IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

CENTRAL RABBINICAL CONGRESS FOR THE USA AND CANADA, *et al.*,	:	Case No.: 12-Civ.-7590
Plaintiffs,	:	Judge Naomi Reice Buchwald
vs.	:	
NEW YORK CITY DEPARTMENT OF HEALTH & MENTAL HYGIENE, *et al.*,	:	
Defendants.	:	

AFFIDAVIT OF DR. BRENDA BREUER, PH.D., M.P.H.

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1. I am the Director of Epidemiologic Research at the Department of Pain Medicine and Palliative Care at the Beth Israel Medical Center in New York, and an Associate Professor of Clinical Neurology at the Albert Einstein College of Medicine in New York. I have previously taught epidemiology, and have had academic appointments in neurology, geriatrics, and public health at Mount Sinai School of Medicine, Cornell University Medical College, and New York University School of Medicine.

2. I have reviewed articles for many peer-reviewed scientific journals, including the leading epidemiology journal, *The American Journal of Epidemiology*.

3. I have reviewed scientific grant proposals for several foundations as well as for the Department of Defense.

4. I have reviewed the report, published in June 2012 in the CDC *Morbidity and Mortality Weekly Report*, entitled "Neonatal Herpes Simplex Virus Infection Following Jewish Ritual Circumcisions that Included Direct Orogenital Suction - New York City, 2000-2011" ("the Report").

5. In my professional opinion, there are several serious methodological flaws in the Report. Those flaws undermine the Report's conclusion that there is a statistically significant association between herpes simplex viral infection ("HSV") and *metzitzah b'peh* ("MBP").

6. First, the researchers who wrote the Report should have begun their project by setting a particular timeframe during which (or sample size across which) they would analyze the number of reported cases of HSV for purposes of inquiring into a link with MBP. Setting these parameters in advance allows for a fair determination of whether the results of the inquiry are statistically significant (meaning that any reported

association is real, rather than simply a matter of chance).

7. The failure to define those parameters in advance of the surveillance was especially problematic here, considering the conclusions of a 2011 report in the *Journal of Sexually Transmitted Diseases*, in which four cases of HSV following MBP were identified. (*See* Exh. 1.) That report concluded that statistical analysis of those cases would be "unstable" (*i.e.*, the level of significance could easily change with the addition or loss of very few cases) due to the "limited number" of cases. (*Id.* at 6.) By waiting until a fifth case occurred, and then including that case in the statistical testing described in the Report, the researchers effectively capitalized on chance, undermining the critical objective of determining whether a finding is statistically significant. As a result, the Report's findings should not be considered statistically significant at a confidence level of 95%.

8. Second, because the Report's analysis was conducted using surveillance data, rather than on data from a controlled study, more stringent criteria would have been required in order to assert statistical significance. In other words, the researchers applied an improper formula to calculate the boundary points for their confidence interval. Correcting this error alone could eliminate the Report's finding of a statistically significant association between HSV and MBP.

9. It is also worth noting that, even setting aside the above methodological flaws, the Report's finding of a link between MBP and HSV was only *barely* statistically significant. Indeed, had the researchers identified only *four* cases of HSV in infants suspected to have received MBP, as opposed to the *five* cases that they claim to have identified—even according to their method of calculations there would have been *no statistically significant association* between HSV and MBP. Thus, any error at all in the identification of these five cases would unquestionably completely eliminate the Report's conclusion that MBP increases the risk of developing an HSV infection.

10. In addition, the Report indicates that in four of the five studied cases of HSV in infants suspected to have undergone MBP, the infants were admitted to the same hospital—Hospital C. If, as is likely, those four infants were also *born* at Hospital C, that raises the real question whether someone at that hospital was the source of the infection for all of those four infants, who constitute the vast majority of the sample size. Yet, while the Report says only that the chance of transmission from health-care workers was "largely excluded," it does not indicate that any robust testing was performed in that regard. The researchers should have tested the hospital staff for HSV before reaching any conclusions about the potential link between HSV and MBP.

11. In light of these methodological flaws in the clinical study that formed the basis for the Report, it is my expert opinion that the Report does not prove any statistically significant association between MBP and HSV.

I declare under penalty of perjury under the laws of the State of New York that the foregoing is true and correct to the best of my knowledge.

Executed this 4th day of October, 2012, at New York, New York.

Brenda Breuer

Brenda Breuer, Ph.D., M.P.H.

STATE OF NEW YORK
COUNTY OF NEW YORK

Subscribed and sworn before me this 4th day of October, 2012.

Hannah Susan Geller

Notary Public

My commission expires on: 3/30/14.

HANNAH SUSAN GELLER
Notary Public, State of New York
No. 01GE4730730
Qualified in New York County
Commission Expires March 30, 2014

EXHIBIT H-1

ORIGINAL STUDY

Population-Based Surveillance for Neonatal Herpes in New York City, April 2006–September 2010

Shoshanna Handel, MPH,† Ellen J. Klingler, MPH,† Kate Washburn, MPH,† Susan Blank, MD, MPH,†‡ and Julia A. Schillinger, MD, MSc†‡*

Background: Population-based data for neonatal herpes simplex virus (HSV) infection are needed to describe disease burden and to develop and evaluate prevention strategies.

Methods: From April 2006 to September 2010, routine population-based surveillance was conducted using mandated provider and laboratory reports of neonatal HSV diagnoses and test results for New York City resident infants aged ≤60 days. Case investigations, including provider interviews and review of infant and maternal medical charts and vital records, were performed. Hospital discharge data were analyzed and compared with surveillance data findings.

Results: Between April 2006 and September 2010, New York City neonatal HSV surveillance detected 76 cases, for an average incidence of 13.3/100,000 (1/7519) live births. Median annual incidence of neonatal HSV estimated from administrative data for 1997 to 2008 was 11.8/100,000. Among surveillance cases, 90.8% (69/76) were laboratory confirmed. Among these, 40.6% (28/69) were HSV-1; 39.1% (27/69) were HSV-2; and 20.3% (14/69) were untyped. The overall case-fatality rate was 17.1% (13/76). Five cases were detected among infants aged >42 days. In all, 80% (20/25) of the case-infants delivered by cesarean section were known to have obstetric interventions that could have increased risk of neonatal HSV transmission to the infant before delivery. Over half (68%, or 52/76) of all cases lacked timely or ideal diagnostics or treatment.

Conclusions: Administrative data may be an adequate and relatively inexpensive source for assessing neonatal HSV burden, although they lack the detail and timeliness of surveillance. Prevention strategies should address HSV-1. Incubation periods might be longer than expected for neonatal HSV. Cesarean delivery might not be protective if preceded by invasive procedures. Provider education is needed to raise awareness of neonatal HSV and to assure appropriate testing and treatment.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Infection with herpes simplex virus type-1 (HSV-1) or type-2 (HSV-2) during the neonatal period, or neonatal herpes (neonatal HSV), causes severe morbidity and high mortality rates even when treated.[1,2] The majority of infections (85%) are acquired perinatally, although postnatal (10%) and congenital (5%) infections do occur.[3] There is evidence that an increasing proportion of adult genital HSV infections are attributable to HSV-1[4,5]; however, approaches for preventing neonatal HSV are limited and focused on HSV-2.[1,2,6]

Experts have advocated for making neonatal HSV a nationally notifiable disease; however, neonatal herpes is currently only reportable in a few jurisdictions in the United States (US).[7–10] Estimates of national incidence from other countries range from 1.15/100,000 to 8/100,000 live births.[11–16] Incidence estimates from different parts of the United States are higher, ranging from 8.4/100,000[17] to 69/100,000 live births[9]; this range includes estimates that are not population based, as well as a nationally representative incidence estimate gleaned from a database of pediatric hospital admissions.[18,19,20] Given variability in the prevalence of genital herpes across geographic regions of the United States,[5] variation in incidence of neonatal HSV is expected. Variations are also likely caused by differences in methods used to measure neonatal HSV disease burden. We present findings from a population-based surveillance system for neonatal HSV for the first time in the United States, and compare these findings with analyses of administrative data for the same population.

MATERIALS AND METHODS

In late March 2006, neonatal HSV infection became a reportable disease in New York City (NYC).[21] Clinical laboratories were required to report positive results for HSV on specimens from infants aged ≤60 days who were residents of NYC, and healthcare providers were required to report diagnoses of neonatal HSV infection for the same age group, regardless of whether laboratory results confirmed infection. Certificates of birth, death, and spontaneous termination of pregnancy (fetal death before delivery) were obtained from the NYC Bureau of Vital Statistics for all cases. To identify cases not reported by a provider or laboratory report, a retrospective search of vital records was performed at regular intervals.

The NYC Department of Health and Mental Hygiene investigated reported cases using a standard form. Investigations included confirmation of laboratory testing, telephone interviews with providers involved with each case, review of infant medical records, and maternal labor and delivery records. Interviews with parents were conducted only where

postnatal infection was considered probable. Data collected regarding infant patients included demographics: gestational age; birth weight; circumcision status and date (males only); whether ill at birth; presence and anatomical distribution of lesions; comorbidities; HSV test and its results; acyclovir treatment; cerebrospinal fluid (CSF) and liver function tests and their results; and dates of: first symptom, first seeking medical attention, hospital admission and discharge, specimen collection, diagnosis, and treatment initiation and completion. Data collected regarding infant patients' mothers included demographics, gravidity and parity, history of HSV infection, prenatal HSV serologic testing status, antiviral medication during pregnancy, and presence of genital herpes lesions at delivery. Data collected regarding delivery of infant patients included presentation (vertex or breech), mode of delivery (vaginal or cesarean section), interval between rupture of membranes and delivery, and artificial rupture of membranes or any invasive obstetric procedures.

We defined a confirmed case of neonatal HSV infection as one occurring in an infant aged ≤60 days who tested positive for HSV by culture, direct immunofluorescence assay or other antigen detection test, or polymerase chain reaction. The upper limit for the age range was 60 days to test our hypothesis that some perinatally transmitted cases may not appear until shortly after the neonatal period. We defined a probable case of neonatal HSV as one occurring in an infant aged ≤60 days with no laboratory confirmation of HSV infection, but who had each of the following: (1) a diagnosis of HSV, (2) treatment with acyclovir for ≥7 days, (3) illness clinically compatible with neonatal HSV, and (4) no alternative diagnosis. In NYC, postnatal HSV-1 infections have occurred after ritual Jewish circumcision practices in which the ritual circumciser (mohel) uses his mouth to suck blood away from the incision on the newly circumcised penis.[22] Infection after ritual circumcision was defined as a confirmed case of HSV-1 or untyped HSV, or a probable case, in a male infant who had been circumcised outside of a hospital, with date of illness onset occurring after circumcision; if the date of illness onset was missing, then the date of first specimen collection for HSV testing was used.

Incidence was calculated for infants aged ≤60 days and for infants aged ≤42 days using the number of cases reported during 4.5 years as the numerator. In the denominator, we added three-quarters the number of live births in 2006 plus the number of live births for 2007 to 2009 plus three-quarters the number of live births in 2009 to estimate the number for January to September 2010. Maternal age and race/ethnicity-specific incidence were calculated using maternal age and race-ethnicity data obtained from birth certificates. To obtain a denominator for these incidence calculations, we used a similar method as described earlier and the number of live births by age and race/ethnicity from 2008 to estimate the numbers for 2009 and 2010, since more current data were not available. Case-fatality rates were calculated overall and by viral type.

Pearson chi-square testing was performed by using SAS 9.1 (SAS Institute, Inc., Cary, NC) to identify statistically significant differences in distribution of characteristics among cases with regard to viral type, fatality, infant sex, clinical manifestation, presence of lesions and fever, delivery mode, maternal race, and age at presentation.

We classified cases as follows: skin, eye, or mucous membranes (SEM) infections were those in which herpetic lesions were present or SEM specimens tested positive for HSV with no evidence of central nervous system (CNS), disseminated, or congenital infection. CNS infections were those that were CSF-positive for HSV with no evidence of disseminated or congenital infection. Disseminated infections were those in which there was no evidence of congenital infection, and both aspartate aminotransferase and alanine aminotransferase levels were elevated.[23] Congenital infections were those with signs of HSV-related illness or those from which HSV-positive specimens were collected within 24 hours of birth, or those with stigmata of congenital infection (e.g., microcephaly, microphthalmia, or retinal scarring) noted at birth.

We measured delays in seeking care, diagnosis, and treatment, as well as instances of inappropriate medical treatment. We defined a delay in seeking medical care as >1 day between date of first symptom and date medical care was first sought, a delay in diagnosis as >1 day between date medical care was first sought and date of diagnosis or first specimen collection for HSV testing, and a delay in treatment as >1 day between herpes diagnosis or first specimen collection and beginning treatment with acyclovir. Cases were classified as adequately evaluated if lumbar puncture and liver-function testing were recorded as performed. Inappropriate treatment was defined as administration of less than the recommended course of acyclovir (60 mg/kg/d of intravenous acyclovir for 14 days for SEM cases and 21 days for CNS and disseminated cases); we considered 21 days appropriate therapy for congenital neonatal HSV.[24]

To explain how HSV might have been transmitted despite the protective effect of cesarean delivery, we recorded obstetric factors that might have increased risk for disease transmission before the cesarean delivery. An interval of >4 hours between rupture of membranes and delivery was considered to pose a risk for HSV transmission,[25] as were artificial rupture of membranes, vacuum extraction, and use of fetal scalp electrodes, intrauterine pressure catheters, or forceps.

We used hospital discharge data to measure number of cases of neonatal HSV diagnosed among infants with an NYC zip code of residence who had been discharged from a New York State hospital during January 1997 to December 2008 and who were aged ≤60 days at time of admission, and included any hospital discharges listing an International Classification of Diseases (ICD) Version 9 (ICD-9) code for herpes (codes 054.0–054.9) as the principal, primary, or other diagnosis code. A unique identifier was created by concatenating the encrypted date of birth, sex, and the zip code of the patient's residence to identify infants with more than one hospital discharge listing a herpes ICD-9 code, and only the first such admission was counted. Annual incidence was calculated using annual neonatal HSV hospital discharges as the numerator and annual number of live births in NYC as the denominator.

RESULTS

During the first 4.5 years (April 2006–September 2010) of neonatal HSV surveillance in NYC, 75 reported cases met our case definitions. One additional case was identified by death certificate search, providing 76 cases for analysis. Overall incidence of neonatal HSV was 13.3/100,000 live births or 1/7519 live births; among infants aged ≤42 days, incidence was 12.4/100,000 live births or 1/8065 live births. Among 72/76 (94.7%) cases with information regarding maternal age at delivery, median maternal age was 25 years (range, 16–43 years). Age-specific incidence was highest among infants born to women aged <20 years (47.4/100,000 live births or 1/2110) and declined thereafter (Table 1). Infants born to black non-Hispanic mothers were 1.5 times as likely to be infected with HSV as those born to white non-Hispanic or Hispanic mothers. Black non-Hispanic mothers had the youngest median age at

TABLE 1. Distribution of Cases by Maternal Age and Race/Ethnicity

	All Race/ Ethnicities			Black Non-Hispanic		Hispanic		White Non-Hispanic		Asian		Other/ Unknown	
Maternal Age (yr)	n	Incidence	%	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence
All ages ($P < 0.0001$)	76	13.3	100.0	23	18.0	24	13.2	18	10.4	4	4.9	7	259.3
<20	18	47.4	23.7	10	79.8	2	9.3	2	72.7	0	0.0	4	2,191.8
20–24	21	18.3	27.6	6	19.4	7	14.4	5	21.5	1	8.6	2	353.1
25–29	15	10.1	19.7	4	12.1	5	10.0	3	7.8	2	7.6	1	135.6
30–34	10	6.7	13.2	0	0.0	5	13.5	5	8.7	0	0.0	0	0.0
>34	12	10.1	15.8	3	12.8	5	19.9	3	5.8	1	5.8	0	0.0

delivery (20 years, as compared with 27.5 years for white non-Hispanic and 26 years for Hispanic mothers).

Among the 76 cases, 69 (90.8%) were confirmed and 7 (9.2%) were probable; all had laboratory testing performed. Among the 69 confirmed cases, 28 (40.5%) patients were infected with HSV-1; 27 (39.1%) with HSV-2; and 14 (20.3%) had positive laboratory results that were not type specific. No statistically significant differences between HSV-1 and HSV-2 cases were identified with regard to sex, fatality, clinical manifestation, presence of lesions or fever, delivery mode, or maternal race. In all, 43 (56.6%) of the cases were boys. Of the 13 deaths, 8 (61.5%) were among girls; 9 (69.2%) occurred within the first 2 weeks of life (Table 2). Although not statistically significant, the fatality rates differed by HSV type (21.4% among HSV-1 cases and 18.5% among HSV-2 cases). Most of the cases (56.5%) were SEM; 23.2% were disseminated, 17.4% were CNS infections, and 2.9% were congenital infections. Lesions were present among 41 (60.3%) of the 68 cases for which lesion data were available. Fever was present among 19 (31.1%) of the 61 cases for which data were available. Among the 61 cases with known fever and lesion data, 19.7% had neither fever nor lesions (Table 3). In all, 27 (69.2%) SEM cases had lesions noted, compared with 5 (41.7%) CNS cases, 7 (43.8%) disseminated cases, and both (100%) of the congenital cases.

Four (9.3%) of the 43 male patients met the definition for infection after ritual Jewish circumcision. All 4 case patients had lesions on the penis or the scrotum (2 on the penis only, 1 on the scrotum only, and 1 on both the penis and the scrotum); 3 of the 4 case-patients were laboratory-confirmed HSV-1 cases. The interval between circumcision and illness onset ranged 2 to 12 days (median, 3.5 days).One of the case-patients had CNS infection, the remaining 3 had SEM disease.

Of all cases, 56 (73.7%) were diagnosed at age ≤14 days; 12 (15.8%) at age 14 to 30 days; 3 (3.9%) at age 31 to 42 days; and 5 (6.6%) at age 43 to 60 days. Case-patients diagnosed at age ≤14 days had a higher fatality rate than those diagnosed at age ≥15 days (21.4% vs. 5%; $P = 0.094$). Of the 5 cases diagnosed among infants >42 days, 2 were HSV-1 (delivered by cesarean section); 2 were HSV-2 (one vaginally, and the other with unknown mode of delivery); and 1 was a probable case (cesarean section). Among the 57 case mothers for whom we had data, 11 (19.3%) had a known history of HSV, and 5/52 (9.6%) of those for whom data were available

TABLE 2. Characteristics of Fatalities

Sex	HSV Type	Syndrome	Mode of Delivery	Obstetric Risk Factors	Maternal History of HSV	Age at Diagnosis (in Days)	Age at Death (in Days)	HSV Indicated on Death Certificate
Male	1	Disseminated	Cesarean	Yes*,†	Unknown	7	12	No
Female	1	SEM	Vaginal	Unknown	Unknown	N/A	0	No
Female	1	Disseminated	Vaginal	Yes‡	No	8	5	Yes‡
Female	1	Disseminated	Cesarean	Yes†,§	Unknown	8	14	Yes‡
Male	2	Disseminated	Cesarean	Unknown	Unknown	11	11	Yes¶
Male	2	Disseminated	Cesarean	Yes†,‖	No	6	12	No
Male	2	Disseminated	Cesarean	Yes†	No	5	8	Unknown
Male	1	SEM	Cesarean	No	No	14	20	Unknown
Female	Unknown	Congenital	Cesarean	Yes§	No	0	3	Unknown
Female	Unknown	Disseminated	Cesarean	No	No	10	23	Yes¶
Female	1	Disseminated	Vaginal	Yes§	No	8	11	Unknown
Female	2	Disseminated	Cesarean	Yes†§	No	12	15	Unknown
Female	2	Disseminated	Vaginal	Yes†§,**	No	16	29	Unknown

*Internal monitor.
†Prolonged rupture of membranes.
‡Underlying cause.
§Artificial rupture of membranes.
¶Immediate cause.
‖Intrauterine pressure catheter.
**Vaccuum extraction.

TABLE 3. Characteristics of Case Infants and Their Births, by Viral Type

	All Cases		Confirmed Cases							Probable Cases	
			Untyped		HSV-1		HSV-2		*P* (HSV-1 vs. HSV-2)		
	N	%*	n	%*	n	%*	n	%*		n	%*
Total	76	100%	14		28		27			7	
Deaths (case-fatality rate)	13	17.1	2	14.3	6	21.4	5	18.5	0.787	0	0
Sex (n = 76)											
Male	43	56.6	8	57.1	16	57.1	13	48.1	0.504	6	85.7
Female	33	43.4	6	42.9	12	42.9	14	51.9		1	14.3
Mean/median age at diagnosis, in days (n = 76)	12.5/9.5		7.9/8.0		13.8/9.5		13.6/11.0		0.957	11.9/7.0	
Clinical manifestation (n = 69)			13		27		23			6	
SEM	39	56.5	9	69.2	17	63.0	8	34.8	0.135	5	83.3
CNS	12	17.4	1	7.7	3	11.1	7	30.4		1	16.7
Disseminated	16	23.2	2	15.4	7	25.9	7	30.4		0	0
Congenital	2	2.9	1	7.7	0	0	1	4.4		0	0
Lesions present (a case can have lesions in multiple sites) (n = 68)			13		27		22			6	
Yes—head	20	29.4	2	15.4	8	29.6	7	31.8	0.951	3	50.0
Yes—trunk	13	19.1	3	23.1	4	14.8	4	18.2	0.804	2	33.3
Yes—genitals/buttocks	13	19.1	5	38.5	4	14.8	1	4.5	0.219	3	50.0
Yes—extremities	12	17.6	4	30.8	2	7.4	6	27.3	0.073	0	0
None	27	39.7	3	23.1	15	55.6	9	40.9	0.308	0	0
Fever present (n = 61)			13		25		18			5	
Yes	19	31.1	2	15.4	8	32.0	9	50.0	0.234	0	0
No	42	68.9	11	84.6	17	68.0	9	50.0		5	100.0
Delivery mode (n = 72)			13		28		24			7	
Vaginal	45	62.5	10	76.9	17	60.7	14	58.3	0.862	4	57.1
Cesarean	27	37.5	3	23.1	11	39.3	10	41.7		3	42.9
Obstetric risk factor† (n = 63)			13		25		19			6	
Yes	52	82.5	11	84.6	22	88.0	13	68.4	0.111	6	100.0
No	11	17.5	2	15.4	3	12.0	6	31.6		0	0
Maternal genital lesions at delivery (n = 52)			12		19		16			5	
Yes	5	9.6	1	8.3	2	10.5	1	6.3	0.653	1	20.0
No	47	90.4	11	91.7	17	89.5	15	93.7		4	80.0

*Column percentages.
†Obstetric risk factors include the following: rupture of membrane >4 h preceding delivery, artificial rupture of membrane, and invasive monitoring or procedures.
HSV indicates herpes simplex virus; SEM, skin, eye, and mucous membrane infection; CNS, central nervous system infection.

had lesions at delivery. None of the 8 cases diagnosed after 30 days of age were born to a mother with a known history of HSV or acyclovir use during pregnancy.

We found a delay in seeking care for 12/59 (20.3%) cases (median: 2 days; range: 2–10 days), a delay in diagnosis for 26/66 (39.4%) cases (median: 4.5 days; range: 2–21 days), and a delay in initiating acyclovir treatment for 18/61 (29.5%) cases (median: 3 days; range: 2–18 days). Overall, 38/54 (70.4%) cases with complete information with which to judge delays had one or more delays. Of the 38 cases where there were delays, 12 (31.6%) had fever, 27 (71.1%) had lesions, and 4 (10.5%) had neither fever nor lesions. Of 66 liveborn infants with complete information regarding lumbar puncture, 57 (86.4%) received lumbar puncture with HSV testing. Of 63 infants, 50 (79.4%) with available information had liver-function tests performed. Only 19 (51.4%) of the 37 patients for whom we had data related to treatment had received an appropriate acyclovir regimen; all of these had received an adequate evaluation. Over half (68%, or 52/76) of all cases lacked timely or ideal diagnostics or treatment.

Length of hospitalization was calculated for 61/76 (80.3%) cases; median was 15 days and varied with clinical manifestation—disseminated cases, median was 11 days (range, 2–39); SEM cases, median was 15 days (range, 0–86 days); and CNS cases, median was 22 days (range, 10–46). The 2 congenital cases were hospitalized for a median of 40.5 days (range, 3–78).

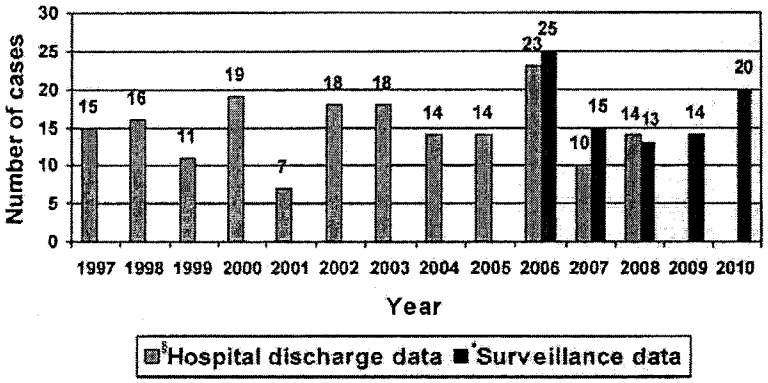

Figure 1. NYC resident neonatal herpes cases identified using an administrative data set of discharges from New York State (including New York City) hospitals during 1997–2008, compared to those reported to New York City through routine public health surveillance during 2006–2010. §Hospital discharge data for 2009 and 2010 are not yet available. *For 2006, and for 2010, the total number of cases was estimated by annualizing 9 months of reported cases.

Where mode of delivery was known, 37.5% (27/72) of the infants were delivered by cesarean section. Among the 25 cases delivered by cesarean for whom we had data related to obstetric risks for HSV transmission, 20 (80.0%) had at least one such risk. (17 had >4 hours between rupture of membranes and delivery, 10 had artificial rupture of membranes, 5 had invasive instrumentation including vacuum extraction, fetal scalp electrodes, intrauterine pressure catheters, or forceps.) Only 2 of the cesarean deliveries were performed because of a perceived risk of HSV transmission. In both cases, the mother had a known history of genital HSV, and active genital lesions were noted at delivery. Among 45 cases delivered vaginally, 31 (68.9%) had at least one known obstetric risk for neonatal HSV transmission. (20 had >4 hours between rupture of membranes and delivery; 16 had artificial rupture of membranes; 12 had invasive instrumentation including vacuum extraction, fetal scalp electrodes, intrauterine pressure catheters, or forceps.)

Administrative Data Findings

During the 12-year interval from 1997 through 2008, a total of 179 infants were discharged with an ICD-9 code for herpes after an admission at age ≤60 days; 84/179 (46.9%) were male. Only 20/179 (11.2%) infants had been admitted at age >42 days. Median duration of admission was 14 days. During 1997 to 2008, annual incidence of neonatal HSV ranged from 5.6/100,000 live births (in 2001) to 18.3/100,000 live births (in 2006); median annual incidence was 11.8/100,000 live births. For infants aged ≤42 days, incidence ranged from 4.8/100,000 live births (in 2001) to 15.1/100,000 live births (in 2006); median incidence was 11.0/100,000 live births (Fig. 1).

DISCUSSION

We present the first population-based surveillance findings for neonatal HSV in the United States, as well as a comparison with findings from an administrative data set for the same population. Both methods yielded similar incidence rates, and were within the range of previously reported estimates. Our findings provide insight into neonatal HSV epidemiology. Laboratory-confirmed cases were diagnosed well after the first 30 days of life, and these included HSV-2 infections, suggesting a longer-than-expected incubation period. Our findings also reveal a substantial proportion of cases attributable to HSV-1.

The similarity in incidence estimates gleaned from NYC surveillance, and administrative data indicate that the latter may provide a reasonable means of measuring HSV disease burden in jurisdictions without resources to implement neonatal HSV surveillance. However, administrative data are often untimely and therefore do not allow for a public health response to epidemiologic findings. In addition, administrative data can be difficult to deduplicate, rely on ICD-9 codes that are not specific to neonatal HSV, and often lack detailed clinical and laboratory information, thereby limiting accuracy and utility.

Disparities in risk for neonatal HSV by maternal age and race/ethnicity were apparent in our findings. Younger mothers might be less likely to be infected with HSV at the start of a pregnancy and at increased risk for acquiring HSV during pregnancy. Moreover, because genital HSV-2 infections are particularly prevalent among black non-Hispanic New York residents,[26] they might be more likely than women of other races/ethnicities to be exposed to HSV.

Our findings differed in several ways from those reported by other North American investigators. We found a lower proportion of CNS cases (17.4%, as compared to 30%) and a higher proportion of SEM cases (56.5%, as compared to 45%) than previously reported.[3] The former was surprising, especially because highly sensitive nucleic-acid amplification tests are increasingly being used to test CSF specimens,[27,28] and the majority of our cases (76.0%) had CSF testing. However, our findings on distribution of cases by clinical manifestation was similar to what was found in Canadian surveillance.[11] Our findings on prevalence of fever (31.1%) was also similar to what has been previously reported.[29] We also found a higher case-fatality rate among disseminated cases (62.5%) than previously reported (29%), but no fatalities among CNS cases, in contrast to previous reports of fatality rates of 4% to 15%[2,29] among CNS cases. These findings may be explained, at least in part, by our use of a definition for disseminated disease which selects for only very severe disease and by the increasing use of highly sensitive tests (polymerase chain reaction) to test CSF, which may classify as CNS disease cases who might have been considered SEM in the past.

Over one-third of the reported case-patients had been delivered by cesarean section, suggesting that the protective effect of cesarean delivery can be undermined when other obstetric risk factors for transmission have already occurred. Because a majority of neonatal HSV cases were among infants born under circumstances that would not prompt provider suspicion of risk for HSV infection, opportunities for intervention are limited. Prenatal screening of pregnant women and their sex partners could enable providers to counsel seronegative women with seropositive partners about abstinence or safer sex during pregnancy,[17] or to recommend acyclovir suppressive treatment during the third trimester to HSV-positive women,[30–32] but

both of these strategies are unproven, expensive, and carry risks (of undue strain on the woman's relationship and possible toxicity to the infant,[1] respectively).

Postpartum infections could be reduced by educating parents and caregivers about ways to avoid transmitting infection. Unfortunately, it is difficult to modify the practice of ritual Jewish circumcision with oral suction because of the religious value attached to it by certain sects.[33] A vaccine for HSV would be the best prevention strategy, but the HSV vaccine in Phase III trials has recently proven ineffective.[6] To prevent the majority of neonatal HSV cases, a vaccine would have to be effective against both HSV types and be administered before sexual debut.

Opportunities to intervene in the progression of disease were missed, evidenced by delays in diagnosis for over 1/3 of cases and delays in initiating antiviral treatment in nearly 1/3 of cases. A majority (89.5%) of those cases where delays in care seeking, diagnosis, and/or treatment were present had fever or lesions, which may support the case for increased caregiver and provider education. Nonspecific presentation, like the 19.7% of cases we found with neither fever nor lesions, does make diagnosis of neonatal HSV difficult, so pediatric providers should be encouraged to consider neonatal HSV in the differential diagnosis of ill infants, to perform SEM testing, lumbar puncture, and liver function tests, and to initiate intravenous acyclovir treatment immediately when neonatal HSV is suspected.

Our study has several limitations. It is likely that neonatal HSV cases were underreported and those reported might be biased toward more severe disease. The relatively limited number of cases limits our ability to make definitive statistical comparisons among our cases and to those reported in other case series and makes certain statistical analyses unstable. Due to missing information on some cases, there may be some misclassification of disease syndrome; however, that is most likely to have resulted in an overestimate of SEM cases. We lack data concerning lumbar punctures performed at the end of treatment; therefore, we were unable to assess whether follow-up treatment was performed when needed. Length of hospitalization for neonatal HSV might have been overestimated because it includes hospitalization for non-HSV illness, and might appear misleadingly short for disseminated cases, which are more likely to result in death. The number of congenital cases might have been overestimated because we may have included infants' ill at birth with conditions other than neonatal HSV who were colonized with HSV, which might have cleared without treatment. Finally, some of our findings may not be generalizable outside of NYC. For example, the incidence is affected by the prevalence of genital HSV in the population, which varies. However, some of our findings (e.g., delays in diagnosis, treatment, and seeking care, and case fatality rates) are likely to be generalizable.

CONCLUSION

Administrative data may provide an adequate and inexpensive means to assess local neonatal HSV burden, although such data lack the detail and timeliness of surveillance data. We believe routine surveillance for neonatal herpes is of value; our data provide new insights, give a baseline incidence from which to evaluate the impact of future prevention efforts, and point to the need for parental and provider education regarding neonatal HSV. Challenges remain for reducing incidence of neonatal HSV, as all current prevention strategies are limited.

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