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The Incidence of Neonatal Herpes Simplex Virus Infections in the United States, 2019

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Abstract

Objective: The objective of this study was to generate updated estimates for the incidence rate, cost burden, and case fatality rate (CFR) of neonatal herpes simplex virus infections (nHSV) in the United States (US) in 2019.

Methods: A nationally representative sample of US pediatric discharges was assessed using data from the Healthcare Cost & Utilization Project Kids' Inpatient Database to estimate the incidence, costs, and fatality of nHSV in 2019. Cases were estimated using herpes simplex virus *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes (B00.xx, A60.xx, or P35.2) among infants aged ≤ 28 days admitted to the hospital and with hospital stays > 5 days or resulting in death. A matching algorithm was developed to deduplicate records of readmissions or transfers from another hospital. Estimates were generated overall, and

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Contributions Statement Page

Matthew Pooser conceptualized the analysis, served as Project Manager, performed initial data exploration, generated initial tables, drafted the manuscript, and critically reviewed and revised the manuscript.

Yan Yuan designed and carried out the data analyses, drafted the manuscript, generated final tables, and critically reviewed and revised the manuscript.

Dr. Saugat Karki offered guidance throughout the study, conceptualized the analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Drs. Kevin O'Callaghan and Kaitlin Hufstetler converted ICD-9-CM codes to ICD-10-CM codes, provided clinical expertise related to the analysis and results, participated in the manual record review for matching potential transfer and readmission records, and critically reviewed and revised the manuscript.

Alejandro Perez offered guidance related to the data analysis and critically reviewed the manuscript.

Andre Berro critically reviewed and revised the manuscript.

Dr. Harrell Chesson offered guidance of cost estimation, such as inflation adjustment for hospital cost, and critically reviewed and revised the manuscript.

Dr. Kristen Kreisel provided advice for the analysis, assisted in interpreting results, and critically reviewed and revised the manuscript.

Conflict of Interest Disclosures: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Mention of company names or products does not imply endorsement by the CDC. The authors have no conflict of interest relevant to this article to disclose.

by sociodemographic factors including race, US region, primary payer, and median household income.

Results: 561 nHSV cases were estimated in the US in 2019, resulting in an incidence rate of 15.7 per 100,000 hospital births. The highest incidence rate was in the South (21.3; 95% confidence interval [CI]: 19.0–23.9) and in infants born to Black birth parents (27.3; 95% CI: 22.8–32.4). The total cost to the US healthcare system was estimated at \$28.9 million. The CFR among infants with nHSV was estimated to be 4.6%.

Conclusion: This study updates the incidence rate, cost burden, and CFR of nHSV in 2019, an increase compared to past estimates and highlights the racial and geographic disparities across the US. Public health interventions for early detection and prevention are critical to mitigate these disparities.

Introduction

Neonatal herpes simplex virus infection (nHSV), caused by herpes simplex virus types 1 (HSV-1) or 2 (HSV-2), is rare but can cause serious morbidity and mortality in neonates.¹ nHSV is most often caused by transmission of HSV-1 or HSV-2 from a person to their neonate during pregnancy or postpartum and is more likely to occur during a pregnancy complicated by a primary genital herpes outbreak than a recurrence.^{1,2} The prognosis for nHSV in neonates depends on the clinical presentation and severity of disease.²

nHSV is classified into 3 main disease categories: skin, eyes, or mouth (SEM) (45% of all nHSV cases); central nervous system (CNS) with or without SEM disease (30% of cases); or disseminated disease involving multiple organs such as the liver or lungs (25% of cases).³ Despite improvements in outcomes, nHSV morbidity and mortality remain high with 45–70% of neonates with CNS disease having neurologic impairment and neonates with disseminated disease having a 30–40% mortality risk.^{3–5}

Few studies have addressed the recent burden of and trends in nHSV in the United States (US) despite the disease's severe morbidity and rising trends in other sexually transmitted infections (STIs). A study by Flagg and Weinstock estimated an nHSV incidence of 9.6 per 100,000 hospital births in 2006.⁶ Donda et al. found increasing rates from 7.9 to 10.0 per 100,000 live births from 2003–05 to 2012–14.⁷ Mahant et al.'s study on Medicaid-enrolled children similarly showed an increase in nHSV incidence from 34 in 2009 to 53 per 100,000 births in 2015.⁸ Both the Donda and Mahant studies noted rising costs, but no significant changes in case fatality rates (CFRs) across study periods.^{7,8} We note that the case definitions of these studies are different from each other. The estimates provided by Flagg, et al, included infants identified with nHSV up to the 60th day of life; the estimates from both Mahant et al. and Donda et al. included infants identified with nHSV up to the 28th day of life. Our objective was to provide updated estimates of the incidence rate, cost burden, and CFR of nHSV utilizing data from the 2019 Healthcare Cost & Utilization Project's Kid's Inpatient database (HCUP KID) provided by the Agency for Healthcare Research and Quality (AHRQ).

Methods

Data Sources

The HCUP KID is the largest publicly available all-payer pediatric inpatient care database in the US, yielding national estimates for hospital stays of patients under 21 years old.⁹ The dataset encompasses approximately 3.1 million hospitalizations (weighted=5.9 million) and includes clinical and resource data extracted from hospital billing discharge records. The KID consists of 10% of normal newborns born within the hospital and 80% other newborns/pediatric cases selected from each hospital.⁹ Its extensive sample size allows for analysis of rare pediatric conditions,⁹ such as nHSV.

Case Definition

The study population included all neonates in the 2019 HCUP KID born in a hospital or admitted ≤ 28 days from birth. nHSV associated hospitalizations were defined as a hospital admission ≤ 28 days of life where the patient had ≥ 1 *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes for HSV infection (Table 1). To address the 2015 transition from ICD-9-CM to ICD-10-CM, codes from the Flag study⁶ were converted using a mapping and deduplication process with the [ICD10Data.com](https://www.icd10data.com) tool and clinical review by two reviewers. Neonates with signs of sepsis may be preemptively diagnosed with nHSV and treated empirically with intravenous acyclovir, the recommended treatment for nHSV, until test results return. To reduce including probable cases and maintain consistency with prior nHSV surveillance studies, we restricted our analysis to patients with a length of stay (LOS) > 5 days or who died ≤ 5 days.⁸

Since each record in the dataset represented a hospital discharge, we combined records associated with readmissions and transfers. For readmissions, we matched records indicating an admission at birth to those indicating admissions ≤ 28 days of life using race, sex, hospital region, patient median household income per ZIP code, admission month, and LOS. Matches were validated through manual review of the Diagnosis Related Group (DRG) and diagnosis codes. Transfers were similarly identified, matching records involving transfers *to* other hospitals with records of transfers *from* other hospitals. In instances of readmission or transfer, we counted matched records for a unique individual as a single record by combining LOS and hospitalization cost.

Incidence Rate Calculations

The crude nHSV incidence rate (per 100,000 hospital births) was calculated by dividing the number of estimated nHSV cases by the total number of hospital births, overall and by hospital region (Northeast, Midwest, South and West). We further stratified by other covariates including: sex (male, female), race/ethnicity (based on AHRQ's uniform coding¹⁰; Non-Hispanic White [NHW], Non-Hispanic Black [NHB], Hispanic, "Additional Race, Non-Hispanic" [combining Asian or Pacific Islander, Native American, and Other due to small case counts]), median household income for patient's ZIP Code ($< \$48,000$, $\$48,000 - \$60,999$, $\$61,000 - \$81,999$, $> \$82,000$), primary payer (public insurance, private insurance, self-pay, no charge/other), and hospital location/teaching status (rural, urban non-teaching, urban teaching).

We also assessed nHSV incidence by gestational age at delivery, using ICD-10-CM codes P07.20-P07.26 for extreme immaturity and P07.30-P07.39 for gestation <37 weeks, classifying a record as preterm birth (gestational age <37 weeks). Records not containing these codes were considered representing term births (gestational age ≥37 weeks). Route of delivery (Cesarean or vaginal) was also evaluated for those infants diagnosed during the birth admission with information on route of delivery.

Healthcare Utilization Calculations and Case Fatality Rate

We assessed nHSV healthcare utilization by examining LOS and associated payments for each case, using variables already included in the 2019 HCUP KID. In addition to estimating hospital charges (amount billed by hospitals) associated with nHSV, we also estimated hospital costs (actual expenses incurred by hospitals), using the HCUP Cost-to-Charge Ratio (CCR).¹¹ We included both hospital charges and costs to allow for fair comparison to Flagg's study and to provide a more realistic cost estimate, respectively. For cases where matched readmissions or transfers were identified, the total LOS and total hospital charges/costs were calculated as the sum of days or costs for all relevant hospitalizations. To make costs comparable across years, we adjusted all cost data to 2019 US dollars using the Personal Consumption Expenditures (PCE) index for hospitals.^{12,13}

Furthermore, we calculated the proportion of nHSV cases diagnosed at birth by dividing the number of cases diagnosed at birth admission by the total number of identified cases. We also determined the CFR for nHSV by dividing the number of deaths during hospitalization by the total number of identified cases.

Statistical Analysis

Incidence rates and 95% confidence intervals (CI) were calculated overall for the US, as well as by US census region of the hospital. We stratified based on all covariates described above. For continuous data, we reported the interquartile range (IQR), mean, median, total values and 95% CIs. All rates and 95% CIs are unadjusted. We inferred statistical significance when 95% CIs did not overlap. All analyses were performed using SAS version 9.4 (SAS Institute Inc) and weighted using HCUP KID discharge weights⁹ for national estimation.

Results

Study Population

We estimated 815 patients were admitted to a US hospital with an associated HSV ICD-10-CM code ≤28 days of life, regardless of LOS (Table 2, Figure 1). Among these, we estimated 561 patients who had a hospital stay of >5 days or died ≤5 days. Nearly half (49.7% [95% CI: 44.9–54.5%]) of the nHSV patients were diagnosed during birth admission.

Incidence Rate

We estimated an incidence rate of nHSV of 15.7 per 100,000 hospital births (95% CI: 14.5 – 17.1) in the US in 2019. All subsequent incidence rates are provided per 100,000 hospital

births. The highest incidence rate was in the South (21.3; 95% CI: 19.0 – 23.9) and lowest in the West (8.7; 95% CI: 6.8 – 11.0, Table 2). Incidence rates for males (16.3; 95% CI: 14.5 – 18.2) and females (15.2; 95% CI: 13.4 – 17.1) were not significantly different (Table 3).

While 23.5% of nHSV cases were NHB infants, the incidence rate among NHB infants (27.3; 95% CI: 22.8 – 32.4) was statistically significantly higher compared to all other race/ethnicity groups, including NHW (14.3; 95% CI: 12.6 – 16.3), Hispanic (15.2; 95% CI: 12.3 – 18.5), and other race/ethnicity groups (13.6; 95% CI: 10.4 – 17.4). Regionally, incidence rates among NHB infants were generally higher than other race/ethnicity groups, with a statistically significant difference observed in the Midwest, where the rate among NHB infants (28.0; 95% CI: 18.2–41.1) significantly exceeded that of NHW infants (10.6; 95% CI 7.7–14.2) (Table 3).

Most (71.6%) infants with nHSV were born to a parent covered by public insurance, with an incidence rate over three times that of those covered by private insurance (25.2, 95% CI: 22.8 – 27.8 vs. 7.5, 95% CI: 6.3 – 9.0) (Table 3). Among infants diagnosed with nHSV, 24.7% were born preterm. The incidence rate in the preterm group (41.4; 95% CI: 34.8 – 49.0) was three times that of infants delivered at term (13.1; 95% CI: 11.9 – 14.4) (Table 3). This pattern was observed for each US region. Only neonates diagnosed with nHSV during birth admission (n=279, 49.7%) had delivery information; of those, 46.6% were delivered by Cesarean section and 53.4% were delivered vaginally; of those delivered vaginally, 38.2% were preterm.

Most infants with nHSV were admitted to urban teaching hospitals (86.2%), with an incidence rate of 18.5 (95% CI: 16.9 – 20.2) which was nearly three times that of infants admitted to rural hospitals (6.5; 95% CI: 4.0 – 9.8), and two times that of infants admitted to urban non-teaching hospitals (9.1; 95% CI: 6.8 – 11.8) (Table 3). Stratified by US census region, the incidence rate of nHSV was highest in Southern urban teaching hospitals (24.4; 95% CI: 21.5 – 27.7) compared to urban teaching hospitals in other regions; the second highest incidence rate was in the Midwest (18.4; 95% CI: 14.9 – 22.5) (Table 3).

Almost half (43.2%) of infants with nHSV were from households in zip codes with a median household income in the lowest quartile, where the incidence rate was 24.5 (95% CI: 21.6 – 27.8), three times that of the highest income category (7.8; 95% CI: 6.0 – 10.0) and nearly double that of the second-highest income category (13.0; 95% CI: 10.8 – 15.6) (Table 3). This same trend was observed when stratified by US census region.

Healthcare Utilization

The median LOS for infants with nHSV was 15 days (95% CI: 14 – 17 days), and the median and mean hospitalization costs were \$27,000 (95% CI: \$23,000– \$31,000), and \$52,000 (95% CI: \$44,000– \$59,000), respectively (Table 4). Total nHSV hospitalization costs were \$28.9 million, and total unadjusted hospitalization charges were \$116.9 million. Stratified by US census region, the South had the highest per-region hospitalization cost, estimated at \$15.2 million, nearly three times that of the next highest region (Midwest, \$5.4 million).

Case Fatality Rate

Of the 561 nHSV cases in 2019, we estimated 26 in-hospital deaths (95% CI: 15–37), for an overall 4.6% CFR (95% CI: 2.6–6.6%), slightly higher than the CFR estimated in 2006 (4.1%, 95% CI: 1.6–6.6%).⁶ There were no significant differences in CFRs by US census region. CFRs were similar between nHSV patients admitted at vs. after birth (Table 5). However, the CFR among patients born prematurely was nearly four times that of those born ≥ 37 weeks (Table 5).

Discussion

We estimated a total of 561 cases of nHSV in the US in 2019, with an incidence rate of 15.7 per 100,000 hospital births and a total cost of \$28.9 million to the US healthcare system. Differences were observed by US census region and race/ethnicity, with the highest rates in the South and in NHB infants. Nearly three quarters of patients were born to parents covered by public insurance and nearly half were born into households in areas with the lowest median household income quartile. The CFR was nearly 5%.

This study provides updates to the first reported estimates of nHSV incidence, mortality, and costs performed by Flagg who used the 2006 HCUP KID. Between 2006 and 2019, the number and incidence rate of nHSV cases increased by 42% and 64%, respectively, for the overall U.S.⁶ The most substantial increase occurred in the South, where the incidence rate increased 139%, from 8.9 (2006) to 21.3 per 100,000 hospital births (2019). These increasing trends align with Donda et al's findings.⁷ One potential explanation for this rise is improved ascertainment and diagnosis of nHSV.⁷ However, changes in the diagnostic codes, available variables in the HCUP KID data, and differences in methodology may have impacted these findings. Comparisons between studies should be interpreted cautiously, as differences between databases and changes within the same database may impact findings.

The first significant difference is the conversion of ICD-9-CM codes to ICD-10-CM codes to align with more recent data. We recommend further investigation to assess the impact of the conversion in diagnostic codes.

The second difference is that the 2019 HCUP KID removed several key variables used in Flagg's 2006 analysis, specifically a variable indicating the patient's age in days. With these limitations, we only identified cases admitted ≤ 28 days of birth, which could result in an underestimation compared to the 60-day window used in Flagg's 2006 analysis. Furthermore, we lowered the LOS threshold (>5 days) for case identification, to align with recent surveillance studies and due to advancements in detecting HSV.¹ This adjustment, in contrast to the former >7 -day threshold in Flagg,⁶ may have led to finding more cases, and thus increased the overall incidence rate.

Prior studies highlight disparities regarding prenatal care, with Black individuals^{14,15} and people with public insurance¹⁶ more likely to receive insufficient prenatal care. These disparities, in addition to studies showing a higher HSV-2 prevalence among Black people,¹⁷ may contribute to higher nHSV rates, as interventions such as patient education and early identification and management of a genital herpes outbreak during pregnancy may reduce

nHSV. We hope our findings will assist clinicians by identifying areas and risk factors for nHSV and highlighting the need for increased efforts to improve prenatal care access and increase awareness.

Nearly half of the nHSV cases studied were diagnosed during the birth admission, a substantial increase from the 24.5% in 2006.⁶ This shift towards earlier detection can likely be largely attributed to the implementation of standardized protocols for managing asymptomatic infants born to mothers with active genital HSV-2, based on the 2013 American Academy of Pediatrics Clinical Report.¹⁸ Timing of detection, whether at birth or after, did not significantly impact the CFR. However, cases diagnosed during the birth hospitalization had a longer mean length of stay (30 days [95% CI, 26–34] vs. 18 days [95% CI, 16–20]) and a higher preterm birth rate (43.9% [95% CI, 37.7%–50.1%] vs. 5.7% [95% CI, 2.5%–8.8%]) compared to those diagnosed after birth. This may reflect greater disease severity among cases diagnosed at birth. Due to data limitations, differences in disease severity and sequelae between the two groups were not assessed. Further studies are needed to investigate whether earlier identification and management have contributed to reduced morbidity in post-birth nHSV cases.

While the median LOS decreased to 15 days (95% CI: 14 – 17 days) in 2019 from 20 days (95% CI: 18 – 20 days) in 2006, the total hospitalization days related to nHSV rose to 13,384 days (95% CI: 11,885 – 14,883) in 2019, marking a 51.2% increase compared to 2006. This increase translated to a greater burden of costs.

The total hospitalization charge we estimated (\$116.9 million in 2019) is substantially higher (148.1%) than estimated in Flagg's study⁶ (\$47.1 million in 2019 dollars, Supplemental Table 1). Notably, despite the South accounting for 39.7% of hospital births in the US, it contributed to 53.9% of nHSV cases and incurred 52.6% of the total associated costs in the country, indicating geographic disparity. Further interventions, such as patient education and increased research on diagnostics and treatment, could address this challenge.

Limitations

The HCUP KID database only includes data from inpatient hospitalizations, potentially missing cases of nHSV treated in outpatient or not in a hospital setting.¹⁹ However, based on national guidance on the management of nHSV and the accepted standard of care, we assumed all identified cases would commence antiviral treatment in a hospital setting.⁵ Our analysis is further limited to hospitalizations admitted ≤ 28 days from birth, and the lack of unique patient identifiers in HCUP KID prevents tracking individuals across multiple hospitalizations. These limitations may lead to underestimation of the incidence rate, costs, and CFR. Specifically, the CFR, derived solely from discharge status, only reflects deaths during hospitalization, potentially underestimating the true CFR associated with nHSV infection.

Another limitation is the reliance on ICD-10-CM diagnosis codes for case identification. Although ICD-10 codes are widely used in healthcare settings, they are subject to coding errors and variations in coding practices, which may impact the accuracy of case identification. Furthermore, the database lacks the ability to classify the type of nHSV

infection (e.g., SEM, CNS, or disseminated), limiting a more detailed analysis of disease severity and outcomes.

nHSV cases were identified from hospital diagnosis charges, including infants born outside hospitals but admitted at 28 days of life or less. Using hospital births as the denominator may have resulted in a 4.7% higher incidence rate (Supplemental Table 3) compared to using all live births.²⁰

Our estimates of the hospital charges and costs of nHSV do not include professional fees and thus could be underestimates.²¹ We estimated the hospital charges and costs of treating infants with nHSV, without regard to whether these expenses were attributable to nHSV. However, a previous study found that >90% of the costs of treating infants with nHSV were “excess costs” compared to the costs associated with healthy infants.²²

Conclusion

We found an increase in the incidence of nHSV and costs to the healthcare system compared to past estimates; however, the CFR did not substantially change. Our findings also highlight racial and geographic disparities. Efforts to improve access to prenatal care and increase provider and patient awareness through nHSV education are needed, especially among patients in areas of high HSV prevalence. Additionally, future studies are needed that investigate the timing of antiviral suppression, causes of healthcare disparities, and mode of delivery to better understand and mitigate the burden of nHSV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AHRQ	Agency for Healthcare Research and Quality
CCR	Cost-to-Charge Ratio
CFR	Case Fatality Rate
CI	Confidence Interval
CNS	Central Nervous System
DRG	Diagnostic Related Group
HCUP	Healthcare Cost and Utilization Project

HSV-1	Herpes Simplex Virus Types 1
HSV-2	Herpes Simplex Virus Types 2
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IQR	Interquartile Range
KID	Kids' Inpatient Database
NHB	Non-Hispanic Black
nHSV	Neonatal Herpes Simplex Virus Infection
NHW	Non-Hispanic White
PCE	Personal Consumption Expenditures
SEM	Skin, Eyes, or Mouth
STIs	Sexually transmitted infections

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Article Summary

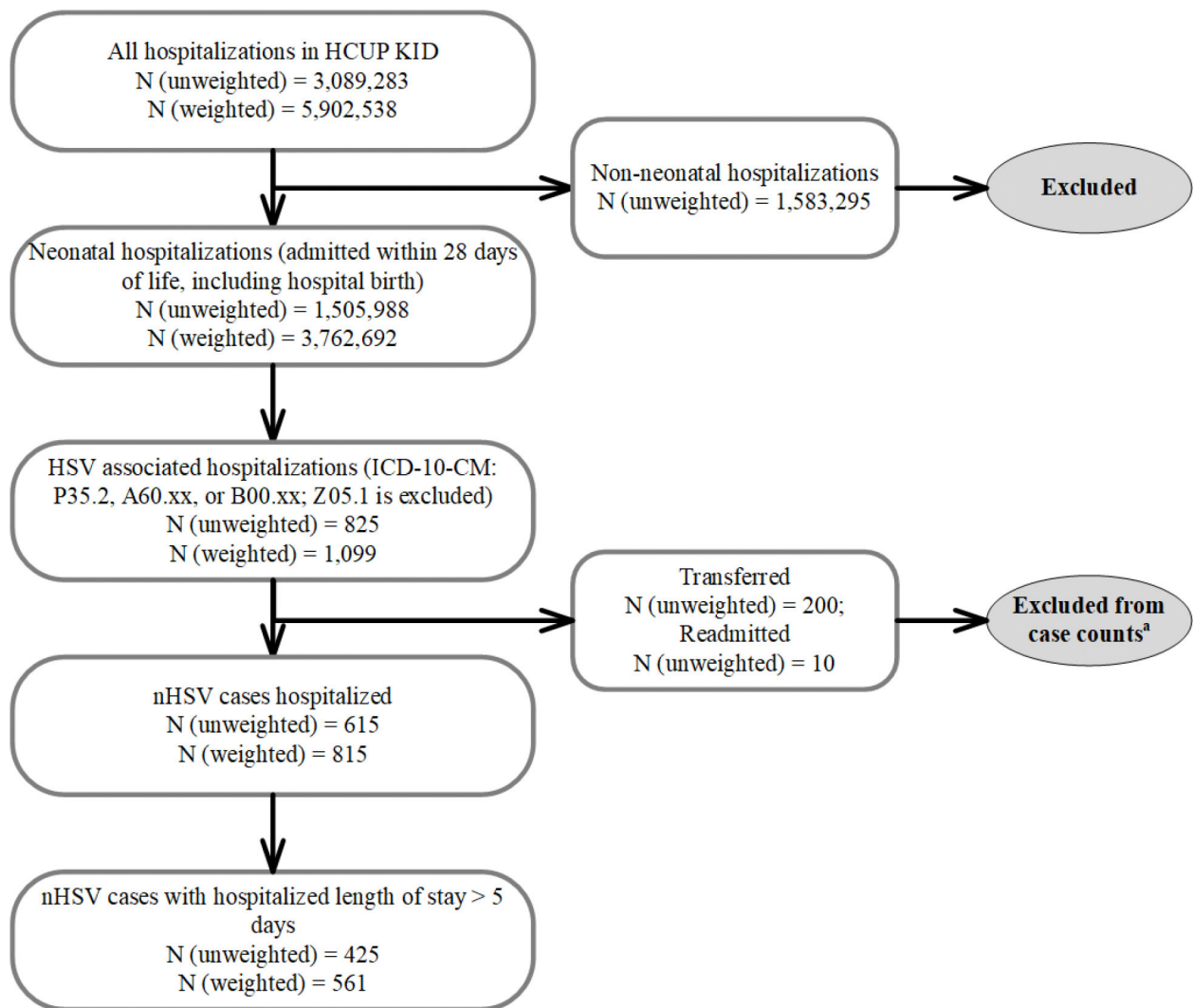
This study assesses current burden of neonatal herpes simplex virus infections in the US using the 2019 HCUP Kids' Inpatient Database (KID).

What's Known on This Subject

Neonatal Herpes Simplex Virus Infection (nHSV) is rare but potentially severe. It is not a nationally notifiable disease, and the latest US incidence estimation is nearly a decade old; thus, to provide an update on nHSV incidence rate is necessary.

What This Study Adds

This study updates the incidence rate, cost burden, and case fatality rate for nHSV using the updated methodology in accordance with the 2019 release of the HCUP KID.

**Figure 1.**

Algorithm for the neonatal herpes simplex virus case definition.

^aAlthough readmissions and transfers were excluded from the case count, the matched records for a unique individual were counted as a single record by combining the matched records' length of stay (LOS), and cost of hospitalization.

Table 1:

ICD-10-CM Codes Used to Define Neonatal Herpes in the 2019 Healthcare Cost & Utilization Project Kids' Inpatient Database.

ICD-10-CM	Descriptor
Inclusion: any ICD-10-CM to identify nHSV	
A60.0	Herpesviral infection of genitalia and urogenital tract
A60.00	Herpesviral infection of urogenital system, unspecified
A60.01	Herpesviral infection of penis
A60.02	Herpesviral infection of other male genital organs
A60.03	Herpesviral cervicitis
A60.04	Herpesviral vulvovaginitis
A60.09	Herpesviral infection of other urogenital tract
A60.1	Herpesviral infection of perianal skin and rectum
A60.9	Anogenital herpesviral infection, unspecified
B00	Herpesviral [herpes simplex] infections
B00.0	Eczema Herpeticum
B00.1	Herpesviral vesicular dermatitis
B00.2	Herpesviral gingivostomatitis and pharyngotonsillitis
B00.3	Herpesviral meningitis
B00.4	Herpesviral encephalitis
B00.5	Herpesviral ocular disease
B00.50	Herpesviral ocular disease unspecified
B00.51	Herpesviral iridocyclitis
B00.52	Herpesviral keratitis
B00.53	Herpesviral conjunctivitis
B00.59	Other herpesviral disease of eye
B00.7	Disseminated herpesviral disease
B00.8	Other forms of herpesviral infections
B00.81	Herpesviral hepatitis
B00.82	Herpes simplex myelitis
B00.89	Other herpesviral infection
B00.9	Herpesviral infection, unspecified
P35.2	Congenital herpesviral [herpes simplex] infection
Exclusion: any ICD-10-CM code below was excluded from case count	
Z05.1	Observation and evaluation of newborn for suspected infectious condition ruled out

Table 2: Case Counts and Incidence Rates per 100,000 Births, Overall and by United States Census Region, United States, 2019

Region of Hospital ^a	Hospital Births ^b	Any P35.2 or B00.xx codes or A60.00 ICD-10-CM (weighted)		Any P35.2 or B00.xx codes or A60.00 ICD-10-CM and LOS >5d (weighted)			
		Estimated no.	%	Incidence Rate ^c (95% CI ^d)	%	Incidence Rate ^c (95% CI ^d)	
United States	3,567,497	815	100	22.9 (21.3–24.5)	561	100	15.7 (14.5–17.1)
Northeast	577,868	112	13.8	19.4 (16.0–23.3)	82	14.5	14.1 (11.2–17.5)
Midwest	743,556	147	18.1	19.8 (16.7–23.3)	105	18.7	14.1 (11.6–17.1)
South	1,416,283	440	53.9	31.1 (28.2–34.1)	302	53.9	21.3 (19.0–23.9)
West	829,790	116	14.2	14.0 (11.6–16.8)	72	12.9	8.7 (6.8–11.0)

^a Due to limitations with the HCUP 2019 KID, the most granular geographic information accessible for this analysis is census region.

^b 95% Hospital births estimated from 2019 KID

^c Per 100,000 hospital births

^d 95% confidence intervals (CIs) were estimated using a Poisson distribution

Table 3:

Case Counts and Incidence Rates per 100,000 Births of Neonatal Herpes Infection by Sociodemographic Factors, Overall and by United States Census Region, United States, 2019

	United States						Region			
	Northeast			Midwest			South		West	
	Case Count ^a	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b
Sex										
Male	297	16.3 (14.5–18.2)	49	16.6 (12.2–21.9)	54	14.3 (10.8–18.7)	163	22.4 (19.1–26.1)	31	7.4 (5.0–10.4)
Female	264	15.2 (13.4–17.1)	33	11.6 (8.0–16.3)	51	13.9 (10.4–18.3)	139	20.2 (17.0–23.9)	41	10.1 (7.3–13.8)
Race/ethnicity^c										
Non-Hispanic White	236	14.3 (12.6–16.3)	34	12.2 (8.5–17.0)	44	10.6 (7.7–14.2)	129	19.9 (16.6–23.6)	29	9.7 (6.5–13.9)
Non-Hispanic Black	132	27.3 (22.8–32.4)	17	27.2 (16.0–43.3)	26	28.0 (18.2–41.1)	83	28.6 (22.8–35.4)	*	16.3 (6.2–34.7)
Hispanic	98	15.2 (12.3–18.5)	16	19.4 (11.0–31.7)	*	9.7 (3.2–22.5)	56	22.4 (16.9–29.0)	21	8.1 (5.0–12.3)
Additional Race, Non-Hispanic	62	13.6 (10.4–17.4)	10	10.6 (5.2–19.2)	*	14.8 (6.8–27.9)	29	19.3 (12.9–27.6)	13	9.2 (5.0–15.7)
Unknown/missing	33	9.7 (6.7–13.7)	*	7.1 (1.9–18.5)	21	17.4 (10.7–26.6)	*	7.1 (2.4–16.2)	*	3.0 (0.5–9.5)
Primary payer^d										
Public insurance	402	25.2 (22.8–27.8)	64	26.8 (20.6–34.2)	86	29.7 (23.7–36.6)	213	29.7 (25.8–34.0)	39	11.2 (8.0–15.3)
Private insurance	127	7.5 (6.3–9.0)	16	5.2 (3.0–8.5)	17	4.5 (2.6–7.2)	71	12.3 (9.6–15.5)	22	5.4 (3.4–8.1)
Self-pay	13	6.9 (3.7–11.7)	*	6.2 (0.3–29.7)	*	2.0 (0.1–9.9)	*	12.5 (5.8–23.5)	*	3.9 (0.3–16.9)
No charge or other	18	18.9 (11.2–29.8)	NA	NA	*	8.4 (0.4–39.7)	*	17.6 (7.3–35.6)	*	34.9 (16.3–65.5)
Gestational age										
< 37 wks	138	41.4 (34.8–49.0)	17	33.1 (19.2–53.2)	30	43.1 (29.1–61.6)	75	52.8 (41.5–66.1)	16	23.1 (13.3–37.2)
≥ 37 wks	423	13.1 (11.9–14.4)	65	12.3 (9.5–15.7)	75	11.1 (8.8–14.0)	227	17.8 (15.6–20.3)	56	7.4 (5.6–9.6)
Location/teaching status of hospital										
Rural	21	6.5 (4.0–9.8)	*	9.6 (1.7–29.7)	*	1.2 (0.1–5.6)	16	11.4 (6.5–18.5)	*	2.6 (0.2–11.2)
Urban- non-teaching	56	9.1 (6.8–11.8)	NA	NA	*	6.7 (2.8–13.4)	42	15.2 (10.9–20.5)	*	3.6 (1.4–7.7)
Urban- teaching	484	18.5 (16.9–20.2)	79	15.7 (12.4–19.6)	96	18.4 (14.9–22.5)	244	24.4 (21.5–27.7)	64	10.8 (8.3–13.8)
Median household income^e										

	United States									
	Region									
	Northeast			Midwest			South		West	
	Case Count ^a	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b	Case Count	Incidence Rate (95% CI) ^b
< \$48,000	242	24.5 (21.6–27.8)	30	25.2 (17.0–35.9)	43	22.4 (16.2–30.1)	147	28.2 (23.8–33.2)	22	14.3 (8.9–21.6)
\$48,000 – \$60,999	135	15.7 (13.1–18.6)	15	12.5 (7.0–20.7)	29	13.4 (8.9–19.2)	78	22.2 (17.5–27.7)	14	7.9 (4.4–13.2)
\$61,000 – \$81,999	117	13.0 (10.8–15.6)	21	13.9 (8.6–21.3)	24	11.8 (7.6–17.6)	53	17.6 (13.2–23.0)	19	7.7 (4.6–12.1)
>\$82,000	62	7.8 (6.0–10.0)	14	7.7 (4.2–12.8)	*	7.0 (3.2–13.2)	22	9.5 (6.0–14.4)	16	6.6 (3.8–10.8)

Note: Abbreviations: CI, confidence interval; NA, not applicable (data not available for sample).

* Sparse data (cell size <10) precluded reporting data.

^a Case restricted to those with Any P35.2 or B00.xx codes or A60.00 ICD-10-CM codes who were hospitalized for > 5 days

^b 95% CIs were estimated using a Poisson distribution

^c 33 cases had unknown or missing Race/ethnicity; we combined Asian or Pacific Islander, Native American, and Other into one category due to the small number of nHSV cases in these race/ethnicity groups.

^d Missing primary payer for 1 case

^e Median household income category for patient's zip code, missing median household income for 5 cases

Table 4: Estimates of Length of Stay, Hospitalization Charges, and Costs Associated with Neonatal Herpes Infections by Census Region, United States, 2019

	United States	Region			
		Northeast	Midwest	South	West
Admitted at Birth					
% (95% CI)	49.7 (44.9–54.5)	47.2 (34.4–60.0)	46.1 (35.1–57.1)	54.1 (47.6–60.7)	39.0 (25.7–52.3)
Length of stay, days					
IQR	11–23	11–24	13–22	11–24	11–22
Mean (95% CI)	24 (22–26)	22 (18–27)	24 (19–30)	25 (22–29)	20 (16–24)
Median (95% CI)	15 (14–17)	15 (12–18)	16 (13–19)	16 (14–18)	14 (11–17)
Total (95% CI)	13,384 (11,885–14,883)	1,832 (1,424–2,240)	2,563 (2,004–3,122)	7,558 (6,268–8,849)	1,430 (1,078–1,782)
Hospitalization charges^{a,b,c}, in 2019 US\$ thousands					
IQR	60–230	60–250	57–175	57–220	89–323
Mean (95% CI)	209 (178–241)	193 (143–243)	182 (125–238)	212 (161–264)	255 (188–322)
Median (95% CI)	110 (100–119)	119 (78–159)	96 (69–122)	104 (91–118)	149 (100–198)
Total (95% CI)	116,852 (99,463–134,241)	15,763 (11,444–20,083)	18,830 (13,007–24,653)	64,220 (48,754–79,686)	18,039 (13,293–22,785)
Hospitalization cost^{b,c,d}(adjusted by CCR), in 2019 US\$ thousands					
IQR	14–53	17–55	17–53	13–46	22–70
Mean (95% CI)	52 (44–59)	50 (34–66)	52 (38–67)	50 (38–62)	59 (46–71)
Median (95% CI)	27 (23–31)	29 (23–36)	25 (20–30)	22 (19–26)	42 (35–50)
Total (95% CI)	28,889 (24,682–33,096)	4,088 (2,766–5,410)	5,439 (3,923–6,955)	15,203 (11,588–18,818)	4,159 (3,255–5,063)

Note: Results reflect weighted estimates with 95% CI computed using Taylor series estimation method.

Abbreviations: CI, confidence interval; CCR, Cost-to-Charge Ratio;

^aHospitalization charge estimated using total charge in HCUP KID

^bLength of stay and hospitalization costs/charges in this table were calculated for all nHSV cases regardless of survival status. Please refer to Supplementary Table 2 to see these results separately for survivors and non-survivors.

^cRounded to the nearest 1,000

^dHospitalization cost is determined by adjusting the hospitalization charge using the HCUP CCR¹¹

Table 5: Estimates of nHSV Fatality Rate by United States Census Region, Gestational Age, Initial Admission Time and Primary Payer, 2019

	Fatality Rate (95% CI)
United States	4.6 (2.6–6.6)
Region	
Northeast	1.6 (0.0–4.8)
Midwest	7.3 (1.9–12.6)
South	4.4 (2.3–6.4)
West	5.5 (0.0–11.7)
Gestational age	
< 37 weeks	10.2 (5.7–14.6)
≥ 37 weeks	2.8 (1.3–4.3)
Initial admission time	
Admitted at birth	5.0 (2.3–7.8)
Admitted after birth	4.3 (1.5–7.0)
Primary payer ^a	
Public insurance	5.8 (4.9–6.8)
Private insurance	2.0 (0.0–4.9)

Note: Results reflect weighted estimates with 95% CI computed using Taylor series estimation method.
Abbreviations: CI, confidence interval; nHSV, Neonatal Herpes Simplex Virus Infection

^aThere were no deaths in self-pay and other categories