Background: Neonatal infection with herpes simplex virus (HSV) is not a nationally reportable disease; there have been few population-based measures of HSV-related infant mortality. We describe infant death rates due to neonatal HSV as compared with congenital syphilis (CS) and HIV, 2 reportable, perinatally transmitted diseases, in New York City from 1981 to 2013.

Methods: We identified neonatal HSV-, CS-, and HIV-related deaths using International Classification of Diseases (ICD) codes listed on certificates of death or stillbirth issued in New York City. Deaths were classified as HSV-related if certificates listed (1) any HSV ICD-9/ICD-10 codes for deaths ≤42 days of age, (2) any HSV ICD-9/ICD-10 codes and an ICD code for perinatal infection for deaths at 43 to 365 days of age, or (3) an ICD-10 code for congenital HSV. CS- and HIV-related deaths were those listing any ICD code for syphilis or HIV.

Results: There were 34 deaths due to neonatal HSV (0.82 deaths per 100,000 live births), 38 from CS (0.92 per 100,000), and 262 from HIV (6.33 per 100,000). There were no CS-related deaths after 1996, and only 1 HIV-related infant death after 2004. The neonatal HSV-related death rate during the most recent decade (2004–2013) was significantly higher than in previous years.

Conclusions: The increasing neonatal HSV-related death rate may reflect increases in neonatal herpes incidence; an increasing number of pregnant women have never had HSV type 1 and are therefore at risk of acquiring infection during pregnancy and transmitting to their infant.

WHAT'S KNOWN ON THIS SUBJECT: Herpes simplex virus causes life-threatening infection during the newborn period; however, there have been few population-based measures of herpes-related infant mortality and no analysis of trends over time in the United States.

WHAT THIS STUDY ADDS: We report population-based measures of infant death due to herpes, syphilis, and HIV over 33 years in the largest US city and show that herpes-related infant deaths increased, whereas deaths due to syphilis and HIV decreased.
Neonatal infection with herpes simplex virus (HSV) type 1 (HSV-1) or HSV type 2 (HSV-2) causes serious illness with potentially devastating consequences, often resulting in death or long-term disability.\(^\text{1,2}\) Before the availability of antiviral treatment, death rates were as high as 85% for disseminated neonatal herpes infection;\(^\text{3}\) however, even with currently recommended high-dose acyclovir treatment, disseminated infection has a death rate of 29%, with 17% of surviving infants left with long-term neurologic sequelae.\(^\text{4}\)

The incidence of neonatal HSV in the United States has been noted to be similar to the incidence of perinatal HIV infection before the routine use of antiretroviral medications in pregnancy and greater than that of congenital syphilis (CS) in nonepidemic years.\(^\text{1}\) However, it is difficult to ascertain the true burden of neonatal herpes infection in the United States because neonatal herpes is not a reportable disease nationally or in most states.\(^\text{5}\)

Estimates of neonatal herpes incidence in the United States vary widely depending on geographic region, the population examined, and the methodology used to capture cases,\(^\text{5-12}\) with most estimates relying on International Classification of Diseases (ICD) codes assigned to hospital discharge diagnoses. In this context, several researchers have advocated making neonatal herpes a reportable disease to better understand the burden of disease, monitor disease trends, evaluate risk factors and interventions, and target preventive measures.\(^\text{10,13,14}\)

Rates of infant death due to nationally reportable sexually transmitted infections such as HIV infection\(^\text{15,16}\) and CS\(^\text{17-18}\) have decreased over the past 2 decades, but there have been few population-based estimates of neonatal HSV-related deaths published in the United States, and none have examined long-term trends.\(^\text{6,12}\) Given the paucity of data for infant death due to neonatal herpes as compared with other perinatally acquired sexually transmitted infections, we sought to describe infant deaths due to neonatal herpes in New York City (NYC) during 1981–2013 compared with deaths due to syphilis and HIV over the same period.

METHODS

Population

The population consisted of the following: (1) infant births; (2) infant deaths within the first year of life for which HSV, syphilis, or HIV was listed as the underlying or contributing cause on the death certificate; and (3) stillbirths in which HSV, syphilis, or HIV was the underlying cause. All occurred from January 1, 1981, through December 31, 2013, in NYC. Stillbirths were defined as fetal deaths occurring after the 20th week of gestational age in which no evidence of life was detected after birth.

Data Sources

The Bureau of Vital Statistics within the NYC Department of Health and Mental Hygiene issues and records certificates for all vital events occurring in NYC, including births, deaths, and stillbirths. For certificates of death, a single underlying cause and up to 7 contributory causes of the event are provided by the physician/certifier; for stillbirths, a single underlying cause was used. International Classification of Diseases, Ninth Revision (ICD-9), codes were used to assign cause of death until 1999, after which International Classification of Diseases, Tenth Revision (ICD-10), codes were used. We identified certificates of stillbirth and death for infants <1 year old with a cause attributable to 1 of the pathogens of interest as indicated by the ICD codes in NYC from 1981 to 2013. Data extracted from death and stillbirth certificates included certificate number, date of death, date of birth, infant age at death (calculated by subtracting date of birth from date of death), infant gender, maternal race/ethnicity, ancestry, zip code, borough, and ICD codes for the diagnoses. We also obtained data on the annual number of live births in NYC during 1981–2013 (including residents and nonresidents) to use as a denominator for infant mortality rate calculations.\(^\text{19}\) Maternal race/ethnicity was classified as white non-Hispanic (NH), black NH, Hispanic, Asian, and other and unknown. Although infants who died within the first year of life would have been included in the denominator of live births, stillbirths were not.

Case Ascertainment

ICD-9 and ICD-10 codes for the 3 diseases of interest were chosen in consultation with a Bureau of Vital Statistics nosologist (Table 1). Because the ICD-9 system did not include a specific code for congenital or perinatal HSV infection, to maximize the probability that the deaths included in our analysis were the result of neonatal herpes (rather than infection that occurred outside the newborn period) we required an additional perinatal infection code for infants >42 days old at the time of death (Table 2). Under the ICD-9 system we included all cases with a general herpes code (054) with or without a code indicating perinatal infection (771.2 or 779.8) for infants ≤42 days old; infants older than 42 days had both a herpes code and a code describing perinatal infection. Under the ICD-10 system, we included all deaths coded as congenital herpes viral infection (P35.2), herpes viral infection (B00), or anogenital herpes (A60) if ≤42 days old. For infants older than 42 days we included deaths coded as congenital herpes (P35.2) and...
only those with other herpes viral infections (B00 or A60) that also had a code describing perinatal infection (P00.2). Although neither ICD-9 nor ICD-10 include a code specifically for perinatally transmitted HIV, we assumed infants who died within a year had contracted it perinatally and therefore included all deaths with codes describing HIV disease. Both ICD-9 and ICD-10 systems included congenital-specific coding for syphilis; however, we searched for all cases of syphilis in infants.

### Analysis

We measured the frequency of deaths related to each disease of interest and calculated disease-specific death rates overall, annually, and in 2-year intervals using the number of deaths related to each disease per year divided by the number of live births in NYC for the corresponding years, expressed as number of deaths per 100,000 live births. We assumed a Poisson process for the counts and used a normal approximation for calculating rate confidence intervals (CIs) for each rate in which the number of deaths was greater than 100 and applied a gamma distribution where the number of deaths was <100. We considered rates with nonoverlapping CIs to be significantly different. Death rates were not calculated for infants of other or unknown race/ethnicity. This analysis did not fall under the purview of the institutional review board because it involved the use of routinely collected surveillance data for the purposes of describing the local burden of disease.
During the 33-year observation, there were 4,138,014 live births in NYC. We identified 34 infant deaths attributed to neonatal HSV, 38 to CS, and 262 to HIV. Table 1 describes the ICD-9 and ICD-10 codes used for case ascertainment and shows the number of deaths associated with each ICD code. None of the deaths were attributed to >1 of the diseases of interest, and no death had >1 disease-specific ICD code. We identified no HSV-related stillbirths, 7 stillbirths due to CS (occurring from 1989 to 1992), and 2 HIV-related stillbirths in 2011 and 2012. One syphilis stillbirth was identified in 2013 through routine surveillance conducted by the NYC Bureau of Sexually Transmitted Disease Prevention and Control; however, this case was not identified by our methods. Review of the infant’s birth certificate showed that the mother was known to have syphilis during pregnancy; however, the infant’s death certificate was coded only as “Fetal death of unspecified cause” (ICD-10 code P95).

**Frequency of Deaths by ICD Code, Gender, and Maternal Race/Ethnicity**

Table 3 presents the number of deaths over the entire 33-year period and overall death rates related to HSV, syphilis, and HIV, stratified by infant gender and maternal race/ethnicity.

**RESULTS**

HSV

Of the 34 deaths with an HSV code, 33 were within 42 days of life; the death that occurred >42 days of age was coded as a congenital herpes viral infection, yielding an overall herpes-related death rate of 0.82 per 100,000 live births. Five additional cases of infant death due to HSV were identified who were >42 days old at the time of death but these did not have an associated code indicating perinatal acquisition of disease. The herpes-related death rate when including all 39 cases was 0.94 per 100,000. Males had a lower herpes-related death rate than females; however, the rates were not significantly different (0.66 and 0.99).
Infants born to black NH women had the highest death rate of all maternal ethnicity groups at 1.08 per 100,000, but this rate was not significantly higher than that for infants in other race/ethnicity groups. Figure 1 shows the distribution of age at death among infants whose deaths were attributable to herpes. Two infant deaths (1 in 2004 and 1 in 2011) were known to be related to ritual Jewish circumcision that included direct orogenital suctioning (metzitzah b’peh). After excluding these cases, the death rate was 0.77 per 100,000.

**Syphilis**

Of the 38 identified syphilis cases, 32 were within 42 days of age at death (Table 3). The overall syphilis-related death rate was 0.92 per 100,000. Male and female infants had similar death rates (0.85 and 0.99 per 100,000, respectively.) Infants born to black NH women had the highest syphilis-related death rates among all maternal ethnicity groups (1.97 per 100,000), which was significantly greater than the rates among infants born to white NH and Hispanic women.

**HIV**

Of the 262 identified HIV cases, 13 were within 42 days of age at death (Table 3). The overall death rate was 6.33 per 100,000 and was similar for male and female infants (6.18 and 6.49 per 100,000, respectively). Infants born to black NH women had the highest death rate among all maternal ethnicity groups (14.18 per 100,000), which was significantly greater than the rates among infants born to white NH and Hispanic women.

**Trends**

Figure 2 shows the number of infant deaths attributable to HSV by year (range: 0–4 deaths/year). Figure 3 compares infant death rates for each of the 3 diseases of interest by 2-year increments during the observation period. Herpes-related death rates remained relatively stable over the first 2 decades, then began to increase in 2001, with an HSV-related death rate of 2.42 per 100,000 during 2005–2006 and 2.78 per 100,000 during 2009–2010. The herpes-related death rate was significantly higher during the most recent decade (2004–2013; 1.68 per 100,000; 95% CI: 1.04–2.57) than during the preceding 23 years (1981–2003; 0.45 per 100,000; 95% CI: 0.24–0.77). The syphilis-related death rate peaked in 1991–1992, with a rate of 4.74 per 100,000; there were no deaths identified from 1997 to 2013. The HIV-related death rate was highest from 1989 to 1990 (24.88 per 100,000), and there were only 3 infant deaths after 2001.
DISCUSSION

We examined disease-specific infant death rates due to 3 perinatally acquired sexually transmitted diseases over a 33-year period in NYC. Overall, the herpes-related death rate (0.82 per 100,000) was very similar to that due to syphilis (0.92 per 100,000); however, both were almost an order of magnitude lower than the HIV-related death rate over the same period. Although syphilis- and HIV-related infant deaths decreased over the 33-year observation period, the number and rate of infant deaths due to HSV increased over the later part of the observation period.

The decreases in infant deaths due to HIV and CS observed over the past 2 decades in NYC are consistent with national trends. In NYC, HIV-related infant deaths steadily decreased beginning in the mid-1990s, coinciding with the availability of highly active antiretroviral therapy for HIV infection and the national implementation of protocols to prevent mother to child transmission of the virus. CS-related deaths also decreased during the mid-1990s. Decreases in CS deaths reflect trends in syphilis infection among women of child-bearing age in NYC; currently, newly acquired syphilis is relatively uncommon among NYC women (∼25 cases of primary and secondary syphilis per year). The decreases in CS deaths could be due to improved screening and treatment during pregnancy; however, there has been at least 1 infant death due to CS as recently as 2013 (not captured in our methods). In a previous analysis that abstracted the medical records of infants discharged from NYC hospitals, we found that among a sample of infant hospitalizations coded only as 771.2, 8.5% (n/N) had laboratory-confirmed HSV. Therefore, relying on only the HSV-specific ICD-9 code of 054 could risk of acquiring HSV-1 during their child-bearing years. HSV-1 causes an increased proportion of new genital herpes infections in young adults, and infections newly acquired during pregnancy are more likely to be transmitted to neonates than are existing infections. Indeed, in NYC more than half of neonatal herpes cases are due to HSV-1.

The observed increases in neonatal herpes-related deaths may also reflect improved case ascertainment, an artifact of the change from the ICD-9 to ICD-10 system. Under the ICD-9 system, neonatal herpes-related deaths could have been given nonspecific codes indicating perinatal infection (771.2 or 779.8), and thus not identified as herpes-related. In the most recent NHANES show that HSV-1 seroprevalence has declined among adolescents, resulting in more young women at risk of acquiring HSV-1 during their child-bearing years. HSV-1 causes an increased proportion of new genital herpes infections in young adults, and infections newly acquired during pregnancy are more likely to be transmitted to neonates than are existing infections. Indeed, in NYC more than half of neonatal herpes cases are due to HSV-1.

The increases could be linked to the changing epidemiology of HSV-1 in adolescents and young adults. Data from the most recent NHANES show that HSV-1 seroprevalence has declined among adolescents, resulting in more young women at risk of acquiring HSV-1 during their child-bearing years. HSV-1 causes an increased proportion of new genital herpes infections in young adults, and infections newly acquired during pregnancy are more likely to be transmitted to neonates than are existing infections. Indeed, in NYC more than half of neonatal herpes cases are due to HSV-1.
have underestimated the herpes-related infant deaths during the years that the system was in use.\textsuperscript{31} The ICD-10 system, implemented in 1999, may allow for more precise case ascertainment because it includes a specific code for congenital herpes infection. Morris et al\textsuperscript{6} also found a higher herpes-related death rate (0.83 per 100,000) in California during the latter part of their observation period (1999–2003) when ICD-10 was in use compared with that measured during 1995–2003 (0.64 per 100,000).

Another possible explanation for the increasing neonatal herpes-related death rate is the introduction of highly sensitive diagnostic tests for HSV, primarily polymerase chain reaction testing, which became increasingly available during the latter part of the observation period. These have likely improved the detection of HSV in ill infants or at autopsy.\textsuperscript{32}

Although interventions have been implemented to prevent mother to child transmission of syphilis and HIV, neonatal herpes-prevention strategies are lacking.\textsuperscript{1} In moving forward, several steps should be taken to decrease the overall incidence of neonatal HSV and related deaths. First, a reduction in maternal-child transmission and early treatment of neonatal HSV must be a priority. Achieving this goal will include performing cesarean delivery and providing maternal antiviral therapy when indicated,\textsuperscript{33} ensuring appropriate management of asymptomatic infants born to women with genital herpes lesions at delivery,\textsuperscript{34,35} and using high-dose acyclovir to treat infants with HSV infection.\textsuperscript{4}\n
Until there is consensus on the use of type-specific herpes serologic screening during pregnancy,\textsuperscript{37–39} other avenues for prevention must be explored and efforts made to fill gaps in knowledge. In populations who practice religious Jewish circumcisions, health care providers should educate parents about the risk of direct orogenital suction (\textit{metzitzah b’peh}) during ritual Jewish circumcision, a practice that resulted in at least 17 cases of laboratory-confirmed neonatal herpes in NYC during 2000–2014, including 2 deaths.\textsuperscript{21,22} Finally, health departments may wish to consider the utility of making neonatal HSV a reportable disease, because this could aid in measuring local disease burden, identifying and quantifying risk factors for infection, evaluating interventions, and targeting preventive measures toward vulnerable populations.\textsuperscript{10,13,14,21,22}

Current guidelines are focused on women with known HSV or active lesions during delivery; however, a majority of neonatal HSV occurs in women who do not know they have HSV and do not have lesions at the time of delivery.\textsuperscript{40} In addition, at least 1 report found that the interval between the onset of clinical disease and diagnosis has not changed in decades,\textsuperscript{41} highlighting the importance of early identification and treatment of infected infants. Point-of-care testing to diagnose genital HSV at the time of delivery, even in women without lesions, may allow more at-risk infants to be identified. However, given the inherent challenges in identifying and treating neonatal HSV, a childhood vaccine would probably be the best tool for reducing genital herpes infections, and thereby neonatal herpes infections. Although several trials have been promising there remain barriers to both the development of a vaccine and its implementation.\textsuperscript{42–47}

The chief limitation to this analysis was our reliance on ICD codes, which are subject to misclassification and provide no information on the characteristics of the infection, such as the infecting viral type. Some researchers have used broader ICD-9 coding and included probable cases of HSV on the basis of signs and symptoms suggestive of herpes infection.\textsuperscript{7} We may be underestimating the number of deaths by relying solely on ICD diagnostic codes, because we are aware of at least 1 CS stillbirth that was not identified by our methods. Previous studies have shown that among cases that were diagnosed as HSV by ICD code, a high proportion had laboratory confirmation.\textsuperscript{12} Therefore, whereas ICD codes may miss some neonatal herpes-related deaths, among those with an HSV ICD code the diagnosis is fairly specific. Because we relied on ICD codes, we had only crude information regarding the manner of disease acquisition and therefore cannot estimate how many deaths could have been prevented. For example, it is not possible to determine how many of the male herpes deaths resulted from direct orogenital suction during ritual Jewish circumcision.\textsuperscript{21,22}

CONCLUSIONS

In summary, although our 33-year observation in NYC shows a promising reduction in infant deaths due to congenital HIV and syphilis, infant deaths due to HSV appear to be increasing. We have several hypotheses to explain this finding and suggest that routine surveillance for neonatal herpes could be of value. The development of a vaccine that is effective against both HSV-1 and HSV-2 will be vital to reduce HSV transmission to newborns. The dramatic reduction in neonatal deaths due to HIV and syphilis after universal prevention strategies were put into place provides hope that if the control of neonatal HSV is also made a public health priority, infant death and morbidity due to HSV may also be significantly reduced.

ABBREVIATIONS

CI: confidence interval
CS: congenital syphilis
HSV: herpes simplex virus
ICD: International Classification of Diseases
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, Tenth Revision
NH: non-Hispanic
NYC: New York City
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