TRENDS IN HERPES SIMPLEX VIRUS CASES IN BRITISH COLUMBIA, 1992 – 2006

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INTRODUCTION

Genital herpes is the second most prevalent sexually transmitted viral infection in Canada and throughout the world (Silversides, 1999), and the most common cause of genital ulceration in the developed world (Mindel, 1998). While most genital herpes are caused by herpes simplex virus type 2 (HSV-2), genital infections with HSV-1 are increasingly recognized (Ross et al., 1993; Langenberg et al., 1999).

Primary genital HSV infection caused by either HSV-1 or HSV-2 can cause vesiculation and painful ulcers that may recur at intervals. Recurrences take place at a higher frequency with HSV-2 (Lafferty et al., 1987), yet many individuals with genital herpes have an atypical presentation or are asymptomatic shedders. Consequently, up to 75% of people with serologic markers of HSV-2 infection are not aware of being infected (Wald et al., 1997). Viral shedding from the genital tract occurs both in those with a diagnosis of genital herpes and in seropositive people with subtle or even no symptoms (Wald et al., 2000).

In addition to concerns about direct morbidity, genital herpes infections have three important public health implications. First, sexual transmission from both diagnosed and undiagnosed cases, and the paucity of definitive preventive interventions contributes to ongoing incidence of HSV. Second, perinatal transmission to the neonate may result in disseminated disease, neurologic damage, and high mortality (Patrick et al., 2001). Third and finally, HSV-2 and associated ulcers facilitates the transmission of human immunodeficiency virus (HIV) (Wald et al, 1997; Halioua & Malkin, 1999; Corey et al., 2004).

EPIDEMIOLOGY

The annual incidence in Canada of genital herpes due to HSV-1 and -2 infections is not known. In the United States, it is estimated that about 1,640,000 HSV-2 seroconversions occur yearly (730,000 men and 910,000 women, or 8.4 per 1,000 persons) (Armstrong et al., 2001). The United States National Health and Nutrition Examination Surveys (NHANES) (Xu et al., 2006) indicates that the overall age-adjusted HSV-2 seroprevalence was 21.0% in 1988-1994 and 17.0% in 1999-2004, a significant relative decrease of 19.0% between the two surveys. Decreases in HSV-2 seroprevalence were especially evident in persons aged 14 to 19 years between 1988 and 2004, which the authors attributed to changes in sexual behaviors in this age cohort. Among those infected with HSV-2, the percentage who reported having been diagnosed with genital herpes was low in both time periods (9.9% in 1988-1994 and 14.3% in 1999-2004). Seroprevalence of HSV-1 decreased from 62.0% in 1988-1994 to 57.7% in 1999-2004, a significant relative decrease of 6.9% between the two surveys.

Among persons infected with HSV-1 but not with HSV-2, the proportion reporting a diagnosis of genital herpes was low in both time periods (0.4% in 1988-1994 and 1.8% in 1999-2004).

In British Columbia (BC) in 1999, the seroprevalence of HSV-2 antibody in serum originally submitted for antenatal testing was 17.3%, ranging from 7.1% in women 15-19 years old to 28.2% in those 40-44 years (Patrick et al, 2001). In Ontario, the overall age- and gender-standardized seroprevalences of HSV-1 and HSV-2 were 51.1% and 9.1%, respectively (Howard et al., 2003). In attendees at an Alberta STI clinic in 1994 and 1995, the seroprevalence of HSV-1 and -2 was 56% and 19%, respectively (Singh et al., 2005).

The incidence and prevalence of HSV-1 genital infection, and the relative prevalence of HSV-1 genital infections (compared with those caused by HSV-2) are increasing globally, with marked variation between countries (Lafferty et al., 2000). In Norway, a recent study found that 90% of genital infections were due to HSV-1 (Nilsen & Myrmel, 2000). In Australia, the percentage of all genital infections caused by HSV-1 rose from 15.8% in 1980 to 34.9% by 2003 ($p<0.001$) (Tran et al.,2004). In England and Wales, Vyse et al. found that HSV-1 seroprevalence increased in individuals between 15 and 24 years of age, suggesting HSV-1 transmission in adolescence and young adulthood may be due to sexual activity (Vyse et al., 2000). In Canada, a recent study indicated that HSV-1 is the predominant isolate (1,213 vs. 1,045) from genital specimens submitted in Nova Scotia (Forward & Lee, 2003). In women, 58.1% of 1,790 HSV isolates from genital lesion cultures were HSV-1, while in men, 36.7% of 468 isolates were HSV-1. This trend was particularly striking in young women 30 years of age or less, in whom 70.8% of isolates were HSV-1.

RISK FACTORS AND GROUPS AT HIGH RISK

Both sexual behavior and a variety of demographic factors appear to influence the sexual transmission of genital HSV. Similar to other STIs, high-risk sexual behaviors such as unprotected oral, genital or anal intercourse are the primary risk factors for genital herpes (PHAC 2006). Condom use reduces transmission of genital HSV-2 from infected men to women by 50% and may reduce transmission from infected women to men to a similar degree (Wald et al., 2001). However, condoms are only effective if used and their effectiveness may also be limited because of the location of lesions outside the zone of protection and the risk of transmission during oral-genital sex.

Epidemiologic studies have shown a direct association between numbers of sexual partners and HSV-2 seroprevalence (Xu et al., 2006; Fleming et al., 1997; Nahmlas et al., 1990; Smith et al., 2001). The age-specific increase in HSV-2 seroprevalence in North American populations, which plateaus with individuals in their thirties (Armstrong et al., 2001; Fleming et al., 1997; Patrick et al., 2001), likely reflects exposure to different sexual partners in early adulthood (Steben et al., 1997). In addition, younger age at first intercourse has been independently associated with increased HSV-2 seroprevalence (Xu et al., 2006; Smith et al., 2001).

HSV-2 antibody prevalence is higher in some groups, such as persons attending STI clinics (Koutsky et al., 1997) and men who have sex with men (MSM) (Nahmias et al.,1990).

In the United States, the prevalence of HSV-2 infection among HIV-negative MSM varied from 26% (Tabet et al., 1998) to 40% (Siegel et al., 1992), higher than the 22% estimated for the general population in that period (Fleming et al., 1997). HSV-2 seroprevalence is considerably higher, up to 70%, among HIV-infected MSM (Handsfield et al., 1987; Stamm et al., 1988), whereas up to 95% of HIV-positive persons have antibodies to HSV-1, HSV-2, or both (Enzensberger et al., 1991).

Populations using recreational drugs are at a high risk for acquiring STIs as a result of factors such as high risk sexual partners and increased levels of high risk sexual behaviors associated with stimulants such as crack cocaine (Cohen et al., 1994; Kim et al., 1993). These risks are often escalated among women because of the biological efficacy of STI transmission and the elevated prevalence of risk behaviors, such as the exchange of sex for drugs or money (Henderson et al., 1994; Powis et al., 1996). Based on a recent study conducted among young drug users in Maryland (Plitt et al., 2004), the seroprevalence of HSV-2 among females and males were 58.7% and 22.0% respectively, which were higher than those reported for the general population (25.6% and 17.8% respectively) (Fleming et al., 1997). Older age, African-American race, being incarcerated, over 30 lifetime partners of the opposite sex, current HIV infection, and previous self reported gonorrhea infection were associated with HSV-2 for both genders. There were no significant differences in the proportion of HSV-2 seroreactivity between injecting drug users (IDUs) and non-injecting drug users (Plitt et al., 2004).

Females are at higher risk of acquiring genital herpes from a male partner than males are from a female partner. Studies have found that among discordant heterosexual couples with a source partner who had symptomatic recurrent genital HSV-2 infection, the annual transmission rates were 11-17% in couples with male source partners and 3-4% in couples with female source partners (Corey et al., 2004; Mertz et al., 1992). Socio-economic factors also are possible determinants of differences in the seropositivity ratios of HSV-2. People living below the poverty level have been shown to have higher HSV-2 seroprevalence in the United States (Xu et al., 2006; Fleming et al., 1997). In addition, genital herpes has emerged as a leading cause of genital ulceration in many developing countries (O'Farrell, 1999). Countries with significant heterosexual HIV epidemics also appear to have rapidly increasing numbers of genital herpes cases (O'Farrell, 1999). In some parts of sub-Saharan Africa, where HIV is of great concern, the prevalence of HSV-2 among women is as high as 75% (WHO 2001; Celum et al., 2004).

NEONATAL HERPES

The most serious direct consequence of genital HSV infection is neonatal herpes, which results from perinatal transmission from mother to infant (Whitley & Arvin, 1995; Prober et al., 1987; Brown et al., 1991). The majority of transmission events are intrapartum through infant contact with HSV in the genital tract (80%); intrauterine (ascending) infection accounts for 5% of neonatal HSV infection, and postnatal infection (usually HSV-1, from maternal oral-labial lesions) for 15% (Kimberlin et al., 2001; Enright & Prober, 2002; Koskiniemi et al., 1989). Transmission is greatly influenced by the mother's serologic status. Fifteen percent to 50% of

vaginally delivered infants from seronegative mothers who acquired gential HSV-1 or HSV-2 in the third trimester may become infected. However, the risk of perinatal transmission is less than 1% among seropositive women with long-standing infection (Brown et al., 1991). Infants delivered vaginally by women with genital lesions or asymptomatic HSV genital virus shedding at parturition had a 2% risk of becoming infected (2 of 92 cases) (Brown et al., 2003). Cesarean delivery has been shown definitively to protect against neonatal transmission of HSV, and suppressive acyclovir after 36 weeks gestational age may also be of benefit (PHAC 2006). Thus, the opportunity for preventing neonatal HSV relates more to identifying and preventing maternal genital infection late in pregnancy than to interventions for women with existing genital HSV infection, providing reassurance for pregnant women with a history of genital herpes (Brown et al., 2003; PHAC 2006).

The incidence of neonatal herpes in Canada for 2000-2003 inclusive was 5.85 per 100,000 live births. The majority (62.5%) of these infections were attributed to HSV-1 (Kropp et al., 2006). While studies from other countries have reported that 55-80% of neonatal herpes are due to HSV-2 (Whitley et al., 1988; Kimberlin et al., 2001; Enright & Prober, 2002; Koskiniemi et al., 1989), these studies also report an increasing proportion of cases due to HSV-1, and infection with HSV-1 may be more severe (Roberts et al., 2003; Lafferty et al., 2000). Additionally, asymptomatically shed genital HSV-1 has been shown to be more infectious to the neonate and is more likely to produce neonatal herpes than HSV-2 (Brown et al., 2003; Brown et al., 2007).

Clinically, neonatal infection is classified as skin-eye-mouth (SEM), central nervous system (CNS) or disseminated infection, with accompanying mortality of 0%, 15% and 47%, respectively, and a possible predisposition for abnormal development (Whitley et al., 1988; Kimberlin et al., 2001; Koskiniemi et al., 1989). However, overlap occurs, and up to 30% of babies presenting with SEM will progress to CNS disease. In the Canadian study by Kropp et al (2006), 63.8% of cases had localized (SEM) disease, while 34.5% had infection that disseminated to the CNS or other organ. With acyclovir therapy, the mortality of neonatal herpes has been reduced to 10%, but neurological sequelae remain common (Whitley et al., 1980; Whtley et al., 1991).

GENITAL HERPES AND HIV TRANSMISSION

In the late 1980s, soon after the viral etiology of AIDS was defined, it began to be appreciated that genital ulcer disease was a risk factor for sexual acquisition and transmission of HIV infection (Greenblatt et al., 1988; Holmberg et al., 1988; Hook et al., 1992; Castro et al., 1988). Herpes is by far the most common cause of genital ulcer disease in the developed world (Mindel, 1998). In addition to the high titers of HIV found in genital herpes ulcerations and the likely effect of this on increasing HIV transmission (Schacker et al., 1998), plasma HIV viral load rises when HSV-2 infection reactivates in persons with HIV infection (Mole et al., 1997) providing further biological evidence for increased risk of transmission of HIV and suggests that herpes may adversely affect the course of HIV disease (Corey & Handsfield, 2000).

The prevalence of HSV-2 infection in populations at risk for HIV is extremely high (Corey & Wald, 1999; Koutsky et al., 1992; Wald et al., 1997). To determine the contribution of HSV-2 infection to the risk of HIV acquisition, Wald and Link (2002) conducted a systematic review of literature and data synthesis and identified 31 studies which addressed the risk of HIV infection in HSV-2–seropositive persons. For nine cohort and nested case-control studies that documented HSV-2 infection before HIV acquisition, the risk estimate was 2.1 (95% confidence interval, 1.4–3.2). Thus, the attributable risk percentage of HIV infection due to HSV-2 was 52%, and the estimated population attributable risk percentage was 19% (in populations with 22% HSV-2 prevalence) to 47% (at 80% HSV-2 prevalence. For 22 case-control and cross-sectional studies, the risk estimate was 3.9 (95% confidence interval, 3.1–5.1), but the temporal sequence of the two infections cannot be documented. Based on these findings, control strategies for HSV-2 should be considered a strategy for HIV prevention (Wald & Link, 2002).

The underlying biologic plausibility of mechanisms by which HSV-2 increases the risk of HIV-1 acquisition has been strengthened considerably in the past several years by studies indicating that subclinical genital mucosal reactivations occur in approximately 90% of HSV-2 seropositive women and 80% of seropositive men, that such reactivations are common (20% of days with daily sampling), and that these “shedding episodes” are associated with microscopic ulcerations and the influx of activated CD4+ T cells to the ulcerative region (Wald et al., 1997; Wald et al., 2002; Krone et al., 2000; Gupta et al., 2004; Corey et al., 2004; Magaret et al., in press; Wald et al., 1999; Koelle et al., 1994; Cunningham & Dwyer, 2004). The higher risk between incident HSV-2 and HIV acquisition can be explained by the even higher rates of subclinical reactivation (35-40% of days) in early versus more chronic HSV-2 infection (Wald et al., 1997; Koelle et al., 1992; Benedetti et al., 1994). In addition to these biological factors, there are mutually reinforcing behavioral and epidemiologic links between genital herpes and HIV infection (Fleming & Wasserheit, 1999).

LABORATORY DIAGNOSIS

Isolation in cell culture is the most common method currently used in public health laboratories in BC and the rest of Canada for viral identification in order to confirm the clinical diagnosis of HSV. It is sensitive (70% from ulcers, 94% from vesicles) and permits identification of HSV type (Corey & Holmes, 1983). Polymerase chain reaction (PCR) has increased sensitivity compared to HSV culture and is 100% specific (Wald et al., 2003). However, at this time, mainly due to their higher costs, PCR assays have been used to a more limited extent and have not yet replaced culture for routine diagnosis of genital herpes in most public health laboratories in Canada (PHAC 2006). PCR assays are substantially more sensitive than isolation in cell culture.

Serologic tests detect antibodies to HSV, and when reactive, indicate that the person is infected even when there are no symptoms or viral shedding,,hence these assays are a very effective way to detect active or latent herpes infections. The sensitivity and specificity of serology is better than isolation in cell culture, but there are two important factors to consider. First, if this is the first exposure to herpes, a person may take 3-6 weeks to develop

antibodies, while by 12 weeks, more than 70% will have seroconverted (Lopez et al., 1993; Ashley et al., 1999). The antibody response to primary infection is characterized by early appearance of IgM, followed subsequently by IgG antibody. IgM antibody usually wanes within a few months of infection (Kohl et al., 1982); therefore, the presence of IgM antibody is an indirect indication of "recent" infection. However, the value of this indicator is negated by the potential reappearance of IgM during reactivations of established disease. Because the interpretation of these results is very difficult in BC as in some other provinces IgM antibody testing has been discontinued[1].

Second, standard HSV IgG/IgM serology cannot distinguish between antibody to HSV-1 and HSV-2. Immune responses to these viruses can be appropriately identified through type-specific antibody testing. Such information will permit practitioners to counsel individuals with genital herpes and their partners (PHAC 2006). Detection of HSV-2 antibody is considered to be accurate for detecting silent genital HSV-2 infection, but detecting HSV-1 antibody is not useful in the same way, because asymptomatic HSV-1 oral-labial infections are common (Ashley, 1994). Type-specific antibody is best detected by Western blot analysis, although this is costly and has limited availability in Canada. New commercial enzyme immunoassays (EIA) with improved sensitivity and specificity are available (Ashley, 1994) and need not be routinely confirmed by Western blot analysis. At this time, type-specific HSV antibody assays are available only in a few laboratories in Canada (PHAC 2006) and are in limited use in BC.

CURRENT BC SURVEILLANCE FOR HERPES SIMPLEX

Genital herpes is reportable in BC by laboratories, according to Schedule B of the Health Act Communicable Diseases Regulation (Health Act 2007). Congenital herpes simplex infection is reportable by all sources under Schedule A of the regulation. However, the current reporting by laboratories and physicians occurs on an *ad hoc* basis. To date, herpes data have not been routinely analyzed or reported.

Recent studies have identified that HSV is highly prevalent in certain subgroup populations in BC (Patrick et al., 2001) and in other provinces of Canada (Howard et al., 2003; Singh et al., 2005). These findings, combined with the epidemiological evidence and biological plausibility of the interaction between HIV and HSV-2, the knowledge of the changing relative prevalence of HSV-1 and HSV-2 genital infections, and their implications for HIV prevention, herpes control, vaccine development, and neonatal herpes morbidity and mortality, provide a strong rationale for establishing ongoing herpes surveillance and control strategies in BC.

[1] Martin Petric, Clinical Virologist, BCCDC, personal communication, 2008.

OBJECTIVES

The purpose of this report is to provide a provincial and regional summary of recent trends in herpes infections and related medical services in British Columbia through analysis of existing laboratory and health care utilization datasets, with a focus on genital herpes and neonatal herpes cases. The intention of this preliminary analysis is to provide the context necessary to inform current and future control strategies for genital herpes in British Columbia. In particular, the value of these data for ongoing genital and neonatal HSV surveillance will be assessed.

METHODS

DATA SOURCES

Sources of data used for this analysis included:

1. **Laboratory Data (Viral identification, serology)**
   a. PHSA Laboratory Viral Identification Test Data, BCCDC STI Information System (LIS Lawiso data: 01-Jan-1993 to 21-Feb-2006; MISYS culture data: 22-Feb-2006 to 31-Dec-2006)
   b. PHSA Laboratory Serologic Test Data, BCCDC STI Information System (LIS Lawser data: 01-Jan-1992 to 21-Feb-2006; MISYS serology data: 22-Feb-2006 to 31-Dec-2006)
   c. STI clinic viral identification test data, BCCDC STI Information System (1989-2007)
   d. STI clinic serologic test data, BCCDC STI Information System (1996-2007)
2. **Health care utilization data (Physician billing, Hospital discharges)**
   a. Physician Billing Data, Ministry of Health Utilization Data (Medical Services Plan (MSP): 01-Jan-1992 to 31-Dec-2006)
   b. Hospital Discharge Data, Ministry of Health Utilization Data (Discharge Abstract Database (DAD) ICD-9 data: 01-Jan-1992 to 31-Mar-2001; DAD ICD-10 data: 01-Apr-2001 to 31-Dec-2006)
3. **Demographic data**
   a. STI Surveillance Cube (Number of background population, cube accessed on 16-Jan-2008)
   b. BC Vital Statistics Agency (Number of live births, 1992 to 2005)

It should be noted that the MSP data also includes data from some non-physicians (e.g. massage therapists, naturopaths, etc) billings, although MSP billings related to herpes ICD

codes are unlikely to originate from non-physicians. Similarly, the DAD data in addition to discharges from inpatient stay (the majority), includes discharges from day surgery procedures, transfers between facilities, and deaths occurring in hospital.

DATA ANALYSIS

Data were analyzed in Excel and SAS 9.1 for windows, by standard descriptive epidemiologic methods and appropriate statistical tests (Independent samples t-test, Chi-square test for trends).

1. Provincial and Health Authority Trends

Laboratory positive viral identifications of HSV (1993 – 2006), positive serologic test reports for HSV (1992 – 2006), volume of serologic tests (1992 – 2006), physician billing data (1992 – 2006), and hospital discharge data (1992 – 2006) were analyzed by year. Volume of viral identification tests (01-Apr-2006 to 30-Sep-2007) were analyzed by quarter between the second quarter (Q2) of 2006 and the third quarter (Q3) of 2007.

The identification of HSV was defined as a laboratory diagnosis of HSV-1, HSV-2, or HSV (not-typed), by either viral culture or PCR. A serodiagnosis of HSV was defined as laboratory detection of anti-HSV IgG antibody, anti-HSV IgM antibody, anti-HSV-1 antibody, or anti-HSV-2 antibody.

Detailed analysis of trends by viral type was conducted using laboratory viral identification test data, 1993 to 2006. Trends in identifications of HSV-1 and HSV-2 have been analyzed separately. In total, there were 24 co-infection reports with HSV-1 and HSV-2; these were counted separately as reports for both HSV-1 and HSV-2. Since 2004, type-specific serology reports were also available in the laboratory database. However, given the extremely low volume of type-specific serologic tests performed between 2004 and 2006 (N=193), these test data were not used to describe type-specific serologic trends.

Given that physician visits within 30 days after a client's last visit may be accounted for by treatment follow-up these records (N=44,084, out of 340,442 original physician billing records) have been excluded from the analysis. Similarly, hospital discharges, which were recorded within 30 days after a patient's last hospital discharge date (N=307, out of 9,913 original hospital discharge records), have been excluded from the analysis.

Annual rates per 100,000 population were calculated for the following: total clients billed and clients with first visits billed for herpes simplex related physician services; total patients discharged and patients with first hospital discharges with herpes simplex related diagnosis; and positive laboratory viral identifications. Due to the absence of unique patient identification in PHSA laboratory data, first and repeat tests for each person could not be identified in these data.

Health Authority was assigned to each case according to the following descending criteria: 1) case residence, or 2) clinic, hospital or ordering physician address. Age at date of specimen received at BCCDC was used in laboratory data analysis. Age at physician

service date was used in physician billing data analysis. Age at hospital discharge date was used in the general hospitalization data analysis, while age at admission date was used to analyze neonatal herpes-related hospitalization. Women of reproductive age were defined as women who were aged 15-44 years. Because only "year and month" of date of birth were recorded in the original MSP and DAD datasets, the "day" of date of birth has been tentatively valued as "01" for calculation purposes. This process likely has an impact on identification of neonatal cases from the physician billing and hospital discharge data sources.

2. Analysis of Trends by Site of Viral Identification

Information regarding specimen site(s) were available in the laboratory viral identification test data and records were divided into eight categories: genital sites (i.e., sites labeled as penis, vagina, vulva, cervix, clitoris, introitus, labia, perineum, anus, perianal region, rectum, groin, and pubic), oral-labial sites, skin lesion, ocular sites, cerebrospinal fluid (CSF), nasal sites, other sites (including multiple sites), and site-unspecified. Trends by sites of viral identification were analyzed by year, with a focus on genital identifications of HSV-1 and HSV-2.

3. Analysis of ICD Codes

ICD-9 diagnosis codes[2] were used to classify the infection or diseases caused by HSV in the physician billing data (1992 to 2006) and the early hospital discharge data (Jan 1992 to Mar 2001). ICD-10-CA[3] diagnosis codes were used in the recent hospital discharge data (Apr-2001 to Dec-2006). To produce comparability of the diagnosis classification, all diagnostic codes were re-classified into 11 categories (Appendix 2). In the hospital discharge data analysis, individuals who had any diagnosis of herpes simplex related disease (including the most responsible diagnosis (MRDx) were included in the overall trend analysis of HSV cases in BC. More specific analysis by age, gender, diagnosis type, and duration of hospitalizations were focused on patients who had MRDx related to herpes. Trends were analyzed by year, with a focus on genital herpes and neonatal herpes cases.

4. Analysis of Neonatal Herpes Cases

Datasets were analyzed to provide a comprehensive description of trends in neonatal herpes infection in BC from 1992 to 2006. A case definition of neonatal herpes simplex infection was developed to capture neonatal cases and reports in BC between 1992 and 2006 (Appendix 3). For this study, the neonatal period was extended to 60 days of life to include late diagnoses outside of the conventionally defined neonatal period (0-28 days).

[2] ICD9.chrisendres.com. access on January 16, 2008 at: http://icd9cm.chrisendres.com

[3] World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision. Version for 2007. Website access on January 16, 2008 at: http://www.who.int/classifications/apps/icd/icd10online

Given the confounding influence of maternal antibodies, serologic test results were not used for developing a case definition of neonatal herpes infection.

Based on the case definition, neonatal herpes cases were identified from physician billing and hospital discharge data. However, due to the absence of unique patient identifiers, only laboratory reports of HSV in neonates, but not unique cases, can be identified from laboratory data. The number of neonatal herpes cases and positive test results were analyzed by year. The rate of neonatal herpes cases and positive test results were calculated per 100,000 live births.

5. Analysis of Repeat Visits and Hospitalizations

Analysis related to frequency of and the interval between repeat visits and hospitalizations can help indicate the frequency of service utilization attributable to herpes. The frequencies and number of repeat physician visits were described in general, and in specified subgroups by five and one year cohorts for individuals with a first physician billing after 2000. Earlier cohorts were excluded from the analysis because the study period (1992 – 1999) may not capture the majority of first visits of clients in these cohorts.

RESULTS

PROVINCIAL TRENDS IN HSV LABORATORY TESTS

1. Trends in Serologic Tests

Between 1992 and 2006, 45,052 HSV serologic tests were performed by PHSA Laboratory Services in BC. In general, serum with a positive IgG result would be followed by an IgM test and the combined results would be reported. Type-specific serologic tests were introduced in 2004 and a small volume was performed in the following two years. In total, 37,836 IgG tests, 26,999 IgM tests, and 193 type-specified serologic tests were conducted during the study period.

In total, antibody to HSV was detected in 24,744 (54.9%) tests (combined results), the majority of which were positive for anti-HSV IgG antibody (N=24,357), with or without other positive test results (Figure 1). The number of HSV serologic tests and positive reports increased approximately five-fold in BC in the study period. Considering IgG tests only, the percentage of positive tests was stable before 1999 (69.0% in 1999) and decreased slowly thereafter (61.1% in 2006). Positive IgM tests remained in small number (ranged from 35 to 171 per year) over the study period. Although the number of type-specific serologic tests performed has been low since the introduction of these tests in 2004, the number of positive HSV-1 serologic test results remained twice as large as that of HSV-2 in the recent three-year period (Figure 1). Similar trends in rates of positive serologic tests are shown in Figure 2.

Serologic test results among STI clinic attendees (a known high risk group for HSV acquisition) from the STI clinic database has been analyzed for the period of 1996 to 2007

(Figure 3). While overall the number of serologic tests performed has increased, particularly in 2007 following expanded availability of type-specific testing, the overall percentage of positive tests has decreased over time.

2. Trends in Viral Identification Tests

Between 1993 and 2006, a total of 66,410 identifications of HSV were reported by PHSA Laboratory Services, including 30,945 (46.6%) HSV-1, 34,966 (52.6%) HSV-2, and 523 (0.8%) HSV (type-unspecified). Trends in total rate and rates by viral type are shown in Figure 4. Dramatic variable rates were observed before 1997, which likely reflects poor quality of laboratory data (i.e., due to different data collection procedures). Since 1997, the rate of total identifications of HSV remained relatively stable (2006 Rate: 125.7 per 100,000 population), reflecting the combination of an increasing trend in HSV-1 and the slightly declining trend in HSV-2 identifications in this period (Figure 4-5). The percentage of identifications of HSV-1 increased steadily throughout the study period, from 37.9% in 1993 to 49.6% in 2006, while the percentage of HSV-2 decreased from 61.7% to 48.3% in the same period (Figure 6).

Detailed data regarding the total quantity of HSV culture or PCR tests were only available since February 2006 and the quarterly volume of testing appears to be stable between Q2 2006 and Q3 2007 (data not shown). It has been estimated that approximately 20,000 diagnostic tests for HSV are performed per year by the PHSA laboratory.[4] As changes in test quantity may influence rates of viral identification, we looked at data from the BC STI Clinic database from which total test volume can be measured. It was evident that approximately 500-700 HSV diagnostic tests were performed among STI clinic attendees per year since 1997, and that the percent positive test results remained relatively stable at approx. 28% throughout the study period (Figure 7). These tests would primarily have been performed on swabs of genital lesions.

3. Gender- and Age-specific Trends

Throughout the study period and in any single year, significantly more laboratory-confirmed HSV-1 and HSV-2 infections were reported in females than males in BC (For any single year, $p<0.001$; Figure 8-9). The overall increasing trends in HSV infection were evident for all age groups (Figure 10) with the highest rates among persons 15-44 years of age. In 2006, people aged 20-24 years had the highest rates of HSV-1 positive test results, while the 20-29 age groups had the highest rates of HSV-2 positive test results (Figure 11). Identifications of HSV-2 were rare in people who were younger than 15 years.

Similar trends were observed among women of reproductive age, with overall increased rates of positive serologic test results (2006 Rate: 172.7 per 100,000 population) and viral identifications (2006 Rate: 310.4 per 100,000 population) throughout the study period (Figure 12-13).

[4] Annie Mak. PHSA Laboratory Service, BCCDC. Personal Communication, 2008.

4. Trends by Site of Viral Identifications

The trend for viral identifications by specimen site showed substantial variation in 2006 compared to previous years (indicated by dashed lines, Figure 14-15), which is attributed to changes in requisition form processing instituted in 2006.[5] For this reason, and due to possible data quality issues prior to 1997, detailed trend analyses by specimen site focused only on identifications of HSV-1 and -2 between 1997 and 2005 in BC.

Throughout 1997 to 2005, the largest overall number and rates of detection of HSV were detected in genital specimens, followed by skin lesion and oral-labial specimens (2005 rates per 100,000 population: 69.5, 16.2, and 11.7, respectively; Figure 16). The number and rates of genital HSV identifications increased over this time period, from 2,128 (53.9 per 100,000) in 1997 to approx. 3,000 (more than 70 per 100,000 population) in recent years. In 2005, 52.1% of HSV identifications were due to genital herpes. Oral-labial identifications of HSV-1 increased 2-fold in the same period. However, HSV-2 has been rarely detected in oral-labial specimens (Figure 14-15, 17).

In children aged 0-14 years, the largest number of identifications of HSV were from oral-labial specimens, followed by skin lesion specimens (Figure 18). The percentage of genital identifications of HSV in this age group was approximately 5% (Total N=251), the majority of which were identified in older children (i.e. 10 to 14 years old). In the same period, approximately 60% and 40% of HSV cultures were from genital specimens in the 15-44 and 45+ age groups, respectively (Figure 19-20).

Caution should be advised in the certainty applied to interpretation of these trends, as specimen site information was missing for a relatively large number of HSV identifications throughout this time period (22.9% of all identifications; Figure 16).

TRENDS IN GENITAL IDENTIFICATIONS OF HSV

Data were analyzed on a total of 25,216 viral diagnostic tests with HSV-1 and HSV-2 detected in genital sites during the period 1997 to 2005 in BC. Of these, 10,001 (39.7%) were HSV-1 and 15,215 (60.3%) were HSV-2. The number of genital HSV diagnoses increased to a peak in 2003 and slightly decreased thereafter (Figure 22). Similar trends are evident in each Health Authority (HA) in BC, with the highest rates of both HSV-1 and HSV-2 observed in Vancouver Coastal Health (VCH), followed by Vancouver Island HA (VIHA) and Fraser HA (FHA) (Figure 24-25).

More laboratory-confirmed genital HSV-1 and HSV-2 infections were identified in females than males (Figure 26). Female rates of genital HSV-1 increased significantly (significant trend, $p<0.001$), from 28.3 to 50.7 per 100,000 population between 1997 and 2005, while the rates of genital HSV-2 in females did not change significantly ($p=0.30$). In males, the rates of genital HSV-1 and -2 both increased significantly during this time period

[5] Annie Mak. PHSA Laboratory Service, BCCDC. Personal Communication. 2008

(p=0.002 and p=0.02, respectively), but were not as dramatic as the trends observed in female HSV-1 infection.

The highest rates of laboratory diagnosis of genital HSV occurred in those aged 15-29 years, followed by the 30-44, and 45+ age groups. Genital HSV infections were rarely reported in children younger than 15 years old (Figure 28). In regard to age-specific rates by viral type, the greatest increase in rates of genital HSV-1 occurred in the 15 to 29 age group, followed by the 30 to 44 age group (Figure 29), while the rates of genital HSV-2 were relatively stable in these two age groups during the same period (Figure 30). In addition, people in the older age groups (i.e. 30-44 and 45+ years old) have significantly higher rates ($p<0.05$) of genital HSV-2 infection than that of HSV-1, which was not observed in the 15 to 29 year age group.

In 1997, 32.8% of all genital infections were caused by HSV-1. This percentage rose to 45.1% by 2005 ($p<0.001$; Figure 23). The trend in percentage increase of genital HSV-1 occurred similarly in both males and females (Figure 27) and in all the three adult age groups (i.e. 15-29, 30-44, and 45+ years old) (Figure 31). The trend among the 5 to 29 age group is significantly greater ($p<0.05$) compared to older age groups. Women of reproductive age experienced similar trends in number of total genital identifications of HSV (Figure 32) and in the percentage of genital HSV-1 infection (from 37.0% in 1997 to 51.6% in 2005) (Figure 33).

TRENDS IN PHYSICIAN UTILIZATION

Between 1992 and 2006, there were 296,358 herpes-related physician billings in BC, which occurred in 208,560 persons. The trend in physician visits increased over the study period (Figure 34), implying an increased burden of herpes simplex related diseases on the health care system. As in our analysis we excluded visits occurring within 30 days of an earlier visit, these figures underestimate the total number of physician billings. The number of unique client billings in 2006 (N=25,041) was almost two times larger than that in 1992, while the 2006 rate (580.9 per 100,000 population) was 1.5 times higher than the 1992 rate (Figure 35).

The rate of persons with a first herpes-related visit (new client billing) appears to be significantly increasing since 2002 ($p=0.005$; Figure 35). Similar trends were observed in both genders, with significantly higher annual rates reported in females than males ($p<0.001$; Figure 36). While the rate of first herpes-related visits prior to 2002 showed a decreasing trend, it is more likely that persons with a first herpes-related visit between 1992 and 2001 had a herpes-related visit prior to 1992 (particularly closer to 1992, before the study period) and are misclassified as a first visit. The age distribution of persons with a first herpes-related visit in 2006 was similar with the age distribution shown in laboratory viral diagnosis data (Figure 11), but with higher rates in all age groups (Figure 37).

Of 208,560 total clients, 22.8% had more than one physician visit between 1992 and 2006. A similar result (21-22%) was found when this analysis was performed with persons with first herpes-related visits in 2000-2002 and repeat visits determined over the following five years (Table 1). Using a one-year period of follow-up, 9-10% of persons with a first

herpes-related visit between 2000-2005 had a repeat visit (Table 1). Surprisingly, in all analyses performed the median number of physician visits per person was one visit, with a similar maximum number of repeat visits observed in each cohort of observation.

The proportion of physician billings by diagnosis type is shown in Figure 38. Given the large proportion (86.0%) of physician billings with the non-specific ICD code "054" ("Herpes Simplex") in the MSP dataset, further analysis of physician billings related to genital herpes were not conducted.

TRENDS IN HOSPITAL UTILIZATION

Between 1992 and 2006, there were a total of 9,606 herpes-related hospital discharges reported in BC among 8,846 patients. Among these, 1,694 hospital discharges had a most responsible diagnosis (MRDx) related to herpes. Both the number and rate of total discharges related to herpes have declined since 1993, while the number and rate of discharges with a herpes-related MRDx decreased slightly before 1998 and has remained stable thereafter (2006 rate: 2.0 per 100,000 population) (Figure 39-40).

With regard to the associated diagnostic codes for the 1,694 discharges with a herpes-related MRDx, the largest proportion were due to oral-labial herpes (33.9%), followed by neurological herpes (17.7%), genital herpes (14.5%), and ocular herpes (12.6%). In patients aged 0-14 years (N=686), 70.4% had MRDx related to oral-labial herpes, while in patients aged 15 years and older (N=1008), neurological (26.8%), genital (23.3%), and ocular (18.1%) herpes MRDx were the most common (Table 2).

Figure 41 indicates the detailed age distribution of patients discharged from hospital with herpes MRDx in BC throughout the study period. Children aged 1 to 4 years had the largest number of discharges (Total N=435), which were mainly attributable to oral-labial herpes (83.0%). Persons in the 15 to 29 age groups had the largest number of discharges with genital herpes MRDx (45.2% in average), while people in the older age groups (i.e. 40+ years old) were more likely to have their hospitalizations caused by neurological (33.6% in average) and ocular (30.0% in average) herpes conditions (Table 3).

From 1992 to 2006, a generally decreasing trend was observed in the rate of patients discharged with a genital herpes-related MRDx (Figure 42), and the majority (89.1%) of these hospitalizations occurred in female patients (Figure 43).

NEONATAL HERPES SIMPLEX INFECTION

The annual number and rates of probable and possible neonatal herpes cases are shown in Table 4. Between 1993 and 2006, a total of 76 neonatal positive test results were reported in BC, including 34 HSV-1, 38 HSV-2, and four HSV positive, type not specified. Of the 76 positive test findings, 34 (44.7%) HSV strains were detected in clinically relevant specimens (i.e. skin, eye, mouth, and nose – probable cases), 22 (29.0%) were detected in genital specimens, and 20 (26.3%) were detected in other or unspecified sites (Table 5). Among the 34 viral laboratory diagnoses which met the probable case definition, there were

twice as many HSV-1 (N=22) as HSV-2 identified (N=12); the rate of probable neonatal cases based on viral identifications ranged from 0.0 to 22.1 per 100,000 per year. In this same time period, 279 possible neonatal cases were identified from physician billing data (range 26.4 to 51.3 billings per 100,000 live births), and 26 probable and 18 possible neonatal cases were identified from hospital discharge data (range 0 to 13.1 discharges per 100,000 live births). Of the 44 neonatal hospital discharges identified between 1992 and 2006, four infants had a hospital diagnosis of congenital herpes simplex and 23 infants had a most responsible diagnosis related to herpes (Table 6). However, whether these four infants had laboratory confirmed HSV disease is unknown.

Due to the lack of a common, unique identifier between laboratory, physician billing and hospital discharge data, it was impossible to determine overlap between these data sources to derive a total probable or possible neonatal case rate.

DISCUSSION

This report describes the first systematic analysis of herpes-related laboratory and utilization data for British Columbia, and describes trends in HSV infections and related service utilization. This study reviewed existing HSV data from multiple sources, including data for approximately 90-95% of all HSV laboratory tests performed in BC[6], and a complete extract of all herpes-related physician billing and hospital discharge data in BC between 1992 and 2006, with a particular focus on data related to genital and neonatal herpes infections. Below the key findings from, and the observed value and limitations of these data sources are discussed. Finally, we propose recommendations for improving herpes-related surveillance in British Columbia.

HSV-RELATED DISEASE BURDEN IN BC

Overall, laboratory trends have been relatively stable over this period of analysis, with a stable percentage of laboratory diagnosis by serology, number and rate of isolation in cell culture, and percentage of diagnoses by isolation in cell culture among STI clinic attendees. Trends in testing of genital specimens by isolation in cell culture have varied; however, the number with unknown specimen sites makes these trends more difficult to interpret. Isolations of HSV from genital specimens are representative of active lesions and are the best indicator of active or incident genital herpes infection.

While the total volume of tests performed for HSV has been increasing in BC since 1995, the interpretation of these results is problematic. The majority of testing by serology has been for IgG antibody which is diagnostic for infection with either HSV-1 or HSV-2, and is not specific to genital infection. The percentage of STI clinic attendees manifesting IgG antibody to HSV is less than seen in the overall province-wide population. This may be explained by the fact that testing for antibody to HSV is performed for many different clinical

[6] Mel Krajden. PHSA Laboratory Services, BCCDC. Personal Communication. 2008.

indications and not just as part of STI workup, and that STI attendees likely have a younger age distribution compared to the provincial population and may be less likely to have acquired HSV infection in the past.

While the utilization of the health care system for HSV, as monitored through physician billings shows an increase over time, hospital discharges (including discharges for genital herpes) have declined. These trends may be explained by an increasing incidence of HSV infection (as suggested by recent trends in number of clients with a first herpes-related physician billing), but may also be explained by the shift from inpatient to outpatient treatment, increased patient awareness leading to increased visits to physicians, and changes in physician coding practice. Overall, these data suggest an increasing outpatient burden of HSV-related diseases on the health care system in BC. Similar trends are evident in all Health Authorities in BC, with the largest disease burden been consistently evident in women and young adults.

In all analyses, females were disproportionately affected compared to males, possibly due to increased risk of disease, regular gynecologic exams, and health-seeking behaviors. Based on the number of specimens received over the 23 years analyzed, Tran et al. found that females were more likely to seek treatment than males, and whether this was due to a higher level of symptomatic infection in females could not be ascertained (Tran et al., 2004). Additionally, the higher proportion of women than men with a positive genital culture for HSV-1 versus HSV-2 may reflect a greater susceptibility of the female genital tract or a greater propensity to transmit HSV-1 by male-to-female oral-genital spread compared with the female-to-male route (Forward and Lee, 2003; Corey et al., 2004; Mertz et al., 1992).

This study reported approx. 9.1%-10.7% repeat visits rates in six recent 1-year cohorts after symptomatic first-episode infection, with the majority of clients over varying time periods having a single physician billing. This pattern of service utilization differs from reported clinical recurrence rates, as in the prospective cohort study of Benedetti et al. 1994, which reported 38% of patients with HSV-2 symptomatic first-episode had at least 6 recurrences during the first year and 20% had more than 10 recurrences. Given that recurrent episodes tend to be less severe (PHAC 2007), it is reasonable that individuals with recurrent genital herpes have decreased need for physician care. It is also likely that clients receive herpes-related care at physician visits assigned another diagnostic code. Additionally, as visits within 30 days of an earlier visit were excluded in this analysis, repeat visits may have been underestimated. This analysis suggests that service utilization data is a poor proxy for clinical recurrence and may underestimate the total service utilization related to herpes. Few other Canadian studies have looked at herpes-related health care utilization data, and our study has provided a valuable contribution to the published information on herpes in this respect.

From the health economic point of view, Szucs et al., 2001, using two costing approaches estimated the economic burden of genital herpes in the United States. In the cross-sectional study, based on an estimated 3.1 million symptomatic episodes per year in the USA, the annual direct medical costs were estimated at a maximum of $984 million. Of these costs, 49.7% were caused by drug expenditures, 47.7% by outpatient medical care and 2.6% by hospital costs. Indirect costs accounted for further $214 million. The analysis of

1,565 genital herpes cases from the claims database yielded a minimum national estimate of $283 million direct medical costs. Due to lack of relevant data, our study did not estimate the economic burden of genital herpes in BC. However, given the increased yearly physician billings and serologic test volume, it is likely that BC is undergoing an increasing trend in direct costs related to HSV.

Several limitations need to be taken into account in interpretation of the study findings. The first and most important limitation is that both the true prevalence and incidence of HSV infection and genital herpes cases can not be measured in the present study due to the following reasons. Firstly, it is well known that a large proportion of people with serologic markers of HSV infection are asymptomatic, and many cases of genital herpes are subtle in their presentation (Corey & Handsfield, 2000). Based on the antenatal seroprevalence study conducted in Canadian women, a large number of people are infected with HSV-2 but are not aware of it as they are asymptomatic (Patrick et al., 2001). In a study conducted in the United States, Wald et al. has reported up to 75% of people with serologic markers of HSV-2 infection have not had their infection status diagnosed (Wald et al., 1997). Furthermore, the natural history of genital HSV-1 infection is relatively more mild compared to that of HSV-2 (Engelberg et al.,2003). These may help explain the different rates and age distribution of HSV cases demonstrated in this study from those findings based on seroprevalence surveys (Howard et al., 2003; Patrick et al., 2001).

The second reason is that HSV infection is a chronic infection and includes intermittent virus reactivation with or without associated recurrent symptoms (Corey & Spear, 1986; Corey et al., 1983). Benedetti et al., 1994, reported that almost all persons with initially symptomatic HSV-2 infection have symptomatic recurrences. More than 35% of such patients have frequent recurrences. The average recurrence rate decreases over time by around 0.8 outbreaks per year, every year (no matter how high the initial outbreak rate was). However, approx. 25% of patients reported more recurrences in year 5 than year 1, evidence again of the substantial inter-individual differences in recurrence rates (Benedetti et al., 1999). Due to this recurrent nature of this infection, it is possible that our laboratory data includes individuals with more than one positive test result. Due to a lack of unique identifying information we were unable to determine whether positive laboratory tests were from primary or recurrent infections and therefore cannot estimate how closely our numbers reflect incident infections.

In the physician billing data analysis, the rate of persons with first HSV-related physician visit appears to be significantly increasing since 2002 in BC, and trends observed in recent years likely reflect the profile of trends in first physician visits for HSV infection in BC. Of all potential indicators identified in this analysis, first physician visits may be the best proxy for the incidence of HSV infections. However, given the limitations of utilization data discussed above, further research validating the association of this indicator with HSV incidence is required.

The third limitation concerns the potential for testing and utilization biases to affect these results, and it is difficult to predict the direction of these biases. For example, groups at risk of HSV infection may differ in their health-seeking behaviors which would affect both testing and utilization trends. This study also analyzed data from a 15 year period, and unrecognized

changes in health seeking behavior, health care accessibility, and improvements in laboratory diagnosis may have affected these results. Furthermore, without a unique patient identifier in laboratory data it was impossible to link serologic and viral identification data. As a result, to what extent the two types of test influenced patient uptake and frequency of testing is unknown. Such issues may be even more complex when considering the different sensitivity and specificity of different test protocols.

The fourth major limitation is data quality, which affect prospects for future surveillance of HSV cases in BC. Several barriers have been encountered in the present study. The large number of non-specific diagnosis coding presented in the physician billing data source has negated any analyses related to genital herpes-related physician visits.

Due to the data quality issues, some analyses of viral identification data had to be restricted to the time period following 1997 due to uncharacterized data quality issues before this year. Furthermore, the analysis of viral identification data by specimen site has been restricted to the period before 2005, as a result of the dramatic change in documentation of specimen sites following the institution of a new laboratory report system in 2006 and unreliability of specimen site data after this time. However, even prior to this date there is a relatively large number of specimens where the site has not been documented, which may potentially bias the trends observed in genital HSV identifications in BC. As information regarding to annual volume of viral identification tests was unavailable, results on positive viral identifications are difficult to interpret.

Finally, more detailed information, such as demographic information (e.g. ethnicity, immigration status, etc), risk factor information (e.g. number of sexual partners, condom use, HIV infection status, history of other STI, etc), maternal information for neonatal cases (e.g. maternal age, intra-partum genital HSV lesions present, etc), and economic information (e.g. direct cost of physician services), were not available from current data sources. Such data should be sought for future research

CHANGING DISTRIBUTION OF GENITAL HERPES

This study demonstrates an increase in the proportion of genital HSV cases due to HSV-1 in BC. In 1997, 32.8% of all genital infections were caused by HSV-1. This percentage rose to 45.1% by 2005 ($p<0.001$). This result confirms those from other regions in Canada and other countries. In a recent study conducted in Nova Scotia, Forward and Lee reviewed 6,529 HSV genital cultures taken between 1998 and 2001 and found that HSV-1 was the predominant isolate from genital specimens (Forward & Lee, 2003). In a retrospective study conducted in Melbourne, Australia, Tran et al. reported that in 1980 only 15.8% of HSV positive genital specimens were HSV-1 compared to 35.9% in 2003 (Tran et al., 2004). In a review of cultures submitted to a Kentucky virology laboratory, Ribes et al noted a trend of increasing HSV-1 rates in both men and women. Between 1994 and 1999, the proportion of genital cultures positive for HSV-1 rose from approximately 27% to 45% (Ribes et al., 2001).

Our study indicates that the greatest increase in the proportion of genital HSV-1 cultures is occurring in females, and younger adults, particularly the 15-29 year age group. People 30 years of age or older had significantly higher rates of genital HSV-2 infection than that of HSV-1. However, in the 15 to 29 age group, rates of HSV-1 and -2 tended to be equally

distributed in recent years in BC, particularly in females. Similar findings have been reported in the recent Nova Scotia study (Forward & Lee, 2003) and Tran et al.'s Australia study (Tran et al., 2004). In addition, Vyse et al. found that HSV-1 seroprevalence increased in individuals between 15 and 24 years of age, suggesting HSV-1 transmission in adolescence and young adulthood may be due to sexual transmission (Vyse et al., 2000). They concluded that a significant proportion of the HSV-1 seropositivity was due to genital infection and that HSV-1 was the predominant cause of genital herpes in the United Kingdom.

Factors which may explain the changing epidemiology of HSV genital infection include a reduction in the acquisition of HSV-1 in childhood associated with improved hygiene or living conditions. Evidence exists that immunity resulting from HSV-1 infection reduces the likelihood of symptomatic genital HSV-2 infection (Xu et al., 2002) and prevents subsequent genital HSV-1 infection. As a result, more individuals may reach adulthood without specific immunity to HSV-1, and may be more susceptible to HSV-1 genital infection more likely to present with a clinically apparent infection (Gibson et al., 1990; Christenson et al., 1992). In the United Kingdom and Holland the prevalence of antibodies to HSV-1 has fallen since the late 1980s (Cowan, 2001). In the Netherlands, the decrease in HSV-1 seroprevalence was most striking in individuals younger than 25 years of age (60% in 1993 versus 50% in 1998) (Roest et al., 2001). This corroborates observations by others who have reported a decreased incidence of childhood oral-labial HSV infections in Europe (Stanberry et al., 1999; Vyse et al., 2000). While similar seroprevalence data is not available for BC, overall similarities in living standards existing in these countries/regions suggests a similar trend may be occurring here. A seroprevalence study would be useful to better examine these trends in BC.

Changes in sexual practices to include a greater frequency of oral sex (i.e. transmission of HSV-1 present in the oral-labial region to a genital area) may also contribute to the changing epidemiology of genital herpes. In teenagers, this may be due to avoidance of unwanted pregnancies or the perception that sexually transmitted infections are not transmitted by oral sex (Samra et al., 2003). Receptive oral sex within the previous two months has been associated with an increased likelihood of genital infection with HSV-1 (Lafferty et al., 2000). While these hypotheses may be related to the trends observed in BC in this report, information regarding sexual practices and other risk factors was not available in the data sources used. Further analytic studies are required to further understand the likely mode of acquisition of genital HSV-1 and -2 infections, as well as determine possible prevention strategies.

The current study has several limitations regarding the analysis of the changing distribution of genital herpes in BC. First, testing bias may present. Patients with genital HSV-1 are likely to have different clinical outcomes compared to patients with HSV-2 infection (Tran et al., 2004). The natural history of HSV-1 infection is relatively mild, particularly regarding the likelihood of recurrence, which has been estimated to be approximately one fifth that of HSV-2 during the first year after primary infection (Engelberg et al.,2003). As a result, it is possible that more patients with HSV-2 infection have accessed clinical care and laboratory testing, which may have a conservative effect and under-estimate the increasing proportion of HSV-1 genital herpes in BC. On the other hand, individuals with

a first episode of genital herpes due to HSV-2 when HSV-1 antibody is present are clinically less severe (Xu et al., 2002), and may be less likely to get tested. This would bias away from the null and may result in an over-diagnosis of genital HSV-1 if clinical presentation with first episode is a major driver of diagnostic testing. Unfortunately, similar to the barriers encountered by the Nova Scotia study (Forward and Lee, 2003), due to lack of total test volume we do not have access to information on the frequency of identification of HSV-1 and HSV-2 from genital specimens before 2006 in BC, and we do not have data on whether the positive identifications were from primary or recurrent infection. In addition, individuals seeking STI tests may differ in risk practices or health seeking behaviors. Therefore, the changing epidemiology of genital herpes infection demonstrated in this study may not reflect the true trend in the general population in BC.

NEONATAL HERPES

Given the potential for serious and even fatal outcomes, neonatal herpes simplex infection is a significant public health concern in Canada and throughout the world. This analysis reviewed data from multiple sources in order to provide a comprehensive description of recent neonatal herpes epidemiology in BC. On the basis of the total 76 positive viral identification tests and BC birth statistics for the study period, the annual rates of neonatal positive HSV tests ranged from 2.4 to 29.5 per 100,000 live births between 1993 and 2005. Lower rates of neonatal herpes cases (ranged from 0 to 13.1 per 100,000 live births) were identified from hospital discharge data, and higher rates (ranged from 26.4 to 51.3 per 100,000 live births) were identified from physician billing data.

From October 2000 to September 2003, a total of four neonatal cases were identified from hospital discharge data in BC, which was consistent with the finding of the first national neonatal herpes incidence study conducted by the Canadian Pediatric Surveillance Program (CPSP), in which reports of neonatal herpes cases were solicited actively from all Canadian pediatricians and pediatric subspecialists in that period (Kropp et al.,2006). However, we cannot determine if we have identified the same four cases without a formal chart review, although the sexes of the cases we identified from those of the CPSP study differ. Our finding of less than 6 discharges per 100,000 live births found in BC in 2000-2003 resembles the national rate of 5.9 cases per 100,000 live births, and is similar to rates reported for European nations such as the United Kingdom (1.65 cases per 100,000 live births) (Tookey & Peckham, 1996) and Sweden (6.5 cases per 100,000 live births) (Malm et al., 1995). However, this rate has increased to 9.8 discharges per 100,000 live births in 2005 in BC. Moreover, in the ICD-10-CA coded data source, the neonatal herpes code was not part of the set of diagnosis codes used to create the initial data extract. Cases with this code were identified only if they had another diagnostic code(s) related to herpes simplex. To consider the potential for under-reporting, physician billing and viral identification test data were also examined resulting in much higher rates, comparable to rates reported for some jurisdictions in the United States (Whitley, 1990).

Overall, there was no significant difference in HSV-1 and HSV-2 infections among neonatal cases identified through viral identification data. However, when focusing on those

viral identifications that met the probable case definition, HSV-1 infection (N=22) occurred twice as frequently as HSV-2 infection (N=12), a finding consistent with the CPSP study that reported the majority of infant cases were typed as HSV-1 (Kropp et al., 2006), and incongruent with a number of older studies that found HSV-2 infection to be more prevalent (Whitley et al., 1988; Selin et al., 1988; Koskinimei et al., 1989; Fleming et al., 1989). In this report women of reproductive age also experienced an increase in the percentage of genital HSV-1 infection from 38% in 1997 to 51% in 2005 in BC (Figure 33) and one might expect to observe an increase in neonatal herpes cases due to HSV-1 in our analysis.

In addition, as mentioned in the CPSP study, an important consideration when interpreting the distribution of HSV-1 and HSV-2 cases is that it is difficult to demonstrate definitively when HSV transmission occurred. Some HSV-1 infected infants in this study might have acquired their infections from oral HSV-1 infections of family members and friends, but we are unable to determine what role, if any, this type of transmission played in this study. In fact, when the neonatal period of interest was narrowed from 0-60 days to 0-28 days, a dramatic decrease in cases identified from physician billing data source were observed, from 279 to 168 cases in total, while the decrease in cases identified from hospital discharge (from 44 to 34) and laboratory (from 76 to 63) data sources were not as obvious. This may be imply that with increasing age, infants acquire their infections from oral-labial HSV-1 infections of caregivers and developed less severe conditions and did not require hospital care. However, with limited information this assumption cannot be further tested.

There are a number of limitations to this study that need to be taken into account in interpretation of the results pertaining to neonatal herpes simplex infection in BC. First, the main limitation is related to the potential under-reporting and mis-reporting of cases. Because only “year and month” of date of birth were recorded in the original MSP and DAD datasets, the “day” of date of birth has been tentatively valued as “01” for calculation purposes. As a result, age in days presented in the analysis results may not be the real age (days) of a patient. This may lead to the potential failure to capture all neonatal cases from physician billing and hospital discharge data sources. In addition, due to the absence of a diagnosis code specific to congenital herpes simplex infection in the ICD-9 system, and the incomplete extraction of records with P35.2 code in the ICD-10-CA system, congenital herpes cases may have been missed. Furthermore, 29% of HSV infections in neonatal cases were classified as genital specimens, which is unlikely to be true and likely represents miscoding. The extent to which mis-reporting may occur and bias the results needs to be evaluated.

Second, given the absence of standard patient identifiers in all data sources and the absence of data on infant and maternal clinical information, we could not fully apply our case definition as we would likely be double- or triple-counting some infants who have simultaneous physician billings, hospital discharges, or laboratory results.

Third, because of the small number of cases reported, low statistical power made it difficult to demonstrate whether statistically significant associations existed between groups, and we cannot determine whether a statistically significant increase in the percentage of HSV-1 infection between 1993 and 2006 occurred.

Overall, these limitations suggest that the findings of this analysis with respect to neonatal herpes infection must be interpreted with caution, and should not be considered to be accurate indications of incidence trends without further validation.

RECOMMENDATIONS

Based on this analysis, recommendations for improving the future analysis of these datasets, and for surveillance for genital and neonatal herpes in BC as follows:

1. In future analyses of laboratory data, to request a data extract which includes unique patient identifiers in order to distinguish between first and recurrent results and link isolation or PCR data to serologic testing. Currently analysis of serologic testing is of limited value as type-specific testing is not widely available (this may change with increased use).
2. To consider the formal linkage of PHSA laboratory data to Ministry of Health databases (physician billing, discharge data) using nominal identifiers, as this linkage should allow for more accurate description of the burden of herpes-related disease in BC. This data linkage could also include linkage to pharmacare data to look at antiviral drug usage patterns.
3. This analysis has identified concerns with historic and prospective analysis of laboratory data due to data quality. Analysis of STI clinic data may be a more feasible and accurate approach for future surveillance, as this dataset has comprehensive information on clinical presentation, risk information, and demographics and focuses on a high risk group for HSV acquisition.
4. To improve the quality of the site of specimen collection field in laboratory data, through standardization of laboratory reporting procedures or through improvements to laboratory requisition forms, in order to reduce the number of records with missing or mis-reported specimen sites.
5. In further requests for MSP and DAD data from the Ministry of Health, to include full date of birth (for improved analysis of neonatal herpes case) and to specify that ICD-10CA codes for congenital herpes are also desired.
6. To conduct seroprevalence surveys in populations known to be at higher risk of HSV and HIV. For example, inclusion of HSV testing in newly formed second generation HIV surveillance systems in BC and in stored specimens from existing high risk cohorts (e.g., MSM, IDU), and repeating the anonymous seroprevalence survey in prenatal sera to identify the seroprevalence of HSV-1 and HSV-2 and examine changes in seroprevalence trends.
7. In general, these sources of data may be of less use in monitoring neonatal herpes infections in BC without further validation. Enhanced surveillance for neonatal herpes would likely be most successful if based on reported positive viral

identifications in infants under 60 days of age, with public health follow-up to collect corroborating clinical data and correctly identify neonatal herpes cases.

8. Given the demonstrated synergy between HSV-2 and HIV, a potential area for future surveillance would be to estimate the prevalence and attributable risk of HSV-2 among individuals with HIV infection in BC, through sero-prevalence studies or through linkage of provincial HSV and HIV-related laboratory data.

SUMMARY

This study suggests an overall increased burden of HSV disease on the health care system in BC, particularly among women. Overall, trends in laboratory testing have been relatively stable over this period of analysis, with a stable percentage of positive serology tests, number and rate of positive identifications, and percentage of positive cultures among STI clinic attendees. Trends in diagnosis of infection in genital specimens by isolation in cell culture have increased to a peak in 2003 and slightly decreased thereafter. We have also identified an increase in the proportion of genital herpes infection caused by HSV-1, similar to reports from elsewhere.

Recommendations for improving future analyses and enhancing surveillance for genital and neonatal herpes in BC have been proposed. These include recommendations to: improve the quality of future data extracts; initiate data linkage projects to link laboratory to utilization (physician billing, hospital discharge, pharmacare) data to better characterize the burden of herpes-related disease in BC; to conduct seroprevalence studies in populations at risk of HIV and HSV; and to further validate these data sources with clinical data prior to use as indicators of neonatal herpes incidence. Diagnosis by isolation in cell culture, although widely practiced is less sensitive than by PCR. Laboratories should be encouraged to convert to the latter platform for testing for HSV.

This analysis provides a comprehensive overview of these recent trends in BC, and serves as a baseline for the guidance and evaluation of ongoing and future herpes control initiatives. While the data sources used in this analysis have not proved sufficiently discriminatory to accurately measure trends in neonatal herpes infection, the disease burden in women of reproductive age and the approximately equal distribution of genital herpes caused by HSV-1 and HSV-2 in this population indicates that efforts to reduce neonatal herpes infection is of continued importance.

With limited data for this analysis, information regarding HIV infection and other risk factors were not available. However, given the consistent epidemiological evidence and biological plausibility of a significant interaction between HIV and HSV-2 (Corey 2007), reducing the impact of HSV-2 on HIV incidence would also be considered an important goal for provincial herpes prevention strategies.

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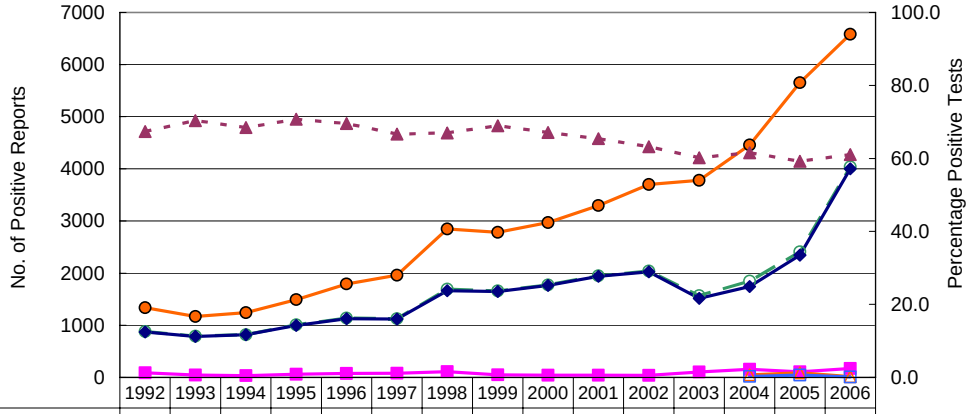
APPENDIX 1: TABLES AND FIGURES

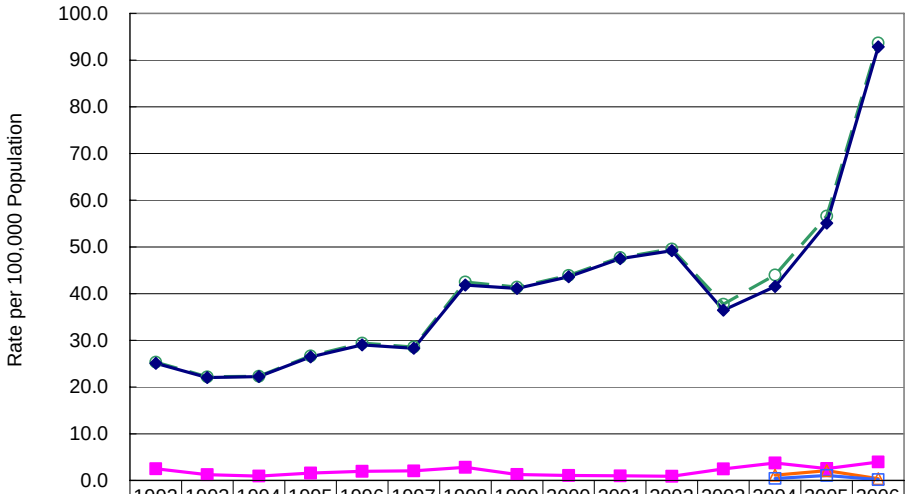
Figure 1 HSV Serologic tests (N=45,052), percent positive tests, and positive serologic reports (N=24,744) by test type, BC, 1992 to 2006
(Anti-IgG(+): N=24,357; Anti-IgM(+): N=1,202; HSV-1(+): N=154; HSV-2(+): N=71)



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
(+) Serologic Reports	879	792	820	1007	1139	1128	1692	1661	1774	1947	2040	1569	1848	2410	4038
Anti-IgG (+)	870	786	817	998	1125	1118	1665	1648	1761	1936	2026	1515	1745	2345	4002
Anti-IgM (+)	87	44	35	60	75	80	112	51	43	40	37	102	157	108	171
HSV-1 (+)													49	89	16
HSV-2 (+)													18	46	7
Serologic Test Volume	1336	1170	1240	1491	1792	1960	2846	2781	2968	3295	3698	3781	4459	5652	6583
% Positive IgG tests	67.4	70.4	68.5	70.7	69.6	66.7	67.0	69.0	67.1	65.4	63.2	60.2	61.6	59.2	61.1

Year

Figure 2 Rates of positive serologic tests by test type, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
(+) Serologic Reports Rate	25.3	22.2	22.3	26.7	29.4	28.6	42.5	41.4	43.9	47.7	49.6	37.8	44.0	56.6	93.7
Anti-IgG (+) Rate	25.1	22.0	22.2	26.4	29.0	28.3	41.8	41.1	43.6	47.5	49.2	36.5	41.5	55.1	92.8
Anti-IgM (+) Rate	2.5	1.2	1.0	1.6	1.9	2.0	2.8	1.3	1.1	1.0	0.9	2.5	3.7	2.5	4.0
HSV-1 (+) Rate													1.2	2.1	0.4
HSV-2 (+) Rate													0.4	1.1	0.2

Year

Figure 3 Trends in herpes serologic tests, BC STI Clinic database, 1996-2007

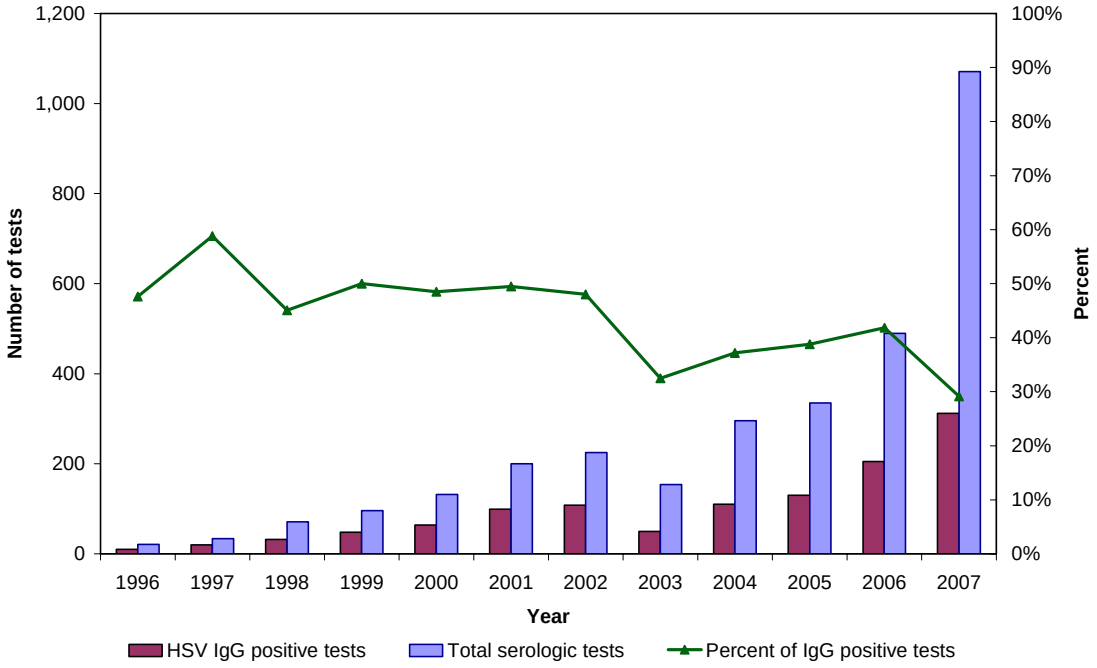
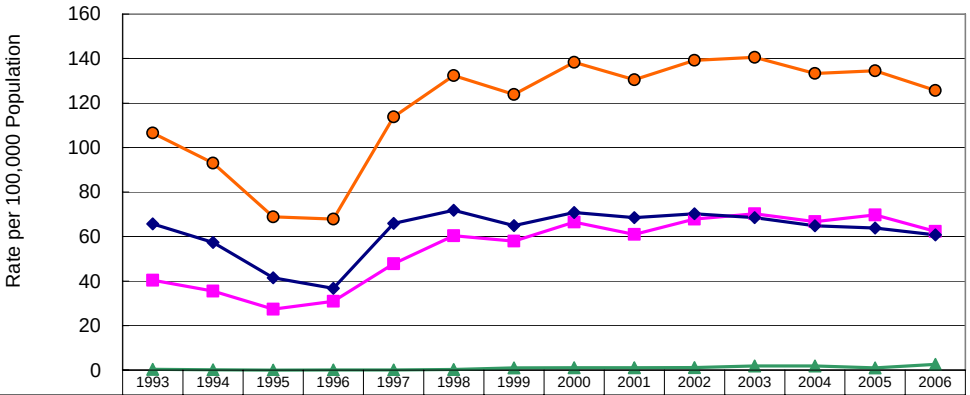


Figure 4 Rates of positive identifications of HSV (N=66,410) by viral type, BC, 1993 to 2006
(HSV-1: N=30,945; HSV-2: N=34,966; Type-unspecified: N=523)



	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# HSV-1(+)	1442	1306	1033	1200	1888	2404	2327	2687	2487	2793	2920	2803	2968	2687
# HSV-2(+)	2345	2108	1565	1424	2601	2861	2605	2862	2792	2893	2846	2726	2720	2618
# Type-unspecified HSV(+)	14	5	1	4	4	9	38	42	44	49	79	79	42	113
# Total (+)	3801	3419	2599	2628	4493	5272	4968	5589	5320	5730	5842	5606	5726	5417
HSV-1(+) Rate	40.4	35.5	27.3	31.0	47.8	60.4	58.0	66.5	61.0	67.9	70.3	66.7	69.7	62.3
HSV-2(+) Rate	65.7	57.3	41.4	36.8	65.9	71.8	64.9	70.9	68.5	70.3	68.5	64.9	63.9	60.7
Type-unspecified HSV(+) Rate	0.4	0.1	0.0	0.1	0.1	0.2	0.9	1.0	1.1	1.2	1.9	1.9	1.0	2.6
Total (+) Rate	106.5	93.0	68.8	67.8	113.8	132.4	123.8	138.4	130.4	139.2	140.6	133.4	134.5	125.7

Figure 5 Number of positive identifications of HSV by viral type, BC, 1993 to 2006

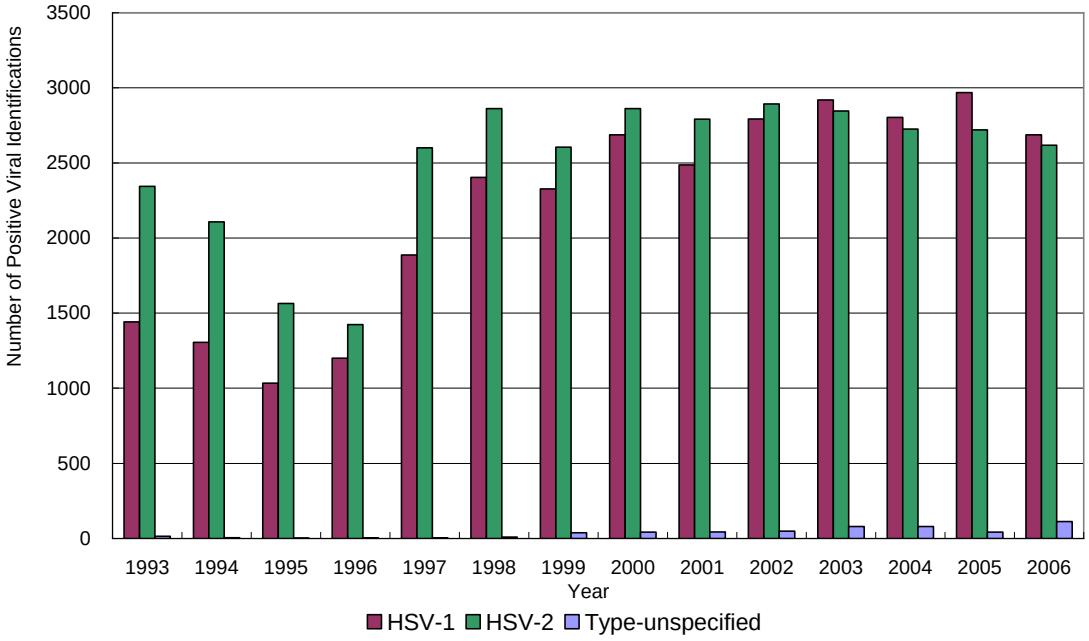


Figure 6 Percentage of positive identifications of HSV by viral type, BC, 1993 to 2006

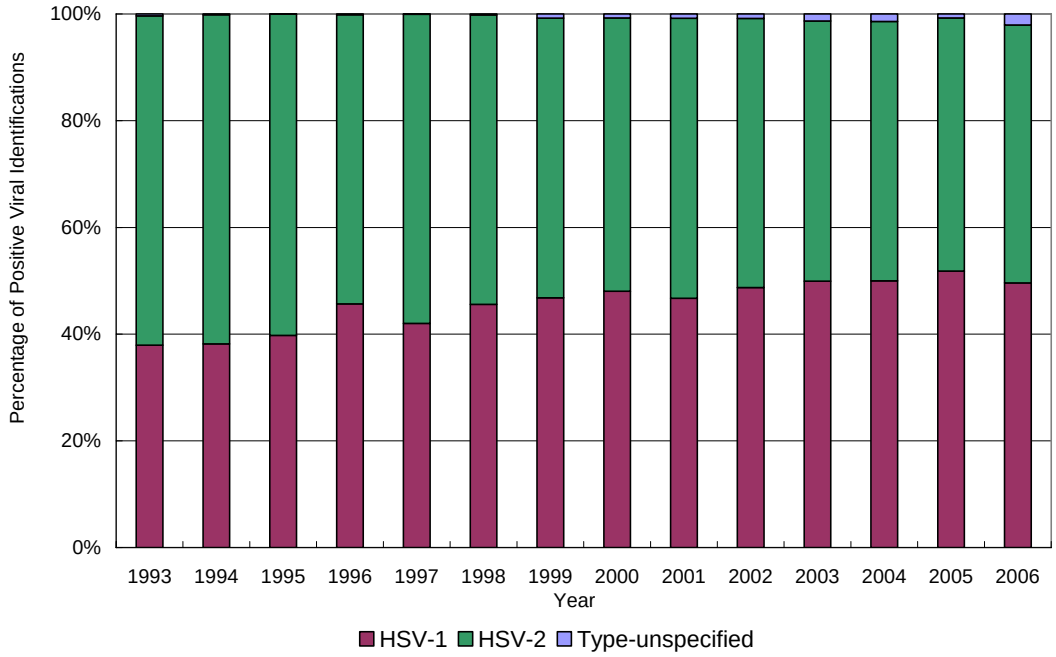


Figure 7 Trends in HSV identification tests, BC STI Clinic database, 1989-2007

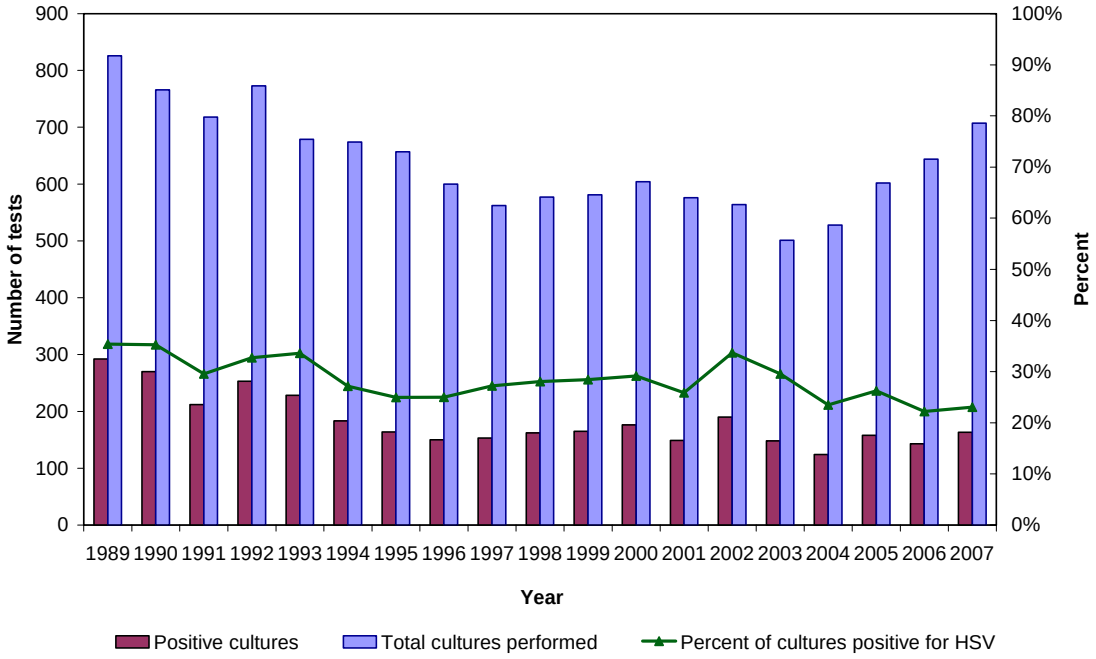
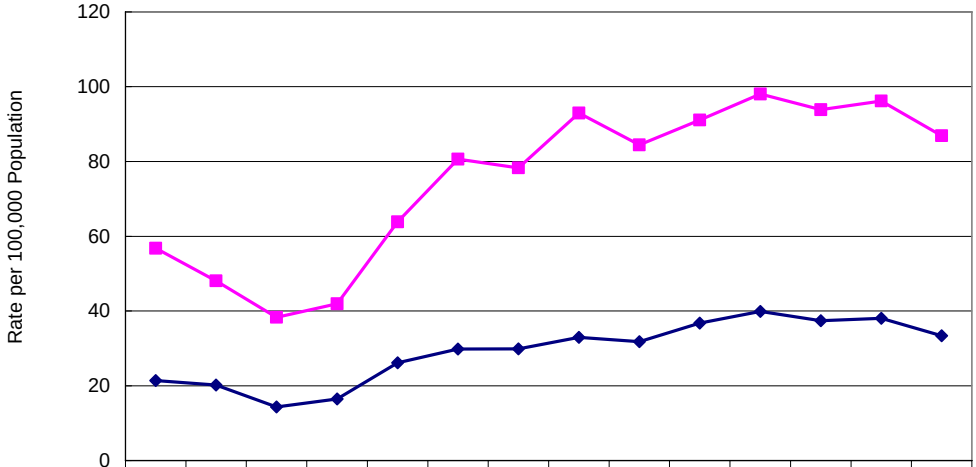
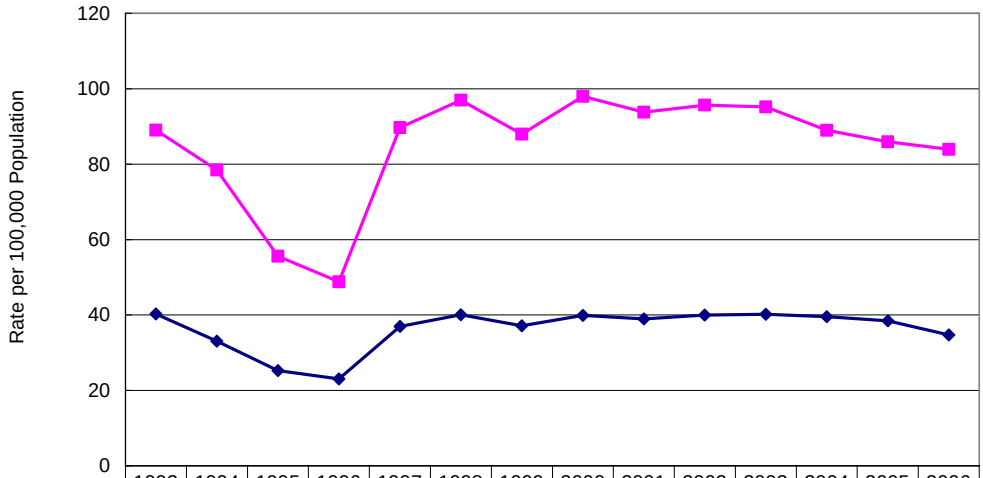


Figure 8 Rates of positive identifications of HSV-1 by gender, BC, 1993 to 2006



	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# Female	1016	887	726	815	1266	1614	1580	1889	1735	1889	2053	1989	2064	1888
# Male	380	370	270	318	514	591	596	661	644	751	822	780	803	713
Female Rate	56.8	48.1	38.3	41.9	63.8	80.6	78.3	92.9	84.5	91.1	98.0	93.8	96.1	86.9
Male Rate	21.4	20.2	14.4	16.5	26.2	29.8	29.9	33.0	31.8	36.8	39.9	37.4	38.0	33.4

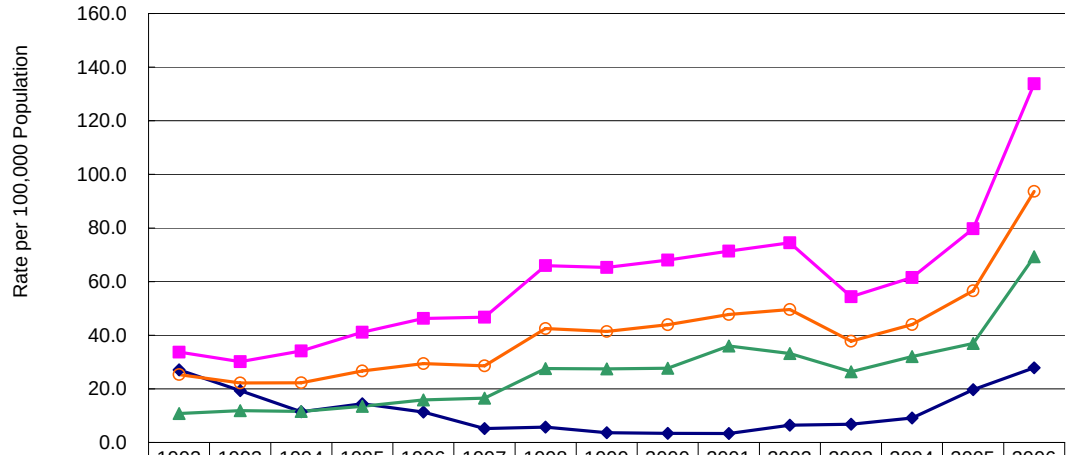
Figure 9 Rates of positive identifications of HSV-2 by gender, BC, 1993 to 2006



	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# Female	1593	1447	1054	949	1780	1942	1775	1992	1927	1985	1994	1886	1845	1824
# Male	716	606	476	445	726	794	740	801	789	816	828	824	811	742
Female Rate	89.0	78.5	55.6	48.8	89.7	97.0	88.0	98.0	93.8	95.7	95.2	89.0	85.9	83.9
Male Rate	40.3	33.1	25.3	23.1	36.9	40.1	37.1	39.9	39.0	40.0	40.2	39.5	38.4	34.7

Year

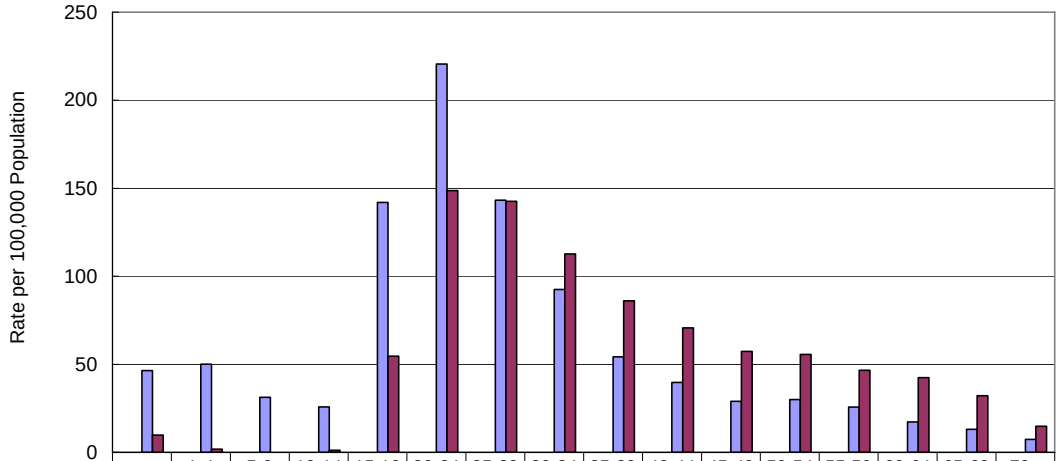
Figure 10 Rates of HSV positive serologic tests by age, BC, 1992 to 2006 - Both Gender



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
<15 yrs	27.1	19.3	11.5	14.4	11.3	5.2	5.7	3.6	3.4	3.3	6.4	6.8	9.1	19.7	27.8
15 - 44 yrs	33.7	30.2	34.1	41.1	46.3	46.7	66.0	65.3	68.1	71.4	74.5	54.3	61.6	79.8	133.8
45+ yrs	10.8	11.8	11.5	13.5	15.9	16.5	27.5	27.4	27.7	36.0	33.2	26.4	32.1	36.9	69.3
Total	25.3	22.2	22.3	26.7	29.4	28.6	42.5	41.4	43.9	47.7	49.6	37.8	44.0	56.6	93.7

Year

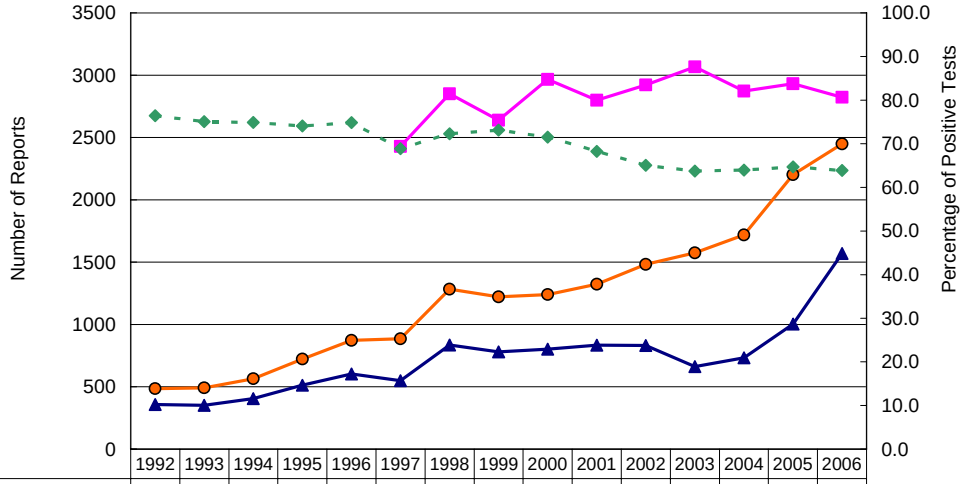
Figure 11 Rates of positive identifications of HSV-1 and HSV-2 by age, BC, 2006 -- Both Gender



	<1 yrs	1-4 yrs	5-9 yrs	10-14 yrs	15-19 yrs	20-24 yrs	25-29 yrs	30-34 yrs	35-39 yrs	40-44 yrs	45-49 yrs	50-54 yrs	55-59 yrs	60-64 yrs	65-69 yrs	70+ yrs
# HSV-1(+)	19	83	70	67	398	678	408	265	172	140	103	98	75	37	22	32
# HSV-2(+)	4	3	0	3	153	457	406	323	273	249	204	182	136	91	54	64
HSV-1(+) Rate	46.5	50.0	31.2	25.9	141.9	220.6	143.2	92.4	54.2	39.7	28.9	29.9	25.7	17.2	13.1	7.4
HSV-2(+) Rate	9.8	1.8	0.0	1.2	54.6	148.7	142.5	112.7	86.0	70.7	57.3	55.6	46.6	42.4	32.2	14.8

Age Group

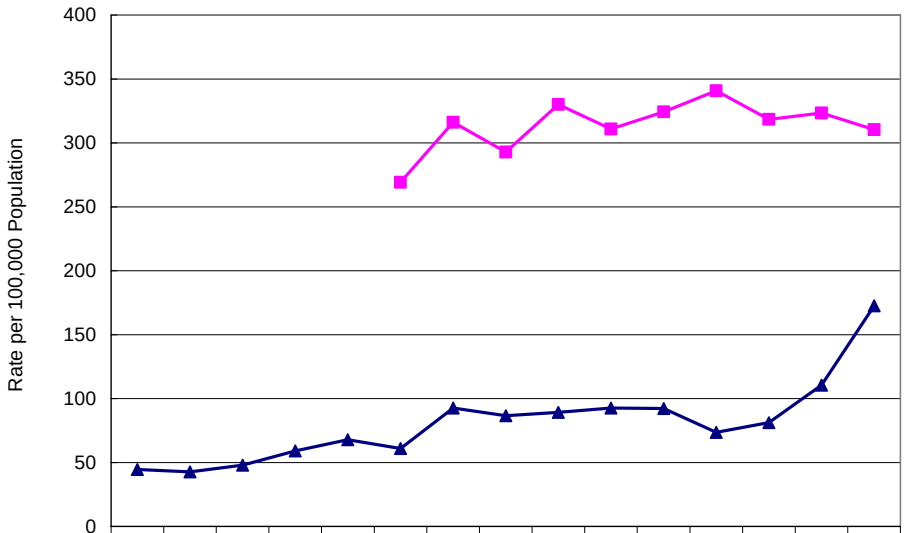
Figure 12 Positive identifications of HSV (N=28,302), HSV serologic test volume (N=18,524), positive serologic tests (N=10,835), and percent positive serologic test in women of reproductive age, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
(+) HSV Identifications						2429	2851	2639	2967	2799	2922	3067	2873	2932	2823
Serologic Test Volume	485	492	566	723	873	886	1284	1222	1241	1324	1483	1575	1718	2203	2449
(+) Serologic Reports	359	352	406	512	604	550	836	780	802	835	831	662	733	1003	1570
% (+) Serologic Tests	76.45	75.05	74.91	74.05	74.84	68.90	72.31	73.13	71.53	68.26	65.07	63.72	63.97	64.71	63.89

Year

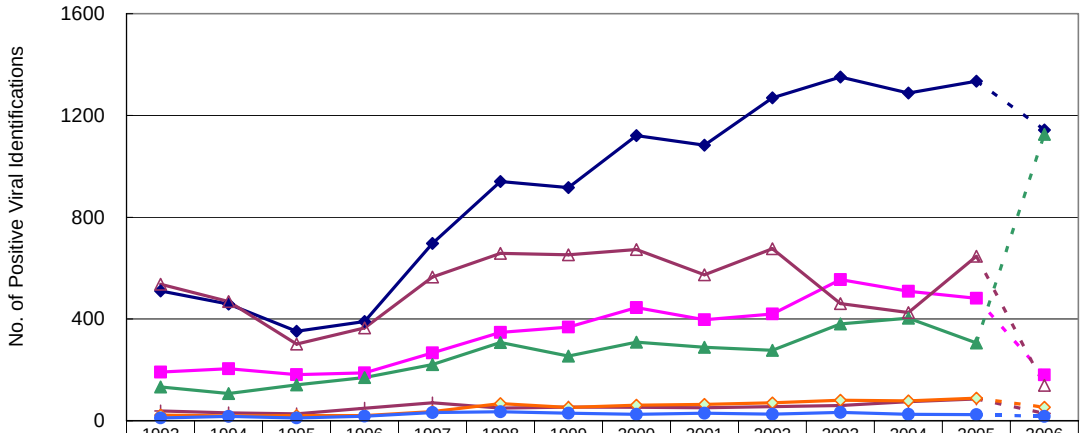
Figure 13 Rates of positive identifications of HSV and rates of positive serologic tests, in women of reproductive age, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Rate - (+) HSV Identifications						269.2	316.1	292.9	330.1	310.8	324.4	340.9	318.4	323.4	310.4
Rate - (+) Serologic Reports	44.5	42.7	48.0	59.1	67.9	61.0	92.7	86.6	89.2	92.7	92.2	73.6	81.2	110.6	172.7

Year

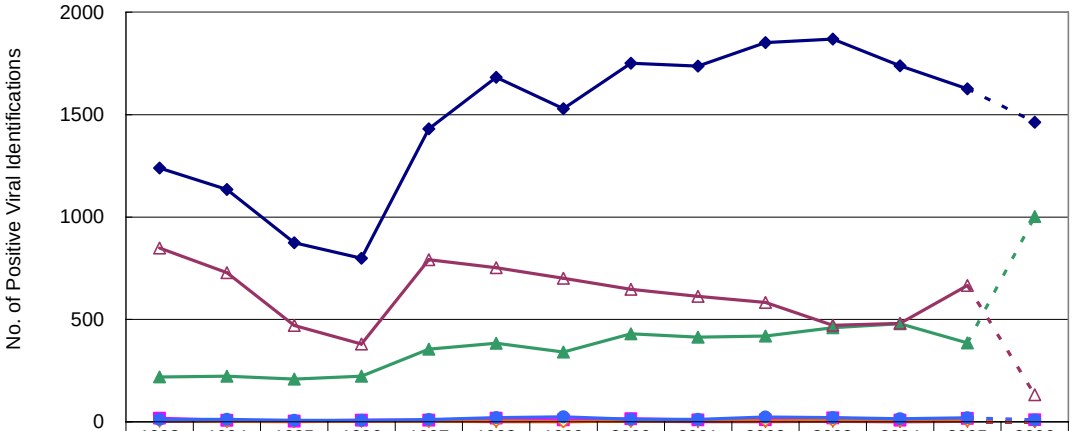
Figure 14 Positive identifications of HSV-1 by specimen site, BC, 1993 to 2006



	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Genital	510	459	352	390	697	940	917	1121	1083	1269	1351	1288	1335	1143
Oral-labial	191	204	181	188	267	347	368	445	397	420	555	509	481	180
Skin Lesion	133	107	141	170	221	307	254	309	289	277	381	403	306	1126
Eye	38	31	27	49	70	50	54	53	51	55	60	75	86	29
Nasal	22	19	20	20	36	67	52	61	64	70	80	78	89	53
Other sites	11	17	11	18	32	35	30	25	30	26	33	25	24	17
Unknown	537	469	301	365	565	658	652	673	573	676	460	425	647	139

Year

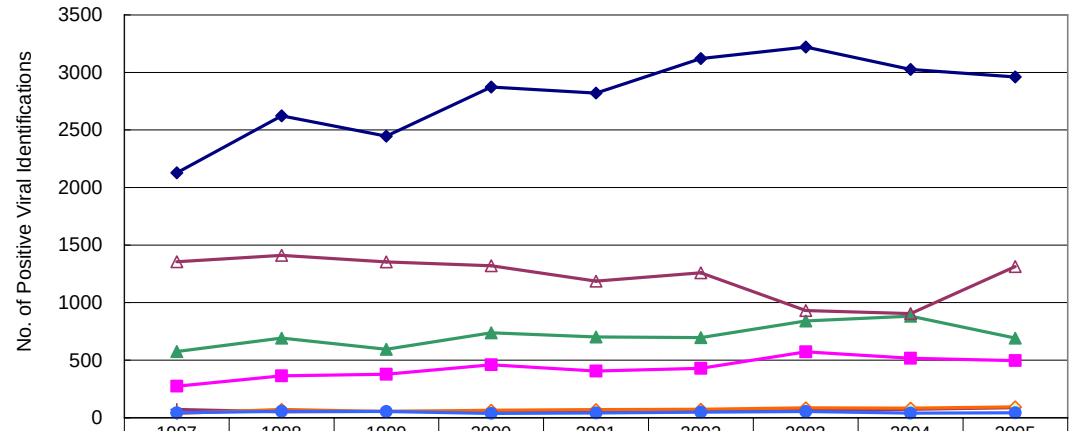
Figure 15 Positive identifications of HSV-2 by specimen site, BC, 1993 to 2006



	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Genital	1239	1134	874	799	1431	1682	1529	1751	1737	1852	1869	1738	1626	1463
Oral-labial	17	7	3	8	8	17	9	15	9	10	18	8	16	10
Skin Lesion	219	223	208	223	355	384	340	429	413	419	460	479	385	1002
Eye	3	2	1	4	3	1	1	3	1	1	2	0	2	0
Nasal	7	2	2	3	2	5	1	4	7	5	6	5	6	2
Other sites	12	12	7	7	11	20	24	13	12	23	20	15	19	9
Unknown	848	728	470	380	791	752	701	647	613	583	471	481	666	132

Year

Figure 16 Total positive identifications of HSV by specimen site, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
Genital	2128	2622	2446	2872	2820	3121	3220	3026	2961
Oral-labial	275	364	377	460	406	430	573	517	497
Skin Lesion	576	691	594	738	702	696	841	882	691
Eye	73	51	55	56	52	56	62	75	88
Nasal	38	72	53	65	71	75	86	83	95
Other sites	43	55	54	38	42	49	53	40	43
Unknown	1356	1410	1353	1320	1186	1259	931	906	1313

Year

Figure 17 Positive oral-labial identifications of HSV-1 (N=3,789) and HSV-2 (N=110), BC, 1997 to 2005

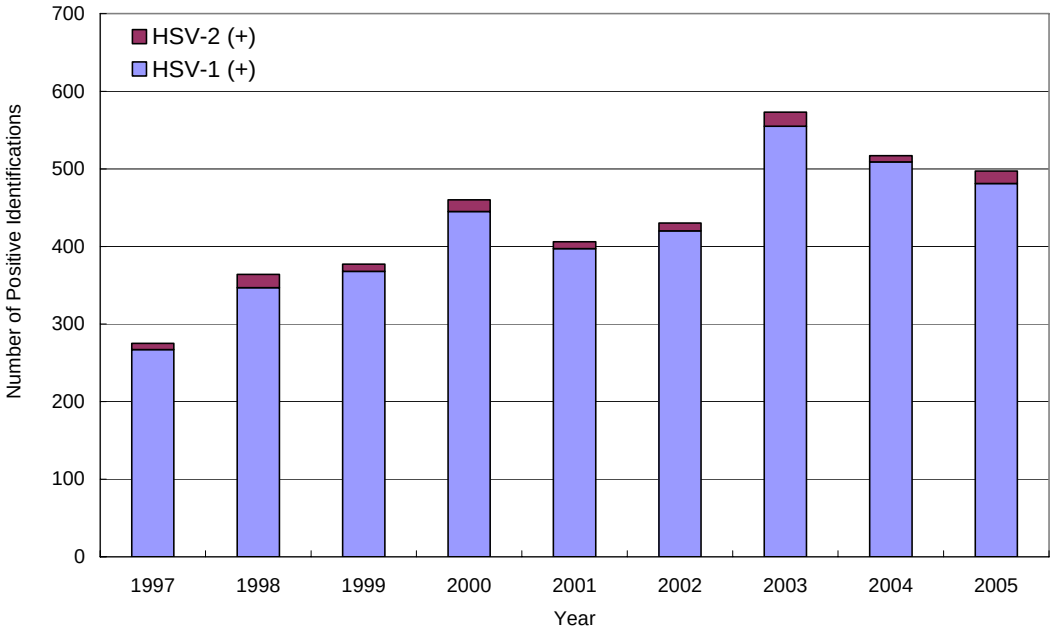


Figure 18 Positive identifications of HSV in 0-14 age group, by specimen site, BC, 1997 to 2005

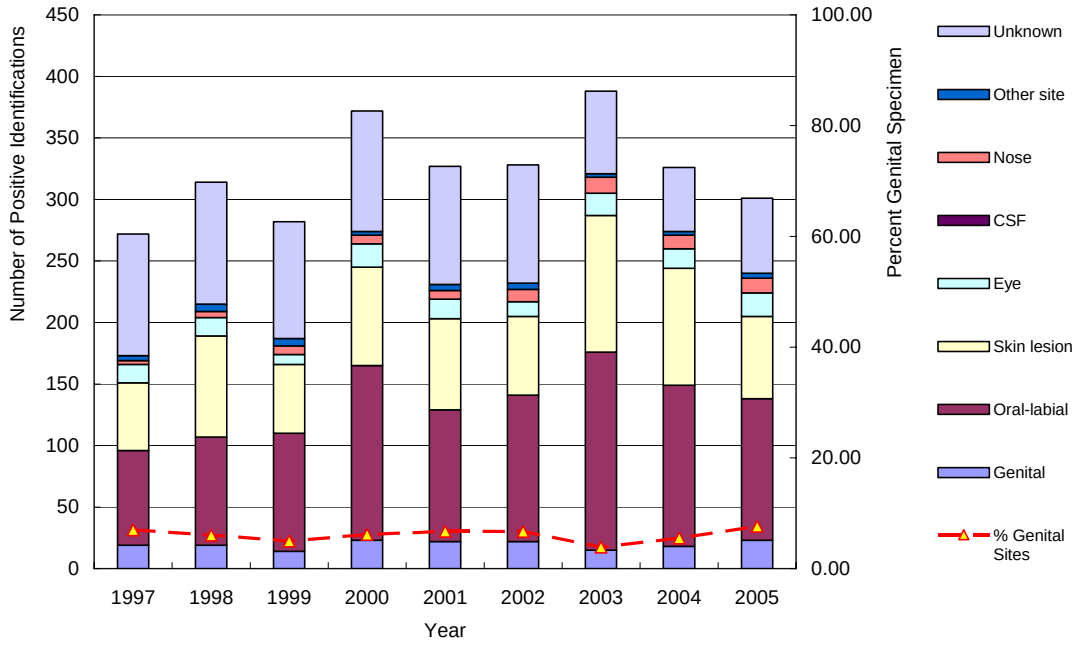


Figure 19 Positive identifications of HSV in 15-44 age group, by specimen site, BC, 1997 to 2005

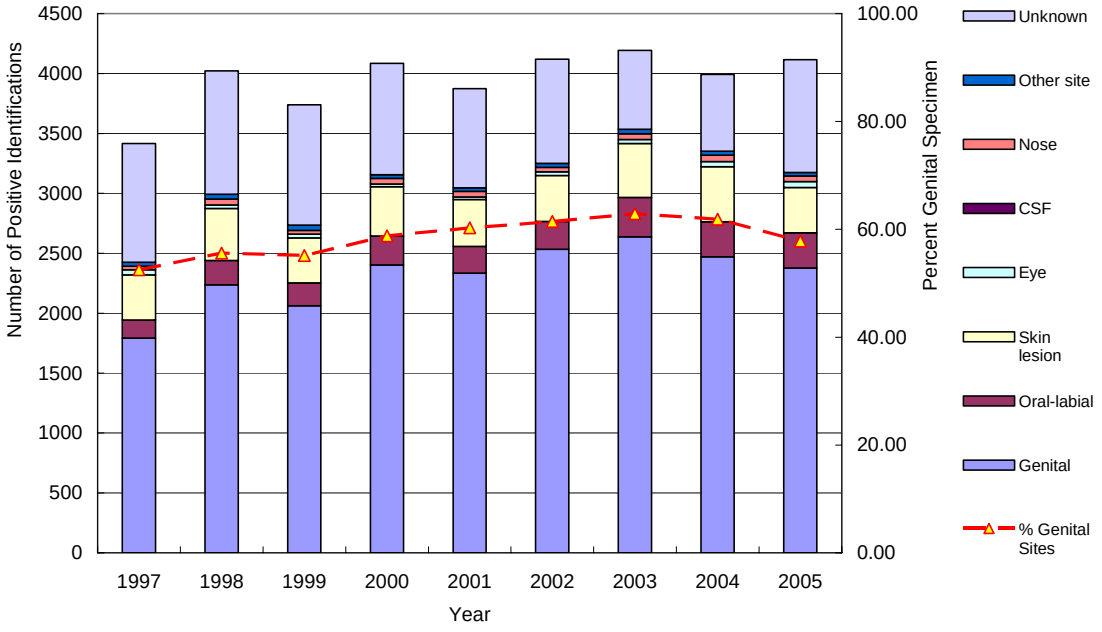


Figure 20 Positive identifications of HSV in 45+ age group, by specimen site, BC, 1997 to 2005

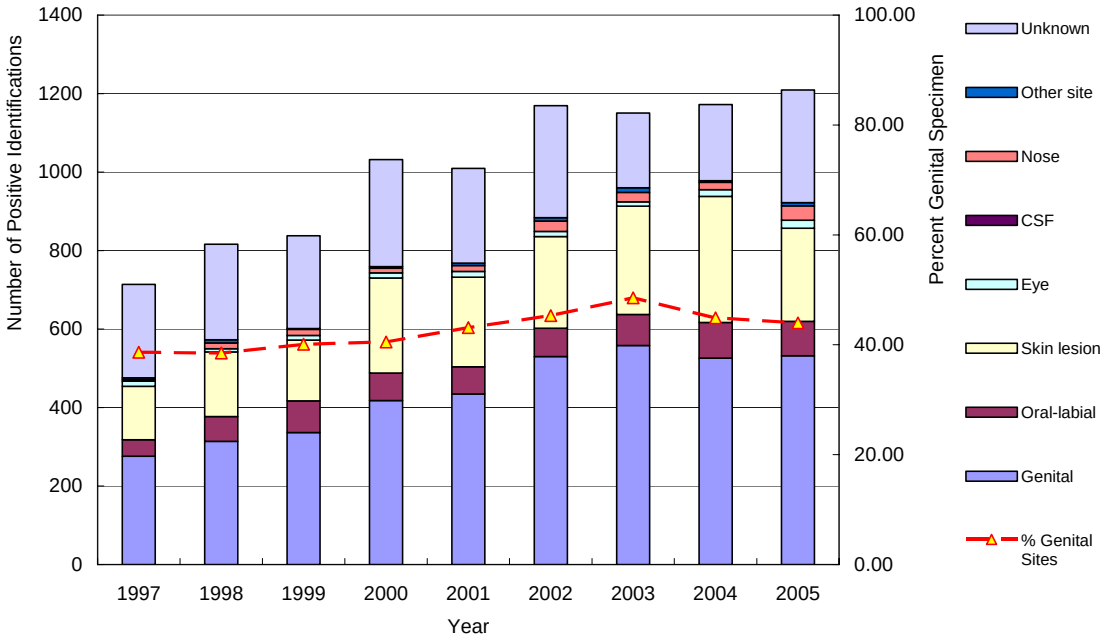


Figure 21 Positive identifications of HSV in women of reproductive age, by specimen site, BC, 1997 to 2005

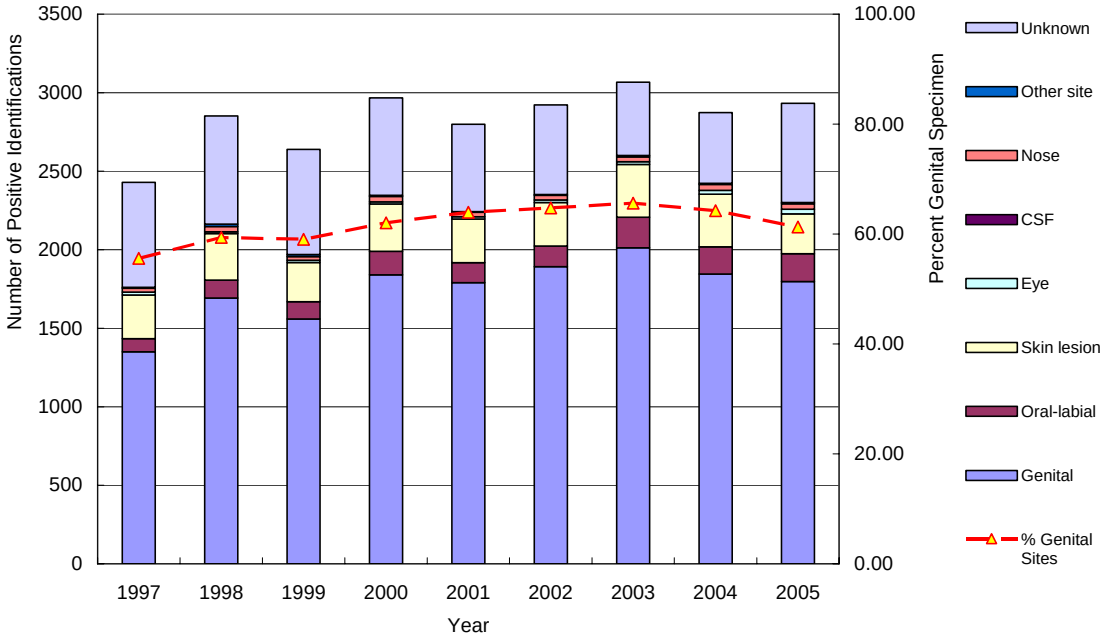


Figure 22 Positive genital identifications of HSV-1 (N=10,001) and HSV-2 (N=15,215), BC, 1997 to 2005

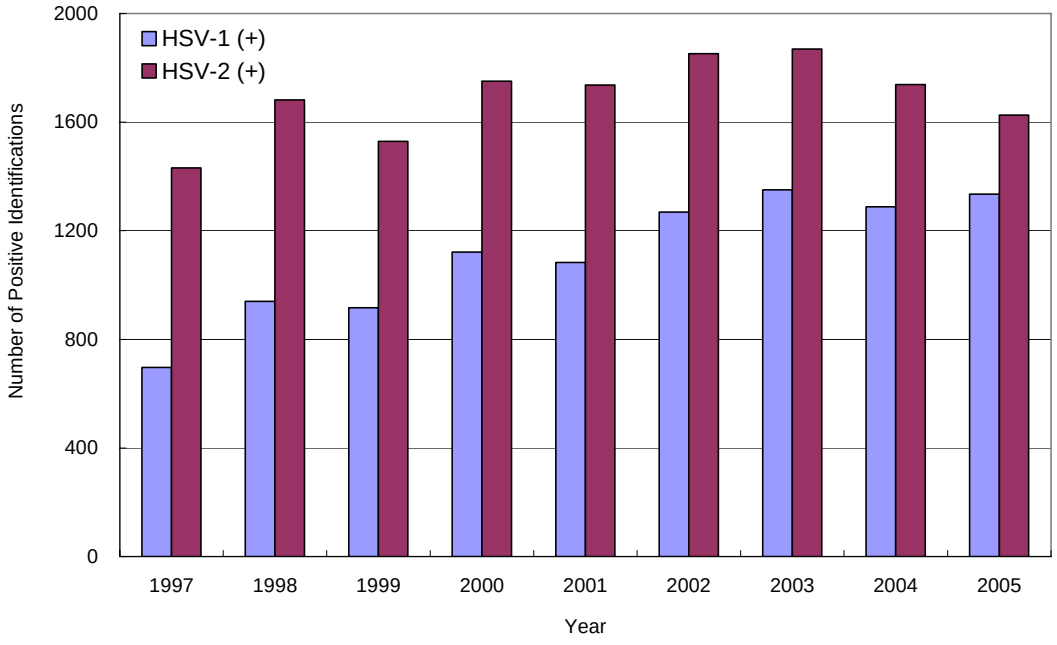


Figure 23 Positive genital identifications of HSV, by percent viral type, BC, 1997 to 2005

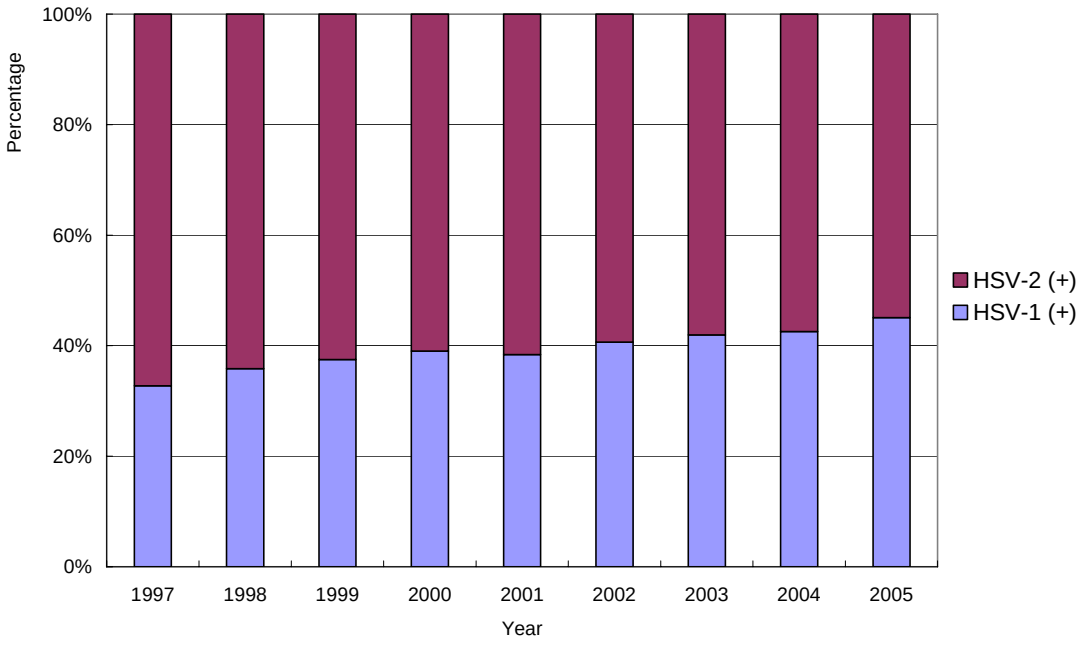
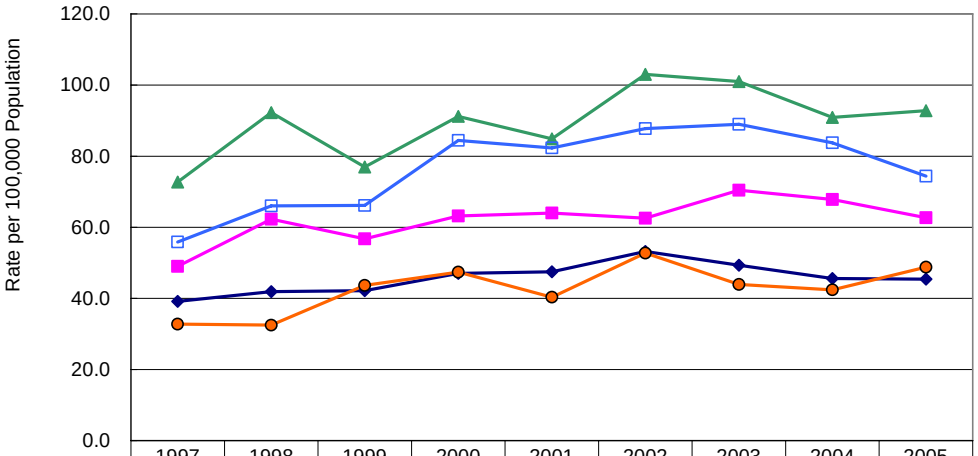


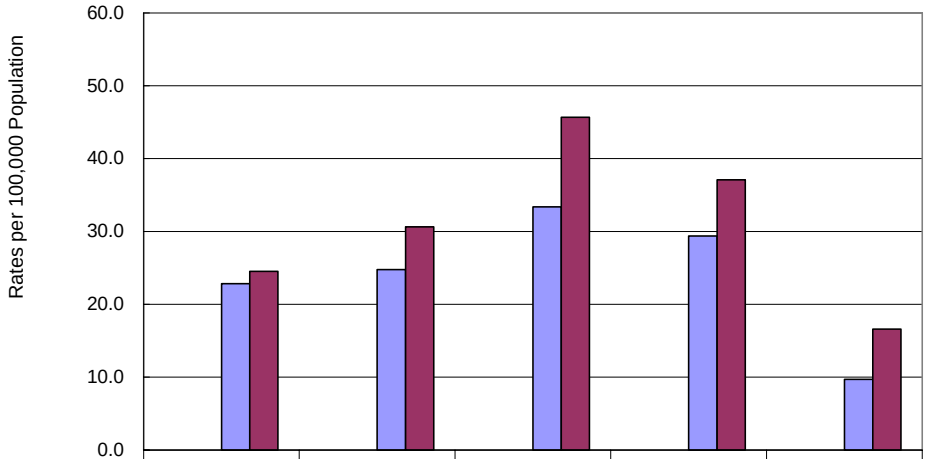
Figure 24 Rates of genital identifications of HSV by Health Authority, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
Interior	39.2	41.9	42.2	47.1	47.5	53.2	49.3	45.6	45.4
Fraser	49.0	62.3	56.8	63.2	64.0	62.6	70.4	67.8	62.7
Vancouver Coastal	72.7	92.3	77.0	91.2	84.9	103.1	101.0	90.9	92.8
Vancouver Island	55.9	66.0	66.1	84.5	82.3	87.8	89.0	83.8	74.4
Northern	32.8	32.5	43.7	47.4	40.3	52.8	43.9	42.4	48.8

Year

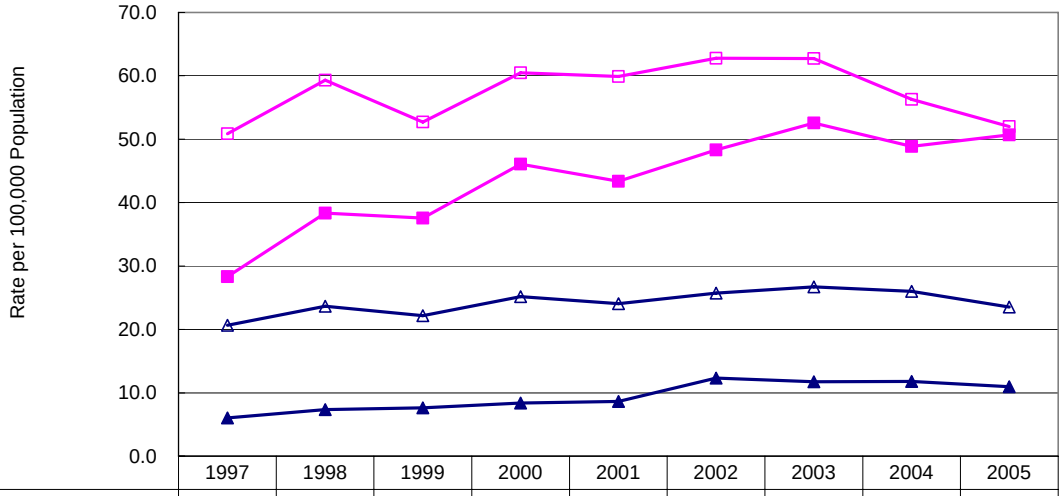
Figure 25 Rates of positive genital identifications of HSV, by viral type and Health Authority, BC, 2006



	Interior	Fraser	Vancouver Coastal	Vancouver Island	Northern
HSV-1(+) Identifications	162	371	359	217	28
HSV-2(+) Identifications	174	459	491	274	48
HSV-1(+) Rate	22.8	24.8	33.4	29.4	9.7
HSV-2(+) Rate	24.5	30.6	45.7	37.1	16.6

Health Authority

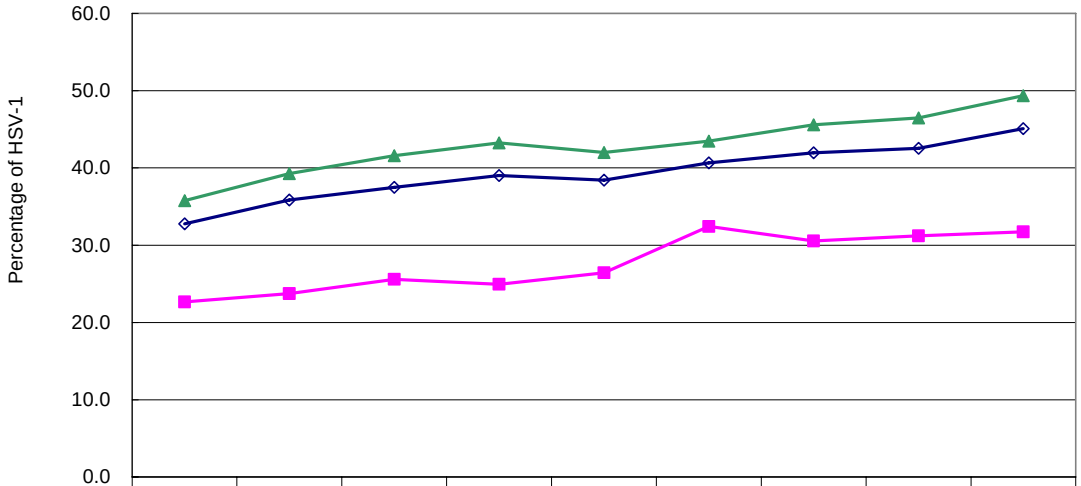
Figure 26 Rates of positive genital identifications of HSV by gender and viral type, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
Male HSV-1(+)	6.1	7.4	7.6	8.4	8.6	12.3	11.7	11.8	10.9
Male HSV-2(+)	20.7	23.7	22.2	25.2	24.1	25.7	26.7	26.0	23.5
Female HSV-1(+)	28.3	38.4	37.6	46.1	43.4	48.3	52.6	48.9	50.7
Female HSV-2(+)	50.9	59.3	52.7	60.5	59.9	62.8	62.7	56.3	52.0

Year

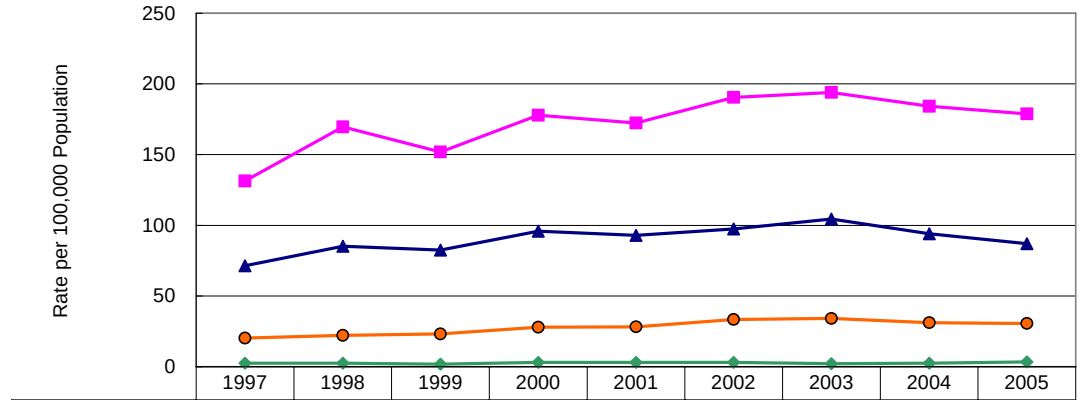
Figure 27 Percentage of positive genital identifications of HSV-1 by gender, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
Female	35.8	39.3	41.6	43.2	42.0	43.5	45.6	46.5	49.4
Male	22.7	23.7	25.6	25.0	26.4	32.4	30.6	31.2	31.7
Total	32.8	35.9	37.5	39.0	38.4	40.7	42.0	42.6	45.1

Year

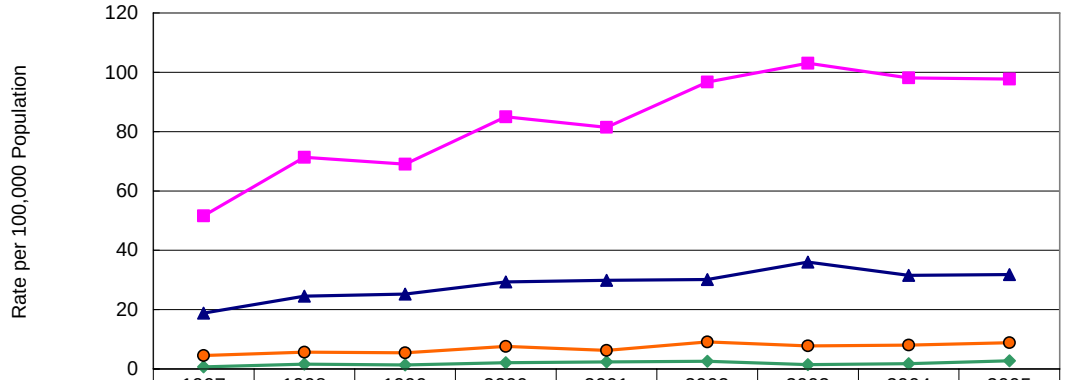
Figure 28 Age-specific rates of total positive identifications of HSV from genital specimen, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
# 0-14 yrs	19	19	14	23	22	22	15	18	23
# 15-29 yrs	1074	1381	1237	1448	1412	1575	1620	1562	1541
# 30-44 yrs	719	856	825	954	923	958	1017	909	837
# 45+ yrs	276	314	336	418	435	530	558	526	532
Rate 0-14 yrs	2.5	2.5	1.9	3.1	3.0	3.1	2.1	2.6	3.3
Rate 15-29 yrs	131.4	169.5	151.9	177.9	172.4	190.4	193.9	184.2	178.8
Rate 30-44 yrs	71.5	85.2	82.5	95.8	93.0	97.4	104.4	94.0	87.0
Rate 45+ yrs	20.2	22.2	23.1	27.9	28.2	33.3	34.1	31.2	30.6

Year

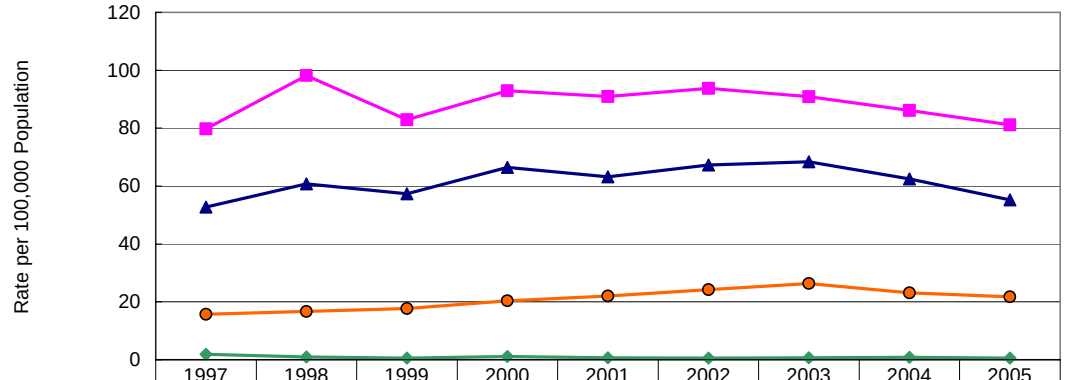
Figure 29 Age-specific rates of positive identifications of HSV-1 from genital specimen, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
# 0-14 yrs	5	12	10	15	17	18	10	12	19
# 15-29 yrs	422	581	562	692	667	800	861	832	842
# 30-44 yrs	189	246	252	292	296	296	351	305	306
# 45+ yrs	61	79	79	113	96	145	127	136	154
Rate 0-14 yrs	0.7	1.6	1.3	2.0	2.3	2.5	1.4	1.7	2.7
Rate 15-29 yrs	51.6	71.3	69.0	85.0	81.4	96.7	103.1	98.1	97.7
Rate 30-44 yrs	18.8	24.5	25.2	29.3	29.8	30.1	36.0	31.6	31.8
Rate 45+ yrs	4.5	5.6	5.4	7.6	6.2	9.1	7.8	8.1	8.9

Year

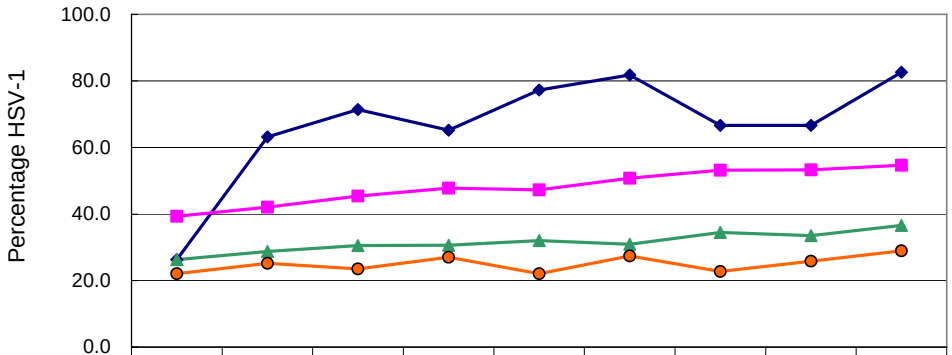
Figure 30 Age-specific rates of positive identifications of HSV-2 from genital specimen, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
# 0-14 yrs	14	7	4	8	5	4	5	6	4
# 15-29 yrs	652	800	675	756	745	775	759	730	699
# 30-44 yrs	530	610	573	662	627	662	666	604	531
# 45+ yrs	215	235	257	305	339	385	431	390	378
Rate 0-14 yrs	1.9	0.9	0.5	1.1	0.7	0.6	0.7	0.9	0.6
Rate 15-29 yrs	79.8	98.2	82.9	92.9	91.0	93.7	90.9	86.1	81.1
Rate 30-44 yrs	52.7	60.7	57.3	66.5	63.2	67.3	68.4	62.5	55.2
Rate 45+ yrs	15.7	16.6	17.7	20.4	22.0	24.2	26.3	23.1	21.8

Year

Figure 31 Percentage of positive genital identification of HSV-1 and HSV-2 by age, BC, 1997 to 2005



	1997	1998	1999	2000	2001	2002	2003	2004	2005
# HSV-1(+) 0-14 yrs	5	12	10	15	17	18	10	12	19
# HSV-1(+) 15-29 yrs	422	581	562	692	667	800	861	832	842
# HSV-1(+) 30-44 yrs	189	246	252	292	296	296	351	305	306
# HSV-1(+) 45+ yrs	61	79	79	113	96	145	127	136	154
% HSV-1(+) 0-14 yrs	26.3	63.2	71.4	65.2	77.3	81.8	66.7	66.7	82.6
% HSV-1(+) 15-29 yrs	39.3	42.1	45.4	47.8	47.2	50.8	53.1	53.3	54.6
% HSV-1(+) 30-44 yrs	26.3	28.7	30.5	30.6	32.1	30.9	34.5	33.6	36.6
% HSV-1(+) 45+ yrs	22.1	25.2	23.5	27.0	22.1	27.4	22.8	25.9	28.9

Year

Figure 32 Positive genital identifications of HSV-1 (N=7,177) and HSV-2 (N=8,602) in women of reproductive age, 1997 to 2005

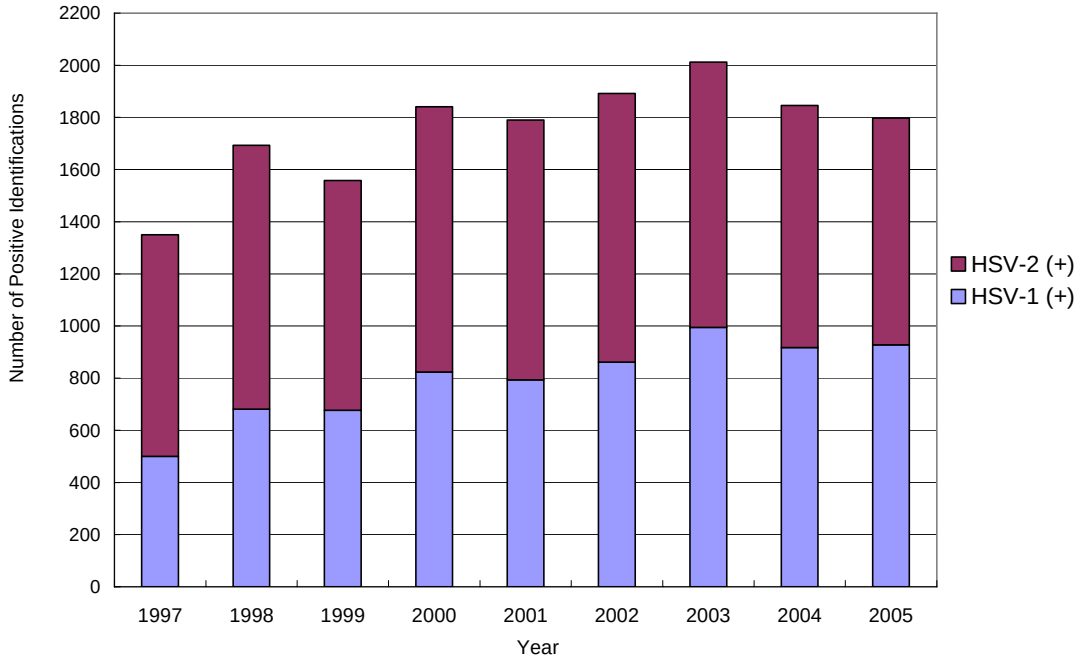


Figure 33 Positive genital identifications of HSV in women of reproductive age, by percent viral type, 1997 to 2005

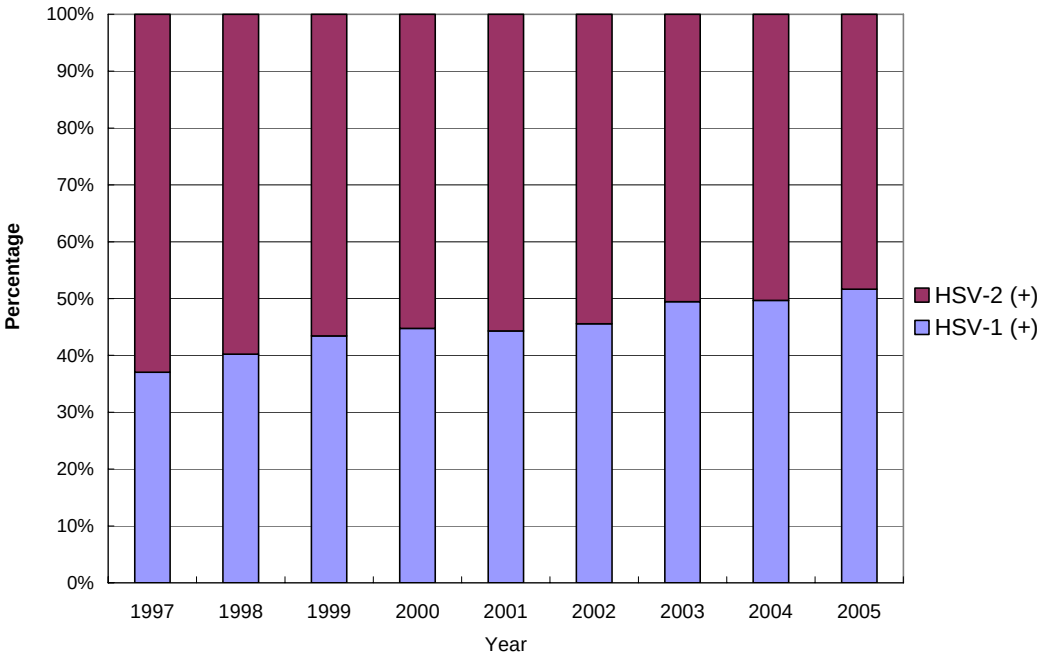
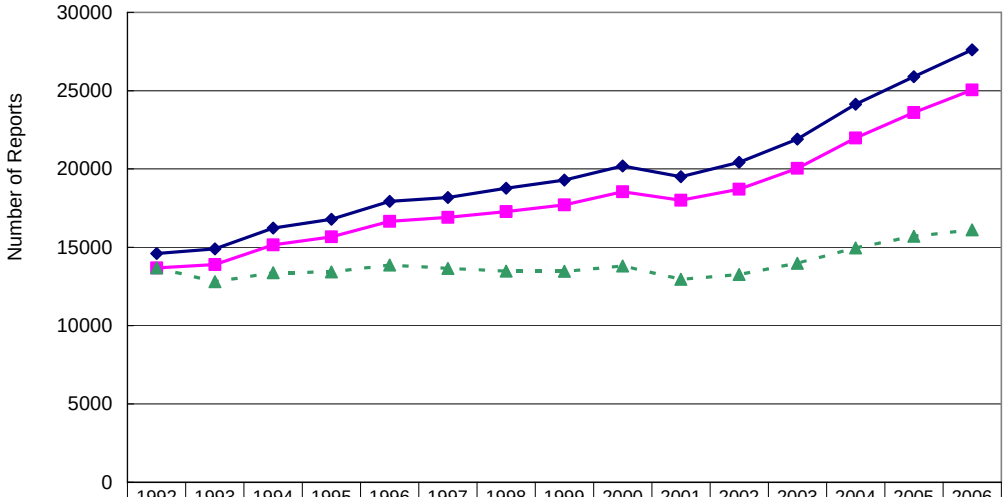
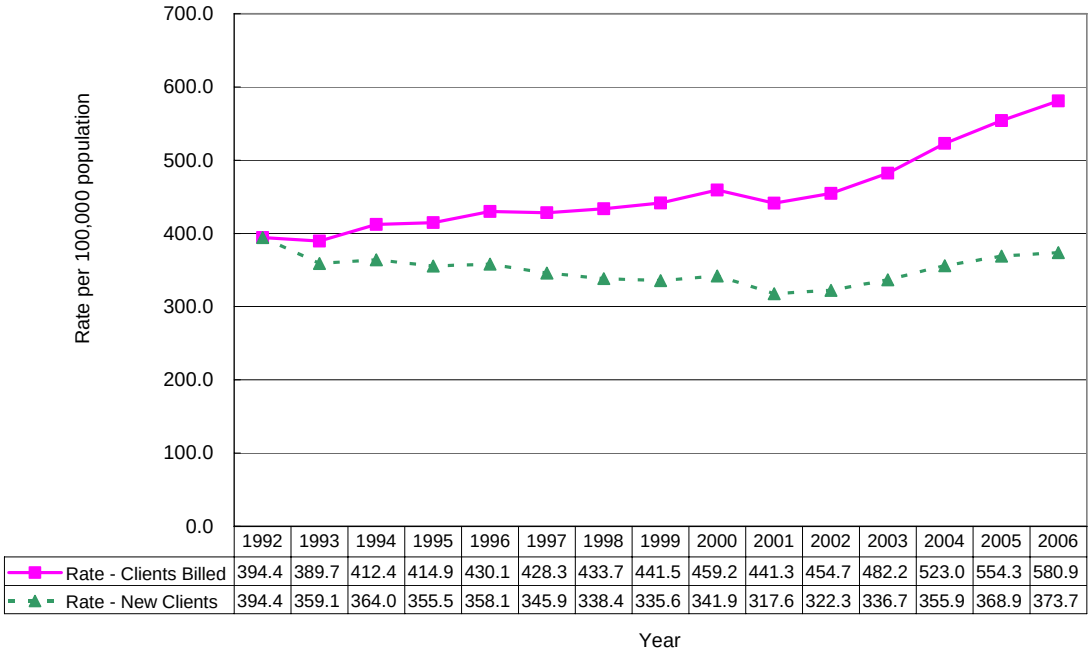


Figure 34 Number of physician billings (N=296,358), clients billed (N=272,886), and clients with first visit (N=208,560) billed for herpes simplex related physician services, BC, 1992-2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# Physician Billings	14608	14903	16235	16782	17937	18178	18770	19290	20190	19504	20422	21910	24134	25892	27603
# Clients Billed	13678	13901	15158	15670	16662	16912	17276	17712	18548	17997	18711	20036	21984	23600	25041
# New Clients Billed	13678	12809	13379	13426	13872	13657	13478	13464	13811	12955	13263	13990	14959	15709	16110

Figure 35 Rates of clients billed (N=272,886), and clients with first visit (N=208,560) billed for herpes simplex related physician services, BC, 1992-2006

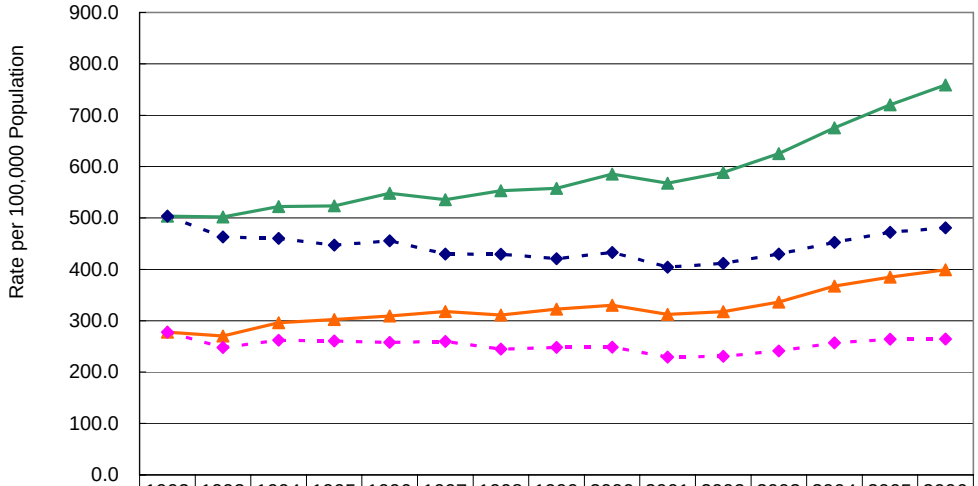


	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Rate - Clients Billed	394.4	389.7	412.4	414.9	430.1	428.3	433.7	441.5	459.2	441.3	454.7	482.2	523.0	554.3	580.9
Rate - New Clients	394.4	359.1	364.0	355.5	358.1	345.9	338.4	335.6	341.9	317.6	322.3	336.7	355.9	368.9	373.7

Table 1 Repeat visit rates and number of physician visits per person - By five and one year cohorts in BC, based on year of first visit

Population	Periods	Repeat visit rate (%)	N	Number of physician visits per person				
				Median	Q1	Q3	Min	Max
Total clients	1992-2006	22.76	208560	1	1	1	1	36
2000 cohort	First 5 years	21.02	13811	1	1	1	1	16
2001 cohort	First 5 years	21.93	12955	1	1	1	1	13
2002 cohort	First 5 years	22.06	13263	1	1	1	1	19
2000 cohort	First 1 years	9.16	13811	1	1	1	1	6
2001 cohort	First 1 years	9.09	12955	1	1	1	1	7
2002 cohort	First 1 years	9.83	13263	1	1	1	1	7
2003 cohort	First 1 years	10.39	13990	1	1	1	1	6
2004 cohort	First 1 years	10.17	14959	1	1	1	1	6
2005 cohort	First 1 years	10.65	15709	1	1	1	1	6

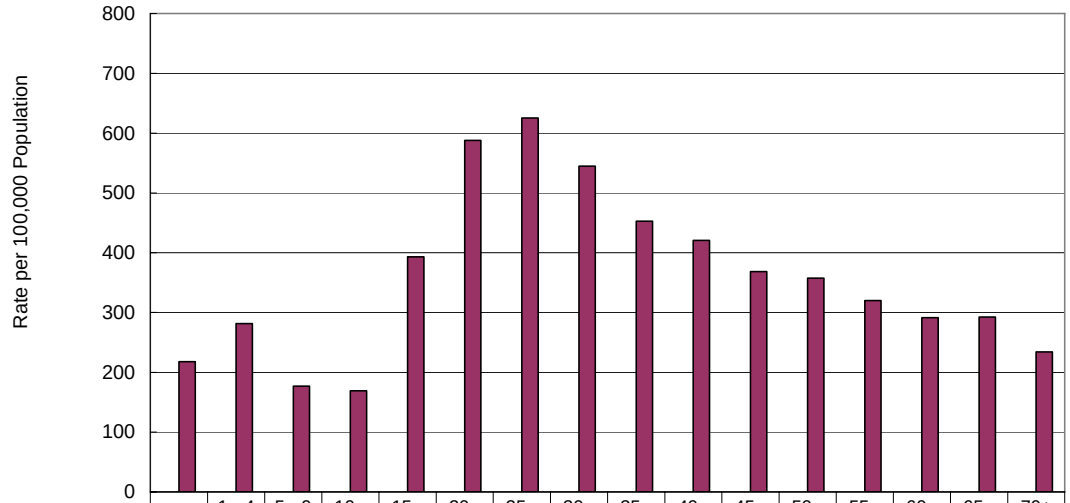
Figure 36 Rates of clients billed and clients with first visits billed for herpes simplex related physician services by gender, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Total Female	503.6	501.8	522.1	523.7	547.9	535.6	553.0	557.5	585.3	567.4	588.5	625.1	675.4	720.4	758.9
Total Male	277.9	270.0	296.1	302.1	309.2	318.2	311.1	322.4	330.0	312.1	317.5	336.0	367.3	384.9	399.2
Female with first visit	503.6	463.0	460.1	447.0	455.7	429.5	429.2	420.7	432.9	404.0	411.5	429.8	452.6	472.0	480.7
Male with first visit	277.9	247.8	261.9	260.3	257.7	259.6	244.6	248.0	248.5	228.9	230.5	241.2	256.8	263.7	264.4

Year

Figure 37 Rates of clients with first visits billed for herpes simplex related physician services, BC, 2006



	<1 yrs	1 - 4 yrs	5 - 9 yrs	10 - 14 yrs	15 - 19 yrs	20 - 24 yrs	25 - 29 yrs	30 - 34 yrs	35 - 39 yrs	40 - 44 yrs	45 - 49 yrs	50 - 54 yrs	55 - 59 yrs	60 - 64 yrs	65 - 69 yrs	70+ yrs
# New Clients	89	467	397	438	1102	1807	1782	1562	1437	1482	1311	1170	934	626	491	1015
Rate - New Clients	217.8	281.5	176.9	169.1	393.0	587.9	625.4	544.8	452.9	420.7	368.4	357.5	320.1	291.5	292.5	234.1

Age Group

Figure 38 Proportion of diagnosis type-specific physician billings for herpes simplex related physician services (N=296,358), BC, 1992 to 2006

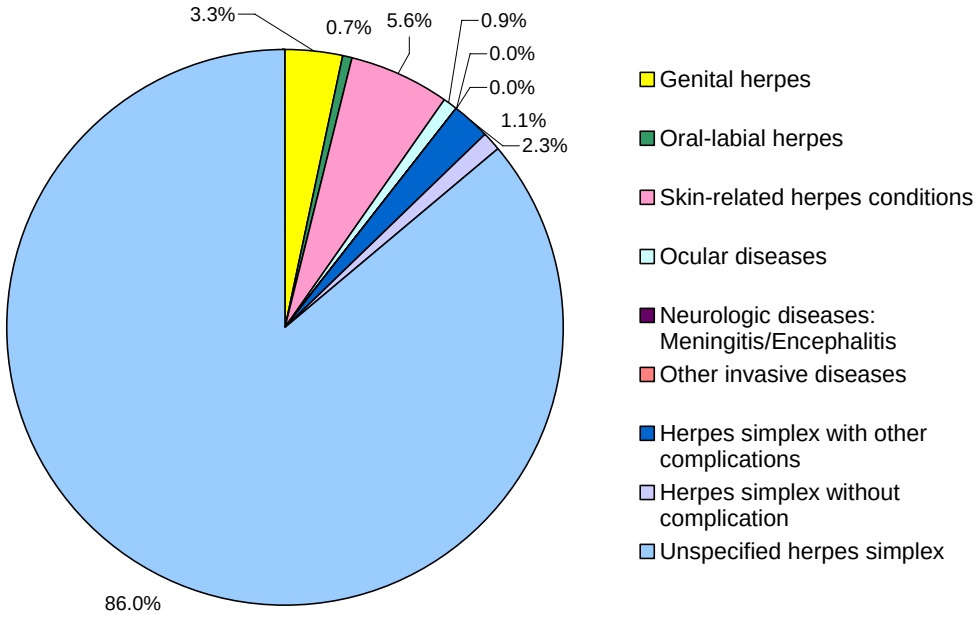
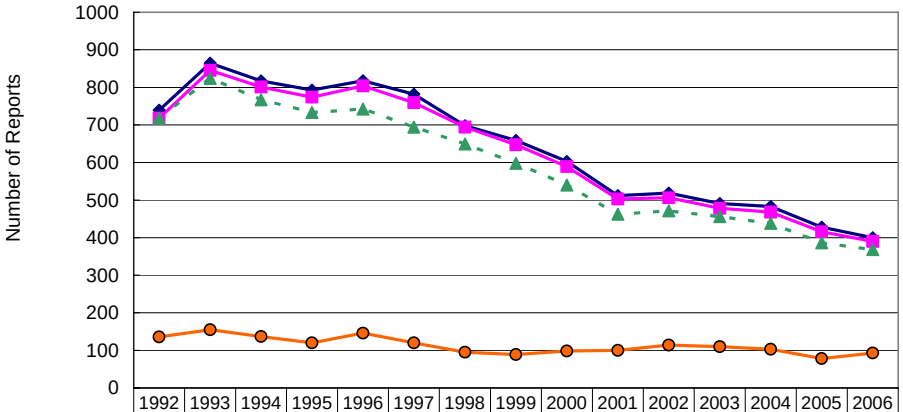
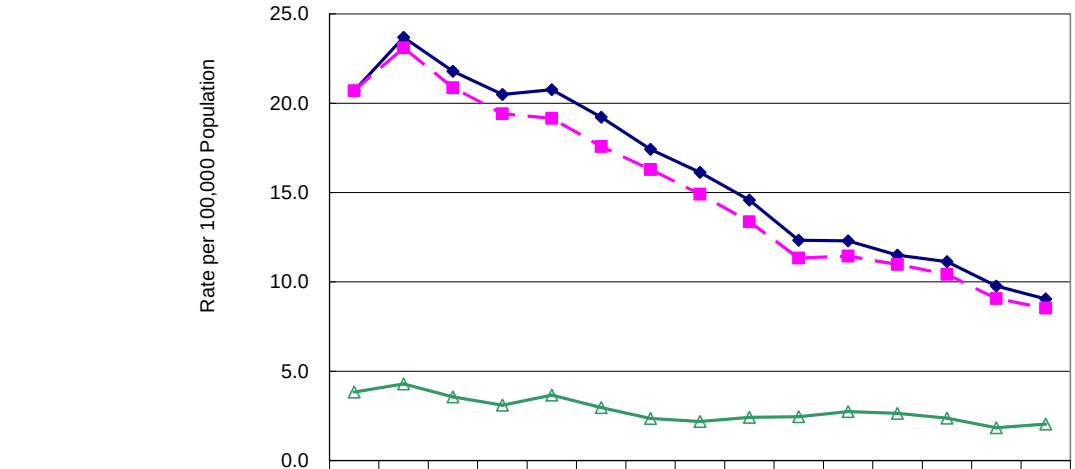


Figure 39 Number of hospital discharges (N=9606), patients discharged (N=9392), patients with first discharges (N=8846) with herpes simplex related hospital diagnosis, and with herpes MRDx (N=1694, N=1662, N=1644, respectively), BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# Hospital Discharges	739	864	817	793	818	782	698	659	603	512	519	491	483	428	400
# Patients Discharged	718	845	801	774	804	759	694	647	589	503	506	478	468	416	390
# New Patients Discharged	718	824	767	733	742	694	649	598	540	462	471	456	438	386	368
# Discharges with Herpes MRDx	136	155	137	120	146	120	95	89	98	100	114	110	103	78	93
# Patients with herpes MRDx	133	153	131	117	142	117	94	88	98	100	113	110	100	78	88
# Patients with first herpes MRDx	133	150	129	116	140	116	93	87	97	100	113	110	98	77	85

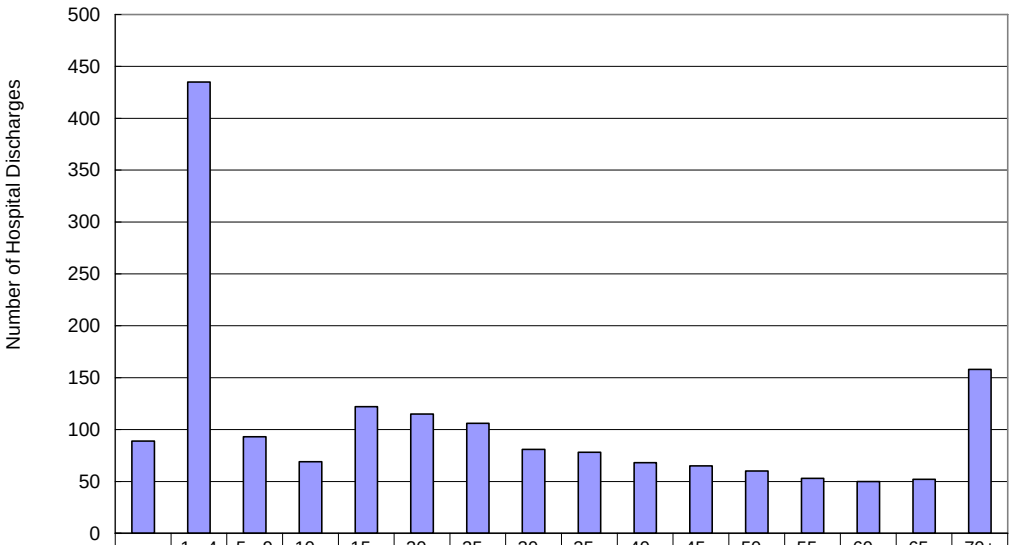
Figure 40 Rates of patients discharged and patients with first discharges from hospital with herpes simplex related diagnosis and with herpes MRDx, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Patients Discharged	20.7	23.7	21.8	20.5	20.8	19.2	17.4	16.1	14.6	12.3	12.3	11.5	11.1	9.8	9.0
New Patients Discharged	20.7	23.1	20.9	19.4	19.2	17.6	16.3	14.9	13.4	11.3	11.4	11.0	10.4	9.1	8.5
Patients with herpes MRDx	3.8	4.3	3.6	3.1	3.7	3.0	2.4	2.2	2.4	2.5	2.7	2.6	2.4	1.8	2.0
Patients with first herpes MRDx	3.8	4.2	3.5	3.1	3.6	2.9	2.3	2.2	2.4	2.5	2.7	2.6	2.3	1.8	2.0

Year

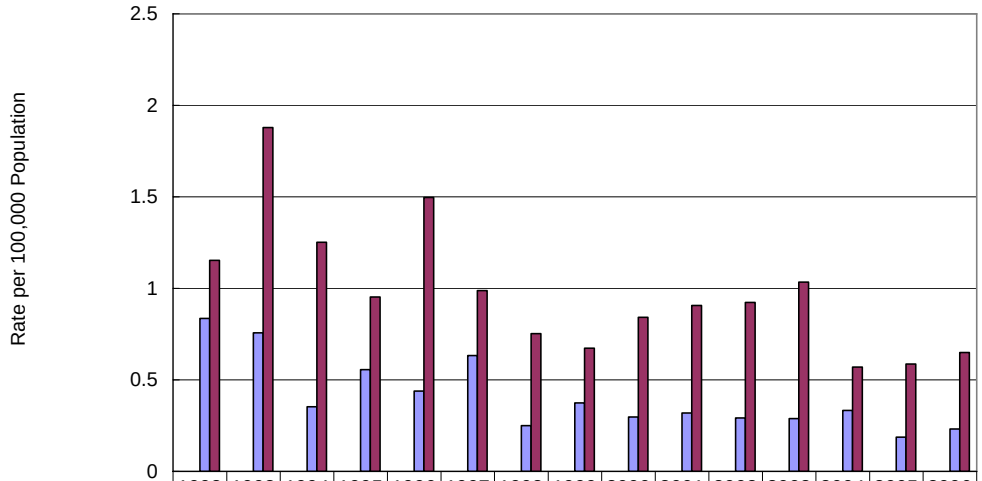
Figure 41 Number of hospital discharges with herpes MRDx (N=1694) by age, BC, 1992 to 2006



	<1 yrs	1 - 4 yrs	5 - 9 yrs	10 - 14 yrs	15 - 19 yrs	20 - 24 yrs	25 - 29 yrs	30 - 34 yrs	35 - 39 yrs	40 - 44 yrs	45 - 49 yrs	50 - 54 yrs	55 - 59 yrs	60 - 64 yrs	65 - 69 yrs	70+ yrs
# Hospital Discharges	89	435	93	69	122	115	106	81	78	68	65	60	53	50	52	158

Age Group

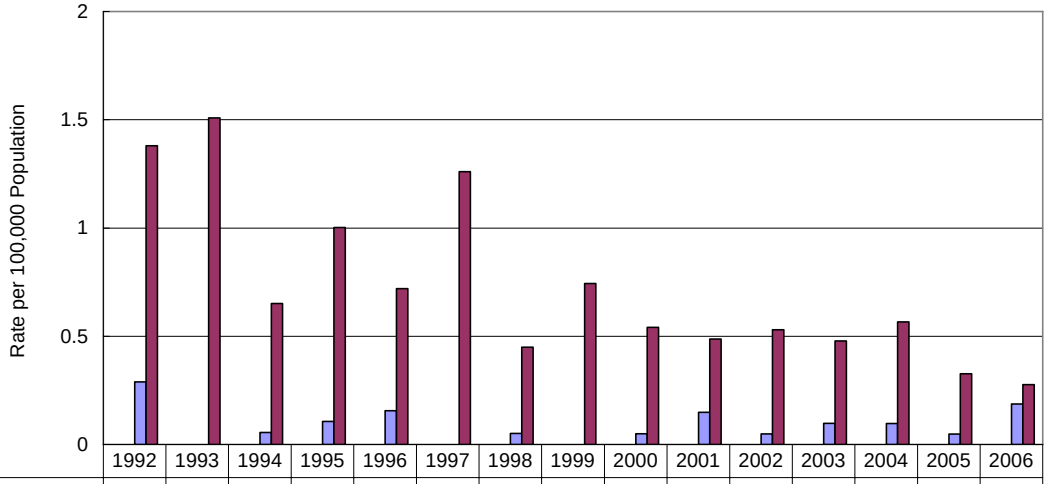
Figure 42 Rates of patients discharged from hospital with genital (N=238) and oral-labial (N=572) herpes MRDx, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# Patients - Genital MRDx	29	27	13	21	17	25	10	15	12	13	12	12	14	8	10
# Patients - Oral MRDx	40	67	46	36	58	39	30	27	34	37	38	43	24	25	28
Patient Rates - Genital MRDx	0.8	0.8	0.4	0.6	0.4	0.6	0.3	0.4	0.3	0.3	0.3	0.3	0.3	0.2	0.2
Patient Rates - Oral MRDx	1.2	1.9	1.3	1.0	1.5	1.0	0.8	0.7	0.8	0.9	0.9	1.0	0.6	0.6	0.6

Year

Figure 43 Rates of patients discharged from hospital with genital herpes MRDx (N=238) by gender, BC, 1992 to 2006



	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
# Male	5	0	1	2	3	0	1	0	1	3	1	2	2	1	4
# Female	24	27	12	19	14	25	9	15	11	10	11	10	12	7	6
Male Rates	0.3	0.0	0.1	0.1	0.2	0.0	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.2
Female Rates	1.4	1.5	0.7	1.0	0.7	1.3	0.4	0.7	0.5	0.5	0.5	0.5	0.6	0.3	0.3

Year

Table 2 Proportion and duration of hospitalizations by type of herpes most responsible diagnosis (MRDx), BC, 1992 to 2006

Type of MRDx	Total Patients		Patients aged 0-14 yrs		Patients aged 15+ yrs		Duration of Hospitalization* (days) in Total Patients					
	N	%	N	%	N	%	Mean	Median	Min	Max	Q1	Q3
Total hospitalizations	9606	-	1108	-	8498	-	10.61	4	1	654	3	10
Hospitalizations with herpes MRDx	1694	100.00	686	100.00	1008	100.00	7.24	4	1	654	2	7
Genital herpes	246	14.52	11	1.60	235	23.31	4.48	4	1	59	2	5
Oral herpes	574	33.88	483	70.41	91	9.03	3.86	3	1	28	2	5
Skin-related herpes	86	5.08	57	8.31	29	2.88	5.19	3	1	54	2	6
Ocular herpes	213	12.57	31	4.52	182	18.06	2.37	1	1	22	1	3
Neurological herpes	299	17.65	29	4.23	270	26.79	21.20	13	1	654	6	22
Other invasive disease	11	0.65	3	0.44	8	0.79	9.36	4	2	53	3	9
HS with other complications	117	6.91	24	3.50	93	9.23	6.71	5	1	51	2	8
HS without complication	143	8.44	47	6.85	96	9.52	5.15	4	1	27	2	7
Congenital herpes	1	0.06	1	0.15			14.00	14	14	14	14	14
Herpes gestationis	4	0.24			4	0.40	3.50	4	3	4	3	4

* If the time between admission and discharge date less than 2 days, the duration of hospitalization will be counted as 1 day, no matter if the discharge occurred on the same or the next day of admission.

Table 3 Age-specific number of hospital discharges by type of herpes most responsible diagnosis (MRDx), BC, 1992 to 2006

Type of Herpes MRDx	Age Group																	Total
	0-28 days	29d -1y	1-4 y	5-9 y	10-14y	15-19y	20-24y	25-29y	30-34y	35-39y	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70+y	
Genital herpes	0	0	1	2	8	58	66	31	19	21	7	11	7	5	1	2	7	246
Congenital herpes simplex infection	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Herpes gestationis	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	4
Oral Herpes	0	31	361	56	35	28	14	10	1	8	6	4	2	1	2	3	12	574
Skin-related herpes conditions	1	17	22	9	8	4	4	6	3	1	1	1	0	2	2	2	3	86
Ocular diseases	0	2	16	9	4	3	2	6	15	4	10	15	15	19	18	15	60	213
Neurological herpes	2	14	4	5	4	20	11	21	24	24	26	21	19	16	19	23	46	299
Other invasive herpes conditions	0	1	2	0	0	1	0	1	2	1	1	0	0	0	0	2	0	11
Herpes simplex with other complications	0	6	11	3	4	0	11	18	9	10	14	5	8	4	3	2	9	117
Herpes simplex without complication	3	11	18	9	6	8	6	10	8	9	3	8	9	6	5	3	21	143
Total	7	82	435	93	69	122	115	106	81	78	68	65	60	53	50	52	158	1694

Table 4a. Number and rates (per 100,000 live births) of neonatal (Aged 0-60 days) positive identifications of HSV, BC, 1992 to 2006

Neonatal Cases		Year															Total
		1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	N
Probable cases	# HSV-1	-	1	1	0	0	1	1	0	1	2	1	3	0	6	3	20
	# HSV-2	-	0	0	4	2	1	0	0	0	0	0	1	1	2	1	12
	# un-specified	-	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
	# total	-	1	1	4	2	2	1	0	1	2	1	4	1	9	5	34
	Rate (probable cases)	-	2.18	2.14	8.57	4.35	4.50	2.33	0.00	2.47	4.95	2.51	9.92	2.48	22.14	N/A	
Possible cases	# HSV-1	-	3	1	1	2	1	0	1	0	2	2	0	0	0	1	14
	# HSV-2	-	6	1	3	3	1	3	0	0	2	2	2	0	2	1	26
	# un-specified	-	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
	# total	-	9	2	4	5	2	3	1	0	4	4	2	1	3	2	42
	Rate (possible cases)	-	19.58	4.27	8.57	10.88	4.50	7.00	2.40	0.00	9.90	10.02	4.96	2.48	7.38	N/A	
Total cases	# HSV-1	-	4	2	1	2	2	1	1	1	4	3	3	0	6	4	34
	# HSV-2	-	6	1	7	5	2	3	0	0	2	2	3	1	4	2	38
	# un-specified	-	0	0	0	0	0	0	0	0	0	0	0	1	2	1	4
	# total	-	10	3	8	7	4	4	1	1	6	5	6	2	12	7	76
	Rate (total cases)	-	21.76	6.41	17.13	15.23	9.01	9.33	2.4	2.47	14.85	12.53	14.89	4.96	29.52	N/A	

Table 4b. Number and rates (per 100,000 live births) of neonates billed for herpes-related physician services, and neonates admitted for herpes-related hospitalizations, BC, 1992 to 2006

Data Source	Neonatal Cases		Year														Total
			1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	N
Physician billings	Possible cases	#	23	21	35	19	23	16	22	11	17	13	17	15	18	13	16	279
		Rate	49.97	45.7	74.73	40.68	50.04	36.03	51.32	26.35	41.98	32.18	42.6	37.22	44.62	31.98	N/A	
	Probable cases	#	2	1	1	5	3	1	1	0	0	0	2	2	4	3	1	26
		Rate	4.34	2.18	2.14	10.71	6.53	2.25	2.33	0.00	0.00	0.00	5.01	4.96	9.92	7.38	N/A	
Hospital discharges	Possible cases	#	0	1	3	1	3	4	1	2	0	0	0	0	1	1	1	18
		Rate	0.00	2.18	6.41	2.14	6.53	9.01	2.33	4.79	0.00	0.00	0.00	0.00	2.48	2.46	N/A	
	Total cases	#	2	2	4	6	6	5	2	2	0	0	2	2	5	4	2	44
		Rate	4.34	4.35	8.54	12.85	13.05	11.26	4.67	4.79	0.00	0.00	5.01	4.96	12.39	9.84	N/A	

Table 5 Neonatal positive viral identifications of HSV - By site of specimen, BC, 1993 to 2006

Specimen Sites	Neonates	
	N	%
Genital (Anal)	2	
Genital (groin)	1	
Genital (Genitalia)	16	
Genital (site unspecified)	3	
Total Genital	22	28.95
Oral	5	6.58
Skin lesion	23	30.26
Eye	2	2.63
Nose	4	5.26
Other sites	1	1.32
Unknown	19	25.00
Total	76	100.00

Table 6 Number of neonatal herpes cases identified from hospital discharge dataset - By diagnosis type, BC, 1992 to 2006

Diagnosis type	Neonates aged 0-60 days or P35.2 coded			
	Total Herpes Diagnosis (N=44)		Herpes MRDx (N=23)	
	N	%	N	%
Genital herpes	6	13.64		
Congenital herpes	4	9.09	1	4.35
Oral herpes	1	2.27		
Skin-related herpes conditions	2	4.55	2	8.70
Ocular herpes	3	6.82	1	4.35
Neurological herpes	15	34.09	11	47.83
Other invasive diseases	1	2.27		
Herpes simplex with other complication	2	4.55	1	4.35
Herpes simplex without complication	15	34.09	7	30.43
Total*	44		23	

* Patient could have multiple herpes simplex related diagnosis in each hospitalization, thus, total number is not equal to sum of the above.

APPENDIX 2: DIAGNOSIS TYPES AND CORRESPONDING DIAGNOSIS CODES IN ICD-9 AND ICD-10-CA SYSTEM

Type of Diagnosis		ICD-9	ICD-10-CA
Herpes simplex related diseases	Genital herpes	054.1 (Genital herpes)	A60.0 (Herpesviral infection of genitalia and urogenital tract) A60.1 (Herpesviral infection of perianal skin and rectum) A60.9 (Anogenital herpesviral infection, unspecified)
	Neonatal herpes	N/A	P35.2 Congenital herpesviral [herpes simplex] infection
	Herpes gestationis	N/A	O26.4 (Herpes gestationis)
	Oral-labial herpes	054.2 (Herpetic gingivostomatitis)	B00.2 (Herpesviral gingivostomatitis and pharyngotonsillitis)
	Skin-related herpes conditions	054.0 (Eczema herpeticum) 054.6 (Herpetic whitlow)	B00.0 (Eczema herpeticum) B00.1 (Herpesviral vesicular dermatitis)
	Ocular herpes	054.4 (Herpes simplex with ophthalmic complications)	B00.5 (Herpesviral ocular disease)
	Neurological herpes	054.3 (Herpetic meningoencephalitis)	B00.3 (Herpesviral meningitis) B00.4 (Herpesviral encephalitis)
	Other invasive herpes	054.5 (Herpetic septicemia)	B00.7 (Disseminated herpesviral disease)
	Herpes simplex with other complication	054.7 (Herpes simplex with other specified complications) 054.8 (Herpes simplex with unspecified complications)	B00.8 (Other forms of herpesviral infection)
	Herpes simplex without complication	054 (Herpes simplex) 054.9 (Herpes simplex without complication)	B00.9 (Herpesviral infection, unspecified)
Diseases not caused by HSV			

Note: In the ICD-9 system, there are no diagnosis codes available to specify congenital herpes simplex infection and herpes gestationis. In the ICD-10-CA coded data source, codes O26.4 and P35.2 were not part of the set of diagnosis codes scanned by the discharge abstract. Cases with these codes would have to contain other diagnosis code(s) related to herpes simplex (i.e. A60 or B00 codes). Therefore, results pertaining to congenital herpes simplex infection and herpes gestationis would be under counted.

APPENDIX 3: CASE DEFINITION OF NEONATAL HERPES SIMPLEX INFECTION

This case definition was based on case definitions developed by Kropp et al. in their three-year national prospective surveillance study regarding neonatal herpes simplex virus infections in Canada (Kropp et al., 2006), and a case definition developed by Alberta Health and Wellness (June 2005). This definition was tailored to the available data.

For this analysis, a case definition of neonatal herpes simplex infection was defined as following:

Probable Case

An infant (aged 0-60 days) with either of the following:

(1) Laboratory-confirmed HSV infection, confirmed with:

Positive viral identification of HSV (by culture test or NAAT) from an appropriate clinical specimen (i.e. skin, eye, mouth, nose, cerebrospinal fluid (CSF) and other specimen from the central nervous system (CNS)); or

(2) At least one hospital admission followed by a diagnosis coded by "P35.2" (i.e. ICD-10-CA diagnosis code specified to congenital herpes simplex infection); or

(3) At least one hospital admission with hospital MRDx related to herpes simplex.

Possible Case

An infant (aged 0-60 days) with either of the following:

(1) Laboratory-confirmed HSV infection, confirmed with:

Positive viral identification of HSV (by culture test or NAAT) from a less appropriate clinical specimen (i.e. other than skin, eye, mouth, nose, CSF and other specimen from CNS); or

(2) Billed for at least one physician service with a diagnosis related to herpes; or

(3) Had a hospital admission(s) with a non-MRDx related to herpes simplex.

Note: In the ICD-10-CA coded data source, the code P35.2 was not part of the set of diagnosis codes scanned by the discharge abstract. Cases with this code would have to contain other diagnosis code(s) related to herpes simplex. Therefore, the result would be an undercount.