Variable	HSV-2 Antibody Positive (n = 75) Number	Percent	Negative (n = 353) Number	Percent	No Sera (n = 138) Number	Percent
Socioeconomic						
Further Education or Training						
Yes	37	49.33	223	63.17	75	54.35
No	38	50.67	130	36.83	63	45.65
Total Number of Years of Education						
$\leq$ 12	46	61.33	151	43.02	70	52.24
$\geq$ 13	29	38.67	200	56.98	64	47.76
Household Annual Income						
$\leq$ $24,999	56	78.87	187	54.52	71	56.35
$\geq$ $25,000	15	21.13	156	45.48	55	43.65
Residence						
Residence Status						
Rent	46	61.33	87	24.65	56	40.58
Own	29	38.67	266	75.35	82	59.42

Table F continued

Variable	HSV-2 Antibody Positive (n = 75)		Negative (n = 353)		No Sera (n = 138)	
	Number	Percent	Number	Percent	Number	Percent
Residence continued						
Type of Dwelling						
Single Family House	15	20.27	178	51.74	63	47.01
Multiple Family House	35	47.30	118	34.30	48	35.82
Apartment Building	24	32.43	48	13.95	23	17.16
Contraception						
Ever Used Contraception						
Yes	57	76.00	276	79.31	100	74.63
No	18	24.00	72	20.69	34	25.37
Sexual Factors						
Ever had Sexual Intercourse						
Yes	75	100.00	348	98.58	133	98.52
No	0	0.00	5	1.42	2	1.48

Table F continued

Variable	HSV-2 Antibody Positive (n = 75) Number	Percent	Negative (n = 353) Number	Percent	No Sera (n = 138) Number	Percent
Sexual Factors continued						
Age at First Intercourse						
≤ 19	51	68.92	150	43.35	65	49.62
≥ 20	23	31.08	196	56.65	66	50.38
Total Numbers of Sexual Partners in a Lifetime						
≤ 1	17	23.94	161	48.06	61	50.41
> 2	54	76.06	174	51.94	60	49.59
Number of Sexual Partners in the Year Preceding the Interview						
≤ 1	64	86.49	312	90.96	113	89.68
≥ 2	10	13.51	31	9.04	13	10.32

Table F continued

	HSV-2 Antibody					
	Positive (n = 75)		Negative (n = 353)		No Sera (n = 138)	
Variable	Number	Percent	Number	Percent	Number	Percent
Sexual Factors continued						
Sexual Preference						
Heterosexual	74	98.67	346	100.00	130	99.24
Bisexual	0	0.00	0	0.00	1	0.76
Homosexual	1	1.33	0	0.00	0	0.00
Lifestyle and General Factors						
Ever Smoked Cigarettes						
Yes	54	72.00	237	67.14	93	67.39
No	21	28.00	16	32.86	45	32.61
Ever Donated Blood						
Yes	21	28.00	143	40.74	26	18.98
No	54	72.00	208	59.26	111	81.02

Table P continued

Variable	HSV-2 Antibody Positive (n = 75)		Negative (n = 353)		No Sera (n = 138)	
	Number	Percent	Number	Percent	Number	Percent
Lifestyle and General Factors continued						
Ever Participated in a Previous Survey						
Yes	31	41.33	173	49.43	56	40.88
No	44	58.67	177	50.57	81	59.12

Table G

Percentage Distribution of Variables between HSV-2 Seropositive and Seronegative Participants

MEN
(n=320)

Variable	HSV-2 Antibody Positive (n = 41)* Number	Percent**	Negative (n = 279)* Number	Percent
Demographic Factors				
Descriptive				
Age at Interview				
≤ 38	16	39.02	102	36.56
39-43	15	36.59	85	30.47
≥ 44	10	24.39	92	32.97
Birthplace				
Canada	21	51.22	157	56.27
Other	20	48.78	122	43.73
Paternal Birthplace				
Canada	18	45.00	117	42.24
Other	22	55.00	160	57.76

* Numbers may vary throughout the table because of missing information for some of the variables.

** Indicates column percentages.

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	HSV-2 Antibody Negative (n = 279) Number	Percent
Demographic Factors - Descriptive continued				
First Language as a Child				
English	28	68.29	200	71.94
French	1	2.44	10	3.60
Other	12	29.27	68	24.46
Marital Status				
Previously Married	7	17.07	43	15.41
Never married,	10	24.39	41	14.70
Married, Common Law	24	58.54	195	69.89
Number of Marriages				
None	10	24.39	41	14.70
1	21	51.22	187	67.03
≥ 2	10	24.39	51	18.27
Age at First Marriage				
≤ 24	13	44.83	108	45.76
≥ 25	16	55.17	128	54.24
Age Marriage Ended				
≤ 29	4	40.00	10	43.93
≥ 30	6	60.00	57	56.07

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Socioeconomic				
Highest Grade of School				
≤ 12	27	65.85	170	61.15
≥ 13	14	34.15	108	38.85
Further Education or Training				
Yes	31	75.61	202	72.66
No	10	24.39	76	27.34
Type of Further Education or Training				
No Further Education or Training	10	24.39	78	27.96
Non-University Education or Training Post Primary	3	7.32	14	5.02
Non-University Education Post Secondary	9	21.95	63	22.58
University	19	46.34	124	44.44
Total Number of Years of Education				
≤ 11	11	27.50	79	28.62
12-15	11	27.50	63	22.83
16-18	13	32.50	72	26.09
≥ 19	5	12.50	62	22.46

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Socioeconomic continued				
Household Annual Income				
≤ $16,999	9	24.32	57	20.96
$17,000-29,999	13	35.14	87	31.99
$30,000-39,999	10	27.03	59	21.69
≥ $40,000	5	13.51	69	25.37
Occupation				
Unemployed	4	10.00	19	8.09
Blue Collar	10	25.00	72	30.64
White Collar	4	10.00	39	16.60
Professional	6	15.00	32	13.62
Administrative Professional	16	40.00	73	31.06
Residence				
Residence Status				
Rent	22	53.66	74	26.52
Own	19	46.34	205	73.48
Duration of Residence				
≤ 10 years	37	90.24	213	76.34
≥ 11 years	4	9.76	66	23.66

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	HSV-2 Antibody Negative (n = 279) Number	Percent
Residence continued				
Duration in Toronto				
≤ 10 years	14	34.15	62	22.22
≥ 11 years	27	65.85	217	77.78
Type of Dwelling				
Single Family House	13	33.33	134	49.63
Multiple Family House	14	35.90	108	40.00
Apartment Building	12	30.77	28	10.37
Household Crowding				
Ratio of Rooms/Person in Current Household				
≤ 4.5	22	53.66	131	46.95
≥ 4.6	19	46.34	148	53.05
Ratio of Rooms/Persons in Childhood Household				
≤ 3.5	19	46.34	153	54.84
≥ 3.6	22	53.66	126	45.16

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Contraception				
Ever Used Contraception (Condom)				
Yes	31	75.61	199	72.36
No	10	24.39	76	27.64
Years of Condom Use				
None	10	24.39	78	28.26
1-5	7	17.07	45	16.30
6-9	4	9.76	23	8.33
10	20	48.78	130	47.10
Consistency of Condom Use				
Never	10	24.39	77	28.21
Occasionally	20	48.78	119	43.58
Consistently	11	26.83	77	28.21
Sexual Factors				
Circumcised				
Yes	22	55.00	115	41.67
No	18	45.00	161	58.33

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Health and Illnesses continued				
Illnesses				
Mumps				
Yes	23	57.50	179	67.80
No	17	42.50	85	32.20
Chicken Pox				
Yes	22	56.41	158	59.85
No	17	43.59	106	40.15
Whooping Cough				
Yes	14	35.90	60	22.39
No	25	64.10	208	77.61
Scarlet Fever				
Yes	3	7.32	30	11.07
No	38	92.68	241	88.93
Infectious mononucleosis				
Yes	4	10.00	10	3.58
No	36	90.00	269	96.42

Table C continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Sexual Factors continued				
Number of Sexual Partners in the Year Preceding the Interview				
≤ 1	18	51.43	194	73.48
2	5	14.29	26	9.85
3,4	3	8.57	22	8.33
≥ 5	9	25.71	22	8.33
Number of Sexual Partners in Teenage Years				
≤ 1	9	22.60	125	46.30
2	6	15.00	27	10.00
3,4	7	17.50	63	23.33
5	18	45.00	55	20.37
Number of Sexual Partners during Twenties				
≤ 1	4	10.00	76	29.12
2,3	6	15.00	54	20.69
4-10	14	35.00	72	27.59
≥ 11	16	40.00	59	22.61

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Sexual Factors continued				
Number of Sexual Partners during Thirties				
≤ 1	12	30.77	129	49.24
2,3	5	12.82	47	17.94
4,5	4	10.26	26	9.92
≥ 6	18	46.15	60	22.90
Number of Sexual Partners in Forties				
≤ 1	8	38.10	98	67.12
2,3	5	23.81	21	14.38
4,5	2	9.52	9	6.16
≥ 6	6	28.57	18	12.33
Sexual Intercourse Preceded or Occurred without Marriage				
Yes	37	94.90	240	88.90
No	2	5.10	30	11.10

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Sexual Factors continued				
Sexual Preference				
Heterosexual	38	92.68	273	99.64
Bisexual	1	2.44	0	0.00
Homosexual	2	4.88	1	0.36
Health Factors and Illnesses				
Hernia Operation				
Yes	3	7.32	34	12.23
No	38	92.68	244	87.77
Ever had Cancer				
Yes	0	0.00	1	0.36
No	41	100.00	278	99.64
Illnesses				
Ever had Tuberculosis				
Yes	0	0.00	4	1.45
No	41	100.00	271	98.55
Measles				
Yes	30	78.95	205	78.24
No	8	21.05	57	21.76

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Health and Illnesses continued				
Illnesses				
Mumps				
Yes	23	57.50	179	67.80
No	17	42.50	85	32.20
Chicken Pox				
Yes	22	56.41	158	59.85
No	17	43.59	106	40.15
Whooping Cough				
Yes	14	35.90	60	22.39
No	25	64.10	208	77.61
Scarlet Fever				
Yes	3	7.32	30	11.07
No	38	92.68	241	88.93
Infectious mononucleosis				
Yes	4	10.00	10	3.58
No	36	90.00	269	96.42

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Health and Illnesses continued				
Illnesses				
Viral Meningitis				
Yes	2	4.88	3	1.08
No	39	95.12	275	98.92
Shingles				
Yes	3	7.32	10	3.58
No	38	92.68	269	96.42
Pneumonia				
Yes	7	17.07	69	25.09
No	34	82.93	206	74.91
Other Viral Illness				
Yes	2	4.88	10	3.61
No	39	95.12	267	96.39
Liver Disease (including hepatitis)				
Yes	10	24.39	22	7.91
No	31	75.61	256	92.09

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	HSV-2 Antibody Negative (n = 279) Number	Percent
Health and Illnesses continued				
Illnesses				
Colds and Influenza				
Number of Colds or Flu Each Year: Current				
≤ 1	22	53.66	150	53.76
≥ 2	19	46.34	129	46.24
Number of Colds or Flu Each Year: Teens				
≤ 1	28	68.29	170	60.93
≥ 2	13	31.71	109	39.07
Colds and Influenza				
Number of Colds or Flu Each Year: Twenties				
≤ 1	26	63.41	159	56.99
≥ 2	15	36.59	120	43.01
Symptoms of Infection				
Sore Throat				
Yes	38	92.68	263	94.27
No	3	7.32	16	5.73

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Health and Illnesses continued				
Symptoms of Infection				
Swollen Glands				
Yes	21	51.22	159	56.99
No	20	48.78	120	43.01
Mouth Sores				
Yes	21	51.22	150	53.76
No	20	48.78	129	46.24
Cold Sores				
Yes	23	56.10	149	53.60
No	18	43.90	129	46.40
Frequency of Cold Sores in a Lifetime				
None	18	43.90	129	46.57
1,2	13	31.71	52	18.77
≥ 3	10	24.39	96	34.66
Genital Blisters				
Yes	8	19.51	28	10.04
No	33	80.49	251	89.96

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Health and Illnesses continued				
Symptoms of Infection				
Genital Sores				
Yes	5	12.20	8	2.87
No	36	87.80	271	97.13
Other Genital Problems				
Yes	1	2.44	28	10.04
No	40	97.56	251	89.96
Total Number of Genital Problems				
≤ 1	33	80.50	256	91.80
≥ 2	8	19.50	23	8.20
Lifestyle and General Factors				
Ever Smoked Cigarettes				
Yes	36	87.80	209	75.18
No	5	12.20	69	24.82
Ever taken Vitamins as an Adult				
Yes	28	68.29	180	64.98
No	13	31.71	97	35.02

Table G continued

Variable	HSV-2 Antibody Positive (n = 41) Number	Percent	Negative (n = 279) Number	Percent
Lifestyle and General Factors continued				
Received Blood Transfusion				
Yes	6	15.38	30	11.11
No	33	84.62	240	88.89
Ever Donated Blood				
Yes	25	60.98	164	58.99
No	16	39.02	114	41.01
Ever Participated in a Previous Survey				
Yes	20	48.78	120	43.48
No	21	51.22	155	56.52

Table H

Percentage Distribution of Variables between HSV-2 Seropositive and Seronegative Participants

WOMEN
(n=428)

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Demographic Factors				
Descriptive				
Age at Interview				
≤ 38	23	30.67	107	30.31
39–44	31	41.33	131	37.11
≥ 45	21	28.00	115	32.58
Birthplace				
Canada	52	69.33	200	56.66
Other	23	30.67	153	43.34
Paternal Birthplace				
Canada	37	52.11	142	40.34
Other	34	47.89	210	59.66

* Numbers may vary throughtout the table because of missing information for some of the variables.

** Indicates column percentages.

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Descriptive continued				
First Language as a Child				
English	50	66.67	250	70.81
French	8	10.67	11	3.12
Other	17	22.66	92	26.07
Marital Status				
Previously Married	27	36.00	67	18.98
Never Married	5	6.67	22	6.23
Married, Common Law	43	57.33	264	74.79
Number of marriages				
None	5	6.67	22	6.23
1	48	64.00	287	81.30
≥ 2	22	29.33	44	12.47
Age First Marriage				
≤ 21	41	59.42	153	46.50
≥ 22	28	40.58	176	53.50
Age Marriage Ended				
≤ 29	4	17.39	11	16.92
≥ 30	19	82.61	54	83.08

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Reproductive Factors				
Age at Menarche				
≤ 12	33	45.21	140	39.66
≥ 13	40	54.79	213	60.34
Menopause Status				
Still Menstruating	50	67.57	287	81.30
Ceased Menstruating	24	32.43	66	18.70
Ever Pregnant				
Yes	63	84.00	308	87.50
No	12	16.00	44	12.50
Total Number of Pregnancies				
None	12	16.00	45	12.75
1, 2	24	32.00	133	37.68
≥ 3	39	52.00	175	49.57
Number of Live Births				
None	2	3.17	14	4.55
1	16	25.40	48	15.58
≥ 2	45	71.43	246	79.87

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Socioeconomic				
Highest Grade of School				
$\leq$ 11	47	62.67	146	41.36
$\geq$ 12	28	37.33	207	58.64
Further Education or Training				
Yes	37	49.33	223	63.17
No	38	50.67	130	36.83
Type of Further Education or Training				
No Further Education	38	50.67	131	37.11
Non-University Education or Training Post Primary	2	2.67	8	2.27
Non-University Education or Training Post Secondary	19	25.33	122	34.56
University	16	21.33	92	26.06
Total Number of Years of Education				
$\leq$ 9	23	30.67	62	17.66
10-12	23	30.67	89	25.36
13-15	10	13.33	87	24.79
$\geq$ 16	19	25.33	133	32.19

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Socioeconomic continued				
Household Annual Income				
≤ $8,999	27	38.03	38	11.08
$9,000-24,999	29	40.85	149	43.44
$25,000-34,999	6	8.45	74	21.57
≥ $35,000	9	12.68	82	23.91
Occupation				
Unemployed	34	45.33	135	39.71
Blue Collar	16	21.33	66	19.41
White Collar	9	12.00	41	12.06
Professional	7	9.33	56	16.47
Administrative Professional	9	12.00	42	12.35
Residence				
Residence Status				
Rent	46	61.33	87	24.65
Own	29	38.67	266	75.35
Duration of Residence				
≤ 10 Years	54	72.00	227	64.31
≥ 11 Years	21	28.00	126	35.69

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Residence continued				
Duration in Toronto				
≤ 10 Years	12	16.00	67	18.98
≥ 11 Years	63	84.00	286	81.02
Type of Dwelling				
Single Family House	15	20.27	178	51.75
Multiple Family House	35	47.30	118	34.30
Apartment Building	24	32.43	48	13.95
Household Crowding				
Ratio of Rooms/Persons in Current Household				
≤ 4.5	51	68.00	168	47.59
≥ 4.6	24	32.00	185	52.41
Ratio of Rooms/Persons in Childhood Household				
≤ 3.5	42	56.00	197	55.81
≥ 3.6	33	44.00	156	44.19
Contraception				
Ever Used Contraception				
Yes	57	76.00	276	79.31
No	18	24.00	72	20.69

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Contraception continued				
Years of Condom Use				
None	42	56.00	170	49.28
1-5	18	24.00	73	21.16
6-9	7	9.33	29	8.41
≥ 10	8	10.67	73	21.16
Consistency of Condom Use				
Never	41	54.67	170	49.28
Occasionally	22	29.33	103	29.86
Consistently	12	16.00	72	20.86
Years of Diaphragm Use				
None	59	78.67	246	70.69
1-5	12	16.00	50	14.37
6-9	2	2.67	20	5.75
≥ 10	2	2.67	32	9.20
Years of IUD Use				
None	60	80.0	277	79.8
1-5	11	14.7	46	13.3
6-9	2	2.7	17	5.2
≥ 10	2	2.7	6	1.7

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Contraception continued				
Years of Oral Contraceptive Use				
None	28	37.33	135	38.79
1-5	21	28.00	115	33.05
6-9	7	9.33	57	16.38
≥ 10	19	25.33	41	11.78
Sexual Factors				
Ever had Sexual Intercourse				
Yes	75	100.00	348	98.58
No	0	0.00	5	1.42
Age at First Intercourse				
≤ 17	24	32.43	72	20.81
18-19	27	36.49	78	22.54
20-22	11	14.86	105	30.35
≥ 23	12	16.22	91	26.3

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	HSV-2 Antibody Negative (n = 353)* Number	Percent
Sexual Factors continued				
Total Number of Sexual Partners in a Lifetime				
≤ 1	16	22.86	161	48.06
2-3	16	22.86	65	19.40
4-6	15	21.43	47	14.03
≥ 7	23	32.86	62	18.51
Number of Sexual Partners in the Year Preceding the Interview				
0	12	16.22	24	7.00
1	52	70.27	288	83.97
2	7	9.46	20	5.83
≥ 3	3	4.05	11	3.21
Number of Sexual Partners in Teenage Years				
0	26	35.14	198	57.23
1	25	33.78	108	31.21
2	8	10.81	26	7.51
≥ 3	15	20.27	14	4.05

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Sexual Factors continued				
Number of Sexual Partners in Twenties				
≤ 1	38	50.67	243	70.23
2	12	16.00	37	10.69
3	8	10.67	28	8.09
≥ 4	17	22.67	38	10.98
Number of Sexual Partners in Thirties				
≤ 1	45	61.64	258	75.22
2	10	13.70	30	8.75
3,4	7	9.59	27	7.87
≥ 5	11	15.07	28	8.16
Number of Sexual Partners in Forties				
≤ 1	35	83.33	176	82.24
2	3	7.14	20	9.35
3,4	2	4.76	10	4.67
≥ 5	2	4.76	8	3.74

Table H continued

Variable	HSV-2 Antibody			
	Positive (n = 75)*		Negative (n = 353)*	
	Number	Percent**	Number	Percent
Sexual Factors continued				
Sexual Intercourse Preceded or Occurred without Marriage				
Yes	48	65.80	180	52.00
No	25	34.20	166	48.00
Unmarried Pregnancy				
Yes	8	12.90	32	10.40
No	54	87.10	275	89.60
Sexual Preference				
Heterosexual	74	98.67	346	100.00
Bisexual	0	0.00	0	0.00
Homosexual	1	1.33	0	0.00
Health Factors and Illnesses				
Hysterectomy				
Yes	19	25.33	39	11.05
No	56	74.67	314	88.95
Ever Had Cancer				
Yes	7	9.33	10	2.83
No	68	90.67	343	97.17

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Health and Illnesses continued				
Cancer Site				
Breast	0	0.00	3	30.00
Cervix	6	85.71	1	10.00
Uterus	1	14.29	3	30.00
Skin	0	0.00	2	20.00
Endocrine	0	0.00	1	10.00
Illnesses				
Ever had Tuberculosis				
Yes	2	2.70	13	3.70
No	72	97.30	338	96.30
Measles				
Yes	63	87.50	288	87.01
No	9	12.50	43	12.99
Mumps				
Yes	43	60.56	207	60.70
No	28	39.44	134	39.30
Chicken Pox				
Yes	56	76.71	231	70.64
No	17	23.29	96	29.36

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	HSV-2 Antibody Negative (n = 353)* Number	Percent
Health and Illnesses continued				
Illnesses				
Whooping Cough				
Yes	25	34.72	100	29.85
No	47	65.28	235	70.15
Scarlet Fever				
Yes	12	16.22	36	10.34
No	62	83.78	312	89.66
Infectious Mononucleosis				
Yes	10	13.51	23	6.53
No	64	86.49	329	93.47
Viral Meningitis				
Yes	2	2.67	3	0.87
No	73	97.33	349	99.13
Shingles				
Yes	3	4.05	16	4.53
No	71	95.95	337	95.47
Pneumonia				
Yes	26	34.67	81	23.08
No	49	65.33	270	76.92

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Health and Illnesses continued				
Illnesses				
Other Viral Illness				
Yes	4	5.33	6	1.73
No	71	94.67	341	98.27
Liver Disease (Including Hepatitis)				
Yes	11	14.67	32	9.07
No	64	85.33	321	90.93
Colds and Influenza				
Number of Colds or Flu Each Year: Current				
$\leq$ 1	42	56.00	214	60.62
$\geq$ 2	33	44.00	139	39.38
Number of Colds or Flu Each Year: Teens				
$\leq$ 1	51	68.00	203	57.51
$\geq$ 2	24	32.00	150	42.49
Number of Colds or Flu Each Year: Twenties				
$\leq$ 1	44	58.67	185	52.41
$\geq$ 2	31	41.33	168	47.59

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	HSV-2 Antibody Negative (n = 353)* Number	Percent
Health and Illnesses continued				
Symptoms of Infection				
Sore Throat				
Yes	74	98.67	344	97.45
No	1	1.33	9	2.55
Swollen Glands				
Yes	45	60.81	207	58.64
No	29	39.19	146	41.36
Mouth Sores				
Yes	33	44.00	177	50.14
No	42	56.00	176	49.86
Cold Sores				
Yes	39	52.00	180	50.99
No	36	48.00	173	49.01
Frequency of Cold Sores in a Lifetime				
None	36	48.00	173	49.01
1, 2	12	16.00	66	18.70
$\geq$ 3	27	36.00	114	32.29

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	HSV-2 Antibody Negative (n = 353)* Number	Percent
Health and Illnesses continued				
Symptoms of Infection				
Genital Blisters				
Yes	10	13.33	25	7.08
No	65	86.67	328	92.92
Genital Sores				
Yes	3	4.00	11	3.12
No	72	96.00	342	96.88
Other Genital Problems				
Yes	12	16.00	59	16.71
No	63	84.00	294	83.29
Total Number of Genital Problems				
1	15	20.30	47	13.50
≥ 2	59	79.70	301	86.50
Lifestyle and General Factors				
Ever Smoked Cigarettes				
Yes	54	72.00	237	67.14
No	21	28.00	116	32.86

Table H continued

Variable	HSV-2 Antibody Positive (n = 75)* Number	Percent**	Negative (n = 353)* Number	Percent
Lifestyle and General Factors continued				
Ever Taken Vitamins as an Adult				
Yes	39	52.00	217	61.47
No	36	48.00	136	38.58
Received Blood Transfusion				
Yes	30	40.54	84	24.28
No	44	59.46	262	75.72
Ever Donated Blood				
Yes	21	28.00	143	40.74
No	54	72.00	208	59.26
Ever Partiċipated in a Previous Survey				
Yes	31	41.33	173	49.43
No	44	58.67	177	50.57

Table I

Percentage Distribution Tables for Participants with Complete Information for all Variables

MEN

Variable	HSV-2 Antibody			
	Positive		Negative	
	Number	Percent	Number	Percent
a) Variables Maintained in the Logistic Models				
Age at Interview				
≤ 38	11	33.33	90	36.14
39-44	13	39.39	87	34.94
≥ 45	9	27.27	72	28.92
Total Number of Sexual Partners in a Lifetime				
≤ 9	8	24.24	126	50.60
≥10	25	75.76	123	49.40
Age at First Intercourse				
≤ 17	23	69.70	114	45.78
≥ 18	10	30.30	135	54.22
Years of Condom Use				
≤ 9	15	45.45	131	52.61
≥ 10	18	54.55	118	47.39
Total Number of Years of Education				
≤ 15	16	48.48	128	51.41
≥ 16	17	51.52	121	48.59

Table I continued

Variable	HSV-2 Antibody			
	Positive		Negative	
	Number	Percent	Number	Percent
Residence Status				
Rent	17	51.52	66	26.51
Own	16	48.48	183	73.49
Marital Status				
Unmarried	19	57.58	89	35.74
Married	14	42.42	160	64.26
Duration of Residence				
≤ 10	29	87.88	192	77.11
≥ 11	4	12.12	57	22.89
Duration in Toronto				
≤ 10	10	30.30	57	22.89
≥ 11	23	69.70	192	77.11
Household Crowding Ratio of Rooms/ Persons in Current Household				
≤ 4.5	16	48.48	116	46.59
≥ 4.5	17	51.52	133	53.41

Table I continued

Variable	HSV-2 Antibody			
	Positive		Negative	
	Number	Percent	Number	Percent
b) Additional Variables				
Type of Education				
None & Non-University	17	51.52	134	53.82
University	16	48.48	115	46.18
Household Annual Income				
≤ $29,999	17	54.84	125	51.23
≥ $30,000	14	45.16	119	48.77
Type of Dwelling				
Apartment	9	28.13	26	10.70
House	23	71.88	217	89.30

Table J

Percentage Distribution Tables for Participants
with Complete Information for all Variables

WOMEN

Variable	HSV-2 Antibody			
	Positive		Negative	
	Number	Percent	Number	Percent
a) Variables Maintained in the Logistic Models				
Age at Interview				
≤ 38	20	28.99	19	29.94
39-44	30	43.48	121	37.35
≥ 45	19	27.54	106	32.72
Total Number of Sexual Partners in a Lifetime				
≤ 1	15	21.74	157	48.46
≥ 2	54	78.26	167	51.54
Age at First Intercourse				
≤ 19	49	71.01	142	43.83
≥ 20	20	28.99	182	56.17
Years of Condom Use				
≤ 9	63	91.30	254	78.40
≥ 10	6	8.70	70	21.60
Years of Oral Contraceptive Use				
≤ 9	51	73.91	258	87.96
≥ 10	18	26.09	39	12.04

Table J continued

Variable	HSV-2 Antibody			
	Positive		Negative	
	Number	Percent	Number	Percent
Total Number of Years of Education				
$\leq$ 12	42	60.87	138	42.59
$\geq$ 13	27	39.13	186	57.41
Residence Status				
Rent	42	60.87	75	23.15
Own	27	39.13	249	76.85
Marital Status				
Unmarried	33	47.83	88	27.16
Married	36	52.17	236	72.84
Duration of Residence				
$\leq$ 10	50	72.46	203	62.65
$\geq$ 11	19	27.54	121	37.35
Duration in Toronto				
$\leq$ 10	10	14.49	62	19.14
$\geq$ 11	59	85.51	262	80.86
Household Crowding Ratio of Rooms/ Persons in Current Household				
$\leq$ 4:5	48	69.57	154	47.53
$\geq$ 4.6	21	30.43	170	52.47

Table J continued

Variable	HSV-2 Antibody Positive Number	Positive Percent	Negative Number	Negative Percent
Hysterectomy Status				
Yes	19	27.54	36	11.11
No	50	72.46	288	88.89
Received Blood Transfusion				
Yes	28	40.58	82	25.31
No	41	59.42	242	74.69
Birthplace				
Canada	48	69.57	188	58.02
Other	21	30.43	136	41.98
b) Additional Variables				
Type of Education or Training				
None & Non-University	55	79.71	237	43.15
University	14	20.29	87	26.85
Household Annual Income				
≤ $24,999	52	78.79	174	54.04
≥ $25,000	14	21.21	148	45.96
Type of Dwelling				
Apartment	22	31.88	41	12.69
House	47	68.12	282	87.31

Table K
Comparison of Adjusted Odds Ratios
Basic Model and Single Entry Models
Men
(n=282)

Variable[1]	Basic	1	2	3	4	5	6
Number of Sexual Partners in a Lifetime							
≥ 10	2.63*	2.63*	2.41	2.13	2.36	2.56*	2.67*
Age at First Intercourse							
≤ 17	2.08	2.35*	1.79	2.15	2.12	2.12	2.06
Condom							
≤ 9	0.90	0.95	0.78	0.82	0.89	0.88	0.87
Years of Education							
≤ 15		0.66					
Residence Status							
Rent			2.45				
Marital Status							
Unmarried				2.08			
Duration of Residence							
≤ 10 years					1.71		
Duration in Toronto							
≤ 10 years						1.51	
Houshold Crowding							
≤ 4.5 Rooms/Person							1.18

1 Age at interview included   * $P < 0.05$

Table L

Logistic Regression Results Basic Model:
Primary Variables

Men
(n=282)

Variable[1]	Beta	S.E.	$\left(\frac{\beta}{S.E._{\beta}}\right)^2$	Odds Ratio	95% Confidence Interval	P Value
Number of Sexual Partners in a Lifetime $\geq$ 10	0.9670	0.4482	4.66	2.63	(1.09, 6.33)	0.0310
Age at First Intercourse $\leq$ 17	0.7299	0.4172	3.06	2.08	(0.92, 4.70)	0.0802
Years of Condom Use $\leq$ 9	-0.1071	0.3836	0.08	0.90	(0.42, 1.91)	0.7800

1 Age at interview included

Table M
Comparison of Adjusted Odds Ratios
Basic Model and Single Entry Models
Women
(n=393)

Variable[1]	Basic	1	2	3	4	5	6	7	8	9
Number of Sexual Partners in a Lifetime										
≥ 2	2.43**	2.82**	2.22**	1.95	2.33*	2.48**	2.81**	2.47**	2.61**	2.33*
Age at First Intercourse										
≤ 19	2.43**	1.88*	2.16*	2.48**	2.53**	2.39**	2.14*	2.35**	2.20**	2.43**
Condom										
≤ 9	2.99*	2.81*	2.61*	3.01*	2.97*	2.92*	3.08*	3.22*	2.91*	3.04*
Oral Contraceptive										
≥ 10	2.31*	2.54**	2.60**	2.30*	2.27*	2.32*	2.62**	3.05**	2.52**	2.32*
Years of Education										
≤ 12		2.23*								
Residence Status										
Rent			4.50**							
Marital Status										
Unmarried				1.69						
Duration of Residence										
≤ 10 years					1.46					
Duration in Toronto										
≤ 10 years						0.71				
Household Crowding										
≤ 4.5 Rooms/Person							2.79**			
Hysterectomy Status										
Yes								3.98**		
Blood Transfusion										
Yes									2.00	
Birthplace										
Canada										1.48

1 Age at interview included
* $P \leq 0.05$
** $P \leq 0.01$

TABLE N
Comparison of Adjusted Odds Ratios
Basic Model including Years of Education and Single Entry Models
WOMEN

Variable[1]	Basic + Education	Residence Status	Marital Status	Duration in Residence	Duration in Toronto	Household Crowding	Hyster-ectomy	Blood Transfusion	Birth-place
Total Number of Sexual Partners in a Lifetime	2.82**	2.32*	2.05*	2.49**	2.63**	2.85**	2.60**	2.99**	2.52**
Age at First Intercourse	1.88*	1.86	1.99*	2.00*	1.93*	1.88*	1.92*	1.72	1.94*
Years of Condom Use	2.81*	2.10	2.38*	2.35	2.41*	2.45*	2.52*	2.70**	2.44**
Years of Oral Contraceptive Use	2.54**	2.72*	2.39*	2.41*	2.43**	2.65**	3.14**	2.72**	2.44**
Total Years of Education	2.23*	1.89	2.33**	2.56**	2.36**	1.85	2.27**	2.14*	2.28**
Residence Status		4.40**	-	-	-	-	-	-	-
Marital Status			1.81	-	-	-	-	-	-
Duration in Residence				1.78	-	-	-	-	-
Duration in Toronto					0.99	-	-	-	-
Household Crowding						2.51**	-	-	-
Hysterectomy							3.71**	-	-
Received a Blood Transfusion								1.91*	-
Birthplace									1.31

1 Age at interview included * P · 0.05 ** P · 0.01

Table 0

Logistic Regression Results Basic Model:
Primary Variables

Women
(n=393)

Variable[1]	Beta	$S.E._{\beta}$	$\left(\frac{\beta}{S.E._{\beta}}\right)^2$	Odds Ratio	95% Confidence Interval	P Value
Number of Sexual Partners in a Lifetime ≥ 2	0.8899	0.3298	7.28	2.43	(1.28, 4.64)	0.0070
Age at First Intercourse ≤ 19	0.8913	0.3034	8.63	2.43	(1.35, 4.42)	0.0032
Years of Condom Use ≤ 9	1.0969	0.4621	5.64	2.99	(1.21, 7.41)	0.0176
Years of Oral Contraceptive Use ≥ 10	0.8394	0.3439	5.96	2.31	(1.18, 4.54)	0.0146

[1] Age at interview included

TABLE P
Comparison of Adjusted Odds Ratios
Original Full Model, Type of Education, Years of Education

MEN
(n=282)

Variable[1]	Original	Type of Education Substituted for Years of Education	Both Type of Education and Years of Education
Total Number of Sexual Partners in a Lifetime ≥ 10	2.09	1.75	2.10
Age at First Intercourse ≤ 17	2.24	2.37	2.26
Years of Condom Use ≤ 9	0.76	0.83	1.31
Total Years of Education ≤ 15	0.58	-	0.61
Residence Status Rent	2.32	2.34	2.33
Marital Status Unmarried	1.61	1.56	1.62
Duration of Residence ≤ 10	1.11	1.10	1.09
Duration in Toronto ≤ 10	1.33	1.58	1.31
Household Crowding 4.5 Rooms/Person	0.99	0.89	0.99
Type of Education Non-University	-	0.63	0.92

1 Age at interview included

TABLE Q
Comparison of Adjusted Odds Ratios
Original Full Model, Household Annual Income, Years of Education

MEN
(n=275)

Variable[1]	Original	Household Annual Income Substituted for Years of Education	Both Household Annual Income & Years of Education
Total Number of Sexual Partners in a Lifetime ≥ 10	2.25	1.87	2.34
Age at First Intercourse ≤ 17	2.07	1.98	2.11
Years of Condom Use ≤ 9	2.77	0.78	0.74
Total Years of Education ≤ 15	0.55	-	0.48
Residence Status Rent	1.93	1.78	1.80
Marital Status Unmarried	1.63	1.54	1.56
Duration of Residence ≤ 10	1.36	1.49	1.43
Duration in Toronto ≤ 10	1.37	1.52	1.43
Household Crowding ≤ 4.5 Rooms/Person	1.07	0.87	1.03
Household Annual Income ≤ $29,999	-	1.25	1.50

1 Age at interview included

TABLE R
Comparison of Adjusted Odds Ratios
Original Full Model, Type of Dwelling, Residence Status

MEN
(n=275)

Variable[1]	Original	Type of Dwelling Substituted for Years of Education	Both Type of Dwelling & Years of Education
Total Number of Sexual Partners in a Lifetime $\geq$ 10	2.07	1.99	2.04
Age at First Intercourse $\leq$ 17	2.81	2.20	2.12
Years of Condom Use $\leq$ 9	0.83	0.86	0.83
Total Years of Education $\leq$ 15	0.55	0.63	0.56
Residence Status Rent	2.17	–	1.86
Marital Status Unmarried	1.55	1.62	1.48
Duration of Residence $\leq$ 10	1.15	1.27	1.09
Duration in Toronto $\leq$ 10	1.35	1.47	1.44
Household Crowding $\leq$ 4.5 Rooms/Person	1.11	0.94	0.91
Type of Dwelling Apartment	–	2.38	1.80

1 Age at interview included

TABLE 5
Comparison of Adjusted Odds Ratios
Original Full Model, Type of Education, Years of Education

WOMEN
(n=393)

Variable[1]	Original	Type of Education Substituted for Years of Education	Both Type of Education and Years of Education
Total Number of Sexual Partners in a Lifetime ≥ 2	2.56*	2.41*	2.49*
Age at First Intercourse ≤19	1.80	2.04*	1.83
Years of Condom Use ≤9	2.40	2.54	2.38
Years of Oral Contraceptive Use ≤10	3.44**	3.29**	3.44**
Total Years of Education ≤12	1.68	-	1.88
Residence Status Rent	3.38**	3.42**	3.49**
Marital Status Unmarried	0.99	0.97	1.02
Duration of Residence ≤10	1.26	1.19	1.24
Duration in Toronto ≤10	0.65	1.37	0.61
Household Crowding ≤4.5 Rooms/Person	1.16	1.30	1.16
Hysterectomy Yes	2.93**	2.93**	2.88**
Received a Blood Transfusion	1.20	1.21	1.21
Birthplace Canada	0.94	1.03	0.93
Type of Education Non-University	-	1.00	0.73

1 Age at interview included
* $P < 0.05$
** $P \leq 0.01$

TABLE T
Comparison of Adjusted Odds Ratios
Original Full Model, Household Annual Income, Years of Education
WOMEN
(n=380)

Variable[1]	Original	Household Annual Income Substituted for Years of Education	Both Household Annual Income & Years of Education
Total Number of Sexual Partners in a Lifetime ≥ 2	2.17*	2.10	2.13
Age at First Intercourse ≤ 19	1.95	2.15*	2.10
Years of Condom Use ≤ 9	2.32	2.20	2.19
Years of Oral Contraceptive Use ≤ 10	3.37**	3.57**	3.59**
Total Years of Education ≤ 12	1.42	-	1.10
Residence Status Rent	3.13*	2.79*	2.81*
Marital Status Unmarried	1.09	0.91	0.92
Duration of Residence ≤ 10	1.20	1.28	1.29
Duration in Toronto ≤ 10	0.69	0.73	0.73
Household Crowding ≤ 4.5 Rooms/Person	1.38	1.32	1.30
Hysterectomy Yes	2.98**	2.99**	3.00**
Received a Blood Transfusion	1.16	1.15	1.16
Birthplace Canada	1.04	1.16	1.13
Household Annual Income $\leq$\$24,999	-	2.13	2.06

1 Age at interview included
* $P \leq 0.05$
** $P \leq 0.01$

TABLE U
Comparison of Adjusted Odds Ratios
Original Full Model, Type of Dwelling, Residence Status
WOMEN
(n=383)

Variable[1]	Original	Type of Dwelling Substituted for Residence Status	Both Type of Dwelling & Residence Status
Total Number of Sexual Partners in a Lifetime ≥ 2	2.42*	2.37*	2.36*
Age at First Intercourse ≤19	1.79	1.98*	1.85
Years of Condom Use ≤9	2.39	2.64*	2.41
Years of Oral Contraceptive Use ≤10	3.27**	3.28**	3.27**
Total Years of Education ≤12	1.70	1.79	1.74
Residence Status Rent	3.35**	-	3.06**
Marital Status Unmarried	1.09	1.17	1.08
Duration of Residence ≤10	1.31	1.61	1.34
Duration in Toronto ≤10	0.64	0.65	0.64
Household Crowding ≤4.5 Rooms/Person	1.15	1.70	1.10
Hysterectomy Yes	2.69*	2.69*	2.63**
Received a Blood Transfusion	1.22	1.29	1.22
Birthplace Canada	0.96	1.12	0.97
Type of Dwelling Apartment	-	2.00	1.28

1 Age at interview included
* $P \leq 0.05$
** $P \leq 0.01$

THE UNIVERSITY OF WESTERN ONTARIO

DEPARTMENT OF EPIDEMIOLOGY AND PREVENTIVE MEDICINE

C O N F I D E N T I A L

SAMPLE SIZE CALCULATION

Based upon estimates from Adam et al 1973b

Number of Sexual Partners and HSV-2 Antibody

Caucasian and Negro Control Patients Combined

Number of Sexual Partners	Number Tested	% HSV-2 Positive
Few	128	34
Many	154	44

$\alpha = 0.05$ (two sided) $\quad Z_\alpha = 1.96$

$\beta = 0.20 \quad Z_\beta = 0.84$

Proportion without trait but with HSV-2 antibody $0.34 = P_1$

Proportion with trait and with HSV-2 antibody $0.44 = P_2$

$$n = \frac{\left[Z_\alpha\sqrt{2\bar{p}\bar{q}} + Z_\beta\sqrt{P_1(1-P_1) + P_2(1-P_2)}\right]^2}{(P_1 - P_2)^2}$$

where $\bar{P} = \dfrac{P_1 + P_2}{2} \qquad \bar{q} = 1-\bar{P}$ Schlesselman 1974

$$\bar{P} = \frac{0.34 + 0.44}{2} = 0.39 \qquad \bar{q} = 1 - 0.39 = 0.61$$

$$N = \frac{\left[1.96\sqrt{2 \times 0.39 \times 0.61} + 0.84\sqrt{0.34 \times (1-0.34) + 0.44(1-0.44)}\right]^2}{(0.34 - 0.44)^2}$$

$$= \frac{(1.96 \times 0.6898 + 0.84 \times 0.6861)^2}{(-0.1)^2}$$

$$= \frac{(1.352 + 0.576)^2}{0.01}$$

$$= \frac{(1.928)^2}{0.01}$$

$$= \frac{3.717}{0.01}$$

$$= 371.7$$

$$\simeq 372 \text{ in each group}$$

∴ A total of 744 participants required

POWER CALCULATION

$$Z_\beta = \frac{\sqrt{N_1 N_0 (P_1 - P_0)^2} - Z\alpha \sqrt{(N_1 + N_0)\bar{p}\bar{q}}}{\sqrt{N_0 P_1 q_1 + N_1 P_0 q_0}}$$

Z_β. This is then found in the Table of Normal Distribution $1-\beta$.

Power $= 1 - \beta = P(Z \leq Z\beta)$

$\alpha = 0.05$ (two sided) ⟶ $Z\alpha = 1.96$ = desired level of significance

$$P_0 = \frac{1}{1 + \frac{q_0}{P_0(R)}}$$

$q_1 = 1 - P_1$

$$\bar{P} = \frac{N_1 P_1 + N_0 P_0}{N_1 + N_0}$$

$\bar{q} = 1 - \bar{P}$

N_1 = Number with the outcome (HSV-2 antibody)

N_0 = Number without the outcome

P_1 = Proportion with the trait (regardless of the outcome)

e.g., $\geq$ age 41

R = "population" theoretical Relative Risk

Schlesselman (1982)

APPENDIX VIII

QUESTIONNAIRE AND CONSENT FORMS

THE UNIVERSITY OF WESTERN ONTARIO

DEPARTMENT OF EPIDEMIOLOGY AND PREVENTIVE MEDICINE

C O N F I D E N T I A L

Subject Code No. ____________

MALE ONLY

MALE

10. Have you ever had an operation to correct a hernia?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

a) When was this? ____________ year

(Note If respondent states age, work out year with him.)

b) Why was this done?

____

11. Have you ever been circumcised?

Yes	☐
No	☐
Don't know	☐
N.A.	☐

12. ARE YOU PRESENTLY MARRIED ?

YES ☐

NO ☐ → GO TO QUESTION 14

Interview Code

Subject Code Number

Time Interview Began

Gender M F

Time

Date of Interview

Date

day month year

Sampling Schedule Assignments

EC	CT	E.A.	Target Dwelling

Subject's Address

Interview Occurrence.

1. Immediate
2. Appointment

Subject Code No. ________________ 2

Residence

1. How long have you lived in this home?

Less than 1 year	1	☐
1 year - less than 2 years	2	☐
2 years - less than 5 years	3	☐
5 years - less than 10 years	4	☐
10 years - less than 20 years	5	☐
20 years +	6	☐
Don't know	8	☐
N.A	9	☐

☐

1a. Do you rent or own this (house, apartment)?

Rent	1	☐
Own	2	☐
Don't know	8	☐
N.A.	9	☐

☐

Subject Code No. ____________

2 How many years have you lived in Toronto?

Less than 1 year	1	☐
1 year - less than 2 years	2	☐
2 years - less than 5 years	3	☐
5 years - less than 10 years	4	☐
10 years - less than 20 years	5	☐
20 years +	6	☐
Don't know	8	☐
N.A.	9	☐

Birthplace

3. In what country were you born? ____________

(If Canada, GO TO Q._4)

a) When did you come to Canada? ____________

No. of years

4. In what country was your father born? ____________

5. What language did you first speak as a child? ____________

Birthdate:

6. When were you born? ____ ____ ____
day month year

Day

Month

Year

a) That makes you how old now? ____
age

Religion:

7. What was your religion when you were a child? ____________

Subject Code No. ____________ 4.

Health.

There are a number of health problems that I would like to ask you about.

8. Have you ever had tuberculosis?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

9. Have you ever had cancer?

Yes	1	☐
No	2	☐ — GO TO Q. 10
Don't know	8	☐
N.A.	9	☐

a) What part of your body did it affect?

____

(Note: Respondent may state type of cancer, e.g. Leukemia, etc. Write out response. Probe until general area of body or cancer type specified)

b) When was this? ________ year

(If age given, work out year with respondent: e.g., "if you were ____ years old, that would have been 19__?")

Subject Code No. ______________

MALE ONLY

MALE

10. Have you ever had an operation to correct a hernia?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

a) When was this? ______________ year

(Note If respondent states age, work out year with him.)

b) Why was this done?

____

11. Have you ever been circumcised?

Yes	☐
No	☐
Don't know	☐
N.A.	☐

12 ARE YOU PRESENTLY MARRIED?

YES ☐

NO ☐ → GO TO QUESTION 14

Subject Code No. ______________ FEMALE ONLY

10 Have you ever had an operation to remove your uterus? (Prompt. "A Hysterectomy?")

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

a) When was this? ____________
year

(Note: If respondent states age, work out year with her)

b) Why was this done?

____

Menstrual History:

We would like to know about your menstrual periods.

11. How old were you when your menstrual periods began?

____
Age

a) When was your last period? ______ ______ ______ We would like to know exactly when your last period began.
day month year

If Periods Have Stopped

Less than 2 months ago	1	☐
2-6 months ago	2	☐
7 months ago	3	☐
Don't know	8	☐
N.A.	9	☐

(Interviewer prompt: if there is trouble remembering, suggest: "More than 1 year ago", less than 6 months ago?, etc.")

Subject Code No. ___________

FEMALE ONLY

Offspring

Now I would like to ask you about pregnancies that you may have had and the health of the children. (PROMPT IF NECESSARY: "The number of pregnancies a woman may have and the health of the children may affect illnesses related to viruses in other family members.") We are interested in all pregnancies whatever the outcome. This would include miscarriages, stillbirths, abortions, as well as full term pregnancies.

12. Have you ever been pregnant?

Yes	1	☐	
No	2	☐	GO TO Q. 14
Don't know	8	☐	
N.A.	9	☐	

☐

13 Starting with your first pregnancy

(FOR EACH PREGNANCY) (USE CHART)

a) How old were you when the (first) pregnancy ended?

b) How did it end? Was it full-term, premature birth, still-birth, miscarriage or abortion?

c) How long was the pregnancy? (Or how long did you carry the child?)

(For each ~~live~~ BIRTH)

d) On the whole, how was the health of this baby as a tiny baby? (up until it was 1 month old)

GOOD	1	☐	
NOT GOOD	2	☐	GO TO i)
Don't know	8	☐	
N.A.	9	☐	

☐

i) If no, what was the problem?

Subject Code No. ____________

e) On the whole, how was the health of this baby as a small child?

(up until age 5)

GOOD	1	
NOT GOOD	2	GO TO i)
Don't know	8	
N.A.	9	

i) If no, what was the problem?

After each pregnancy:

"How old were you when your next pregnancy ended?"

NOTE: If the respondent appears not to fully understand about our interest in all pregnancies or becomes confused in remembering, ask the pregnancies in this way:

"How old were you when your first baby was born?"

e.g. 1st
2nd
3rd pregnancy
etc.

Then:

"Did you have any other pregnancies such as miscarriages, stillbirths, abortions..., premature births...?"

Record each in turn.

Subject Code No. ______________

Question 13

Pregnancies, Health of Children

	a	b	c	d	d_1	e	e_1
	Age	Outcome	Length of Preg. in Months	Health of Baby	Problem	Health of Child	Problem
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							

Subject Code No. ______________

CODES FOR PREGNANCIES, HEALTH OF CHILDREN

Question 13

a) Age in years

b) Outcomes:

1 = live birth
2 = stillbirth
3 = miscarriage
4 = abortion
8 = don't know
9 = N.A.

c) Length of pregnancy in total months

d) Health of baby (child)

e) 1 = yes
2 = no
8 = don't know
9 = N.A.

Summary:

Pregnancies

- Age, 1st pregnancy ended
- Age, list live birth
- Total live births
- Total stillbirths
- Total miscarriages
- Total abortions
- Total pregnancies
- Age last pregnancy

Health of Children

- Total babies, ill health
- Total babies, ill health apparently due to non-viral conditions
- Total babies, ill health due to potentially viral disease
- Total babies, ill health due to encephalitis, meningitis, or virus specified
- Total children, ill health
- Total children, ill health apparently due to non-viral conditions
- Total children, ill health due to potentially viral disease
- Total children, ill health due to encephalitis, meningitis, or virus specified

Subject Code No. ____________ 10.

Viral Illness

14. We are interested in knowing about any illnesses that you have had that may have been caused by viruses.

(FOR EACH)

a) Have you ever had ____________?

b) How old were you when you first had ____________?
(Probe: "Younger than age 10, older than age 10?")

c) Since the first time you had (first episode) ____________, how frequently have you had this?
(Probe: "Ever again, once each year, etc.")

(RECORD TOTAL NUMBER, INCLUDING FIRST EPISODE, IN LIFE SO FAR. BE SURE THAT RESPONDENT STATES TIMES IN LIFE, NOT TIMES PER YEAR)

If other than Never:

d) How old were you the last time you had ____________?
(RECORD AS MOST RECENT EPISODE)

e) In all, how many times in your life have you had this?

Subject Code No. ______________ 11.

Question 14
Viral Illnesses

	a	b	c	d
	Ever had	Age at first episode	Frequency (incl. 1st episode)	Age at most recent episode
1. Red Measles				
2. German Measles				
3. Mumps				
4. Chicken Pox				
5. Whooping Cough				
6. Scarlet Fever				
7. Infectious Mononucleosis				
8. Liver Disease, such as hepatitis				
9. Viral Meningitis or Encephalitis				
10. Shingles				
11. Pneumonia				
12. Polio				
13. Other				
14. Other				

Subject Code No. _______________ 17.

Colds, Influenza:

Colds and influenza may be caused by viruses.

We would like to know about how often you may have had colds, influenza or flu.

The common cold - (define as runny nose, stuffy nose, sneezing, and sometimes sore throat or coughing).

15. At present (say, think of the past 3-4 years)

How often do you have a common cold?

Less than 1 per year 1 ☐
1 per year 2 ☐
2 per year 3 ☐
More than 2 per year 4 ☐

☐

16. During your 20's:

How often did you have a common cold?

Less than 1 per year 1 ☐
1 per year 2 ☐
2 per year 3 ☐
More than 2 per year 4 ☐

☐

17. How often did you have a common cold during your teenage years? (through age 19)

Less than 1 per year 1 ☐
1 per year 2 ☐
2 per year 3 ☐
More than 2 per year 4 ☐

☐

Subject Code No ____________ 13

Now, about influenza, and by this I mean fever, muscle aches and pain, headache, sometimes also sore throat and cough.

18 At present (say, think of the past 3-4 years)

How often do you have influenza

Less than once a year	1	☐
1 per year	2	☐
2 per year	3	☐
More than 2 per year	4	☐

19 "During your 20's

How often did you have influenza"

Less than once a year	1	☐
1 per year	2	☐
2 per year	3	☐
More than 2 per year	4	☐

20 How often did you have influenza during your teens?

Less than once a year	1	☐
1 per year	2	☐
2 per year	3	☐
More than 2 per year	4	☐

Subject Code No ______________

Viral illnesses also frequently affect the stomach and bowels, that is, they may cause nausea, vomiting, stomach cramps and diarrhea. Sometimes there will be fever as well.

21. At present (say, think of the past 3-4 years)

How often do you have a stomach flu?

- Less than once a year 1 ☐
- 1 per year 2 ☐
- 2 per year 3 ☐
- More than 2 per year 4 ☐

☐

22. During your 20's

How often did you have a stomach flu?

- Less than once a year 1 ☐
- 1 per year 2 ☐
- 2 per year 3 ☐
- More than 2 per year 4 ☐

☐

23. How often did you have a stomach flu during your teens?

- Less than once a year 1 ☐
- 1 per year 2 ☐
- 2 per year 3 ☐
- More than 2 per year 4 ☐

☐

Subject Code No ___________

Other Symptoms of Viral Infection

24. Have you ever had any of the following problems?

(FOR EACH)

a) Have you ever had ___________?

b) When was the last time you had ___________?
(If one episode only, indicate this

c) How old were you when you first had ________?
(Probe "Younger than 20, older than, etc.")

(IF MORE THAN ONE EPISODE, USE AGE PARAMETERS REPORTED AND CONTINUE e.g. if respondent states that his first episode was around age 6, and the most recent age 24, then state "From the time you were age six until you were 10, how frequently would you say you had _______? etc.")

d) How frequently (how many times) would you say you experienced ___________ between the ages of

i) ≤ 1-10

ii) 11-19

iii) 20-29

iv) 30-39

v) 40+

Interviewer does not have to fill

e) How many episodes of _________ would you say you've had in all? (Help respondent add these up.)

PROMPT: "During this time period would you say you had this as much as once a year?"

If Yes: "Was this more than once a year?"
No ⟶ record as 1/year
Yes: ⟶ "Was this as much as twice a year?"
No ⟶ Record as > 1/year (greater than 1/year)
Yes: ⟶ "Was this twice a year?"
Yes ⟶ Record as 2/year
No
"Was this more than twice a year?"
Yes.
Continue as above taking the respondents to the next level.

Subject Code No ______________

Question 24

Viral Symptoms

	a	b	c	d					e	f
	Ever had	Age at first episode	Age at most recent episode	Frequency During Ages					Total episodes	Comments
				i	ii	iii	iv	v		
				0-10	11-19	20-29	30-39	40+		
1. Sore throat										
2. Swollen glands										
3. Ulcers or sores in the mouth "Canker Sores"										
4. Cold sores or blisters on the lips, mouth or nose										
5. Blisters or sores in the genital area										
6. Other sores or problems in the genital area										
7. Eczema or Skin Rashes										
8. Other										

Subject Code No ______________ 17

Vaccinations and Injections

The vaccinations or medications that we receive may affect our susceptibility to viruses

25. a) Have you been immunized vaccinated against ______?

b) When? (i.e. at what age?) Were you first vaccinated against ______?

	(a)	Approx. Age (e.g. 5 age 20, >20)
1. Polio		
2. Smallpox		
3. Tetanus		
4. Typhus		
5. Diptheria		
6. Flu Shots (Cold shots)		
7. Other (specify)		

(a)	(b)

Blood Transfusion

26. Have you ever had a blood transfusion?

Yes	1	
No	2	GO TO Q. D)
Don't know	8	
N.A.	9	

a) How old were you when you first had a blood transfusion? (Probe Before age 10, 20, etc.) ____________

b) Approximately how many blood transfusions have you had since then ? (Probe More than 10, less than 3, etc)

____
Specify

c) What was the reason for the transfusion ____________?
Specify

d) Have you ever donated blood?

Yes	1	
No	2	
Don't know	8	
No answer	9	

Viral Exposure:

Family size may affect our chance of exposure to viruses. For example, children may catch colds or flu from school-mates.

27. How many persons live in your home at present? (Including respondent)

____

28. How many rooms are there in your home, not counting bathrooms and kitchen?

____

Please try to think back to when you were age thirteen.

29. How many persons lived with you in your home then? (Including respondent)

____

30. How many rooms, not counting bathrooms and kitchen were there in your home then?

____

Sexual Intercourse

We are trying to assess all of the ways in which viral exposure may occur. One of these ways is through the close physical contact of sexual intercourse.

31. Have you ever had sexual intercourse?

Yes	1	☐	
No	2	☐	← GO TO Q.44
Don't know	8	☐	
N.A.	9	☐	

☐

Contraception:

The types of protection used during intercourse may affect our opportunity for exposure to viruses at different times of life. So that we may estimate your chance of exposure, I will ask you about various types of protection at different times of life. We are interested in the commonly used kinds of protection between you and your partner such as the condom or diaphragm, intrauterine device and birth control pill.

32. Have you or your partner ever used any form of protection during intercourse?

Yes	1	☐	
No	2	☐	← (GO TO COITAL QUESTIONS, PAGE 25)
Don't know	8	☐	
N.A.	9	☐	

☐

Subject Code No ______________

20. MALE ONLY

USE CHART.

32. CONDOM

FOR EACH METHOD USED
(Question 32)

a) How old were you when you first used ______________?
(Probe "younger than 16, older than 20, etc.")

b) When did you last (most recently) use ______________?

c) During your (age interval), when you had intercourse regularly, did you use this? **(SEE EXAMPLE)**

Would you say this was used

1) Regularly (all of the time)

e.g. nearly every sexual encounter

2) Often (most of the time)

e.g. most of the month, except around menses, etc

3) Occassionally (some of the time)

e.g. only during certain times

4) Rarely (once in a while)

e.g. experimental use, or with one specific partner

Tried method out, but not used as a regular method

Subject Code No. ______________

20. FEMALE ONLY

For each method that you have used, we will want to know when you first used this, how frequently and how long this was used.

33. Has your partner ever used a condom during intercourse?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

34. Have you ever used a diaphragm during intercourse?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

35. Have you ever used an intra-uterine (I.U.D.) device during intercourse?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

36. Have you ever taken the birth control pill?

Yes	1	☐
No	2	☐
Don't know	8	☐
N.A.	9	☐

Subject Code No. ______________

(USE CHART. SELECT EACH METHOD USED.)

37. CONDOM

38. DIAPHRAGM

39 I.U.D.

40. BIRTH CONTROL PILL

FOR EACH METHOD USED
(Questions 37-40)

a) How old were you when you (your partner)first used ____________?
(Probe: "younger than 16, older than 20, etc.") Note For Condom "How old were you when a condom was first used during intercourse?"
b) When did you last (most recently) use ________________?

c) During your (age interval), when you had intercourse how regularly would you say this method was used? (SEE EXAMPLE) Suggest

Would you say this was used

1) Regularly (all of the time)

e.g. nearly every sexual encounter.

2) Often (most of the time)

e.g. most of the month, except around menses, etc.

3) Occassionally (some of the time)

e.g. only during certain times (such as ovulation)

4) Rarely (once in a while)

e.g. experimental use, or with one specific partner.

Tried method out, but not used as a regular method.

Subject Code No. ______________ 22

EXAMPLE: AGE INTERVALS

FOR EACH METHOD, TO RECORD FREQUENCY OF USE, TAKE AGES REPORTED IN DECADE INTERVALS, FROM AGE AT FIRST USE TO LAST.

E.G.

- Condom
- Age at first use: 16
- Age at most recent use: 34

1) "From the time you were 16, until you were out of your teens, say before the age of 20, how frequently was the condom used?"
2) "When you were in your twenties, how frequently was the condom used?"
3) "When you turned thirty, until you were 34, when you stopped using the condom, how frequently was this used?"

USE AS APPROPRIATE. (Age intervals

Question 37-40, Part c)

During your teens, how frequently was the ________ used?

During your twenties, how often was the ________ used?

During your thirties, how frequently was the ________ used?

During your forties, how often was the ________ used?

CODES FOR CONTRACEPTIVE USE
Questions 37-40
(2 digit)

Interval	Portion of the Year	Degree of Use
Use (✓) check mark the age at first and most recent use	(If respondent states that the method was used for only PART, e.g. the first 6 months of a year)	1 = Regularly 2 = Often 3 = Occasionally 4 = Rarely
	0 = Entire year	
	1 = Part of the year (less than 6 months)	

EXAMPLE

Age	Interval	P	D
18	✓	0	2

Indicates method was often used for the entire year.

Subject Code No. ______________ 24.

CONTRACEPTION

	Q.37			Q.38			Q.39			Q.40			
	CONDOM			DIAPHRAGM			I.U.D.			BIRTH CONTROL PILL			
Age at Use	(a-b) Interval	(c) P	D	(a-b) Interval	(c) P	D	(a-b) Interval	(c) P	D	(a-b) Interval	(c) P	D	Comments
≤12													
13													
14													
15													
16													
17													
18													
19													
20													
21													
22													
23													
24													
25													
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36													
37													
38													
39													
40													
41													
42													
43													
44													
45													
46													
47													
48													
≥49													

Subject Code No. ____________ 25

There are a number of questions regarding sexual intercourse that we must ask.

So that the answers to these questions may remain COMPLETELY confidential, even from the interviewer, we are asking that you complete this portion of the questionnaire yourself.

When you have finished answering all of the questions (to the best of your memory), please fold this form, place it in the envelope provided, seal it and give it to me.

This will be returned to the Study Centre and coded separately from the rest of the questionnaire. Therefore, neither I nor any members of the study staff, will be able to identify your answers to these questions.

If you should have any difficulty in answering any of the questions, please let me know.

Provide COITAL QUESTIONNAIRE AND ENVELOPE

There is a great variation in the population as to when each person begins having intercourse. Some people begin early in life and some people begin later on.

Futhermore, over the years, many people may have a number of sexual partners.

(Respondent is given a pencil, clipboard and is instructed to begin the questionnaire).

Please keep in mind that you are free to not answer any question that you wish.

Begin End

49. ______________
Specify ages

a). During your (20's ______) how much did you smoke?

More than 2 packs per day	1
2 packs per day	2
more than 1 pack, but less than 2 per day	3
1/2-1 pack per day	4
less than 1/2 pack per day	5
occasionally (not every day)	6
Don't know	8
N.A.	9

b). Did you smoke filter or non-filter cigarettes during this time

Filter	1
Non-filter	2
Both	3
Don't know	8
N.A.	9

Subject Code No. ____________ 26.

Please look at the questionnaire.

As you can see, we are asking about the number of sexual partners during various life periods. Therefore a partner you are with for many years may be counted several times.

For example, someone who has been your sexual partner over your lifetime would be counted again in your 20's, again in your 30's, and so on.

41. Do you have any questions?

Specify Question ____________________

____

____

Please begin:

(At the end of the Coital Questionnaire)

42. Were there any questions that you were unable to answer?

Yes 1 ☐

No 2 ☐

☐

a) What was the number of the question(s)?

(e.g. 1-8)

____

(Explain question to respondent and allow a second try)

43. Have you answered all of the questions which apply to you?

Yes 1 ☐

No 2 ☐

Don't know 8 ☐

N.A. 9 ☐

☐

Ask Respondent if you can be of assistance in helping them to answer the questions. If this is refused or otherwise, collect the Coital Questionnaire, thank the respondent and continue the interview without comment.

COLLECT COITAL QUESTIONNAIRE

Subject Code No. __________

Smoking History:

It is possible that the condition of our lungs may affect our chance of respiratory infection due to viruses. Smoking can affect our lungs.

44. Have you ever smoked cigarettes?

Yes	1	☐	
No	2	☐	GO TO Q. 52
Don't know	8	☐	
N.A.	9	☐	

☐

45. How old were you when you first smoked cigarettes? ☐☐

____
Specify Age

46. Do you still smoke cigarettes?

Yes	1	☐	GO TO Q. 48
No	2	☐	
Don't know	8	☐	
N.A.	9	☐	

☐

47. How old were you when you stopped ☐☐

____

(Go to appropriate age category: e.g. If respondent started smoking at age 17 and stopped at age 35, state: "From the time you started smoking until you were age 20, how much did you smoke?" USE Decade Categories: e.g. smoking began at age 17, age 20 is the cut-off point).

Subject Code No. ___________ 29.

Smoking History

48.

Specify Age (e.g. 17-20)

Begin		End	

a). During your (teens _____) how much did (do) you smoke?

More than 2 packs per day	1	
2 packs per day	2	
more than 1 pack, less than 2 packs per day	3	
½ - 1 PACK PER DAY	4	
less than 1/2 pack per day	5	
occasionally (not every day)	6	
Don't know	8	
N.A.	9	

b). Did you smoke filter or non-filter cigarettes during this time?

filter	1	
non-filter	2	
both	3	
Don't know	8	
N.A.	9	

Subject Code No. ____________ 30.

Begin End

49. ____________
Specify ages

a). During your (20's ______) how much did you smoke?

More than 2 packs per day 1
2 packs per day 2
more than 1 pack, but less than 2 per day 3
1/2-1 pack per day 4
less than 1/2 pack per day 5
occasionally (not every day) 6
Don't know 8
N.A. 9

b). Did you smoke filter or non-filter cigarettes during this time

Filter 1
Non-filter 2
Both 3
Don't know 8
N.A. 9

Subject Code No. ____________ 31.

Begin End

50.

Specify Ages

a). During your thirties (the present or age stopped) how much did you smoke?

More than 2 packs per day 1
2 packs per day 2
more than 1 pack, but less than 2 packs per day 3
1/2-1 packs per day 4
less than 1/2 pack per day 5
Occasionally (not every day) 6
Don't know 8
N.A. 9

b). Did you smoke filter or non-filter cigarettes during this time?

Filter 1
Non-filter 2
Both 3
Don't know 8
N.A. 9

Subject Code No. ________________ 32.

Begin End

51.

____
Specify Ages

a). From the time you turned 40, how much did you smoke?

More than 2 packs per day	1	
2 packs per day	2	
more than 1 pack, but less than 2 packs per day	3	
½-1 pack per day	4	
less than ½ pack per day	5	
occasionally (not every day)	6	
Don't know	8	
N.A.	9	

b). Did you smoke filter or non-filter cigarettes during this time?

Filter	1	
Non-filter	2	
Both	3	
Don't know	8	
N.A.	9	

VITAMINS:

52 As an adult, say since you were in your twenties, have you ever taken a vitamin supplement such as a multiple vitamin or vitamin C?

- [ ] yes
- [ ] no ⟶ Go to question 53
- [ ] other

For each:

a) What kind of vitamins are these?

b) When did you start taking them?

c) When did you last take them? (can be present time)

d) How frequently do you take them? Suggest
1) Daily
2) Only at Special Times (e.g. as colds)
3) Occasionally

After Each:

e) What other vitamins have you taken? (Go back to a) - d).

a) Vitamin	b) When 1st taken	c) Last taken	d) Frequency of Use
1			
2			
3			

Subject Code No. ____________ 34.

General Information:

I'd like to ask you some general questions.

(PROMPT IF NECESSARY: "We ask these questions because our work or marital status may affect our health.")

Marital Status:

We would like to know your present marital status.

53. Are you married, widowed, divorced, separated, living common-law, or single?

Consider as ever married	Married	1	
	Widowed	2	
	Divorced	3	
	Separated	4	
	Living common-law	5	
	Single	6	GO TO Q. 54
	Don't know	8	
	N.A.	9	

(IF EVER MARRIED)

a). Have you ever been married before?

Yes	1
No	2

b). How many times have you been married?

(including present marriage) ____ (Total including this one)

If once only, GO TO Q. 53

(IF MARRIED)

c). How old were you when you were first married?

Specify age ________

Subject Code No. ____________

(IF MORE THAN ONE MARRIAGE)

d). How old were you when you married for the (2nd, 3rd, etc. time)?

i) marriage number 2 Specify age _____

ii) marriage number 3 Specify age _____

iii) marriage number 4 Specify age _____

Ask if ever married or living common law:

e). Was your partner ever married before his marriage to you?

Yes	1	
No	2	→ GO TO Q. 54
Don't know	8	
N.A.	9	

f). How many marriages did he have in all? (Including this one)

If separated, divorced, or widowed:

g). How old were you when ____________ (separated, divorced widowed) Specify age ____________

Education

54. What was the highest grade of public or high school that you completed?

____

a). Did you have any schooling or training after that?

Yes	1	
No	2	GO TO Q. 55

i) If yes, what was that (specify)

____

____

ii) How long did it take? ____________________ (years, months)

Subject Code No. ____________

55. In all, how many years of schooling and training did you have? ____________

Education of current or most recent spouse - if widowed or divorced.

Ask if ever married or living common-law:

56. What was the highest grade of public or high school that your partner completed? ____________

a). Did he have any schooling or training after that?

Yes 1

No 2

i) If yes, what was that? Specify -

____

____

ii) How long did it take? ____________ (years, months)

iii) In all, how many years of schooling or training did he have? ____________ years

Work: (Respondent)

57. What kind of work do you do now? Specify -

____

a). If not working for pay now (e.g. unemployed, housewife, student):

i) What was the last job you worked at for pay?

Specify - ____________

Subject Code No. ____________ 37.

Ask only if presently married or presently living common law:

b). Does your work require that you stay away from home frequently? (Say about as much as four times each year?) (For periods of time outside the city)

- Yes 1
- No 2
- Don't know 8
- N.A. 9

IF EVER MARRIED

58. What kind of work does your spouse (or most recent spouse) do now?

Specify - ____________________

a). (If spouse not working for pay now)

What was the last job that he worked at for pay?

Specify - ____________________

IF PRESENTLY MARRIED or presently living common law:

b). Does his work require that he stay away from home frequently? (Say ~~as~~ much as four times per year) (for periods of time outside the city)

- Yes 1
- No 2
- Don't know 8
- N.A. 9

c). How is his health?

- Good 1
- Not good 2
- Don't know 8

Subject Code No. ____________

d). Would you say that he catches colds or flu more or less frequently than you do?

More	1	
Less	2	
Same	3	
Don't know	8	

Parents' Occupation: (If parents retired or deceased: "What did they do before that?")

59. What does (did) your father do for a living?

____

60. What does (did) your mother do for a living?

____

Income:

61. Lastly, could you please tell me which number corresponds to the income group of your total combined family income (before taxes):

01 - Less than $4,500 per year

02 - $5,000 - $8,999 per year

03 - $9,000 - 16,999 per year

04 - $17,000 - $24,999 per year

05 - $25,000 - $29,999 per year

06 - $30,000 - $34,999 per year

07 - $35,000 - $39,999 per year

08 - $40,000 or more per year

77 - Refused

88 - Don't know

99 - N.A.

Time at this portion of the interview

Subject Code No. ________

62. As I have mentioned earlier, this is a study of viral illnesses. It is often possible to tell whether or not we have in the past, had a cold or virus, by examining the blood.

The persons that we talk with are asked to give a small blood sample. This is taken by me, as I am certified in this procedure.

May I take a sample of your blood at this time?

Yes	1	☐
No	2	☐
Other, specify	3	☐

Would this be more convenient at another time?

____

Specify

Subject Code No. ______________

63. Since the age of 35, have you ever been hospitalized (that is stayed over night in a hospital) for any reason?

yes
no
don't know

64. Have you ever participated in a survey before

Yes
No
Don't Know

65. Are there any questions about our inquiries that you would like to ask me?

Yes
No

Specify: (write out respondent's comments)

____

____

You have been very kind to take the time to talk with me. I would like to thank you on behalf of Dr. K. Stavraky, the principal investigator of this study.

I will leave this note with you (provide Thank You Note). Please feel free to contact us if you should have any comments or questions with regard to the study.

Time:

Length in Minutes:

Subject Code No. ____________ 41.

INTERVIEWER'S COMMENTS

TO BE COMPLETED OUTSIDE THE HOME, AFTER THE INTERVIEW

1. Was the interview done in complete privacy?

   Yes 1 ☐
   No 2 ☐
   Don't know 8 ☐ ☐

   Specify - ____________________________

2. Were there any distractions during the interview?

   Yes 1 ☐
   No 2 ☐ ☐

   Specify - ____________________________

3. Was anyone else in the home during the interview?
   (other rooms, etc.)

   Yes 1 ☐
   No 2 ☐
   Don't know 8 ☐ ☐

   Specify - ____________________________

4. Did the respondent have any difficulty in remembering facts or in answering any of the questions?

   Yes 1 ☐
   No 2 ☐ ☐

   All of the questions ____________________

   Some of the questions (specify) ____________________

   ____

Subject Code No. ______________ 42

5. How do you think the respondent found the interview?

Enjoyable 1 [ ]

Acceptable 2 [ ]

Uncomfortable 3 [ ]

Intrusive 4 [ ]

6. Do you think that the answers are:

Often incorrect 1 [ ]

Sometimes incorrect 2 [ ]

Usually correct 3 [ ]

Completely correct 4 [ ]

7. How would you describe the respondent's cooperation?

Poor 1 [ ]

Fair 2 [ ]

Good 3 [ ]

Excellent 4 [ ]

8. Please comment on the cleanliness of the rooms you were able to see ______________________________

Rate the cleanliness on a scale of 1 - 10.

1 = very dirty

10= extremely clean ________ Rate

9. Rate the tidiness on a scale of 1 - 10.

1 = very untidy

10= extremely tidy ________ Rate

10 Other comments on the interview

____

____

Subject Code No. ____________

Type of Dwelling:

11. What sort of dwelling does the respondent live in?

Single House	☐	☐☐
Attached House		
Duplex	☐	☐☐
Triplex	☐	☐☐
Townhouse	☐	☐☐
Apartment		
"Old" (≥ 30 yrs.)	☐	☐☐
"New" ("modern" type)	☐	☐☐
Room (Rooming house)	☐	☐☐
Mobile Home	☐	☐☐
Other	☐	☐☐

QUESTIONS REGARDING

SEXUAL INTERCOURSE

Form A

Code Number

So that the answers to these questions may remain completely confidential, even from the interviewer, we are asking that you complete this part of the questionnaire yourself.

WHEN YOU HAVE FINISHED ANSWERING ALL OF THE QUESTIONS, PLEASE FOLD THIS FORM, PLACE IT IN THE ENVELOPE PROVIDED, SEAL IT, AND GIVE IT TO THE INTERVIEWER.

THERE ARE 8 QUESTIONS TO BE ANSWERED. IF ANY QUESTION DOES NOT APPLY TO YOU, PLEASE CHECK THE BOX THAT STATES: "DOES NOT APPLY".

1. How old were you when you first had sexual intercourse?

   Age at first intercourse ________.

PLEASE BEGIN ANSWERING THE QUESTIONS FROM THE AGE CATEGORY WHEN YOU FIRST HAD INTERCOURSE.

2. During your teenage years, how many different persons did you have sexual intercourse with?

   Number of sexual partners ________.

   Does not apply to me as I had not yet begun having intercourse in my teens. ☐

3. During your twenties, how many different persons did you have sexual intercourse with?

   Number of sexual partners ________.

   Does not apply to me as I had not yet begun having sexual intercourse in my twenties. ☐

Form A Code Number

4. During your thirties, how many different persons did you have sexual intercourse with?

Number of sexual partners ______________.

5. From the time you became age 40 until the present time, how many different persons did you have sexual intercourse with?

Number of sexual partners ______________.

Does not apply to me as I am not yet 40. ☐

6. During your whole lifetime so far, how many different persons have you had sexual intercourse with?

Number of sexual partners ______________.

7. In the last year, that is 12 months ago from today, how many different persons have you had sexual intercourse with?

Number of sexual partners ______________.

8. Have you answered all the questions that apply to you?

Yes

No

If no: Please state the reason below:

____

____

____

IF YOU HAVE HAD ANY DIFFICULTY WITH ANY OF THESE QUESTIONS, PLEASE ASK THE INTERVIEWER FOR HELP.

Thank you for answering these questions. Please fold this form, seal it in the envelope provided, and give it to the interviewer.

1878-1978
The University of
Western Ontario

PERMISSION FOR INTERVIEW

I, ______________________________, agree to be interviewed for a survey of the frequency of common illness due to viruses, such as the common cold, especially with regard to things which make people susceptible to these illnesses. I understand that a few of these questions are of an intimate nature, such as contraceptive use and sexual partners, as these factors may affect exposure to viruses. I also understand that all information gathered will be kept in the strictest confidence.

I understand that this information will be used solely for the purpose of scientific research.

Signature ______________________________

Date ______________________________

Department of Epidemiology & Preventive Medicine
Faculty of Medicine Kresge Building
London, Canada N6A 5B7

1878-1978
The University of
Western Ontario

PERMISSION FOR BLOOD SAMPLE

I agree to have a small sample of blood taken as part of my participation in this survey.

I understand that a small sample of blood (10cc, or less than 1 oz.) will be taken from a superficial vein (blood vessel) in my arm with a needle and syringe according to customary medical procedure. I know that some people feel momentarily faint from the necessary pin prick and this could happen to me.

I understand that the blood sample will make the information gathered in the interview useful, because the purpose of taking blood is to examine it for evidence of past illnesses due to viruses.

Signature ______________________________

Date ______________________________

Department of Epidemiology & Preventive Medicine
Faculty of Medicine Kresge Building
London Canada N6A 5B7

The University of Western Ontario

Department of Epidemiology &
Preventive Medicine
Faculty of Medicine
Kresge Building
London Canada
N6A 5B7

Dear Participant:

We appreciate the opportunity to talk with you in our survey of the frequency of illness and the spread of viruses.

All of the information gathered will be kept in the strictest confidence. When the information you have given is combined with that given by other survey participants, we hope to learn about the patterns of viral illness in Toronto.

If you should have any questions or comments with regard to our study, please feel free to contact me.

We are grateful for your cooperation.

Yours sincerely,

Kathleen M. Stavraky, M.D., Ph.D.
Associate Professor

Telephone: (519)679-3896

APPENDIX IX

ASSESSMENT OF THE EFFECTS OF ASSAY VALIDITY, NON-RESPONSE ON STUDY RESULTS

APPENDIX IX

Table

A	Total Years of Education and HSV-2 Antibody: WOMEN: Original and Adjusted Estimates Based upon Previous Investigations
B	Non Response: Theoretical Estimates. Reallocation of Participants Without Serologic Information

APPENDIX IX

TABLE A

Comparison of RIA and MN Results from Rawls et al., 1980 and the Present Investigation

WOMEN

HSV-2 ANTIBODY

		POSITIVE	NEGATIVE	
YEARS OF EDUCATION	$\leq$ 12	1) 46 (+45)	106	197
	$\geq$ 13	2) 29 (+45)	200	229
		120	306	426

1) 30% reallocated to low educational level

$$O.R. = \frac{a(d)}{c(b)}$$

$$= \frac{91(200)}{29(106)}$$

$$= \frac{18200}{3074}$$

$$= \underline{5.92}$$

Observed odds ratio from study data = 2.10

2) 30% reallocated to high educational level

$$O.R. = \frac{46(200)}{74(106)}$$

$$= \underline{1.17}$$

APPENDIX IX

TABLE B

Non-Response: Theoretical Estimates: Reallocation of Participants without Serologic Information

MEN

Variable: Total Number of Sexual Partners in a Lifetime

EXPOSURE		HSV-2 ANTIBODY POSITIVE	NEGATIVE	NO SERA	TOTAL
NUMBER OF SEXUAL PARTNERS	Many ($\geq$10)	a=25	b=125	e=28	R_1= 178
	Few ($\leq$9)	c=9	d=129	f=31	R_2= 169
	Total	C_1=34	C_2=254	C_3=59	T= 347

Odds Ratio for those with Sera

$$O.R. = \frac{ad}{bc} = \frac{25(129)}{125(9)} = \underline{2.87}$$

ESTIMATES OF THE POSSIBLE EFFECTS UPON THE MEASURE OF ASSOCIATION (THE ODDS RATIO) THROUGH THE HYPOTHETICAL ALLOCATION OF THOSE WITHOUT SEROLOGIC INFORMATION TO THE ANTIBODY GROUPS.

MEN: Number of Sexual Partners

Original Odds Ratio = 2.87

ALLOCATION OF THOSE WITHOUT SERA TO	ODDS RATIO	EFFECT UPON THE ORIGINAL ESTIMATE
I Number of Sexual Partners Distributed as known in the No Sera Group		
1. To HSV-2 Negative		
$\text{O.R.} = \frac{(a)(d+f)}{(b+e)(c)} = \frac{(25)(129+31)}{(125+28)(9)} =$	2.90	≈
2. To HSV-2 Positive		
$\text{O.R.} = \frac{(a+e)(d)}{(b)(c+f)} = \frac{(25+28)(129)}{(125)(9+31)} =$	1.37	↓
3. Distributed as Positive to Negative with regard to Antibody Status		
$\text{O.R.} = \frac{[a+P_{mp}(e)][d+P_{fn}(f)]}{[b+P_{mn}(e)][c+P_{fp}(f)]}$		
$= \frac{[25+0.17(28)][129+0.93(31)]}{[125+0.83(28)][9+0.07(31)]} =$	2.91	≈
II Number of Sexual Partners reallocated (as well as Antibody Status)		
1. Proportionately distributed as Sera Group with regard to Antibody Status and Number of Sexual Partners		
$\text{O.R.} = \frac{(a+C_3P_pP_{pm})(d+C_3P_nP_{nf})}{(b+C_3P_nP_{nm})(C+C_3P_pP_{pf})}$		
$= \frac{a+115(d+27)}{b+25\ (c+2)} = \frac{25+5(129+27)}{125+25(9+2)} =$	2.87	=

2. To Many Partners, Distributed as Antibody Groups

$$O.R. = \frac{[a+Pp(C_3)]d}{[b+Pn(C_3)]c}$$

$$= \frac{[25+0.12(59)]129}{[125+0.88(59)]9} = \quad 2.59 \quad \approx$$

3. To Few Partners, Distributed as Antibody Groups

$$O.R. = \frac{a[d+Pn(C_3)]}{b[c+Pp(C_3)]}$$

$$= \frac{25[129+0.88(59)]}{125[9+0.12(59)]} = \quad 2.26 \quad \approx$$

Exposure varying with Antibody Status:

4. To Few Partners, Positive

$$O.R. = \frac{a(d)}{b(c+C3)} = \frac{25(129)}{125(9+59)} = \quad 0.38 \quad +$$

5. To Many Partners, Negative

$$O.R. = \frac{a(d)}{(c+C_3)(c)} = \frac{25(129)}{(125+5)9(\underline{9})} = \quad 1.95 \quad +$$

6. To Few Partners, Negative

$$O.R. = \frac{a(d+C_3)}{b(c)} = \frac{25(129+59)}{125(9)} = \quad 4.18 \quad \dagger$$

7. To Many Partners, Positive

$$O.R. = \frac{(a+C_3)(d)}{b(c)} = \frac{(25+59)(129)}{125(9)} = \quad 9.63 \quad \dagger$$

PROPORTIONATE DISTRIBUTION OF:	MEN
Positive to Negative:	
P_p = Proportion Positive = $\frac{C_1}{C_1 + C_2}$	$P_p = 0.12$
P_n = Proportion Negative = $1 - \frac{C1}{C_1 + C_2}$	$P_n = 0.88$
Sexual Partners: Many to Few	
P_m = Proportion Many = $\frac{a + b}{C_1 + C_2}$	$P_m = 0.52$
P_f = Proportion Few = $1 - \frac{a + b}{C_1 + C_2}$	$P_f = 0.48$
Sexual Partners: Many to Few HSV-2 Positive	
P_{pm} = Porportion Many in Positives = $\frac{a}{C_1}$	$P_{pm} = 0.74$
P_{pf} = Proportion Few in Positives = $1 - \frac{a}{C_1}$	$P_{pf} = 0.26$
Sexual Partners: Many to Few HSV-2 Negative	
P_{nm} = Proportion Many in Negatives = $\frac{b}{C_2}$	$P_{nm} = 0.49$
P_{nf} = Proportion Few in Negatives = $1 - \frac{b}{C_2}$	$P_{nf} = 0.51$
Positive to Negative with Regard to Number of Sexual Partners	
P_{mp} = Proportion Positive in Many $= \frac{a}{a+b}$	$P_{mp} = 0.17$
P_{mn} = Proportion Negative in Many $= 1 - \frac{a}{a+b}$	$P_{mn} = 0.83$
P_{fp} = Proportion Positive in Few $= \frac{c}{c+d}$	$P_{fp} = 0.07$
P_{fn} = Proportion Negative in Few $= 1 - \frac{c}{c+d}$	$P_{fn} = 0.93$

Sexual Partners: Many to Few No Sera Group	
P_{nsm} = Proportion Many in no sera = $\frac{e}{C_3}$	$P_{nsm} = 0.47$
P_{nsf} = Proportion Few in no sera = $1 - \frac{e}{C_3}$	$P_{nsf} = 0.53$

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