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ARTICLE

Neonatal Herpes Simplex Virus Infections in Canada: Results of a 3-Year National Prospective Study

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ABSTRACT

OBJECTIVE. The goal was to determine incidence, determinants, and morbidity and mortality rates of neonatal herpes simplex virus infections in Canada.

METHODS. From October 1, 2000, to September 30, 2003, reports of neonatal herpes simplex virus infection were solicited actively from all Canadian pediatricians and pediatric subspecialists on a monthly basis.

RESULTS. Fifty-eight cases of neonatal herpes simplex virus were reported (5.9 cases per 100 000 live births). Cesarean section was performed in 24.6% of cases, 28.1% of patients were born prematurely, 28.6% had birth weights of <2500 g, and 7.5% had Apgar scores of <7 at 5 minutes of life. Mothers <20 years of age and those reporting Aboriginal ethnicity were affected disproportionately; 40% of mothers had no history of genital herpes before delivery, and intrapartum genital lesions were present in only 1 of 58 cases. Of cases with known herpes simplex virus type, 62.5% were herpes simplex virus-1. Localized infections accounted for 59.6% of cases, whereas disseminated disease and central nervous system disease were reported for 17.5% and 22.8%, respectively. Localized infections were more likely to be herpes simplex virus-1 and disseminated and central nervous system infections herpes simplex virus-2. Nine of 58 cases were fatal. All cases with known treatment information (n = 55) were treated with intravenously administered acyclovir.

CONCLUSIONS. This is the first study to examine the national incidence of neonatal herpes simplex virus in Canada. Many women had no genital herpes simplex virus history before delivery, and the majority of cases were herpes simplex virus-1, which has implications for prenatal screening and vaccine/drug development. Follow-up monitoring of case subjects is being performed annually for 3 years, to be completed in October 2006.

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Key Words
neonatal herpes simplex infection, herpes simplex virus, vertical transmission

Abbreviations
NHSV—neonatal herpes simplex virus
HSV— herpes simplex virus
CNS— central nervous system
CPSP—Canadian Paediatric Surveillance Program
PCR—polymerase chain reaction

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GENITAL HERPES SIMPLEX virus (HSV) is one of the most incident and prevalent sexually transmitted infections in the world; however, because genital HSV infections frequently are asymptomatic, HSV is underdiagnosed. One of the most potentially devastating consequences of genital HSV infection is the perinatal transmission of the infection from mother to infant. A pregnant woman who is infected with either HSV-1 or HSV-2 can pass the infection to her child in utero (estimated 5% of cases), during birth (estimated 85% of cases), or after birth (estimated 10% of cases).[1,2]

The risk of transmitting HSV to the neonate differs depending on when the woman's HSV infection is acquired; a woman who has her first HSV infection late during pregnancy when seroconversion has not occurred is at greater risk of transmission (estimated to be 50%) than a woman experiencing recurrent HSV infection when seroconversion has already been established (<1%).[3] Morbidity and mortality rates for the neonate vary according to whether there are localized or disseminated manifestations of the infection. Approximately 45% of neonatal HSV (NHSV) cases involve only localized lesions of the skin, eyes, or mouth, infections that rarely are fatal and usually respond well to treatment.[2,4] Alternatively, it is estimated that 25% of NHSV cases are disseminated, involving multiple organ systems (eg, central nervous system [CNS], lungs, and liver), and 30% of infected neonates are classified as having CNS disease (clinical manifestations including seizures, irritability, bulging fontanelle, and tremors[2]); ~70% of infants with disseminated infections experience encephalitis,[2] which, if left untreated, has a mortality rate of >80%.[5,6] Although acyclovir therapy can improve the outcomes of this infection greatly,[7] treatment may be delayed because of nonspecific presentation and subsequent late diagnosis.

NHSV infection is not nationally reportable in Canada. Currently, published data in Canada are based on a limited number of small case series, which are neither necessarily representative nor national in scope.[8,9] Data on national incidence, rates of morbidity and death resulting from NHSV infection, and maternal and infant risk determinants are therefore essential for a better understanding of the epidemiologic features of this infection in Canada. National incidence data can be used to promote prevention and control strategies, to further research, and to estimate the national burden of illness. Furthermore, Canadian NHSV data allow for international comparisons of infection rates and provide essential baseline data needed for evaluation of the potential benefits of HSV vaccination. Finally, exploring the knowledge of maternal HSV infection before delivery has implications for prenatal screening recommendations. To this end, the current study aimed to explore the epidemiologic features of NHSV infection in Canada during a 3-year period. Specifically, the objectives of this study were (1) to estimate the incidence rates of NHSV infections in Canada for the years 2000 to 2003, (2) to determine the proportion of HSV-infected infants with localized and disseminated disease, and (3) to identify maternal risk factors, including maternal HSV status before delivery.

METHODS

Study Design

Between October 1, 2000, and September 30, 2003, the Canadian Paediatric Surveillance Program (CPSP), a national surveillance network, sent a form each month to all pediatricians and pediatric subspecialists to report newly diagnosed NHSV infection cases. After receiving a case report, CPSP mailed the reporting physician a questionnaire to complete on the infant case, with demographic and HSV history information regarding the infant's mother. Pediatricians' survey response rate (the proportion of pediatricians reporting a possible case of NHSV who completed the questionnaire) for this study was 97%. CPSP screened all case reports for duplicates, and each case was then assigned a study number. To ensure confidentiality, no personal identifiers were used on the questionnaire and data were collected on a nonnominal basis for both the infant and mother.

Completed questionnaires were forwarded to the principal investigator at the Sexually Transmitted Infection and Sexual Health Section, Health Canada (now part of the Public Health Agency of Canada), who determined whether each report fit with the case definition. For reports that fit the case definition, CPSP retained a copy of the questionnaire, in a secured office, for back-up purposes only. The data for confirmed cases were stored and maintained in a password-protected database at Health Canada. The original reporting forms were kept in a locked cabinet in the principal investigator's office at all times and were accessible only to the principle investigator and project coordinator. The Ottawa Hospital Research Ethics Board granted approval for this project.

Case Definition

To be considered a case subject for this project, the infant had to be ≤2 months of age, born between October 1, 2000, and September 30, 2003, with both of the following: (1) laboratory-confirmed HSV infection, confirmed with culture, HSV IgM, or polymerase chain reaction (PCR) assays, and (2) localized infection involving the skin, eyes, or mouth or disseminated infection involving the CNS or organs other than the CNS. For this study, the neonatal period was extended to 60 days of life, so that late laboratory diagnoses were not missed. For each case, reporting physicians were asked to indicate whether the infection was localized to the skin, eyes, and/or mouth or was disseminated to visceral organs/

systems, including the CNS. On the basis of the information provided, the following classification of cases was used for this study: (1) localized: disease limited to the skin, eyes, and/or mouth; (2) disseminated: visceral organ involvement, with or without CNS or localized infection; (3) CNS: CNS but no other visceral organ involvement. It should be noted that, for some cross-tabulations based on classification, CNS and disseminated disease were grouped because of low cell counts and subsequent inadequate power; where grouping occurred, this is noted in the table footnotes.

Measures

Infant Data Collected

Demographic information included gender, date of birth, and hospital/center where the child's infection was diagnosed. Clinical and laboratory information included the infant's gestational age; weight, height, and head circumference at birth; Apgar score at 5 minutes; delivery method; use of scalp electrodes; birth complications; diagnosis of other congenital infections; clinical signs of HSV (localized and disseminated); site of infection; laboratory test results and date of results; HSV type; and anti-HSV treatment. Outcome data included the child's status at the time of the report (hospitalized, discharged, or dead); information on the date and cause of death and autopsy reports were collected for infants who had died. Physicians reported any obvious sequelae of infection in the first 2 months of life, including hearing loss, visual impairment, seizures, encephalitis, paralysis, microcephaly, and developmental delay (Denver II scale).

Maternal Data Collected

Demographic information included age at delivery, ethnicity, and province/territory of residence. Clinical information included mother's gestational age at delivery, history of HSV infection, HSV type, gestational age when maternal HSV was diagnosed, type of maternal infection (primary or recurrent), and history of other sexually transmitted infections.

RESULTS

Incidence

Table 1 outlines the number of cases reported during the study period, as well as the status of the cases. There are no remaining cases pending review for any of the study years. Between October 1, 2000, and September 30, 2003, 58 confirmed cases of NHSV infection were reported, after duplicate reports were removed (incidence rate of 5.9 cases per 100 000 live births). Forty-four cases were reported in duplicate, that is, reported by >1 physician. A number of potential case reports did not meet the entry criteria (n = 20) and therefore were excluded from the study, specifically because the infants were born before October 1, 2000 (n = 3), had no positive laboratory results (n = 7), or had no laboratory information available (n = 10). The majority of cases were reported from Central Canada (n = 35, 60.4%; incidence: 5.8 cases per 100 000 live births) and Western Canada (n = 14, 24.1%; incidence: 6.0 cases per 100 000 live births), but similar incidence rates were reported by the Prairies (n = 5, 8.6%; incidence: 6.5 cases per 100 000 live births) and Atlantic Canada (n = 4, 6.9%; incidence: 6.1 cases per 100 000 live births). No cases were reported from Northern Canada.

TABLE 1 **NHSV Cases Reported to the CPSP, October 2000 through September 2003**

Status	No.
Confirmed NHSV cases[a]	58
Did not meet entry criteria[b]	20
Duplicate report	44
Total	122

[a] Including fatalities, 2 in 2003, 3 in 2002, 3 in 2001, and 1 in 2000 (9 fatalities).

[b] Excluded from the study because reports did not fit the case definition (17 reports) or the date of birth was before October 2000 (3 reports).

Demographic and Birth Information

Table 2 shows information on the mothers of the 58 infants with NHSV infections. The majority of mothers (75.4%) were white, 10.5% were Aboriginal, and 5.3% were black. Among mothers whose age was known (n = 41), the mean age was 27 years, with 92.7% of mothers being ≤35 years of age. Mothers <20 years of age accounted for 14.6% of cases, whereas mothers ≥35 years of age accounted for only 7.3% of cases. Of the 58 cases, only 1 mother (1.7%) had intrapartum genital HSV lesions. Importantly, of the 20 women with available information on HSV status, 8 women (40.0%) had no HSV history before delivery.

Information on infant demographic features and the birth is presented in Table 3. More than one fourth of the infants (28.1%) were born prematurely (before 37 weeks of gestation). Only 7.5% of infants with available

TABLE 2 **Maternal Demographic Information and HSV Status (n = 58)**

	No. (%)
Age (n = 41)	
<20 y	6 (14.6)
20-24 y	7 (17.1)
25-29 y	15 (36.6)
30-34 y	10 (24.4)
≥35 y	3 (7.3)
Ethnicity (n = 57)	
White	43 (75.4)
Black	3 (5.3)
Aboriginal	6 (10.5)
Other	5 (8.8)
Intrapartum genital HSV lesions present (n = 58)	1 (1.7)
History of HSV infection before delivery (n = 20)[a]	12 (60.0)

Numbers and totals may not add to 58 because of missing information.

[a] Information available from 20 mothers.

TABLE 3 **Demographic and Birth Characteristics of Infant Case Subjects, October 2000 Through September 2003 ($n = 58$)**

	No. (%)
Gender ($n = 58$)	
Female	30 (51.7)
Male	28 (48.3)
Gestational age ($n = 57$)	
<37 wk	16 (28.1)
37–40 wk	32 (56.1)
>40 wk	9 (15.8)
Apgar score ($n = 40$)	
≤3	1 (2.5)
4–6	2 (5.0)
7–10	37 (92.5)
Birth weight ($n = 49$)	
<2500 g	14 (28.6)
≥2500 g	35 (71.4)
Delivery type ($n = 57$)	
Vaginal	43 (75.4)
Cesarean	14 (24.6)
Birth complications ($n = 55$)	
Yes	8 (14.5)
No	47 (85.5)

Numbers and totals may not add to 58 because of missing information.

Apgar score information ($n = 40$) had Apgar scores of <7 at 5 minutes of life. Low birth weight (defined as <2500 g) was present for 14 of the case subjects (28.6%). The majority of births (75.4%) were vaginal, whereas 24.6% of case subjects were born through cesarean section. Cesarean section was performed because of the mother's HSV infection for 3 of the 14 cesarean section births; the rest were performed because of fetal distress ($n = 7$), breech presentation ($n = 1$), high transverse twin ($n = 1$), macrosomia ($n = 1$), and failure to progress ($n = 1$) (data not shown). Scalp electrodes were used in 3 of 25 cases for which information was available regarding their use, 1 of which involved disseminated infection to the CNS (HSV type unknown); the remaining 2 cases involved localized infection of the skin and in 1 case also the oral cavity (HSV-2 and HSV-1, respectively). Intrapartum maternal genital lesions were not present and there was no history of HSV infection before delivery in any of the 3 cases in which scalp electrodes were used. Birth complications were noted in 8 cases (14.5%), with respiratory distress being the most common complication ($n = 4$); early rupture of membranes, breech extraction of twins, and induction because of nonstress test failure were also noted. No infants were reported as being coinfected with toxoplasmosis, rubella, or cytomegalovirus, but 1 infant each was reported as being coinfected with varicella and group B *Streptococcus agalactiae* (late-onset group B *Streptococcus* infection).

Characteristics of Infant HSV Infection

In almost 85% of the cases, culture was used for HSV testing, often in conjunction with PCR testing (39.7%) and less often with serologic testing (IgM) (3.4%). When culture was not used, PCR testing was used by itself (13.8%) or with serologic testing (1.7%), but serologic testing was never the only diagnostic method used (data not shown). The majority of positive cultures (61.0%) were from skin or skin lesions, although positive cultures were also reported from the throat (13%), conjunctiva, mouth, and nasopharyngeal aspirate (7.4% each), and amnion, peritoneal fluid, respiratory secretions, and stool (2.0% each). For the 35 cases in which PCR testing was used, the majority of assays (80.0%) were performed with cerebrospinal fluid, although blood, conjunctiva, and skin lesion samples were used for 2 cases each and liver and nasal samples for 1 case each. Of infants with known age at diagnosis ($n = 55$), 51 (92.7%) were diagnosed within the first 28 days of life; the remaining 4 cases were diagnosed at 29, 30, 33, and 45 days.

The majority of infant HSV cases (62.5%, $n = 30$) with available subtype information were typed as HSV-1, whereas 37.5% ($n = 18$) were typed as HSV-2 (Table 4). Ten cases were missing information on HSV type (virus not isolated, $n = 1$; virus not typed, $n = 5$; missing information, $n = 4$). Approximately 38% of cases ($n = 21$) had the first positive laboratory result within the first 1 week of life, whereas 61.8% of cases ($n = 34$) had a positive laboratory result after 1 week of life, with 4 of these after 4 weeks of life. For infants with known virus type and age of diagnosis ($n = 46$), 19 HSV-1 infections (67.9%) had the first positive laboratory diagnosis after the first 1 week of life, whereas 8

TABLE 4 **Characteristics of Infant HSV Infections ($n = 58$)**

	No. (%)
HSV type[a] ($n = 48$)	
HSV-1	30 (62.5)
HSV-2	18 (37.5)
Age at first positive laboratory diagnosis ($n = 55$)	
0–7 d	21 (38.2)
>7 d	34 (61.8)
Type of infection ($n = 57$)	
Localized	34 (59.6)
Skin	32 (94.1)
Oral cavity	7 (20.6)
Eye(s)	3 (8.8)
CNS	13 (22.8)
With skin, eyes, and/or mouth involvement	8 (61.5)
Disseminated	10 (17.5)
Liver	6 (60.0)
Lung	6 (60.0)
Trachea	2 (20.0)
Spleen	1 (10.0)
Kidney	1 (10.0)
Pancreas	1 (10.0)
Other	1 (10.0)
With CNS involvement	6 (60.0)
With skin, eyes, and/or mouth involvement	2 (20.0)

Numbers and totals may not add to 58 because of missing information.

[a] Ten reports had unknown HSV type (virus not typed, $n = 5$; virus not isolated, $n = 1$; missing information, $n = 4$).

HSV-2 infections (44.4%) had the first positive results in this time frame ($P = .14$) (Table 5).

The majority of HSV infections (59.6%) were localized only, with >90% of these cases being localized to the skin (Table 4). Localized infections of the oral cavity ($n = 7$) and eyes ($n = 3$) were also described. Of the 34 infections localized to the skin, eyes, and/or mouth, PCR assays of the cerebrospinal fluid were performed for 12 (all negative results). Approximately 18% of cases involved disseminated infections ($n = 10$), with dissemination to the liver ($n = 6$), lung ($n = 5$), trachea ($n = 1$), spleen ($n = 1$), kidney ($n = 1$), and pancreas ($n = 1$) being reported; CNS involvement was reported for 6 and skin, eyes, and/or mouth involvement for 2 of the 10 disseminated cases (Table 4). CNS disease was reported for 13 cases (22.8%), 8 of which also had skin, eyes, and/or mouth involvement (61.5%). For infants with known virus type and type of infection ($n = 47$), localized infections were more likely to be caused by HSV-1, whereas disseminated and CNS infections were more likely to be caused by HSV-2 ($P = .01$) (Table 5).

Treatment and Outcomes

Table 6 outlines the treatment and outcome information for the NHSV cases. Of the 56 neonates with known treatment information, all except 1 (98.2%) received treatment for their HSV infections. No reason was given for why 1 infant did not receive treatment. Of those treated ($n = 55$), all were treated with intravenously administered acyclovir, and 14 were also treated with orally administered acyclovir. Of the 51 infants with reported duration of intravenous therapy, 13 were treated for <2 weeks, 18 were treated for 14 days, 19 were treated for 21 days, and 1 was treated for 28 days. Of the 14 infants who also received orally administered acyclovir, 8 were treated for 180 days, 2 were treated for 365 days, and the rest received orally administered acyclovir for 10 to 90 days.

TABLE 5 Comparison of Type of Infection, Age at Positive Laboratory Diagnosis, and Sequelae of Infection According to Virus Type

	No.		*P*[a]
	HSV-1	HSV-2	
Type of infection ($n = 47$)			
Disseminated and CNS[b]	5	10	.01
Localized	24	8	
Age at first positive laboratory diagnosis ($n = 46$)			
0–7 d	9	10	.14
>7 d	19	8	
Obvious sequelae at 2 mo ($n = 48$)			
Yes	2	9	.001
No	28	9	
Fatal infection ($n = 48$)			
Yes	2	6	.04
No	28	12	

[a] *P* values were calculated with Fisher's exact test.
[b] Because of small cell sizes and resultant low power, disseminated and CNS disease were combined for this calculation.

TABLE 6 Treatment and Outcomes for NHSV Cases

	No. (%)
Received treatment ($n = 55$)	
Acyclovir, intravenously only	41 (74.5)
Acyclovir, intravenously and orally	14 (25.5)
Infant died ($n = 9$)[a]	
HSV-1	2 (25.0)
HSV-2	6 (75.0)
Localized	1 (12.5)
Disseminated[b]	4 (50.0)
CNS	3 (37.5)
Obvious sequelae at 2 mo ($n = 14$)	
Physical[c]	
Encephalitis	10 (71.4)
Seizures	9 (64.3)
Microcephaly	2 (14.2)
Blindness	1 (7.1)
Hydrocephaly	1 (7.1)
Developmental[c]	
Gross-motor	3 (21.4)
Fine-motor	2 (14.2)
Personal/social	2 (14.2)
Language	2 (14.2)

[a] One fatality was missing information on HSV type and type of infection.
[b] All 4 fatalities with disseminated infection had CNS involvement.
[c] Percentage of those who had sequelae ($n = 14$).

Nine of the 58 infected infants died, all within the first 27 days of life (range: 3–27 days), resulting in a case fatality rate of 15.5%. Three of those infants were born through cesarean section, although there was no significant difference in likelihood of death according to the type of delivery ($P = .67$). Of the 9 fatal cases, 4 deaths occurred among infants with disseminated infection (all involving dissemination to the CNS), 3 with CNS disease, and 1 with reported localized infection only (respiratory failure secondary to severe CNS insult, with negative HSV cerebrospinal fluid PCR results); for the final fatal case, no information was available regarding the nature of the infant's infection. Death was more likely to occur for those with disseminated or CNS disease than localized infection (30.4% vs 2.9%; $P = .005$) and for those with HSV-2 than HSV-1 (33.3% vs 6.7%; $P = .04$).

In the first 2 months of life, 14 cases (24.1%) demonstrated obvious sequelae of infection. Neonates infected with HSV-2 were significantly more likely to have obvious sequelae of infection than were those infected with HSV-1 (50.0% vs 6.7%; $P = .001$) (Table 5). Similarly, neonates with disseminated or CNS infection were more likely to have obvious sequelae in the first 2 months of life than were those with only localized infection (50.0% vs 5.9%; $P < .001$) (data not shown), although with small sample size this statistical significance should be interpreted with caution. Ten infants had encephalitis, occurring in 7 (53.8%) of 13 CNS cases and 3 (30.0%, all with CNS involvement) of 10 dissem-

inated cases. Other physical symptoms, including seizures ($n = 9$), microcephaly ($n = 2$), hydrocephaly ($n = 1$), and blindness ($n = 1$), were reported. Hearing loss (unilateral, bilateral, conductive, or sensorineural) was not reported for any infant in the first 2 months of life. Developmental delays in gross-motor function ($n = 3$), fine-motor function ($n = 2$), personal/social development ($n = 2$), and language ($n = 2$) were also noted.

DISCUSSION

Given the potential for serious and even fatal outcomes, NHSV infection is a significant public health concern in Canada and throughout the world. As the first national study to examine NHSV incidence in Canada, this study provides valuable data on the national epidemiologic features of this serious infection. On the basis of the 58 confirmed cases and national birth statistics[10] for the study period, the reported NHSV incidence rate in Canada was 5.9 cases per 100 000 live births. A previous retrospective chart review of NHSV cases in Manitoba, Canada, found incidence rates ranging between 0 and 17 cases per 100 000 live births between 1980 and 1986.[9] Compared with other countries, the rate found in this study resembles more closely rates reported for European nations such as the United Kingdom (1.65 cases per 100 000 live births)[11] and Sweden (6.5 cases per 100 000 live births),[12] whereas the United States has higher reported rates of 20 to 50 cases per 100 000 live births.[13]

Forty-four duplicate case reports of NHSV were submitted, that is, >1 physician reported a given case, a reflection of the comprehensiveness of this voluntary reporting system in which case reports were solicited actively from all practicing pediatricians and pediatric subspecialists on a monthly basis. The majority of NHSV cases (60%) were reported in Central Canada, where ~62% of the Canadian population resides; there were no cases reported in the northern region, where only 0.32% of Canadians live.

Although the vast majority of the mothers in this study were reported to be of white ethnicity, >10% of mothers were reported to be of Aboriginal ethnicity. This finding is particularly concerning because Aboriginal women of childbearing age made up only 3.4% of the childbearing population in Canada during the study period. Mothers <20 years of age were also affected disproportionately, accounting for 14.6% of cases with known maternal age information in the study but 5.0% of live births in Canada in 2001.[14] In contrast, mothers ≥35 years of age accounted for only 7.3% of cases, whereas 16.5% of live births occurred in this age group in Canada in 2001. Scalp electrodes were used in 3 of 25 NHSV cases. The use of scalp electrodes has been associated with NHSV infection in a number of studies.[15–17]

Importantly, 8 (40.0%) of 20 mothers were unaware of their HSV infection before delivery, and obvious genital lesions were present in only 1 (1.7%) of 58 cases during the intrapartum period. Other studies showed that between 60% and 100% of infants with NHSV are born to mothers with no history of genital HSV infection,[4,9,18] which has clear implications for prenatal screening and overall prevention of NHSV infection. There is a growing body of research outlining ways to decrease transmission of HSV from mother to child, including studies outlining the safety, effectiveness, and cost-effectiveness of using acyclovir suppression near term to decrease the risk of viral shedding and lesion recurrence,[19–23] as well as studies showing a significant reduction in transmission of HSV through cesarean section for women with primary lesions or active disease near term.[24,25]

There has been much debate regarding the risks and benefits of performing type-specific screening for HSV in prenatal care.[26–31] Proponents of type-specific screening stress that screening would allow potentially all pregnant women to benefit from recommendations to reduce perinatal transmission and from counseling regarding their own HSV infection or safer sex (for HSV-negative women at risk of acquiring HSV during pregnancy, eg, those with a serodiscordant partner). A seronegative pregnant woman whose partner is HSV positive is at risk for primary genital HSV infection, which carries the greatest risk for transmission of the virus to the newborn. It has been argued, however, that screening all pregnant women for HSV may not be cost-effective, has potential psychosocial implications for those diagnosed as HSV positive, may increase rates of cesarean sections unnecessarily, and that behavior modification after counseling of at-risk HSV-negative women is not well supported. Despite these arguments, it is clear that, without screening, a proportion of asymptomatic HSV-infected women would not be identified and therefore would not have the opportunity to benefit from activities to reduce the risk of perinatal HSV transmission.

Importantly, the majority of infant cases in this study were typed as HSV-1, a finding incongruent with a number of older studies that found HSV-2 infection to be more prevalent.[4,9,32,33] However, the results from this study, and recent studies showing an increase in the proportion of genital HSV infections caused by HSV-1,[34,35] have implications for both vaccine and drug development, where effectiveness against both HSV-1 and HSV-2 infection needs to be demonstrated.

An important consideration when interpreting the large proportion of HSV-1 cases in this study 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. It is notable, however, that HSV-1 infections were not significantly more likely to have their laboratory diagnosis after 1 week of life than

were HSV-2 infections. Data on the date of symptom onset, which is a better proxy measure for estimating when transmission might have occurred, were not collected. In this study, 2 intrauterine cases were reported. These 2 case subjects (both HSV-2 positive) were born with severe HSV manifestations at birth, which indicated that most likely intrauterine transmission had occurred. The first neonate had extensive CNS manifestations at birth, including cystic encephalomalacia, and died on the third day of life. The second infant had HSV-2 skin lesions, intracranial and hepatic calcifications, microcephaly, and hypoplatic ribs at birth and was reported to have spastic quadriparesis at the 1-year follow-up assessment.

Approximately 28% of the infants in this study were born before 37 weeks of gestation or were born with low birth weight, but birth complications were rare and Apgar scores were high for >90% of the sample with this information ($n = 40$). The treatment of choice for NHSV infection is acyclovir,[36–38] and all children in this study except 1 were treated with intravenously administered acyclovir or both intravenously and orally administered acyclovir. Although the majority of infections (almost 60%) in this study were localized exclusively to the skin, eyes, and/or mouth, 17.5% were disseminated (60.0% involving the CNS) and 22.8% were classified as CNS disease (61.5% with skin, eyes, and/or mouth involvement). Disseminated and CNS infections were more likely than localized infections to result in obvious sequelae in the first 2 months, to result in death of the infant and were more likely to be caused by HSV-2 than HSV-1. Similar low rates of disseminated and CNS disease and high rates of exclusively skin, eyes, and/or mouth manifestations have been reported in other studies since the availability and use of antiviral therapy.[2] Nine of the 58 infants in this study died, which resulted in a case fatality rate of 15.5%, a rate similar to that found in other studies.[7,32]

In the first 2 months of life, 14 of the 49 surviving infants with NHSV displayed obvious sequelae of infection, both physical and developmental in nature. The reported CNS-related physical sequelae in this study included encephalitis, microcephaly, hydrocephaly, blindness, and seizures, outcomes comparable to those in other studies.[32,39,40] Developmental delays with respect to gross- and fine-motor function, personal/social development, and language skills were reported for a small number of cases. Longer-term assessment of physical and developmental sequelae is needed to assess more adequately the overall impact of NHSV infection. A second phase of this project is currently underway, in which surviving infants from phase I are monitored annually for 3 years, to evaluate the overall health and developmental consequences of NHSV infection. This second phase of the project will end in October 2006.

There are a number of limitations to this study that need to be taken into account in interpretation of the results. First, the main limitation is the potential underreporting of cases, because the study survey was mailed only to pediatricians and pediatric specialists. Therefore, children born with HSV who were treated only by their family physicians might not have been reported. However, it is unlikely that a significant number of NHSV cases, especially disseminated cases, are treated solely by family physicians. In addition, the incidence estimate presented here may also be an underestimate, given that 10 potential cases were excluded from this study because of lack of laboratory results to meet the case definition. Second, because the CPSP network involves only pediatricians, the maternal information provided was limited and often missing. Third, because of the small number of NHSV cases reported, low statistical power made it difficult to demonstrate whether statistically significant associations existed between groups unless differences were large; in many instances, disseminated and CNS infections were grouped in cross-tabulations to provide sufficient power. Finally, because this is the first national examination of NHSV epidemiologic features in Canada, there are few avenues available for validation of the numbers reported.

Prevention of NHSV, the most serious consequence of often-undetected genital HSV infections, provides a challenge for the numerous health care providers who may be involved in the care of both mother and infant before birth, during delivery, and after birth. As the first national epidemiologic study of NHSV in Canada, this study provides valuable data for international comparisons and has implications for prenatal screening, vaccine and drug development, and national prevention strategies for NHSV infection.

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