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Missing Diagnoses of Congenital Cytomegalovirus Infection in Electronic Health Records for Infants with Laboratory-Confirmed Infection

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Congenital cytomegalovirus (CMV) is a leading cause of non-genetic sensorineural hearing loss and neurodevelopmental disabilities in children born in the United States, and is associated with a 7-fold increased prevalence of microcephaly.[1, 2] Although universal newborn screening for CMV in not currently recommended in the United States, a few states and health care systems have implemented targeted screening for infants who do not pass the newborn hearing screening.[3–5]

The prevalence of congenital CMV ascertained through diagnostic codes from the *International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10-CM*) using large healthcare databases in the United States ranges from 0.9 to 3.3 per 10,000 live births.[6] In comparison, the prevalence of symptomatic congenital CMV disease in a retrospective chart review of >30,000 infants was 2.9 per 10,000 live births, with CMV testing performed most consistently for investigating microcephaly and low birth weight.[7] However, the sensitivity of diagnostic codes and the extent to which congenital CMV infection is ascertained through laboratory testing in clinical practice is unknown.

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We used deidentified electronic health records (EHR) to assess the sensitivity of CMV diagnostic codes among infants with laboratory confirmed CMV infection, overall and by geographic region. We used 2010–2017 data from 349 facilities that provided CMV laboratory data to Cerner Health Facts, a nationally distributed EHR data warehouse. A congenital CMV case was defined as an infant with a positive CMV laboratory test (i.e., polymerase chain reaction (PCR), direct fluorescent antibody (DFA), or culture from urine, saliva, respiratory secretion, or blood samples, or IgM serology) within 21 days of life. Prevalence of congenital CMV was calculated as the number of cases per 10,000 infants with encounters within 21 days of life. Among congenital CMV cases, diagnostic data were searched for CMV codes (ICD 9: 078.5, B25.x; ICD10: 771.1 and P35.1) and congenital CMV-related conditions within 90 days of life (up to 6 years for hearing loss). The sensitivity of CMV diagnostic codes was the proportion of congenital CMV cases with a CMV diagnostic code within either 21 or 90 days of life, to allow for delay in diagnostic code assignments.[8] Data analysis was performed using R and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

During 2010–2017, 668 congenital CMV laboratory-confirmed cases were identified among 7,517,207 infants with encounters within 21 days of life, or 0.89 cases per 10,000 infants (Table 1). Most (96%) were identified through just one laboratory method, including 513 (77%) through culture, 60 (9%) PCR, 44 (7%) IgM, 23 (3%) DFA; 28 (4%) had results reported using more than one method. Most (97%) cultures were performed using urine samples. The sensitivity of CMV diagnostic codes assigned within 21 and 90 days of life was 10.3% (95% CI: 8.2, 12.9) and 11.1% (95% CI: 8.9, 13.7), respectively. The most common congenital CMV-related conditions were low birth weight, jaundice, and thrombocytopenia (Table 2).

In this study, we found that just one out of ten infants with laboratory-confirmed congenital CMV infection were assigned a CMV diagnostic code in their EHR. The low sensitivity may be attributable to missing diagnostic code data and varying CMV diagnostic code assignment protocols. Used primarily for billing purposes, diagnostic codes may better reflect administrative practices for reimbursement within health systems than the true number of laboratory-confirmed cases.

Prevalence of congenital CMV and sensitivity of diagnostic codes varied by region (Table 1). The Northeast had the highest prevalence, albeit the lowest sensitivity, which may indicate missing laboratory data in other regions, and possibly, varying testing practices by region. Laboratory data in EHR have the potential to expand previous administrative capabilities in identifying infants with congenital CMV infection. However, gaps in completeness and regional variation due to different EHR utilization practices might be important limitations.[9]

Despite widespread availability of PCR testing, a minority of cases in this study were identified by PCR. Missing or uninterpretable PCR results may have led to a relatively low prevalence compared to other studies using administrative data.[3] Among congenital CMV cases, a very low number was diagnosed by IgM testing or using respiratory secretions which are not recommended for diagnosing congenital CMV; excluding those would have

little effect on the results reported. We could only assess certain, rather non-specific CMV-related conditions through diagnostic codes but not clinical notes to assess whether physicians recorded a diagnosis of symptomatic congenital CMV.

Although most congenital CMV cases were identified through culture within 21 days of life, they were not assigned a CMV diagnostic code, hence the low sensitivity. The turnaround time for culture results in some cases might have been longer than the hospital stay, and a subsequent diagnosis might not have been recorded in the Cerner data. However, available data indicate that the median length of hospital stay for infants with congenital CMV varies from 10 days for infants delivered vaginally[10] to 98 days for very low birth weight and premature infants admitted to neonatal intensive care units.[11] Assessing the specificity and positive predictive value of CMV diagnostic codes, frequency of antiviral treatment and length of hospital stay among infants with congenital CMV was outside the scope of this study but is warranted in the future. Continued caution is needed in interpreting administrative data on congenital CMV, since most children with congenital CMV infection are not assigned diagnostic codes for CMV even if they have laboratory confirmation of the diagnosis.

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Table 1.

Prevalence of congenital CMV infection and sensitivity of CMV ICD-9/10-CM diagnostic codes by region

Census Region[a]	Total Infants	Infants with Congenital CMV[b]	Congenital CMV per 10,000 Infants	ICD-9/10-CM Diagnostic Code[c]	
				No.	Sensitivity, % (95% CI)[d]
Northeast	1,528,303	368	2.41	11	3.0 (1.7, 5.3)
Midwest	2,075,136	132	0.64	12	9.1 (5.2, 15.3)
West	2,016,899	25	0.12	6	24.0 (11.2, 44.2)
South	1,898,718	143	0.75	40	28.0 (21.2, 35.9)
Total	7,517,207	668	0.89	69	10.3 (8.2, 12.9)

Abbreviations: CMV, cytomegalovirus; ICD-9/10-CM, International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification

[a] Data are from 349 facilities that provided CMV data to Cerner Health Facts Database between 2010 to 2017.

[b] An infant with a positive CMV laboratory test (i.e., polymerase chain reaction, direct fluorescent antibody, or culture from urine, saliva, respiratory secretion, or blood samples, or IgM serology) within 21 days of life.

[c] Using 21-day cut-off criteria for encounters, CMV laboratory tests, and ICD-9/10-CM codes.

[d] Confidence intervals were calculated using the logit transformation of the original percentages.

Table 2.

Congenital CMV-related conditions among infants with congenital CMV within 21 and 22–90 days of life

	Infants with congenital CMV[a]	
Conditions	**Within 21 days of life (n= 668) No. (%)**	**Between 22–90 days (n= 170) No. (%)**
Low birth weight	207 (31)	16 (9)
Jaundice	171 (26)	36 (21)
Thrombocytopenia	103 (15)	22 (13)
Microcephaly	30 (4)	6 (4)
Petechiae	24 (4)	5 (3)
Brain abnormalities	26 (4)	9 (5)
Hearing loss (6 years)	40 (6)	13 (8)

Abbreviations: CMV, cytomegalovirus; ICD-9/10-CM, International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification

[a]An infant with a positive CMV laboratory test (i.e., polymerase chain reaction, direct fluorescent antibody, or culture from urine, saliva, respiratory secretion, or blood samples, or IgM serology); 668 congenital CMV laboratory-confirmed cases within 21 days of life, and 170 tested positive between 22–90 days of life.