Original Research

The Economic Burden of Congenital Cytomegalovirus Disease in the First Year of Life: A Retrospective Analysis of Health Insurance Claims Data in the United States

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ABSTRACT

Purpose: Congenital cytomegalovirus (cCMV) infection is the most common congenital infection in the United States; however, limited data exist regarding the economic burden of cCMV disease (cCMVd) among newborns and infants. The purpose of this study was to compare health care resource utilization and costs between infants with cCMVd at birth and during the first year of life versus matched infants without diagnosed cCMVd.

Methods: Retrospective analyses of health insurance claims data from the MarketScan Commercial Claims and Encounters and Multi-State Medicaid databases (January 1, 2011–December 31, 2016) were conducted. Infants with cCMV diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 771.1 or 078.5; *International Classification of Diseases, Tenth Revision, Clinical Modification* code P35.1 or B25) were included. Two mutually exclusive periods were examined: initial hospital stay at birth ("birth" analysis) and subsequent 12 months ("postbirth" analysis). Infants with cCMVd in both periods were matched 1:1 to infants without cCMVd based on demographic and clinical characteristics. All-cause costs for cCMVd in infants versus matched control infants were reported in 2016 US dollars. Multivariable regression analyses controlled for additional confounding factors.

Findings: In the birth analysis, 397 of 404 newborns with cCMVd (167 vaginal deliveries, 230 cesarean deliveries) were matched to control infants; newborns with cCMVd had an additional mean (95% CI) of 9.1 (5.8–12.3) and 9.0 (4.6–13.5) inpatient days and $24,274 (10,082–38,466) and $31,770 (9911–53,630) more unadjusted inpatient costs versus control infants for vaginal and cesarean deliveries, respectively. In the postbirth analysis, 678 of 679 infants with cCMVd were matched with control infants; infants with cCMVd had an additional $58,806 (95% CI, 41,247–76,365) in unadjusted costs versus control infants, with inpatient visits accounting for 85% of the difference. Newborns with cCMVd accrued costs at birth averaging 1.5 to 2.1 times greater than control infants for cesarean and vaginal deliveries. During the first year of life, infants with cCMVd had costs averaging 7 times greater than control infants.

Implications: cCMVd is associated with substantial economic burden from birth and during the first year of life. Our findings support the notion that developing effective prevention of cCMVd and increasing awareness of the disease among women should be a public health priority, given the economic burden of cCMVd. (*Clin Ther*. 2019;41:1040–1056)

Key Words: congenital cytomegalovirus, health care costs, resource utilization.

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INTRODUCTION

Human cytomegalovirus (CMV) belongs to the group of herpes viruses that includes herpes simplex virus, varicella-zoster virus, and Epstein–Barr virus. It is a common infection, occurring in ~6 of 10 people in the United States.[1] It can be transmitted from a pregnant woman to her fetus, termed congenital CMV (cCMV) infection.[2] cCMV infection occurs in ~1 of every 150 births.[3] Transmission of CMV to the fetus may cause an increased risk of fetal loss, and ~1 in 10 may be affected by serious related sequelae such as hearing loss, chorioretinitis, jaundice, hepatosplenomegaly, premature birth, low birth weight, intracranial calcifications, petechiae, seizures, and microcephaly.[2] Furthermore, among children born with cCMV infection, ~1 in 5 may develop permanent disabilities, such as hearing or vision loss, lack of coordination, or developmental disabilities, due to the CMV infection.[3]

Although aspects of the epidemiology of cCMV infection and its related disabilities have been documented in the literature, few studies describe the economic burden associated with cCMV disease (cCMVd) in the United States, despite the fact that cCMVd adversely affects more children in the United States than other prominent childhood diseases and syndromes such as fetal alcohol syndrome, Down syndrome, and spina bifida.[4–8] Three studies have evaluated the inpatient economic burden associated with cCMVd in the United States.[4,6,7] Specifically, Candrilli and Trantham[4] evaluated infants hospitalized with a cCMVd diagnosis who were aged <1 year and observed a mean length of stay (LOS) ranging from 24.5 to 36.7 days and costs ranging from $81,915 to $128,052, depending on year of admission. Inagaki et al[7] evaluated newborns diagnosed with symptomatic cCMVd and reported that mean LOS for the birth was between 15 and 27 days and mean charges for the birth were between $45,771 and $89,846, depending on year of birth. Similarly, Lopez et al[5] also evaluated hospitalized infants with a diagnosis of cCMVd and observed a median LOS of 12.9 days and costs ranging from $7600 to $25,000 per stay, depending on infant age; the authors reported medians as opposed to means, potentially accounting for differences in results relative to the other 2 studies. However, these studies focused on hospital-associated costs, and it is important to account for the burden of disease in and across different care settings. In addition, a small number of studies have examined the burden outside the United States and found substantial costs associated with the disease.[9,10] Another analysis described costs associated with permanent neurologic sequelae in childhood, but it was not specific to cCMVd and was completed >15 years ago.[11]

The primary objective of the current retrospective database analysis therefore was to assess the incremental resource use and costs of diagnosed cCMVd at birth and during the first year of life across care settings in the United States by comparing health care resource utilization and costs between groups of infants with a diagnosis of cCMVd and matched control groups of infants without the condition.

PATIENTS AND METHODS

Overview

This retrospective administrative health insurance claims database analysis reports on incremental health care resource utilization and costs associated with cCMVd in the United States. Because there is no routine screening for cCMV infection in the United States, infants with a claim coded for CMV in the first year of life should have had symptomatic CMV, hence cCMVd. Because costs related to birth were anticipated to be high compared with costs accrued during the first year of life, and cCMVd newborn-related claims may have been included on a mother's insurance policy, this analysis was conducted in 2 stages. In the first stage, admissions related to birth (the "birth analysis") were examined, with the assumption that newborn claims might be included under the mother's and/or newborn infant's record. In the second stage, all subsequent postbirth claims for infants during the first year of life (the "postbirth analysis") were examined, without need for this assumption, as claims should have been included under only the infant's insurance. In both stages, infants with cCMVd were matched to infants without cCMVd based on demographic and clinical characteristics, and the incremental burden of cCMVd was defined as the difference between the cCMVd infants and the matched non-cCMVd cohort infants.

Data Sources

The MarketScan Commercial Claims and Encounters (CCAE) and Multi-State Medicaid (Medicaid) databases, both maintained by IBM Watson, were used for the current study. These

databases provided access to health care data for patients in the United States insured commercially or as part of state Medicaid programs. Both databases contain inpatient, outpatient, and prescription drug claims along with demographic and enrollment details. The CCAE population contains nearly 50 million covered lives and is like that of a nationally representative population of persons with employer-sponsored health insurance. The Medicaid database reflects the health care service use of >28 million Medicaid enrollees in multiple states.

This study used the most recent data available at the time the study was conducted (ie, calendar years 2011−2016 for the CCAE database and 2011−2015 for the Medicaid database). Because the data were de-identified, retrospective, and collected for administrative purposes, RTI International's institutional review board committee determined that this analysis was not research with human participants, and no further review was required.

Patient Selection Criteria and Matching

Birth Analysis

Birth admissions were identified if they had an admission designated as "maternal and newborn admission" based on the IBM Watson−created admission type variable. Newborns were also required to have a diagnosis on the admission indicating a birth (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes V29−V39 or *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] codes Z38 or Z05). From this population of all birth admissions, those that contained information for only the newborns were identified in 2 ways: (1) admissions for patient age equal to zero at the time of admission; and (2) admissions for patient age greater than zero at the time of admission and not containing a diagnosis code for the mother's stay (ie, ICD-9-CM code V27 or ICD-10-CM code Z37). From this population of newborn-only birth admissions, newborns with a diagnosis of cCMVd (ie, the cCMVd cohort) were identified based on a corresponding diagnosis during the inpatient stay (ICD-9-CM codes 771.1 or 078.5 or ICD-10-CM codes P35.1 or B25). Newborn admissions were included in the non-cCMVd cohort if they did not have a diagnosis of cCMVd during the inpatient stay. Admissions containing information for both the mother and the newborn were also identified; however, only 4 cCMVd cases were found among these admissions, and these claims were not further evaluated, as data for these claims would have included costs for both the mother and the newborn.

Admissions for the cCMVd cohort were matched 1:1 to admissions in the non-cCMVd cohort by using direct covariate matching. Matching was based on sex, birth type (ie, vaginal or cesarean), race, plan type, region, birth weight, and gestational age at birth (cCMVd newborns with missing birth weight/gestational age were matched to newborns who also had missing birth weight/gestational age). If > 1 match was available for each case, the match was selected at random.

Postbirth Analysis

In the postbirth analysis, infants were included in the cCMVd cohort if they had at least 1 medical claim with a corresponding diagnosis (ie, ICD-9-CM code 771.1 or 078.5 or ICD-10-CM code P35.1 or B25) and were aged <1 year on the first observed claim for cCMVd (cCMVd diagnosis may have occurred at birth or in the time frame up to 1 year postbirth). The date of the first observed medical claim (cCMVd or otherwise, including the birth admission) defined the index date, and infants were required to have continuous medical and pharmacy enrollment for a minimum follow-up period of 12 months.

Infants were included in the non-cCMVd cohort if they had no medical claims with a diagnosis of cCMVd during the first year of life. The date of the first observed medical claim (including the birth admission) defined the index date, and infants were required to have continuous medical and pharmacy enrollment for 12 months' postindex date. Infants in the non-cCMVd cohort with a diagnosis of HIV, solid organ transplant, or stem cell transplant were excluded from the analysis, as they could be at risk of invasive CMV infection due to immunodeficiency.

Infants in the cCMVd cohort were matched 1:1 to infants in the non-cCMVd cohort by using direct covariate matching. Matching was based on the same list of variables described for the birth analysis, excluding birth type. If > 1 match was available for each case, the match was selected at random.

Study Measures

Birth Analysis

The mean LOS and costs for the admission were reported for each cohort (ie, cCMVd and matched non-cCMVd admissions) stratified according to type of delivery (ie, vaginal or cesarean). The incremental burden of cCMVd at birth was calculated as the difference in LOS and costs between the cCMVd cohort and matched non-cCMVd admissions. All cost data were adjusted to 2016 US dollars by using the Medical Care component of the US Consumer Price Index[12] and represent the reimbursements paid by health plans for each admission.

Postbirth Analysis

All-cause and cCMVd-related health care resource utilization and costs were aggregated and reporting during the 12-month follow-up period. The cCMVd-related inpatient visits were identified based on a primary diagnosis of cCMVd, and cCMVd-related emergency department and outpatient claims were identified by searching medical claims with a primary or secondary diagnosis of cCMVd. The cCMVd pharmacy claims included prescriptions for ganciclovir or valganciclovir.

All-cause and cCMVd-related resource utilization and costs were reported overall and according to care setting. The number and percentage of infants with an admission or claim in each care setting were reported along with number of admissions or claims and per-infant costs. Birth admissions were excluded from the analysis, as these costs were captured in the birth analysis.

The incremental burden of cCMVd was calculated as the difference between infants with cCMV and matched non-cCMVd control infants. All cost data were updated to 2016 US dollars by using the same inflation adjustment method as that for the birth analysis and represent the reimbursements paid by health plans for health care encounters during the postbirth period.

Data Analyses

Descriptive analyses were conducted to evaluate patient demographic and clinical characteristics, comorbidities and sequelae, and health care resource utilization and costs. For the birth analysis, comorbidities and sequelae were limited to diagnosis codes observed on the birth admission. For the postbirth analysis, comorbidities and sequelae were evaluated for the 12-month follow-up period (inclusive of the index date). The statistical significance of descriptive differences in outcomes (ie, LOS, health care resource utilization, costs) between the cCMVd and matched non-cCMVd cohort infants were measured by using paired Student t tests and χ^2 tests.

Multivariable regression analyses to estimate the adjusted incremental burden were conducted and are described in Supplemental Material.

RESULTS

Birth Analysis

Newborn birth admissions on a newborn policy (N = 2,465,931) and those on a mother's policy (N = 84,413) resulted in a total of 2,548,971 newborns who had admission records with information in which newborn costs could be distinguished from mothers' costs, and these were evaluated further. Among these newborns, 457 had a cCMVd diagnosis, of whom 170 (37%) had a vaginal delivery and 234 (51%) had a cesarean delivery. Fifty-three newborns did not have their delivery type recorded and were excluded from further analyses. Correspondingly, 2,548,514 newborns had an admission with no cCMVd diagnosis present, of whom 1,717,801 (67%) had a vaginal delivery and 737,721 (29%) had a cesarean delivery; the remaining newborns did not have their delivery type recorded and were excluded from further analyses.

Before matching, 170 newborns with cCMVd and a vaginal delivery were compared versus 1,717,801 newborns with a vaginal delivery without cCMV; demographic and clinical characteristics for these newborns are reported in Tables I and II, respectively. Briefly, in the vaginal delivery population, a greater percentage of cCMVd newborns were covered by Medicaid insurance compared with newborns without cCMVd. Approximately 36% of newborns with cCMVd had a birth weight category specified versus 6.1% of newborns without cCMVd, and newborns with cCMVd tended to have greater percentages in the lower birth weight categories compared with newborns without cCMVd. Similarly, 60.0% of newborns with cCMVd had a gestational age

Table I. Demographic characteristics according to cohort and birth type: birth analysis.

Characteristic	Vaginal Delivery: Unmatched		Vaginal Delivery: Matched		Cesarean Delivery: Unmatched		Cesarean Delivery: Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
Total no. of admissions	170	1,717,801	167	167	234	737,721	230	230
Admission type (no., column %)*								
Newborn on newborn insurance	167 (98.2%)	1,666,283 (97.0%)	165 (98.8%)	165 (98.8%)	226 (96.6%)	708,225 (96.0%)	225 (97.8%)	225 (97.8%)
Newborn on mother's insurance	3 (1.8%)	51,518 (3.0%)	2 (1.2%)	2 (1.2%)	8 (3.4%)	29,496 (4.0%)	5 (2.2%)	5 (2.2%)
Payer type (no., column %)*								
Commercial	67 (39.4%)	863,658 (50.3%)	65 (38.9%)	65 (38.9%)	103 (44.0%)	413,128 (56.0%)	100 (43.5%)	100 (43.5%)
Medicaid	103 (60.6%)	854,143 (49.7%)	102 (61.1%)	102 (61.1%)	131 (56.0%)	324,593 (44.0%)	130 (56.5%)	130 (56.5%)
Sex of newborn (no., column %)[a]								
Male	75 (44.1%)	831,929 (48.4%)	74 (44.3%)	74 (44.3%)	123 (52.6%)	369,400 (50.1%)	122 (53.0%)	122 (53.0%)
Female	92 (54.1%)	856,455 (49.9%)	90 (53.9%)	90 (53.9%)	107 (45.7%)	355,663 (48.2%)	104 (45.2%)	104 (45.2%)
Unknown	3 (1.8%)	29,417 (1.7%)	3 (1.8%)	3 (1.8%)	4 (1.7%)	12,658 (1.7%)	4 (1.7%)	4 (1.7%)
Health plan type (no., column %)*								
Health maintenance organization	69 (40.6%)	538,832 (31.4%)	68 (40.7%)	68 (40.7%)	85 (36.3%)	222,095 (30.1%)	82 (35.7%)	82 (35.7%)
Preferred provider organization	37 (21.8%)	525,008 (30.6%)	36 (21.6%)	36 (21.6%)	58 (24.8%)	254,743 (34.5%)	58 (25.2%)	58 (25.2%)
Point of service	7 (4.1%)	49,335 (2.9%)	7 (4.2%)	7 (4.2%)	5 (2.1%)	25,040 (3.4%)	5 (2.2%)	5 (2.2%)

Table I. (*Continued*)

Characteristic	Vaginal Delivery: Unmatched		Vaginal Delivery: Matched		Cesarean Delivery: Unmatched		Cesarean Delivery: Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
Other	45 (26.5%)	411,735 (24.0%)	44 (26.4%)	45 (27.0%)	59 (25.2%)	150,679 (20.4%)	59 (25.7%)	59 (25.7%)
Missing/unknown	12 (7.1%)	192,920 (11.2%)	12 (7.2%)	11 (6.6%)	27 (11.5%)	85,183 (11.6%)	26 (11.3%)	26 (11.3%)
Region (no., column %)*								
Northeast	10 (5.9%)	179,106 (10.4%)	10 (6.0%)	10 (6.0%)	18 (7.7%)	88,466 (12.0%)	17 (7.4%)	17 (7.4%)
North Central	15 (8.8%)	243,862 (14.2%)	15 (9.0%)	15 (9.0%)	25 (10.7%)	101,328 (13.7%)	24 (10.4%)	24 (10.4%)
South	24 (14.1%)	280,005 (16.3%)	23 (13.8%)	23 (13.8%)	50 (21.4%)	157,698 (21.4%)	50 (21.7%)	50 (21.7%)
West	12 (7.1%)	144,806 (9.4%)	12 (7.2%)	12 (7.2%)	8 (3.4%)	57,675 (7.8%)	7 (3.0%)	7 (3.0%)
Missing/unknown	109 (64.1%)	870,036 (50.7%)	107 (64.1%)	107 (64.1%)	133 (56.8%)	332,562 (45.1%)	132 (57.4%)	132 (57.4%)
Race (no., column %)*								
White	32 (18.8%)	345,509 (20.1%)	32 (19.2%)	32 (19.2%)	38 (16.2%)	127,451 (17.3%)	38 (16.5%)	38 (16.5%)
Black	27 (15.9%)	224,894 (13.1%)	27 (16.2%)	27 (16.2%)	44 (18.8%)	93,842 (12.7%)	44 (19.1%)	44 (19.1%)
Hispanic	6 (3.5%)	66,033 (3.8%)	6 (3.6%)	6 (3.6%)	7 (3.0%)	19,108 (2.6%)	6 (2.6%)	6 (2.6%)
Other	35 (20.6%)	192,907 (11.2%)	34 (20.4%)	34 (20.4%)	39 (16.7%)	73,871 (10.0%)	39 (17.0%)	39 (17.0%)
Missing/unknown	70 (41.2%)	888,463 (51.7%)	68 (40.7%)	68 (40.7%)	106 (45.3%)	423,450 (57.4%)	103 (44.8%)	103 (44.8%)

cCMVd = congenital cytomegalovirus disease.

*Variable included in the matching of cCMVd cases with non-cCMVd control cases.

[a]Variable included in the matching of cCMVd cases with non-cCMVd controls.

Table II. Clinical characteristics according to cohort and birth type: birth analysis.

Characteristic	Vaginal Delivery: Unmatched		Vaginal Delivery: Matched		Cesarean Delivery: Unmatched		Cesarean Delivery: Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
Total no. of admissions	170	1,717,801	167	167	234	737,721	230	230
Birth weight (no., column %)*								
<500 g	0	992 (0.1%)	0	0	5 (2.1%)	838 (0.1%)	4 (1.7%)	4 (1.7%)
500–999 g	13 (7.7%)	3352 (0.2%)	11 (6.6%)	11 (6.6%)	37 (15.8%)	7321 (1.0%)	36 (15.7%)	36 (15.7%)
1000–1499 g	10 (5.9%)	5295 (0.3%)	9 (5.4%)	9 (5.4%)	43 (18.4%)	10,649 (1.4%)	43 (18.7%)	43 (18.7%)
1500–1999 g	18 (10.6%)	13,272 (0.8%)	18 (10.8%)	18 (10.8%)	30 (12.8%)	15,565 (2.1%)	29 (12.6%)	29 (12.6%)
2000–2500 g	12 (7.1%)	34,487 (2.0%)	12 (7.2%)	12 (7.2%)	20 (8.6%)	24,368 (3.3%)	20 (8.7%)	20 (8.7%)
>2500 g	6 (3.5%)	46,006 (2.7%)	6 (3.6%)	6 (3.6%)	10 (4.3%)	29,488 (4.0%)	10 (4.4%)	10 (4.4%)
Low birth weight status, weight unspecified	2 (1.2%)	1481 (0.1%)	2 (1.2%)	2 (1.2%)	1 (0.4%)	687 (0.1%)	1 (0.4%)	1 (0.4%)
Gestational age (no., column %)*								
<24 completed weeks	1 (0.6%)	124 (0.0%)	0	0	1 (0.4%)	90 (0.0%)	1 (0.4%)	1 (0.4%)
24 complete weeks	2 (1.2%)	723 (0.0%)	2 (1.2%)	2 (1.2%)	11 (4.7%)	1083 (0.2%)	10 (4.4%)	10 (4.4%)
25–26 completed weeks	3 (1.8%)	1472 (0.1%)	3 (1.8%)	3 (1.8%)	9 (3.9%)	2709 (0.4%)	9 (3.9%)	9 (3.9%)
27–28 completed weeks	4 (2.4%)	1961 (0.1%)	3 (1.8%)	3 (1.8%)	22 (9.4%)	3726 (0.5%)	22 (9.6%)	22 (9.6%)
29–30 completed weeks	4 (2.4%)	3109 (0.2%)	4 (2.4%)	4 (2.4%)	12 (5.1%)	5169 (0.7%)	12 (5.2%)	12 (5.2%)
31–32 completed weeks	4 (2.4%)	6280 (0.4%)	4 (2.4%)	4 (2.4%)	15 (6.4%)	8424 (1.1%)	13 (5.7%)	13 (5.7%)
33–34 completed weeks	7 (4.1%)	20,254 (1.2%)	6 (3.6%)	6 (3.6%)	19 (8.1%)	17,480 (2.4%)	19 (8.3%)	19 (8.3%)
35–36 completed weeks	18 (10.6%)	57,649 (1.2%)	18 (10.8%)	18 (10.8%)	30 (12.8%)	37,089 (5.0%)	30 (13.0%)	30 (13.0%)
≥37 completed weeks	37 (21.8%)	129,636 (7.6%)	37 (22.2%)	37 (22.2%)	25 (10.7%)	66,894 (9.1%)	25 (10.9%)	25 (10.9%)
Extreme immaturity, gestational age unspecified	22 (12.9%)	17,988 (1.1%)	22 (13.2%)	22 (13.2%)	39 (16.7%)	18,805 (2.6%)	38 (16.5%)	38 (16.5%)

Table II. (*Continued*)

Characteristic	Vaginal Delivery: Unmatched		Vaginal Delivery: Matched		Cesarean Delivery: Unmatched		Cesarean Delivery: Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
Unspecified gestational age	68 (40.0%)	1,478,60 5 (86.1%)	68 (40.7%)	68 (40.7%)	51 (21.8%)	576,252 (78.1%)	51 (22.2%)	51 (22.2%)
Sequelae observed on birth record (no., column %)								
Prematurity	43 (25.3%)	91,572 (5.3%)	40 (24.0%)	40 (24.0%)	119 (50.9%)	75,770 (10.3%)	116 (50.4%)	116 (50.4%)
Intrauterine growth retardation and small for gestational age	61 (35.9%)	41,729 (2.4%)	61 (36.5%)	20 (12.0%)	90 (38.5%)	27,830 (3.8%)	90 (39.1%)	42 (18.3%)
Purpura and petechiae	5 (2.9%)	20,392 (1.2%)	5 (3.0%)	1s (0.6%)	7 (3.0%)	4560 (0.6%)	7 (3.0%)	0
Hepatitis	2 (1.2%)	88 (0.0%)	2 (1.2%)	0	3 (1.3%)	96 (0.0%)	3 (1.3%)	0
Jaundice and hyperbilirubinemia	52 (30.6%)	255,828 (14.9%)	52 (31.1%)	32 (19.2%)	59 (25.2%)	134,974 (18.3%)	58 (25.2%)	49 (21.3%)
Thrombocytopenia	37 (21.8%)	4,409 (0.3%)	37 (22.2%)	3 (1.8%)	64 (27.4%)	6022 (0.8%)	63 (27.4%)	13 (5.7%)
Renal failure	0	479 (0.0%)	0	1 (0.6%)	2 (0.9%)	754 (0.1%)	1 (0.4%)	3 (1.3%)
Hepatosplenomegaly and splenomegaly	6 (3.5%)	108 (0.0%)	6 (3.6%)	0	7 (3.0%)	149 (0.0%)	7 (3.0%)	0
Microcephaly	18 (10.6%)	966 (0.1%)	18 (10.8%)	1 (0.6%)	13 (5.6%)	517 (0.1%)	13 (5.7%)	2 (0.9%)
Seizures	3 (1.8%)	21 (0.0%)	3 (1.8%)	0	5 (2.1%)	15 (0.0%)	5 (2.2%)	0

cCMVd = congenital cytomegalovirus disease.

*Variable included in the matching of cCMV cases with non-cCMV control cases.

Table III. Unadjusted length of stay (LOS) and costs according to delivery type: birth analysis. Values are given as mean (SD).

Cohort	LOS, days	Costs
Vaginal delivery		
cCMVd admissions (n = 167)	22.1 (28.2)*	$46,994 ($117,619)†
Non-cCMVd admissions (n = 167)	13.0 (24.0)‡	$22,720 ($63,947)§
Difference	9.1 (21.4)‖	$24,274 ($92,889)¶
Cesarean delivery		
cCMVd admissions (n = 230)	37.5 (40.2)#	$98,126 ($191,341)**
Non-cCMVd admissions (n = 230)	28.4 (37.9)††	$66,355 ($144,339)‡‡
Difference	9.0 (34.4)§§	$31,770 ($167,880)‖‖

cCMVd = congenital cytomegalovirus disease.
* Median, interquartile range (IQR): 10, 4 to 26.
† Median, IQR: $10,592, $2887 to $32,117.
‡ Median, IQR: 3, 3 to 8.
§ Median, IQR: $1735, $816 to $9392.
‖ Lower to upper 95% CI, 5.8 to 12.3; $P < 0.0001$.
¶ Lower to upper 95% CI, 10,082 to 38,466, $P = 0.0009$.
# Median, IQR: 21, 8 to 53.
** Median, IQR: $28,506, $4762 to $105,547.
†† Median, IQR: 10, 4 to 43
‡‡ Median, IQR: $5625, $1312 to $72,866.
§§ Lower to upper 95% CI, 4.6 to 13.5; $P < 0.0001$.
‖‖ Lower to upper 95% CI, 9911 to 53,630; $P = 0.0046$.

specified versus 13.9% of newborns without cCMVd, and newborns with cCMVd tended to have a greater percentage in the lower gestational age categories compared with newborns without cCMVd. Finally, a greater percentage of cCMVd newborns had each of the selected sequelae observed on the birth record compared with newborns without cCMVd. In total, 98.2% of newborns with cCMVd and a vaginal delivery (167 of 170) were matched to newborns with a vaginal delivery without cCMVd. Demographic and clinical characteristics of these newborns after matching are also reported in Tables I and II, respectively.

Before matching, 234 newborns with cCMVd and a cesarean delivery were compared versus 737,721 newborns with a cesarean delivery without cCMVd; demographic and clinical characteristics for these newborns are reported in Tables I and II, respectively. In the cesarean delivery population, a greater percentage of cCMVd newborns were covered by Medicaid insurance compared with non-cCMVd newborns. Approximately two thirds of newborns

Table IV. Demographic characteristics: postbirth analysis.

Characteristic	Unmatched		Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
Total no. of patients	679	1,791,493	678	678
Sex (no., column %)*				
Male	368 (54.2%)	915,339 (51.1%)	368 (54.3%)	368 (54.3%)
Female	309 (45.5%)	872,761 (48.7%)	308 (45.4%)	308 (45.4%)
Unknown	2 (0.3%)	3393 (0.2%)	2 (0.3%)	2 (0.3%)
Payer type (no., column %)*				
Commercial	219 (32.3%)	789,908 (44.1%)	219 (32.3%)	219 (32.3%)
Medicaid	460 (67.8%)	1,001,585 (55.9%)	459 (67.7%)	459 (67.7%)
Health plan type (no., column %)*				
Health maintenance organization	271 (39.9%)	650,466 (36.3%)	270 (39.8%)	270 (39.8%)
Preferred provider organization	137 (20.2%)	501,055 (28.0%)	137 (20.2%)	137 (20.2%)
Point of service	22 (3.2%)	50,422 (2.8%)	22 (3.2%)	22 (3.2%)
Other	224 (33.0%)	472,393 (26.4%)	224 (33.0%)	218 (32.2%)
Missing/unknown	25 (3.7%)	117,157 (6.5%)	25 (3.7%)	31 (4.6%)
Region (no., column %)*				
Northeast	47 (6.9%)	155,484 (8.7%)	47 (6.9%)	47 (6.9%)
North Central	26 (3.8%)	176,928 (9.9%)	26 (3.8%)	26 (3.8%)
South	108 (15.9%)	283,192 (15.8%)	108 (15.9%)	108 (15.9%)
West	30 (4.4%)	142,712 (8.0%)	30 (4.4%)	30 (4.4%)
Missing/unknown	468 (68.9%)	1,033,177 (57.7%)	467 (68.9%)	467 (68.9%)
Race (no., column %)*				
White	134 (19.7%)	425,231 (23.7%)	134 (19.8%)	134 (19.8%)
Black	118 (17.4%)	294,908 (16.5%)	118 (17.4%)	118 (17.4%)
Hispanic	27 (4.0%)	63,622 (3.6%)	26 (3.8%)	26 (3.8%)
Other	181 (26.7%)	217,824 (12.2%)	181 (26.7%)	181 (26.7%)
Missing/unknown	219 (32.3%)	789,908 (44.1%)	219 (32.3%)	219 (32.3%)

cCMVd = congenital cytomegalovirus disease.
*Variable included in the matching of cCMVd cases with non-cCMVd control cases.

with cCMVd had a birth weight category specified versus only 12% of newborns without cCMVd, and the cCMVd cohort tended to have a greater percentage of newborns in the lower birth weight categories compared with newborns without cCMVd. Similarly, 78.2% of newborns with cCMVd had a gestational age specified versus 21.9% of newborns without cCMVd, and the cCMVd cohort tended to have a greater percentage in the lower gestational age categories compared with newborns without cCMVd. Finally, a greater percentage of cCMVd newborns had each of the selected sequelae observed on the birth record compared with newborns without cCMVd. In total, 98.2% of newborns with cCMVd and a cesarean delivery (230 of 234) were matched to newborns with a cesarean delivery without cCMVd. Demographic and clinical characteristics of these newborns after matching are also reported in Tables I and II.

Among newborns with vaginal delivery, cCMVd was associated with an ~70% increase in unadjusted LOS (ie, incremental LOS associated with cCMVd of

Table V. Clinical characteristics: postbirth analysis.

Characteristic	Unmatched		Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
Total no. of patients	679	1,791,493	678	678
cCMVd-related sequelae (no., column %)				
Ataxia	65 (9.6%)	12,607 (0.7%)	65 (9.6%)	15 (2.2%)
Chorioretinitis	14 (2.1%)	46 (0.0%)	14 (2.1%)	0
Cognitive disability	155 (22.8%)	33,264 (1.9%)	154 (22.7%)	48 (7.1%)
Hearing loss	202 (29.8%)	48,876 (2.7%)	201 (29.7%)	36 (5.3%)
Microcephaly	66 (9.7%)	4,257 (0.2%)	66 (9.7%)	3 (0.4%)
Paresis/paralysis	9 (1.3%)	1361 (0.1%)	9 (1.3%)	2 (0.3%)
Seizures	91 (13.4%)	27,989 (1.6%)	90 (13.3%)	16 (2.4%)
Vision loss	14 (2.1%)	1,435 (0.1%)	14 (2.1%)	2 (0.3%)
Common comorbidities (no., column %)				
ICD-9-CM codes				
765.xx Disorders relating to short gestation and low birth weight	370 (54.5%)	286,158 (16.0%)	369 (54.4%)	353 (52.1%)
770.xx Other respiratory infection of fetus and newborn	277 (40.8%)	168,106 (9.4%)	276 (40.7%)	206 (30.4%)
783.xx Symptoms concerning nutrition and metabolic development	358 (52.7%)	379,304 (21.2%)	357 (52.7%)	237 (35.0%)
518.xx Other diseases of the lung	155 (22.8%)	45,394 (2.5%)	154 (22.7%)	84 (12.4%)
747.xx Other congenital anomalies of the circulatory system	140 (20.6%)	47,143 (2.6%)	139 (20.5%)	88 (13.0%)
ICD-10-CM codes				
P07.xx Disorders relating to short gestation and low birth weight	17 (2.5%)	3632 (0.2%)	17 (2.5%)	8 (1.2%)
P22.xx Respiratory distress of newborn	2 (0.3%)	1848 (0.1%)	2 (0.3%)	3 (0.4%)
P28.xx Other respiratory diseases originating in the perinatal period	5 (0.7%)	1563 (0.1%)	5 (0.7%)	2 (0.3%)
P61.xx Other perinatal hematologic disorders	2 (0.3%)	532 (0.0%)	2 (0.3%)	1 (0.2%)
P27.xx Chronic respiratory disease originating in the perinatal period	9 (1.3%)	541 (0.0%)	9 (1.3%)	1 (0.2%)
Birth weight (no., column %)*				
<500 g	14 (2.1%)	1416 (0.1%)	13 (1.9%)	13 (1.9%)
500–999 g	79 (11.6%)	8306 (0.5%)	79 (11.7%)	79 (11.7%)
1000–1499 g	51 (7.5%)	13,461 (0.8%)	51 (7.5%)	51 (7.5%)

Table V. (*Continued*)

Characteristic	Unmatched		Matched	
	cCMVd Cohort	Non-cCMVd Cohort	cCMVd Cohort	Non-cCMVd Cohort
1500–1999 g	45 (6.6%)	23,370 (1.3%)	45 (6.6%)	45 (6.6%)
2000–2500 g	41 (6.0%)	41,540 (2.3%)	41 (6.1%)	41 (6.1%)
>2500 g	28 (4.1%)	50,330 (2.8%)	28 (4.1%)	28 (4.1%)
Low birth weight status, weight unspecified	6 (0.9%)	2562 (0.1%)	6 (0.9%)	6 (0.9%)
No birth weight status	415 (61.1%)	1,650,508 (92.1%)	415 (61.2%)	415 (61.2%)
Gestational age (no., column %)*				
<24 completed weeks	0	54 (0.0%)	0	0
24 complete weeks	27 (4.0%)	1777 (0.1%)	27 (4.0%)	27 (4.0%)
25–26 completed weeks	25 (3.7%)	3929 (0.2%)	25 (3.7%)	25 (3.7%)
27–28 completed weeks	36 (5.3%)	5421 (0.3%)	36 (5.3%)	36 (5.3%)
29–30 completed weeks	19 (2.8%)	7661 (0.4%)	19 (2.8%)	19 (2.8%)
31–32 completed weeks	17 (2.5%)	12,746 (0.7%)	17 (2.5%)	17 (2.5%)
33–34 completed weeks	33 (4.9%)	28,740 (1.6%)	33 (4.9%)	33 (4.9%)
35–36 completed weeks	59 (8.7%)	63,347 (3.5%)	59 (8.7%)	59 (8.7%)
≥37 completed weeks	99 (14.6%)	135,063 (7.5%)	99 (14.6%)	99 (14.6%)
Extreme immaturity, gestational age unspecified	0	0	0	0
Unspecified gestational age	364 (53.6%)	1,532,755 (85.6%)	363 (53.5%)	363 (53.5%)

cCMVd = congenital cytomegalovirus disease; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification;* ICD-10-CM = *International Classification of Diseases,* 10th *Revision, Clinical Modification*.
*Variable included in the matching of cCMVd cases with non-cCMVd control cases.

9.1 days) and a nearly 110% increase in costs (ie, incremental costs associated with cCMVd of $24,274) (Table III). Among newborns with cesarean delivery, cCMVd was associated with an ~32% increase in LOS (ie, an incremental LOS associated with cCMVd of 9.0 days) and an ~48% increase in costs (ie, incremental costs associated with cCMVd of $31,770). Adjusted results are presented in the Supplemental Material.

Postbirth Analysis

Demographic and clinical characteristics for the postbirth analysis are presented in Tables IV and V, respectively. Before matching, 679 infants with cCMVd were compared with 1,791,493 infants without cCMVd. In the cCMVd cohort, hearing loss was diagnosed in almost 30% of infants, cognitive disability was diagnosed in 22.8% of infants, 13.4% had a diagnosis of seizures, 9.7% had a diagnosis of microcephaly, and 9.6% had a diagnosis of ataxia.

In total, 678 infants with cCMVd were matched to 678 infants without cCMVd. Demographic and clinical characteristics for the two groups are shown in Tables IV and V, respectively.

During the 12-month follow-up period, ~32% of infants in the cCMVd cohort had at least 1 all-cause hospital admission versus 9.7% of matched non-cCMVd control infants (data not shown). Furthermore, infants with cCMVd had 11.9 more inpatient days versus matched non-cCMVd control infants. Approximately one half of infants with cCMVd had at least 1 all-cause emergency department visit versus 41.6% of matched non-cCMVd control infants. More than 80% of infants in the cCMVd cohort had at least 1 all-cause outpatient hospital visit versus 64% of matched non-cCMVd control infants. Regardless of the cohort, nearly all

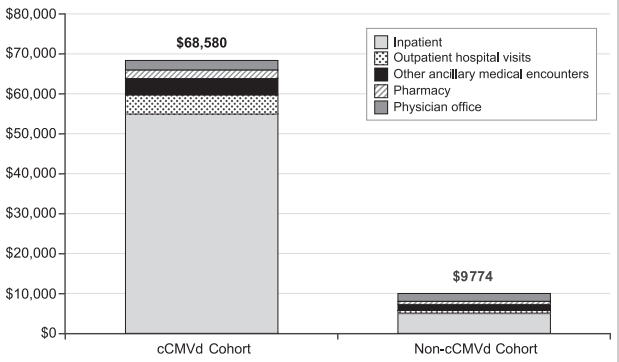

Figure 1. Unadjusted all-cause health care costs according to cohort and place of service: postbirth analysis. Costs for all-cause physical/occupational therapy and emergency department visits represented <1% of total all-cause costs and are not included in figure. $P < 0.0001$ for the difference in all-cause health care costs between infants with congenital cytomegalovirus disease (cCMVd) versus matched non-cCMVd control infants in total and according to place of service. Mean 95% CI difference in all cause health care costs between infants with cCMVd and matched non-cCMVd control infants was $58,806 (95% CI, $41,247-$76,365).

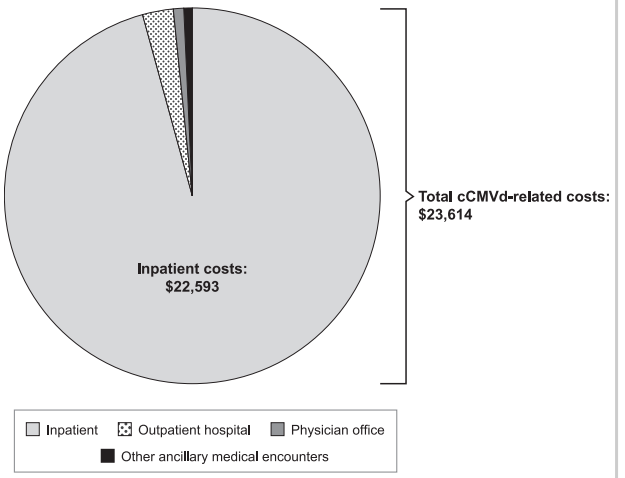

Figure 2. Unadjusted congenital cytomegalovirus disease (cCMVd)-related health care costs according to place of service: postbirth analysis. Costs for cCMVd-related pharmacy, physical/occupational therapy, and emergency department visits represented <1% of total cCMVd-related costs and are not included in figure.

infants had at least 1 all-cause physician office visit, whereas the percentage of infants with an all-cause physical/occupational therapy visit in the cCMVd cohort was approximately twice the percentage of those in the matched non-cCMVd control cohort. Approximately 84% of infants with cCMVd had at least 1 all-cause other ancillary medical encounter (eg, claims for laboratory tests, health care visits in other service settings) versus 68.6% of infants in the matched non-cCMVd cohort, whereas 83.3% of infants in the cCMVd cohort had at least 1 all-cause prescription versus 76.8% of matched non-cCMVd control infants.

Mean (SD) total all-cause health care costs were $68,580 ($228,893) among infants with cCMVd and $9774 ($58,027) among matched non-cCMVd control infants; specifically, infants with cCMVd had, on average, $58,806 more in all-cause costs compared with matched non-cCMVd control infants ($P < 0.0001$) (Fig. 1). More than 85% of the difference in costs between infants with cCMVd and matched control infants was due to inpatient visits, with infants with cCMVd accruing $50,166 more in inpatient costs versus matched non-cCMVd control infants. Infants with cCMVd accrued $3849 more in outpatient hospital visits, $2984 more in other ancillary medical encounters, and $1010 more in pharmacy costs versus matched non-cCMVd control infants.

Among cCMVd infants, 7.5% of infants had a cCMVd-related inpatient admission, with a corresponding mean (SD) of 5.0 (28.4) inpatient days for cCMVd-related inpatient admissions during follow-up. More than one third of infants had a cCMVd-related outpatient hospital visit, 44.3% of infants had a cCMVd-related office visit, and 22.0% of infants had a cCMVd-related other ancillary medical encounter. The percentages of infants with a

cCMVd-related emergency department visit and a cCMVd-related physical/occupational therapy visit were low (both 3.0%), and only 4 infants received a cCMVd-related medication during follow-up.

Total cCMVd-related health care costs were $23,614 (ie, more than one third of all-cause health care costs were directly attributable to cCMVd), with inpatient visits accounting for >95% of all cCMVd-related health care costs (Fig. 2). Adjusted results are presented in the Supplemental Material.

DISCUSSION

Each year in the United States, ~30,000 children are born with cCMV infection, and ~20% of these infants have permanent disabilities.[3] Although published data exist regarding the clinical outcomes and sequelae associated with cCMV infection (eg, Boppana et al,[13] Fowler and Boppana[14]), limited data are available regarding health care resource utilization and costs associated with cCMVd. This retrospective, longitudinal, health insurance claims database analysis evaluated the economic burden of cCMVd in infants at birth and throughout the first year of life. As expected for a serious neonatal condition, it was observed that cCMVd is associated with a significant increase in health care resource utilization and costs both at birth and throughout the first year of life.

Results of this study are in line with previously published US data regarding inpatient costs associated with cCMVd in infants. Specifically, Candrilli and Trantham[4] evaluated infants hospitalized with a cCMVd diagnosis who were aged <1 year using the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample. They found that most hospitalizations with a cCMVd diagnosis were for the birth of the infant, with mean LOS ranging from 24.5 days to 36.7 days, depending on year of admission, and mean costs ranging from $81,915 to $128,052 (2016 USD), depending on year of admission. Similarly, Inagaki et al[7] evaluated birth records of newborns with symptomatic cCMVd using the Healthcare Cost and Utilization Project Kids' Inpatient Database. They found that mean LOS ranged from 15 to 27 days, depending on year of admission, and mean charges ranged from $45,771 to $89,846 (2012 USD), depending on year of admission. Correspondingly, the current study observed for the birth admission a mean LOS between 22.1 and 37.5 days and mean costs between $46,994 and $98,126 (depending on delivery type).

Lopez et al[5] evaluated hospitalizations in the Healthcare Cost and Utilization Project Kids' Inpatient Database that included a diagnosis of cCMVd and stratified results according to infant age (ie, infants aged <1 month vs infants aged 1−12 months). They found an estimated 747 cCMVd-related hospitalizations in a 5-year period, with a median LOS of 12.9 days and costs ranging from $7600 to $25,000 per stay (2012 USD), depending on infant age. Our study found that, postbirth, approximately one third of infants with cCMVd were hospitalized and that infants had an average of 13.7 inpatient days during the 1-year follow-up period. Other recent studies[9,10] have estimated the burden of cCMVd in settings outside the United States and are not comparable to the current analysis.

The current analysis provides a more in-depth examination of the health care resource utilization and costs associated with cCMVd than these earlier studies, as the MarketScan databases track participants over time and provide details on all care settings. Our study observed that inpatient visits were a key cost driver among the cCMVd population and contributed to >80% of total costs among cCMVd infants and ~85% of the difference in costs between cCMVd and matched infants without cCMVd. After inpatient visits, outpatient hospital visits and other medical encounters were the next largest cost drivers and, together with inpatient costs, accounted for almost 97% of the difference in costs between cCMVd infants and matched non-cCMVd control infants.

Regarding permanent disabilities, we observed that nearly 30% and 23% of infants with cCMVd had a diagnosis of hearing loss or cognitive disability, respectively, during their first year of life. Previous authors have noted that cCMV infection accounts for an estimated one third of all hearing loss cases in the United States.[15] Previous authors have also reported that between 22% and 65% of symptomatic and 6% and 23% of asymptomatic infants with cCMV infection develop some degree of hearing loss during their lifetimes, making cCMV infection the leading nongenetic cause of sensorineural hearing loss in children.[14,16]

Beyond the direct economic impact quantified in this study, other aspects of cCMV infection affect both the patient and society. For example, a lifetime burden is

associated with care of children with disabilities, including sequelae of cCMV infection such as hearing loss and cognitive disabilities; previous research has suggested that annual economic costs, both direct and indirect, range between $20,000 and $60,000, with an average of $30,000 per family with a child with a disability.[17] This estimate does not include the additional burden to society associated with Social Security benefits, reported to be $7116 annually per person in 2009.[17]

More specific to cCMVd-associated disabilities, the lifetime societal costs of hearing loss for infants with prelingual hearing loss onset have previously been estimated to exceed $1 million.[18] Correspondingly, the lifetime costs for individuals with cognitive disabilities are estimated to be $870,000.[19] Thus, when considered in totality, the costs associated with cCMVd beyond what were found in the current study for the first year of life analysis are likely to be substantial and require further analysis.

This study was conducted by using administrative health insurance claims data and has limitations common to such analyses. First, diagnoses were taken from administrative billing records, which are subject to miscoding or undercoding, and no clinical or electronic medical records were available to confirm diagnoses or clinical events. Data were missing for birth weight and gestational age. However, given that infants were matched on gestational age and birth weight, we do not expect a bias in our analysis based on these covariates. Newborn birth costs may have been accrued on the mothers' insurance. To mitigate this limitation, we conducted a 2-stage approach. Specifically, we separated birth admissions from all other costs and utilization in the first year of life. Newborns with no delivery type were excluded from the birth analysis, as delivery type (ie, vaginal vs cesarean) was a key cost driver for the birth analysis.

Infants with cCMV infection who were asymptomatic during their first year of life and had no corresponding cCMV infection diagnosis were not included in the analysis; therefore, this study likely overestimated the per-infant costs of cCMV infection in the first year of life, as diagnosis was most likely pursued in more severely affected infants. Infants who died were not included in the postbirth analysis. Because infants who died may have represented the group of patients with the most severe cCMVd, costs may have been underestimated in this analysis. In addition, it was not possible to differentiate between congenital and noncongenital, postnatal infections in the claims data; therefore, all infants with a diagnosis of CMV in the first year of life were assumed to have had a congenital infection. Of note, symptomatic, nursery-acquired postnatal CMV infection is a syndrome restricted to preterm infants and much less common than cCMV infection in the current era.[20]

Cost data were based on health plan–paid amounts, which reflect only the costs incurred by payers. Health care services paid for completely out of pocket or by other supplemental insurance were not observed, nor were any medications that may have been administered on experimental protocols. In addition, this study did not capture indirect costs associated with cCMVd that may be incurred by families (eg, loss of income due to care of the infant). Therefore, although this study captured the costs of cCMVd to payers, the total cost burden associated with cCMVd is most likely underestimated. Previous studies have estimated that ~8% of children with disabilities are covered by both Medicaid and commercial insurers.[21,22] Because this study pooled infants covered by Medicaid and commercial insurers, per-infant cost of illness may be slightly greater than that reported in this analysis, as some infants may have dual insurance coverage.

Because we were able to match >98% of newborns and infants with cCMVd to non-cCMVd control subjects, no alternative matching methods (eg, propensity scores) were explored, and results may vary based on alternative matching covariates and methods. In the postbirth analysis, the index date reflected the first observed health care claim for the infant. It is theoretically possible that infants with cCMVd may have been matched to non-cCMVd control infants at different stages of development. In fact, among both cCMVd cases and non-cCMVd control cases, ~80% of infants had their first health care claim observation in the inpatient setting on a claim indicating birth. In addition, results may be different for uninsured infants, infants with fee-for-service plans, and infants enrolled in Medicaid in states not included in the database. Finally, although previous evidence has linked fetal growth and birth weight with socioeconomic status,[23] no information is available in the MarketScan database on maternal

socioeconomic status (eg, education, income), and adjustments were not able to be made.

In addition to symptomatic congenital disease, CMV infection has been linked to additional birth outcomes.[24–26] For example, cCMV infection has been associated with spontaneous abortion and stillbirth. Because this analysis focused on live births, costs associated with these birth outcomes were not included. CMV infection has also been linked with preterm delivery and intrauterine growth retardation. To estimate the incremental costs associated with cCMVd, we matched infants on gestational age and birth weight (as available, with cCMVd infants with missing gestational age and birth weight values matched to non-cCMVd infants with missing gestational age and birth weight values). Therefore, costs resulting from CMVd-associated preterm delivery or intrauterine growth retardation would not be captured in this analysis.

CONCLUSIONS

This study found that cCMVd is associated with a substantial economic burden both at birth and throughout the first year of life. This study provides important information on the economic burden associated with cCMVd during the first year of life and fills a noted gap in the published literature. We have estimated the direct medical costs associated with cCMVd during a finite period. Although the numbers are substantial, they represent a fraction of the total burden that infants with cCMV will face during their lifetime. Future research is needed to evaluate the burden of cCMVd during childhood, adolescence, and adulthood. Furthermore, studies assessing the societal burden of cCMVd are needed to better understand the total burden of this disease, beyond that borne by payers. In addition, previous studies have shown that awareness of cCMV is limited among women of child-bearing age, and interventions (eg, patient education) may be useful in reducing the incidence of CMV infection.[27] Our findings support the notion that developing effective prevention of cCMVd should be a public health priority and may reduce the economic and societal burdens of the disease.

CONFLICTS OF INTEREST

Ms. Meyers and Dr. Candrilli are employees of RTI Health Solutions. RTI Health Solutions received funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth NJ, USA to conduct this study. Drs. Sinha and Samant are employees of Merck Sharp & Dohme Corp. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The study sponsor was involved in the study design, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

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Ms. Meyers participated in the conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, visualization, and project administration for this project. Dr. Sinha participated in the conceptualization, methodology, investigation, writing, supervision, and funding acquisition for this project. Dr. Samant participated in the conceptualization, methodology, investigation, writing, and project administration for this project. Dr. Candrilli participated in the conceptualization, methodology, validation, investigation, resources, writing, supervision, and funding acquisition for this project.

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APPENDIX A. SUPPLEMENTARY DATA

The following is the supplementary data related to this article:

To estimate the adjusted incremental burden of cCMVd, multivariable regression models were estimated. In this study, the use of regression models in analyzing health care costs controlled for confounding factors (i.e., comorbidities) that were not included in the matching of cases to controls. As available demographic and clinical characteristics including gestational age and birth weight were included in the matching of infants with cCMVd and non-cCMVd controls, it was not necessary to include these in the multivariable regression models as well.

Costs for the initial inpatient stay and for the 1-year postindex date (and LOS for the initial inpatient stay) models were evaluated using a generalized linear model with a log-link function and Poisson (for LOS models) or gamma distributions (for cost models) for the error term, the latter of which helps resolve the issue of skewed cost distribution that is common in claims data(Wedderburn, 1974). Dependent variables included LOS and costs (by setting and overall). Independent variables included a binary indicator for the study cohort (i.e., cCMVd cohort or matched non-cCMVd controls) and binary indicators for the presence of selected comorbidities (i.e., for the birth analysis, the following comorbidities were included in the analysis: intrauterine growth retardation and small for gestational age, purpura and petechiae, hepatitis, jaundice and hyperbilirubinemia, thrombocytopenia, renal failure, hepatosplenomegaly and splenomegaly, microcephaly, and seizures; the postbirth analysis included diagnosis codes that were observed to be common to infants with cCMVd, including ICD-9-CM diagnosis 765.xx [disorders relating to short gestation and low birth weight], 770.xx [other respiratory infection of fetus and newborn], 783.xx [symptoms concerning nutrition and metabolic development], 518.xx [other diseases of the lung], and 747.xx [other congenital anomalies of the circulatory system]).

Before statistical modeling began, each outcome was evaluated regarding the most suitable functional form to use. It was observed that cost values were extremely right skewed, with a small number of infants having very high costs. Upon additional review of the data, it was decided that those infants with extremely high cost values (i.e., infants who had costs greater than $500,000, corresponding to infants in the top fifth percentile) would have their cost value set to approximately the 95th percentile value (i.e., $500,000) (no changes were made to unadjusted cost values). Setting costs to a lower (though still high) value among infants with very high cost values allowed for inclusion of these infants (versus exclusion of these infants and their corresponding data altogether) without the inherent inflation of the mean that would otherwise be present. This methodology, termed *Winsorizing*, is common in analyses of skewed data, as it results in a smaller standard error and correspondingly greater power (at the expense of a reduced correlation matrix) than "un-Winsorized" data (Wilcox, 2017).

For the birth analysis, incremental adjusted LOS associated with cCMVd was 5.9 days among newborns with a vaginal delivery and 11.4 days among newborns with a cesarean delivery, while incremental adjusted costs associated with cCMVd were $15,568 among newborns with a vaginal delivery and $37,199 among newborns with a cesarean delivery (all P values < .0001, Table S1).

For the postbirth analysis, among infants in the cCMVd cohort, mean (SD) adjusted all-cause total health care costs based on multivariable regression analysis (excluding admissions for labor and delivery) were $48,540 ($73,025) versus $9,449 ($17,452) among matched non-cCMVd controls (difference = $39,091, P < .0001) (Table 6). Consistent with unadjusted costs, adjusted inpatient costs remained the largest component of all-cause adjusted total health care costs. As separate models were estimated for each component of health care costs, slightly higher cost values were predicted for inpatient versus total costs among infants with cCMVd (i.e., mean [SD] adjusted all-cause inpatient health care costs were estimated to be $56,610 [$109,028] among infants with cCMVd versus $3,552 [$8,968] among matched non-cCMVd controls [difference = $53,058, P < .0001]).

Table S1. Adjusted LOS and Costs, by Delivery Type: Birth Analysis.

Article I. Cohort	LOS (Days), Mean (SD)	Costs,[a] Mean (SD)
Vaginal delivery		
cCMVd admissions (N=167)	20.5 (4.4)	$39,561 ($13,891)
Non-cCMVd admissions (N=167)	14.6 (1.6)	$23,993 ($4,537)
Difference	5.9 (4.6)[b]	$15,568 ($14,498)[d]
Cesarian delivery		
cCMVd admissions (N=230)	38.6 (8.4)	$93,008 ($32,755)
Non-cCMVd admissions (N=230)	27.3 (3.3)	$55,809 ($12,376)
Difference	11.4 (9.0)[c]	$37,199 ($34,663)[e]

cCMVd = congenital cytomegalovirus disease; CI = confidence interval; LOS = length of stay; SD = standard deviation.

[a] Unadjusted cost values above $500,000 were set equal to $500,000 for the presented regression analysis.

[b] Lower 95% CI - Upper 95% CI: *P* value: 5.2-6.6, <.0001.

[c] Lower 95% CI - Upper 95% CI: *P* value: 10.2-12.5, <.0001.

[d] Lower 95% CI - Upper 95% CI: *P* value: $13,353-$17,783, <.0001.

[e] Lower 95% CI - Upper 95% CI: *P* value: $32,696-$41,703, <.0001.

Table S2. Adjusted All-Cause Health Care Costs by Cohort and Place of Service: Postbirth Analysis.[a]

Characteristic	Cohort				Difference				
	cCMVd Cohort, (SD)		Matched non-cCMVd Cohort, Mean (SD)		Mean	SD	Lower 95% CI	Upper 95% CI	*P* Value
Inpatient services	$56,610	($109,028)	$3,552	($8,968)	$53,058	($107,040)	$44,986	$61,129	<.0001
ED visits	$302	($140)	$167	($71)	$135	($144)	$124	$146	<.0001
Outpatient hospital visits	$4,900	($4,669)	$1,104	($1,133)	$3,796	($4,552)	$3,453	$4,140	<.0001
Physician office visits	$2,136	($1,074)	$1,495	($683)	$641	($1,139)	$555	$727	<.0001
Physical/ occupational therapy visits	$348	($457)	$25	($43)	$323	($444)	$290	$356	<.0001
Other ancillary medical encounters	$4,675	($6,652)	$1,034	($1,872)	$3,642	($6,313)	$3,165	$4,118	<.0001
Pharmacy	$2,710	($3,731)	$928	($1,524)	$1,782	($3,473)	$1,520	$2,043	<.0001
Total health care costs	$48,540	($73,025)	$9,449	($17,452)	$39,091	($70,554)	$33,771	$44,411	<.0001

cCMVd = congenital cytomegalovirus disease; CI = confidence interval; ED = emergency department; SD = standard deviation.
[a] Unadjusted cost values above $500,000 were set equal to $500,000 for the presented regression analysis.