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Identification of congenital CMV cases in administrative databases and implications for monitoring prevalence, healthcare utilization, and costs

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Abstract

Objective: To critically review researchers' use of diagnosis codes to identify congenital cytomegalovirus (cCMV) infection or disease in healthcare administrative databases. Understanding the limitations of cCMV ascertainment in those databases can inform cCMV surveillance and health services research.

Methods: We identified published studies that used diagnosis codes for cCMV or CMV in hospital discharge or health insurance claims and encounters records for infants to assess prevalence, use of services, or healthcare costs. We reviewed estimates of prevalence and of charges, costs, or expenditures associated with cCMV diagnosis codes.

Results: Five studies assessed hospitalizations with cCMV diagnosis codes recorded in hospital discharge databases, from the United States ($n = 3$), Australia ($n = 1$), and the United Kingdom ($n = 1$). Six other studies analyzed claims or encounters data from the United States ($n = 5$) or Japan ($n = 1$) to identify infants with cCMV codes. Prevalence estimates of recognized cCMV ranged from 0.6 to 3.8 per 10,000 infants. Economic analyses reported a wide range of per-hospitalization or per-infant cost estimates, which lacked standardization or comparability.

Conclusions: The administrative prevalence of cCMV cases reported in published analyses of administrative data from North America, Western Europe, Japan, and Australia (0.6–3.8 per 10,000 infants) is an order of magnitude lower than the estimates of the true birth prevalence of 3–7 per 1,000 newborns based on universal newborn screening pilot studies conducted in the same regions. Nonetheless, in the absence of systematic surveillance for cCMV, administrative data might be useful for assessing trends in testing and clinical diagnosis. To the extent that cCMV cases recorded in administrative databases are not representative of the full spectrum of cCMV infection or disease, per-child cost estimates generated from those data may not be generalizable. On the other hand, claims data may be useful for estimating patterns of healthcare use and expenditures associated with combinations of diagnoses for cCMV and known complications of cCMV.

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Keywords

Health services research; cost analyses; congenital CMV

Introduction

Congenital cytomegalovirus (cCMV) infection occurs in an estimated 3–7 per 1000 live births in North America, Western Europe, Japan, and Australia[1,2]. Within the United States, variation in birth prevalence by race/ethnicity, region, and socioeconomic status, is commonly reported[1,3]. Typically, 10–15% of infants with cCMV infection present with clinical signs at birth, such as hepatosplenomegaly, petechiae, chorioretinitis, jaundice, and microcephaly;[1,4–7] therefore, the true prevalence of symptomatic cCMV infection is an order of magnitude lower than that of cCMV overall. Diagnosis of cCMV infection requires laboratory testing of specimens collected within the first 3 weeks of life[8–11]. In the absence of universal screening, relatively few infants are diagnosed with cCMV infection, mostly infants who are tested due to clinical signs present at birth[9]. A minority of infants diagnosed with cCMV are asymptomatic, tested as a result of concerns about maternal infections during pregnancy or of the infant not passing newborn hearing screening[12,13].

Congenital CMV is an important preventable cause of birth defects (microcephaly and brain anomalies) and developmental disabilities[14]. Children with cCMV who are symptomatic at birth are at elevated risk of intellectual disability, cerebral palsy, epilepsy, and other adverse neurosensory and neurodevelopmental outcomes[6,15]. Sensorineural hearing loss (SNHL) is the most common sequela of cCMV infection and may occur regardless of the presence of clinical signs at birth[6,16,17]. The serious sequelae of cCMV and their associated costs[18–20] have prompted the development of a variety of interventions, including antiviral treatments, screening, and candidate vaccines[7,21]. Quantifying the cost-effectiveness of such preventive strategies can be challenging, however[22,23].

A major challenge to quantifying the economic impact of cCMV infection is the paucity of data on healthcare use and costs for children with cCMV infection. A few studies in the United States have used diagnosis codes recorded in healthcare administrative data to ascertain cases of presumed cCMV infection or disease and estimate healthcare utilization and costs[3,24–26]. However, if those cases are not representative of infants with cCMV infection or disease due to under-ascertainment, the estimates of average costs could be of uncertain utility[22]. On the other hand, administrative healthcare data could potentially be used to track from birth children with cCMV who develop serious neurological sequelae and require repeated hospitalizations and costly outpatient care. A relatively small number of children with medical complexity, including conditions such as cerebral palsy, are known to account for a disproportionate share of aggregate pediatric healthcare expenditures[27,28].

In this study, we critically review published studies that have used administrative data to ascertain presumed cases of cCMV infection or disease for various purposes. Administrative data can be used to assess frequency with which a condition such as cCMV is recognized in healthcare encounters, along with comorbid diagnoses, complications, risk factors, healthcare utilization and expenditures or costs. Our intent is to inform future health services

research on cCMV conducted using administrative data sources, both in the United States and in other countries.

Methods

This scoping review used the PubMed database to identify published studies that used billing diagnosis codes for cCMV in administrative healthcare databases. The two major types of administrative healthcare data sources are hospital discharge databases and health insurance claims or encounters databases using reporting forms developed for billing purposes. The International Classification of Diseases (ICD), 9th and 10th Revisions, Clinical Modification (CM) codes for "congenital cytomegalovirus infection" are 771.1 and P35.1, and for "cytomegaloviral disease", independent of age of diagnosis, are 078.5 and B25, respectively. Since 1 October 2015, US healthcare systems have used ICD-10-CM codes to bill payers and record encounters; prior to that date ICD-9-CM codes were used. Our selection criteria were analyses of data collected routinely by healthcare systems and not for the purposes of research or surveillance of disease in which these ICD-9/10 diagnosis codes were used to identify presumed cases of cCMV infection or disease or associated clinical encounters.

Two searches were conducted using the PubMed database. Both search strategies used "congenital cytomegalovirus" in combination with either "hospitalization" or "claims." The searches were updated on 1 June 2020. The hospitalization search identified 32 articles published from 1984 to 2020, of which five met our selection criteria (Table 1)[3,24,25,29,30]. The claims search identified five articles published from 2013 to 2020, all five of which met our selection criteria[8,26,31–33]. References of retrieved articles were also reviewed. An additional search in PubMed on 24 February 2020 using "congenital cytomegalovirus" in combination with "hospital" identified a total of 1061 articles. Of those, 114 articles were published during 2019–2020, none of which met the criteria for full-text review. A full-text search of Google Scholar on "congenital cytomegalovirus" in combination with ICD-9 or ICD-10 did not identify additional published studies. One additional study, which appeared in the December 2020 issue of JAMA Pediatrics, was subsequently identified[34].

For studies that were included in this review, we extracted information on the databases used in the studies, years of analysis, study population, methods used to identify cases of cCMV infection or disease and calculate associated healthcare costs, and outcome measures, such as reported hospitalization rates and prevalence of cCMV, and their associated costs (estimated medical charges, costs, or expenditures) if reported.

Results

Hospital discharges

Three U.S. studies and one study each from Australia and the United Kingdom used hospital discharge databases. The three U.S. studies all used Healthcare Cost and Utilization Project (HCUP) databases to examine hospitalizations associated with a cCMV diagnosis code (ICD-9-CM 771.1)[3,24,25]. All reported average cost or charge per hospitalization, but each used different sample years and different methods for calculating and reporting costs.

Using the HCUP Kids' Inpatient Databases (KID), Lopez et al. identified cCMV diagnosis codes in 1.9 per 10,000 infant hospitalizations during 1997–2009, excluding hospitalizations with human immunodeficiency virus (HIV) or transplant-related diagnosis codes. Of an estimated 3734 cCMV-coded hospitalizations, 55% were in the first month of life, which implies that cCMV was diagnosed in 1.0 per 10,000 neonates. Median costs for cCMV-coded hospitalizations were $19,100 in 2012 US dollars; median costs were higher for those in the first month of life ($25,500) than in the post-neonatal period ($7600)[24].

Inagaki et al. likewise used HCUP KID data and reported 0.9 per 10,000 birth hospitalizations with cCMV diagnosis codes during 2000–2012. The authors reported that 76% of admissions were accompanied by one or more cCMV-associated symptom diagnosis codes, i.e. a prevalence of 0.7 per 10,000 symptomatic cCMV cases. The authors reported geometric mean charges (not costs) of roughly $90,000 in 2012 US dollars for the symptomatic cCMV hospitalizations[3].

Finally, using the HCUP Nationwide Inpatient Samples, Candrilli and Trantham reported a slight decline in cCMV diagnosis codes from 2.1 per 10,000 infant hospitalizations in 2004 to 1.8 per 10,000 in 2013. The arithmetic mean cost for those hospitalizations was $104,000 in 2016 US dollars[25].

Of the two non-US studies that examined hospitalization discharge databases, Seale et al. conducted a retrospective analysis of deidentified Australian hospital discharge records from the National Hospital Morbidity Database to search for pediatric (aged ≤14 years) hospitalizations with an ICD-9 code of 777.1 for the period 1993–1998 or ICD-10 code of P35.1 for the period 1999–2001[30]. CMV-related hospitalization rates at ages 0–4, 5–9, and 10–14 years were 0.94, 0.24, and 0.085 per 10,000, respectively. Most (70%) hospitalizations in the 0–4 age group were during the first 9 months of life. The highest frequency was in the first month of life; 3.7 per 1000 neonatal hospital discharges had a CMV code[30].

A recently published study by Kadambari et al. analyzed hospitalization databases from England (Hospital In-Patient Enquiry, Hospital Episode Statistics, and Oxford Record Linkage Study) to examine trends during 1968–2016 in discharges coded for any of four congenital viral infections. For 1999–2016, national data were linked at the patient level across multiple hospital stays, and cCMV-associated discharges were identified using ICD-10 codes for cCMV at any age or for CMV in a hospitalization at ≤28 days of age. The investigators reported a doubling in the frequency of hospital discharges in infancy associated with cCMV from 1.14 per 10,000 in 1999–2006 to 2.27 per 10,000 in 2007–2016[29]. The incidence or birth prevalence of cCMV diagnoses among unique infants increased from 0.63 per 10,000 infants in 1999–2006 to 1.24 per 10,000 in 2007–2016. In 2016, 92 infants had 149 cCMV discharges, an average of 1.6 discharges per infant.

Health insurance claims and encounters

Although the diagnosis of cCMV should be made by testing samples collected within 3 weeks of life, researchers often use cCMV or CMV-coded diagnoses within 30–90 days of life to account for potential delays in coding of new diagnoses in claims data. Five published

studies, four from the United States and one from Japan, used claims and encounters databases. Three of the U.S. studies examined utilization of selected services by infants with presumed cCMV (either cCMV or CMV diagnosis codes) using health insurance claims from the IBM MarketScan research databases[8,26,31]. These databases include the MarketScan Commercial databases of employer-sponsored insurance (ESI) plans, Medicare Supplemental data for retirees who have ESI-funded supplements to Medicare, and Multi-State Medicaid databases. The commercial and Medicare databases are nationwide, whereas the Medicaid databases include data for a small number of unnamed states. The composition of the databases varies from year to year, which may affect comparability of estimates using different sample years. These databases include unique enrollee identifiers, which allows for tracking individuals' use of services over time as long as they and their health plans remain in the claims database. Thus, it is possible to assess costs per infant with presumed cCMV. Researchers commonly restrict analyses to individuals with continuous enrollment data for at least 12 months.

Leung et al. identified 1.7 per 10,000 infants enrolled in ESI plans with presumed cCMV within the first 30 days of life in 2011, although only 12% had a claim for CMV testing during the same time period[8]. In a second study, Leung et al. analyzed data for infants in ESI or Medicaid plans during 2009–2015[31]. The study population included infants who had continuous enrollment for at least 45 days from the first claim following a live birth. Presumed cCMV was identified within the first 45 days of life in 2.5 per 10,000 ESI-insured infants and 3.3 per 10,000 Medicaid-insured infants. In this study, presumed cCMV rates increased over time in both samples, as did the proportions of infants with filled outpatient prescriptions for valganciclovir antiviral therapy[31]. In 2015, Medicaid-insured infants with presumed cCMV were more likely to have filled valganciclovir prescriptions than those among ESI-insured infants (37% vs. 29%, respectively).

Meyers et al. identified infants with presumed cCMV, pooling MarketScan ESI and Medicaid-insured data from 2011–2016 and 2011–2015, respectively[26]. They reported presumed cCMV in 1.9 per 10,000 birth hospitalizations and 3.8 per 10,000 infants post-birth hospitalization. Cases were matched with controls based on demographic and clinical characteristics, and additional covariates were included in regression analyses (see Table 1).

Meyers et al. also assessed healthcare expenditures associated with cCMV in infancy. In claims data, costs are typically recorded as the sum of expenditures (payments) by health plans and patients to healthcare providers for a defined time period, typically 1 year. In MarketScan claims data, payments are imputed for encounters reported by capitated (e.g. managed care) health plans in the database which paid providers a fixed amount per person per month. Analysts typically calculate the difference in all healthcare spending for individuals with a diagnosis such as cCMV and with matched individuals without the same diagnosis to calculate incremental expenditures attributable to the condition. It is also possible to estimate spending on CMV-related claims, but that would not include spending indirectly caused by cCMV, e.g. services for hearing loss, since the cCMV diagnosis code would typically not be included in most claims. As already noted, Meyers et al. pooled estimates from the ESI and Medicaid databases despite methodological challenges (see Discussion section).

In the birth hospitalization cohort, adjusted costs were estimated to be higher for newborns with presumed cCMV: by $15,568 among those with a vaginal delivery and $37,199 among those with a cesarean delivery. In the post-birth hospitalization cohort, the incremental adjusted cost of presumed cCMV during infancy was estimated to be $39,091; mean adjusted costs for infants with presumed cCMV were four times those of controls.

Messinger et al. analyzed data from MarketScan Commercial data for 2011–2015 with Medicaid Analytic eXtract (MAX) data for 2000–2013 to estimate the prevalence of microcephaly diagnoses among infants with and without cCMV. Unlike other claims studies, the authors ascertained cCMV case study using an algorithm requiring ≥2 ICD-9-CM claims with codes for cCMV infection or disease ≤90 days. Of more than 2 million infants who were enrolled from birth through at least 90 days, 336 had cCMV, a pooled prevalence of 1.4 per 10,000 (1.5 per 10,000 in the Medicaid data and 1.3 per 10,000 in the MarketScan Commercial data). Microcephaly diagnoses were also more common in the Medicaid data, 3.1 per 10,000, than in the MarketScan data, 2.4 per 10,000. The pooled prevalence of microcephaly was 655 per 10,000 infants with cCMV and 2.8 per 10,000 infants without cCMV.

Leung et al. examined the prevalence of congenital CMV-coded diagnosis among American Indian and Alaska Native (AI/AN) infants using the Indian Health Service National Data Warehouse[32]. The database includes data for approximately 1.6 million eligible AI/AN persons who receive healthcare from Indian Health Service (IHS)-operated or IHS-contracted health facilities. Among 354,923 AI/AN infants during October 2000 to September 2017 with a health visit within the first 90 days of life, 54 had a CMV-coded diagnosis ≤90 days, a prevalence of 1.5 per 10,000. Among these 54 infants, 48% had ≥1 diagnosis code associated with clinical signs, such as jaundice, petechiae, thrombocytopenia, or microcephaly. In particular, neonatal jaundice was diagnosed in 28% of infants coded with cCMV, similar to the 24% prevalence in other AI/AN infants.

Finally, Lin et al. analyzed a subset of the Japan Medical Data Center claims database, a proprietary database with information from individuals and their families covered by selected employers that was developed for pharmacoepidemiologic studies[35]. Lin et al. analyzed data for 207,547 infants born April 2010–March 2017 and followed for 8–88 months[33]. They identified 53 (25.5 per 100,000) with a cCMV diagnosis code (ICD-10 code P35.1) in claims ≤6 months from birth, excluding claims with rule-out diagnoses (“suspected case flag”). Most (77%) had a diagnosis code on an inpatient claim, and 44 (83%) had a claim within the first month of life. The researchers assumed that all 53 cases were diagnosed based on clinical symptoms, although only two-thirds (68%) of patients had ≥1 diagnosis code associated with “symptoms” of cCMV within ≤1 month of birth, including SNHL (30%), hepatitis or hepatosplenomegaly (28%), and small for date/low birth weight (19%)[33].

Discussion

Administrative healthcare data are increasingly being used to ascertain cases of cCMV infection or disease for health services research, especially in North America. US

researchers have used hospital discharge and claims databases to assess trends and geographic differences in either hospitalization rates or prevalence, laboratory testing for CMV, use of valcanciclovir therapy, presence of co-occurring diagnoses, and healthcare expenditures during infancy[3,8,24–26,31,32]. Australian and British researchers have used hospital discharge data to assess trends in the frequency of diagnoses in discharges[29,30]. Such changes could reflect improved clinical awareness and increased testing. Notably, Kadambari et al. reported a doubling in the incidence or birth prevalence of cCMV diagnoses, from 0.63 per 10,000 infants in 1999–2006 to 1.24 per 10,000 in 2007–2016, which they tied to the initiation of targeted hearing-based CMV testing[29]. Finally, Japanese researchers used claims data from 2010 to 2017 to assess prevalence of and the presence of diagnoses indicative of symptomatic cCMV[33].

Assessment of the administrative prevalence of cCMV requires data on unique individuals for both the numerator of unique cCMV cases and the denominator of the population at risk. Most hospitalization databases cannot link encounters to unique individuals, which allows the calculation of hospitalization rates but may be problematic for assessing prevalence. Inagaki restricted their analysis to birth hospitalizations, which allowed them to identify unique infants but which excluded infants who were diagnosed with cCMV after discharge from the birth hospitalization[3]. Lopez et al. included all hospitalizations in the first month, which could pick up later diagnoses of cCMV but could not exclude multiple admissions for the same infant with a diagnosis code of cCMV[24]. The overall cCMV frequency was similar between the two studies, 0.9 per 10,000 birth hospitalizations in Inagaki et al.[3] and 1.0 per 10,000 neonates with a cCMV-coded hospitalization in Lopez et al.[24]

Longitudinally-linked claims data can be used to identify cohorts of unique infants with cCMV diagnoses to calculate prevalence. In addition, by following them over the first few years of life, researchers could potentially track the timing of diagnoses of neurosensory impairments and use of services such as hearing amplification along with associated expenditures.

Challenges in identification of congenital CMV cases

Caution in the interpretation of findings of such studies may be warranted due to the undercounting of reported cCMV cases relative to the true prevalence of cCMV. To the extent that recorded cases are not representative of all individuals with cCMV infection or disease, excess healthcare costs for those patients might not be generalizable to the population of infants and children with cCMV and used to estimate aggregate costs associated with cCMV[22]. The administrative prevalence of cCMV, 1–3 per 10,000, is a small fraction of the true prevalence of 30–70 per 10,000 revealed through universal screening studies in the same countries. Researchers have reported that only a minority of the 10–15% of infants with symptomatic cCMV disease are clinically diagnosed in the absence of screening, due to non-specific symptoms and low provider awareness[9,20].

Efforts to classify infants with cCMV recorded in administrative data as symptomatic based on the presence of diagnosis codes associated with clinical signs of cCMV (e.g. petechiae, thrombocytopenia, and microcephaly) are limited by inconsistent recording of clinical signs related to cCMV. Some researchers assume that all infants with cCMV diagnosis codes are

symptomatic, diagnosed based on clinical signs or symptoms[26,33]. However, a minority of infants who receive clinical cCMV diagnoses may have been evaluated and diagnosed for other reasons. Notably, targeted testing for cCMV following referral from newborn hearing screening can contributed to diagnoses with cCMV[12,29].

Another challenge is the lack of information on the frequency of false-positive cCMV diagnosis codes. False-positive diagnoses are especially common in outpatient claims, reflecting either coding errors or “rule-out” diagnoses where a clinician evaluates a patient for a condition, e.g. ordering a laboratory test[36–39]. In the United States, inpatient diagnosis codes receive closer scrutiny because they affect reimbursements to providers, unlike outpatient claims[40]. In an unpublished tabulation of US claims data, Leung et al. found that 33–37% of all infants identified with cCMV in either the first 45 or 90 days were identified solely on the basis of outpatient claims[31].

No assessments of the validity of ICD-CM diagnosis codes in administrative healthcare data for the ascertainment of presumed cCMV have been published, unlike for numerous other conditions[41,42]. For example, a published review of validation studies of ICD-9-CM diagnosis codes for tuberculosis found a positive predictive value (PPV) of less than 0.4 in 8 of 10 studies, meaning that false-positive diagnoses outnumbered true-positives[43]. Consequently, diagnosis codes in inpatient claims usually reflect medical diagnoses; a Canadian validation study found that 97% of pediatric hospital discharges with an ICD-10-CM code for respiratory syncytial virus infection had the diagnosis confirmed in medical charts[44]. However, those medical diagnoses may not have laboratory confirmation. A Canadian study that linked laboratory test results with administrative databases found that the PPV of a diagnosis code for influenza relative to laboratory test results was 70% in hospital discharges, 65% in emergency or urgent care visits, and 56% in outpatient physician claims[45].

Researchers using claims databases have taken various approaches to try to minimize false-positive cCMV diagnoses. Most have required the presence of cCMV or CMV diagnosis codes in claims during the first 30–90 days of life[8,31,32,34]. Although only tests conducted on specimens collected within 21 days of birth can establish a diagnosis of cCMV infection[8–11], researchers allow for delays in conducting tests, submitting claims, and reporting of results outpatient encounters. Nonetheless, infants with postnatal CMV infections may have false-positive diagnosis codes for cCMV owing to the lack of a specific diagnosis code for postnatal CMV infection[46]. In a recent analysis of MarketScan Commercial claims data that required the presence of ≥2 claims on separate dates with cCMV diagnosis codes ≤90 days, Messinger et al. found an administrative prevalence of cCMV of 1.3 per 10,000 infants[34], compared to 2.5 per 10,000 infants in an analysis by Leung et al. that required ≥1 claim ≤45 days[31]. It is not possible to determine how many of the infants with just 1 cCMV claim may have been true cases.

A limitation specific to some analyses of hospital discharge data is that databases may not allow researchers to track individual patients across multiple encounters. Readmissions for infants with cCMV could explain higher cCMV-coded hospitalization rates in the two US studies that considered all hospitalizations in infancy[24,25] compared to an analysis restricted

to birth hospitalizations[3]. Similarly, an Australian study could not determine how many unique infants had cCMV diagnoses[30]. In contrast, a UK study that used linked hospitalization records was able to count unique infants as well as admissions and readmissions[29]. At the two extremes, an average of 3.7 neonatal hospital discharges had a cCMV code per 10,000 Australian infants born during 1993–2001[30], whereas just 0.9 per 10,000 birth hospitalizations in a US study were coded for cCMV[3].

In Japan, 2.1 per 10,000 unique infants born during 2010–2017 had a cCMV code in a hospitalization in the first 6 months of life using linked claims data[33]. However, most claims databases only represent individuals covered by a specific payer type. In the US healthcare sector, there are large differences in the sociodemographic and economic characteristics of people covered by public and private insurers. Consequently, the administrative prevalence of cCMV can also be expected to be heterogeneous, higher among populations with lower socioeconomic status. Not surprisingly, Leung et al. reported a higher prevalence among infants covered by public Medicaid programs than those covered by employer-sponsored insurance plans[31]. However, the MarketScan Medicaid data came from a small number of states and the generalizability of those estimates is uncertain. In contrast, Messinger et al. analyzed Medicaid claims data from 46 states as well as from MarketScan Commercial claims, but they did not report administrative prevalence estimates separately for the two samples, only a pooled rate of 1.4 per 10,000 births. Meyers et al. reported a rate of 1.9 per 10,000 birth hospitalizations in a pooled analysis of MarketScan Commercial and MarketScan Medicaid claims databases[26].

Differences among published estimates of the administrative prevalence of diagnosed cCMV could reflect differences in the true prevalence of cCMV, the state of clinical awareness and testing practices, or analytic methods and data sources. One study reported that the prevalence of cCMV diagnoses among infants born to Native American mothers in IHS deliveries during 2000–2017 was elevated in Alaska, 3.7 per 10,000, relative to the Southern Plains region, 0.9 per 10,000[32]. Kadambari et al. documented a substantial increase in recorded cCMV diagnoses following the implementation of targeted CMV testing in a National Hearing Screening Programme in England in 2006[29]. It would be of interest to assess how the frequency of cCMV codes has changed following implementation of CMV screening policies in other jurisdictions.

Challenges in estimation and reporting of healthcare costs

Differences in methods used in analyses of “costs” in administrative data can make estimates of costs reported by diverse studies difficult to compare. Specific methods discussed in this section include the measures used to describe average costs (e.g. mean or median), the operational definition of “cost”, the distinction between hospital costs and hospitalization costs, standardization of cost estimates for differences in purchasing power between countries and over time, heterogeneous data sources (e.g. type of health insurance claims), possible truncation of cost distributions or identification of statistical outliers, and potential biases resulting from the inclusion or exclusion of covariates in regression analyses of per-child costs. Ultimately, if cCMV per-person attributable cost estimates are to be incorporated in cost-of-illness or cost-effectiveness analyses, they would need to be estimated as the

incremental cost relative to an otherwise similar child who did not experience cCMV infection[22].

Commonly used measures to assess the "average" cost of health care include the arithmetic mean, geometric mean, and median. The arithmetic mean cost is much larger than the median cost because of the long right-hand tail of the distribution of costs. It would be helpful for comparability of estimates if researchers were to report both arithmetic mean and median expenditures or costs[47,48]. The median represents the central tendency of the cost distribution as well as the experience of the "typical" patient, whereas the arithmetic mean allows analysts to estimate aggregate expenditures and the share of spending for components, such as inpatient care. The geometric mean is close to the median.

One US hospital discharge database study analyzed reported charges[24], whereas two other studies estimated costs by multiplying charges by hospital-specific cost-to-charge ratios[3]. Hospital charges (invoice prices) in the United States refer to the facility fee charged by hospitals to reimburse for institutional costs and does not include professional fees billed separately by physicians and other clinicians who are licensed for independent practice[49]. The facility fee is generally a multiple of the actual costs incurred by the hospital[50]. For example, in 2017, the mean cost of an inpatient discharge with a principal diagnosis code of P35.x for congenital viral disease averaged $26,669, which was 23.9% of the mean charge of $111,654[51]. If one applies a 0.24 cost-to-charge ratio to the geometric mean estimate of $90,000 in charges for "symptomatic" cCMV birth hospitalizations (76% of all cCMV-coded birth hospitalizations) reported by Inagaki et al., the estimated cost is similar to the $25,500 median cost for all cCMV-coded neonatal hospitalizations reported by Lopez et al.

The exclusion of professional fees from hospital charges in US hospital discharges databases is desirable if the objective is to assess costs from the perspective of the hospital administrator. However, the exclusion leads to underestimation of hospitalization costs from the perspectives of the patient, healthcare payers, and society. Using both private and public insurance claims data, researchers calculated professional fee ratios relative to facility fees; they estimated that the overall cost of inpatient care inclusive of physician services may be as much as 20–25% higher than the cost calculated on the basis of hospital charges in combination with cost-to-charge ratios[52]. To avoid downward biased estimation of hospitalization costs for conditions such as cCMV, researchers who analyze US hospital discharge databases can apply professional fee ratios to reported costs[53].

Guidelines for economic analyses recommend that patient cost estimates from different years be adjusted in terms of a common currency year, e.g. 2012 US dollars[54]. Within a country, that requires adjustment for inflation. Experts recommend that cost estimates from different years be adjusted for either general price inflation or medical price inflation using an appropriate measure[55]. Many US researchers, including Inagaki et al. and Meyers et al., have used the medical care component of the US Consumer Price Index to adjust cost estimates from different years[3,26]. However, that measure has historically overstated overall medical price inflation relative to accurate measures[55], and its use can overstate estimates of expenditures or costs.

Insurance type (public vs. private) is an important predictor of healthcare costs in the United States. Private insurance payments for physician and hospital services substantially exceed payments by Medicaid programs that insure low-income individuals, varying over time[56,57]. In addition, the relative difference in expenditures between privately and publicly insured persons with the same diagnoses may vary[58,59]. Meyers et al. assumed the association of cCMV with expenditures is the same in publicly and privately insured infants, which may not be the case. In addition, their classification of all individuals for which a matching variable was not available in one data source as "unknown" (e.g. race for commercial and region for Medicaid data) could be statistically problematic since the data were not missing at random[60].

We suggest that researchers avoid modeling practices that can downwardly bias cost estimates. For conditions, such as cCMV, where affected individuals may incur very high costs, truncation of expenditures at the upper 5th percentile can result in substantial underestimation of average costs[61]. Privately-insured US children with co-occurring cCMV and microcephaly can incur more than $1 million in expenditures during the first 3–4 years of life[62], and truncation would exclude those observations.

Finally, the inclusion of causally-associated diagnoses as covariates in regression models, which can result in downward bias in the estimated incremental cost-of-illness associated with the condition of interest[63]. Meyers et al. both truncated expenditures and included as covariates conditions that are causally related to cCMV infection (see Table 1)[26]. For example, cCMV infection often results in preterm birth and low birthweight, which are associated with substantially higher healthcare expenditures[48]. Diagnoses such as intellectual disability, hearing loss, microcephaly, cerebral palsy, and epilepsy, can be appropriately modeled in pathway analyses as mediating the impact of cCMV on healthcare costs rather than be treated as independent predictors[19]. It is important to assess the relative risk of cCMV for these conditions as well as potential interactions among these diagnoses and their average costs.

We acknowledge limitations of this scoping review. Unlike a systematic review, there was no predefined hypothesis. Assessments reflect the professional opinions of the authors, and readers may reach different judgments.

Implications for future research

The lack of formal validation studies of diagnosis codes for cCMV is an important limitation. Researchers can use hospital chart reviews linked to administrative data to identify infants with laboratory-confirmed cCMV and compare to infants with ICD codes for cCMV or CMV in hospital discharges[42,44]. It would also be helpful if those same data could be linked to administrative data inclusive of ambulatory clinic encounters to assess the PPV for cCMV diagnosis codes outside of hospitals. Finally, researchers might use electronic health records data to compare the presence of positive laboratory test results for CMV infants within 21 days of birth with the presence of ICD diagnosis codes for CMV or cCMV.

Future analyses of stand-alone administrative databases on children with recognized cCMV can hopefully benefit from the observations in this review. One is that US-based researchers

can conduct parallel analyses of data for children with different types of health insurance, similar to the analysis by Leung et al. on valganciclovir uptake[31]. Such analyses could potentially reveal differences between children with private and public coverage in the association of cCMV with healthcare use. Children with Medicaid or other public insurance are not only more likely to have cCMV, but they may also have a greater frequency of serious postnatal complications of cCMV and hence increased medical need. To date, no published analyses of US claims data have assessed whether that is the case; existing studies either presumed the same risk for privately and publicly insured children[26,34] or only examined diagnoses recorded in the first 45 days of life[31].

Researchers could also potentially use administrative data with unique individual identifiers to identify and follow cohorts of children coded with cCMV diagnoses soon after birth. Analyses of such data could assess healthcare use and spending in early childhood for children with and without cCMV codes in early infancy. Although the overall sample of children with cCMV diagnoses may not be representative, researchers could identify subgroups of patients with specific combinations of diagnosis codes of interest. However, attrition as a result of either families or health plans leaving databases over time can make it difficult to follow most children for more than a few years. That can make it difficult or impossible to calculate cumulative costs over a period of 5–6 years as in the analyses of longitudinal data from the CROCUS study in the Netherlands[20,64].

Researchers could analyze healthcare costs for infants and children with diagnoses of cCMV and co-occurring administrative diagnoses of neurological or neurodevelopmental conditions such as autism spectrum disorder (ASD), cerebral palsy or epilepsy. Although diagnosed ASD is more common among children with symptomatic cCMV[64], it is not known whether such children have co-occurring diagnoses such as microcephaly, brain anomalies, epilepsy, or cerebral palsy. Researchers might test for potential interactions to quantify the extent to which children with co-occurring diagnoses incur higher expenditures. Children with the highest level of medical complexity account for 0.5% of children in the United States but 15–33% of pediatric health spending[27]. Quantification of the very high costs of care for children with medical complexity attributable to cCMV could be useful for economic evaluations of a hypothetical CMV vaccine, since reductions in numbers of severely affected children and associated costs could potentially offset a considerable part of the cost of the vaccine.

Beyond stand-alone administrative databases, record link-ages of individual-level administrative data on healthcare use and costs matched to cCMV diagnoses confirmed by laboratory test results (i.e. CMV PCR of neonatal dried blood spots) could supersede the limitations of cost estimates from administrative databases. For example, since July 2019, the Ontario Infant Hearing Program and Newborn Screening Ontario have been offering testing for CMV in dried blood spot specimens to parents of all infants born in the province along with testing for genetic risk factors for hearing loss; almost all infants are being tested. If Canadian researchers were to link the CMV test results from this program to administrative records, they could prospectively assess healthcare use and costs for a large, representative cohort of North American children with cCMV infection along with CMV-negative children. Such linked data, once available, might yield accurate, incidence-based

cost-of-illness estimates of expected costs per case with cCMV based on representative data. Such estimates could also inform assessments of the cost-benefit/effectiveness of potential interventions such as vaccination against CMV.

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Table 1.

Studies on congenital cytomegalovirus (cCMV) using administrative healthcare data.

Study	Country	Data source	Study years	Study design/study population	Congenital CMV case definition	Cases or encounters (*n*)	Prevalence of cCMV-coded diagnoses	Cost, charge, or expenditure
Hospital discharges								
Candrilli S et al., 2017[25]	USA	HCUP Nationwide Inpatient Sample	2004–2013	Retrospective cohort/ Hospital discharge records of infants aged *d* < 1 year at hospital admission	ICD-9-CM 771.1	Not available	~2 per 10,000 hospital discharges (decrease from 2.1 per 10,000 hospital discharges in 2004 to 1.8 per 10,000 hospital discharges in 2013	**Costs calculated by multiplying charges by cost-to-charge ratios arithmetic mean cost** of $103,773 (SD $175,737) in 2013 per discharge, in 2016 US dollars (no explanation of method of inflation adjustment)
Inagaki K et al., 2018[3]	USA	HCUP Kids' Inpatient Database	2000, 2003, 2006, 2009, 2012	Retrospective cohort/ 19,638,452 hospital discharge records of in-hospital births	ICD-9-CM 771.1, with in-hospital birth record, and ≥ 1 congenital CMV-related condition[a]	1,773 with cCMV diagnostic code; 1,349 with symptomatic cCMV	0.9 per 10,000 birth Hospitalizations overall 0.7 per 10,000 with symptomatic cCMV	**Geometric mean of total charges** per birth hospital discharge ranged from $45,771 (SE $8,509) in 2000 to $89,846 (SE $10,358) in 2006 and remained stable during 2006–2012, in 2012 US dollars (adjusted using medical care component of the Consumer Price Index)
Kadambari S et al., 2020[29]	England	Hospital In-Patient Enquiry, Hospital Episode Statistics, and Oxford Record Linkage Study	1968–2016	Retrospective cohort/ Hospital discharges and day-case episodes coded with cCMV among infants	ICD-9-CM 771.1 or 078.5; ICD-10-CM P35.1 or B25.9 within *n* ≤ 28 days of birth	Not reported	Hospital discharges: 1.1 per 10,000 hospital discharges in 1999–2006 2.3 per 10,000 hospital discharges in 2007–2016 Unique infants: 0.6 per 10,000 infants in 1999–2006 1.2 per 10,000 in 2007–2016	Not assessed
Lopez AS et al.,2014[24]	USA	HCUP Kids' Inpatient Databases	1997, 2000, 2003, 2006, 2009	Retrospective cohort/ Hospital discharge records of infants aged *d* < 1 year	ICD-9-CM 771.1 without HIV and transplant-related diagnostic codes within *n* < 1 year and *d* < 1 month of age	3734 cCMV-coded hospitalizations 2042 neonatal cCMV-coded hospitalizations	1.9 per 10,000 infants *s* < 1 year of age 1.0 per 10,000 infants *s* < 1 month of age	**Costs calculated by multiplying charges by cost-to-charge ratios. Median** cost for discharges **for infants < 1 year of age:** $19,100, for discharges for infants < 1 month of age: $25,500, and for **discharges for infants 1–11 months of age:** $7600, in 2012 US dollars (no explanation of

Study	Country	Data source	Study years	Study design/study population	Congenital CMV case definition	Cases or encounters (*n*)	Prevalence of cCMV-coded diagnoses	Cost, charge, or expenditure
								method of inflation adjustment)
Seale et al., 2009[30]	Australia	National Hospital Morbidity Database	1993–2001	Retrospective cohort/ Hospital discharge records of children aged ≤ 14 years with a cCMV-coded hospitalization	ICD-9-CM 771.1; ICD-10-CM P35.1	1314 cCMV-coded hospitalizations	0.94 per 10,000 hospital discharges in 0–4-year-olds 0.24 per 10,000 hospital discharges in 5–9-year-olds 0.085 per 10,000 hospital discharges in 10–14-year-olds	Not assessed
Health insurance claims and encounters								
Leung J et al., 2013[8]	USA	IBM MarketScan Commercial databases	2011	Retrospective cohort/ 368,266 infants with ESI ≤ 30 days of age	ICD-9-CM 771.1 or 078.5 within ≤ 30 days of birth	61	1.7 per 10,000 infants with ESI	Not assessed
Leung J et al., 2018[31]	USA	IBM MarketScan Commercial and Multi-State Medicaid databases	2009–2015	Retrospective cohort/ 1,163,112 infants with ESI ≤ 45 days of age with pharmaceutical claims available; 1,357,945 Medicaid-insured infants with known basis of Medicaid eligibility and pharmaceutical claims available	ICD-9-CM 771.1 or 078.5; ICD-10-CM P35.1 or B25 within ≤ 45 days of birth	257 infants with ESI; 445 Medicaid-insured infants	2.5 per 10,000 infants with ESI; 3.3 per 10,000 Medicaid insured infants	Not assessed
Leung et al., 2020[32]	USA	Indian Health Service National Data Warehouse	2000–2017	Retrospective cohort/ 354,923 American Indian and Alaska Native infants with ≥ 1 health visit within the first 90 days of life	ICD-9-CM 771.1 or 078.5; ICD-10-CM P35.1 or B25 within ≤ 90 days of birth	53 infants with cCMV disease within ≤ 90 days of birth	1.5 per 10,000 infants	Not assessed
Lin C et al., 2020[33]	Japan	Japan Medical Data Center claims database	2010–2017	Retrospective cohort/ 207,547 newborns with ≥ 6 months of observation time	ICD-10-CM P35.1 within ≤ 6 months of birth (excluding those coded with "suspected case flag")	53 infants with cCMV disease within ≤ 6 months of birth 44 infants with cCMV disease within ≤ 1 month of birth	2.6 per 10,000 infants within ≤ 6 months of birth 2.1 per 10,000 infants within ≤ 1 month of birth	Not assessed
Messinger et al., 2020[34]	USA	Medicaid Analytic extract (MAX) and IBM MarketScan Commercial databases	2000–2013 (MAX) 2011–2015 (MarketScan)	2,338,580 infants enrolled from birth through 90 days without chromosomal anomalies (1,757,330 Medicaid and 581,250 MarketScan)	2 or more ICD-9-CM 771.1 or 078.5 within 90 days of delivery	336 infants with cCMV within 90 days (259 Medicaid and 77 Commercial)	1.4 per 10,000 infants within 90 days of birth (1.5 per 10,000 Medicaid and 1.3 per 10,000 Commercial)	Not assessed

Study	Country	Data source	Study years	Study design/study population	Congenital CMV case definition	Cases or encounters (*n*)	Prevalence of cCMV-coded diagnoses	Cost, charge, or expenditure
Meyers J et al., 2019[26]	USA	IBM MarketScan Commercial and Multi-State Medicaid databases	2011–2016 (until 2015 for Medicaid)	Case-Control (matched l:l)/Birth Analysis: 2,548,971 newborns (794 included in case-control analysis). Covariates: insurance type (Medicaid or ESI), race (in Medicaid data), region (in Commercial data), birth weight, and gestational age Post-birth analysis: 1,792,172 infants age *d* < 1 year with continuous medical and pharmacy enrollment for 12 months from first medical claim (1,356 included in case-control analysis) Covariates included common sequelae and comorbidities, e.g. cognitive disability, hearing and vision loss, microcephaly, ataxia, and paresis/paralysis	ICD-9-CM 771.1 or 078.5; ICD-10-CM P35.1 or B25 on birth admission (birth analysis) or within *n* < 1 year of age (post-birth analysis)	404 newborns with cCMV disease in birth analysis; 679 infants with cCMV in post-birth analysis	1.9 per 10,000 infants in birth analysis 3.8 per 10,000 infants in post-birth analysis	**Regression-adjusted incremental per-child mean medical expenditure (sum of insurer and out-of-pocket payments) relative to infants without cCMV codes adjusted for covariates** Birth hospitalization: $15,568 with a vaginal delivery ($p<0.001$) and $37,199 with a cesarean delivery ($p<0.001$) Post-birth: $39,091 ($p<0.001$), 4 times non-cCMV infants, in 2016 US dollars (adjusted using medical care component of the Consumer Price Index)

Abbreviations: cCMV, congenital cytomegalovirus infection; ESI, employer-sponsored insurance; HCUP, Healthcare Costs and Utilization Project; HIV, human immunodeficiency virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; SD, standard deviation; SE, standard error.

[a]Congenital CMV symptoms, as defined by Inagaki et al., included thrombocytopenia/platelet transfusion, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis, microcephaly/other central nervous system involvement, hearing loss, and chorioretinitis.

Limitations of all papers using administrative data:

- Reliance on diagnostic coding to identify congenital CMV cases
- No lab results or medical chart review to validate diagnostic coding
- Sensitivity of capturing congenital CMV, and congenital CMV-related symptoms using diagnostic codes; known to be underestimates
- Inability to distinguish between infants with symptomatic congenital CMV disease versus asymptomatic congenital CMV infection based on diagnostic codes for congenital CMV disease or infection