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Epidemiology of cytomegalovirus Infection among mothers and infants in Colombia

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Abstract

We assessed maternal and infant cytomegalovirus (CMV) infection in Colombia. Maternal serum was tested for CMV immunoglobulin G antibodies at a median of 10 (interquartile range: 8–12) weeks gestation ($n = 1501$). CMV DNA polymerase chain reaction was performed on infant urine to diagnose congenital (≤21 days of life) and postnatal (>21 days) infection. Maternal CMV seroprevalence was 98.1% (95% confidence interval [CI]: 97.5%–98.8%). Congenital CMV prevalence was 8.4 (95% CI: 3.9%–18.3%; 6/711) per 1000 live births. Among 472 infants without confirmed congenital CMV infection subsequently tested at age 6 months, 258 (54.7%, 95% CI: 50.2%–59.1%) had postnatal infection.

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Study conception, design and/or oversight: Angelica Rico, Sheila C. Dollard, Diana Valencia, Sheryll Corchuelo, Van T. Tong, Monica Benavides, Maritza Gonzalez, Helena M. Rodriguez, Laura D. Zambrano, Marcela M. Mercado, Suzanne M. Gilboa, Jacqueline Acosta, Jessica Ricaldi, Dioselina Pelaez, Margaret A. Honein, Martha L. Ospina, and Tatiana M. Lanzieri. Data collection, data management, laboratory testing, data analysis and/or interpretation: Angelica Rico, Sheila C. Dollard, Diana Valencia, Sheryll Corchuelo, Van T. Tong, Katherine Laiton-Donato, Minal M. Amin, Monica Benavides, Phili Wong, Suzanne Newton, Marcela Daza, Jordan Cates, Maritza Gonzalez, Laura D. Zambrano, Elizabeth C. Ailes, Helena M. Rodriguez, Suzanne M. Gilboa, Jacqueline Acosta, Jessica Ricaldi, Dioselina Pelaez, and Tatiana M. Lanzieri. Manuscript draft: Angelica Rico, Sheila C. Dollard, Diana Valencia, Van T. Tong, Suzanne Newton, Jordan Cates, and Tatiana M. Lanzieri. Manuscript review and approval: all authors.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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Keywords

CMV; Colombia; congenital infection; cytomegalovirus; newborns; postnatal infection; prevalence; seroprevalence

1 | BACKGROUND

Congenital cytomegalovirus (CMV) infection is mainly associated with sensorineural hearing loss and, in the most severe cases, can result in central nervous system involvement (e.g., microcephaly) or infant death.[1] However, most infants with congenital CMV infection are asymptomatic at birth and have no long-term sequelae.[1] Congenital CMV infection is diagnosed by testing infant's urine, saliva or blood within 21 days of life.[1] After that it is not possible to distinguish congenital from postnatal CMV infection, which occurs in up to 40% of breastfed infants born to CMV-seropositive mothers and is also typically asymptomatic.[2]

Studies conducted in Latin American countries indicate high maternal CMV seroprevalence (≥90%), and prevalence of congenital CMV infection ranging from 6 to 32 per 1000 live births.[3] Limited data exist on the burden of congenital CMV-related sequelae in populations with high maternal CMV seroprevalence, and no data are available for Colombia.[3]

In 2016, the World Health Organization declared a Public Health Emergency of International Concern in response to a cluster of neonates born with microcephaly and neurological disorders likely associated with in utero Zika virus infection.[4] To assess the risk of adverse neurodevelopmental outcomes of Zika virus infection during pregnancy, the *Instituto Nacional de Salud* (National Health Institute [INS]) in Colombia and the US Centers for Disease Control and Prevention (CDC) initiated a prospective cohort study of pregnant women and their infants (in Spanish *"Zika en Embarazadas y Niños* [ZEN]") in 2017.[5] Leveraging on this effort, we assessed CMV infection among mothers and infants in Colombia, including congenital CMV prevalence and outcomes, and postnatal infection at 6 months.

2 | METHODS

The ZEN study was conducted in 13 prenatal care clinics in seven cities in Colombia (Barranquilla, Bucaramanga, Buga, Girón, Palmira, Soledad, and Tuluá). Pregnant women in their first trimester were recruited from February 2017 to January 2018.[5] As part of the ZEN study, maternal serum samples collected at study enrollment and end of pregnancy (delivery or pregnancy loss) were tested for CMV immunoglobulin G (IgG) antibodies by a commercial reference laboratory in Colombia. A subset of mothers' samples was tested at the CDC laboratory for IgG avidity using VIDAS (bioMerieux); five mothers with CMV-negative infants matched on city and age (±2 years) were selected for each mother of an infant with congenital CMV infection. Maternal demographic characteristics were collected during enrollment interviews, and exposures, such as occupations involving bodily fluid contact, regular care for children less than 5 years of age, and contact with bodily fluids from children less than 5 years of age, were added to follow-up interviews during pregnancy.

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Screening for congenital CMV infection was initiated in October 2017, after institutional review boards at both INS and CDC approved the study protocol amendment. Infants whose mothers provided consent had urine samples tested for CMV DNA; infant samples were linked to the mother's identification number and consents were reviewed. Urine samples collected at the first follow-up visit (~10 days of life) were tested both by the INS and CDC laboratories, and urine samples collected at the last follow-up visit (~6 months) were tested at CDC for infants whose parents provided consent for both sample storage and future testing. The INS lab extracted DNA from urine using the MagNA Pure 96 (Roche) and performed quantitative polymerase chain reaction (PCR) using commercial kits (CMV R-gene kit; Argene). The CDC lab extracted DNA from urine using the QiaCube extractor (Qiagen) and performed PCR with an in-house assay targeting the viral immediate early gene.[6] We categorized infants with CMV-positive results in urine samples collected ≤21 days of life as having congenital CMV infection. Because CMV birth prevalence is low and postnatal CMV infection is common, we assumed all infants with first CMV-positive results in urine samples collected greater than 21 days of life as having postnatal CMV infection, though not all infants were tested ≤21 days to reliably rule out congenital infection.

Study nurses collected newborn clinical data by reviewing medical records. As part of the ZEN study, all infants were followed with biweekly visits up to 6 months of life. During follow-up visits, study nurses collected information on infants' feeding, and measured infant head circumference, height/length, and weight; we used the World Health Organization growth curves as the reference curve for calculating growth measurement percentiles. Additionally, infants had a cranial (transfontanellar) ultrasound performed during the neonatal period; routine eye exams within first 3 months of life and at 6 months; hearing screening at approximately 1, 3, and 6 months; and standardized developmental screeners in Spanish language, including Ages & Stages Questionnaire, Third Edition,[7] at 2 and 6 months, and Abbreviated Scale of Development (*Escala Abreviada de Desarollo—3*), a Colombian developmental screener, at 3 months.[8]

We estimated the prevalence of congenital CMV infection using the number of infants tested for CMV within 21 days of life as the denominator, and prevalence of CMV shedding at 3 and 6 months, as the percentage of CMV-positive infants among those tested between 22 and 90 days and 91–197 days, excluding those with confirmed congenital CMV infection. We calculated 95% confidence intervals (CIs) using the Wilson Score method. We compared proportions using χ^2 or Fisher exact tests, and continuous variables using student t or analysis of variance tests. We considered results with $p < .05$ as statistically significant. We conducted data analysis using SAS version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Maternal CMV seroprevalence

A total of 1501 pregnant women enrolled in the ZEN study had a serum sample taken at enrollment tested for CMV IgG. Median gestational age at enrollment was 10 weeks (interquartile range: 8–12). Maternal CMV IgG prevalence was 98.1% (95% CI: 97.5% −98.8%).

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Compared with CMV IgG-negative women (n = 28), CMV IgG-positive women (n = 1473) were more likely to be older, have ≥1 previous live birth, have ≥1 child living in household, and have a lower level of education (Table 1). Only 5.2% of all tested pregnant women had a job involving contact with bodily fluids. Among 619 pregnant women with data collected on exposures to young children, 44.8% (n = 277) reported they regularly cared for children less than 5 years of age, of whom 63.0% (172/273) reported they had contact with children's bodily fluids, with no differences by IgG status.

3.2 | Congenital CMV infection

Of 1108 infants enrolled in the ZEN study, 1023 (92.3%) infants had at least one urine sample tested for CMV (Figure 1). Of these, 711 (69.5%) had a first urine sample collected ≤21 days of life (median: 15 days, interquartile range: 13–17 days); six were CMV-positive, corresponding to a prevalence of congenital CMV infection of 8.4 (95% CI: 3.9–18.3) per 1000 live births. All six infants remained CMV-positive when tested at an age range of 83–181 days. Their mothers were 19–25 years of age at enrollment, all were primipara, though they all lived with ≥1 child in household, and two reported regularly caring for children less than 5 years of age. All six mothers of infants with congenital CMV infection and 30 matched mothers of infants who were uninfected at birth were IgG-positive at enrollment; all but one mother of an uninfected infant had high IgG avidity at enrollment.

All six infants with congenital CMV infection were born at ≥37 weeks gestational age. Among five infants with clinical information, four had no apparent abnormalities on newborn physical exam or eye exams; all passed their hearing screening tests. Three infants were developing as expected for age at 2–3 months, and two (infants A and B) had neurological abnormalities. Infant A had jaundice, seizures, ventriculomegaly, and an abnormal light reflex response during the neonatal period, and at age 2 months, was not able to focus and follow with either eye, was diagnosed with hydrocephaly by cranial ultrasound, and was at risk for gross motor delays. Infant A was also at risk for gross and fine motor delays when screened at 3 months; started holding their head at age 6 months, and had marked hypotonia, did not sit on their own, crawl, stand or walk at age 15 months; neuroimaging studies had shown asymmetric ventricles, with slightly dilated left lateral ventricle. Infant B was at risk for fine motor and psychosocial delays when screened at age 2 months (but not at 3 months), had a normal hearing evaluation at 7 months, but was at risk for language, fine and gross motor delays, and had a diagnosis of macrocephaly at 12 months.

3.3 | Postnatal CMV infection

Among 472 infants who were CMV-negative ≤21 days of life and were tested at approximately 6 months, 258 (54.7%, 95% CI: 50.2%−59.1%) had postnatal CMV infection (Figure 1). Excluding the six infants with confirmed congenital CMV infection, the prevalence of CMV shedding increased from 9.9% (95% CI: 6.4%−15.2%; 18/181) at 3 months of age to 55.9% (95% CI: 52.2%−59.6%; 386/690) at 6 months. Among 218 infants not tested ≤21 days but tested around 6 months, 128 (58.7%) were CMV-positive, and most likely had postnatal CMV infection. The 395 infants who first tested positive at around 3–6 months and the 297 out of 304 (97.7%) infants who were uninfected at 6 months were

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breastfed; with significant differences in mean maternal age (24.7 vs. years, respectively) and mean duration of breastfeeding (24.2 vs. 22.8 weeks) ($p < .001$ for both). Though mothers of infants with postnatal infection were more likely primipara (52.0% vs. 37.8%, $p < .001$), the proportion with ≥1 child living in the household was not significantly different (73.9% vs. 79.9%, $p = .06$).

4 | DISCUSSION

In this multi-city study in Colombia, maternal CMV seroprevalence was high (98%), and the prevalence of congenital CMV infection was per 1000 live births, consistent with studies in other Latin American countries.[3] Our study adds to the limited data on neurodevelopmental outcomes associated with congenital CMV infection in developing countries, where most congenital infections result from non-primary maternal infections.[3] Two of five infants who were assessed had congenital CMV-associated neurological manifestations at 12–15 months of age. Despite the small sample size, all six infants with congenital CMV infection were born to mothers aged 19–25 years who most likely had non-primary infections and were all primipara living with ≥1 child in the household. Studies in developing countries have shown that mothers of infected infants were younger and more likely to be primipara,[3] whereas a French study found that younger age but not parity was associated with increased risk of congenital CMV infection following non-primary maternal infections.[9]

Limited data exist on early acquisition of CMV infection among term infants. The proportion of CMV-positive infants at 3 months of age (9.9%) was consistent with studies showing that 13% to 19% of very low birth weight infants receiving breast milk from their CMV-seropositive mothers acquire CMV infection, with onset of CMV viruria at median 50 days of life.[10] The prevalence of CMV shedding in urine at 6 months of age was 55.9%, which suggests a high incidence of postnatal CMV infection early in infancy, likely from breastfeeding, though transmission from others in the household, including children, was possible.

Our study had limitations. The study findings might not be generalizable to the overall Colombian population because the study sites included populations with lower socioeconomic status where the risk of Zika infection was higher. We were not able to test all infants for CMV infection within 21 days of life. Some of the early “postnatal” CMV infections could have been true congenital infections resulting in a possible underestimate of CMV birth prevalence. Finally, we may have missed infants with postnatal infection shortly after birth who may have stopped shedding before they were tested around 6 months.

Efforts initiated to collect information on outcomes associated with Zika virus infection during pregnancy served as a useful platform to better understand the burden of congenital CMV infection and the dynamics of CMV infection during early infancy. Infants may acquire CMV infection from their mothers, mainly through breastfeeding, and in turn maternal reinfection can occur because young children shed high amounts of virus in urine and saliva.[11] While there are no currently licensed vaccines, mathematical models have shown that infant or toddler vaccination could reduce CMV transmission and would have the highest impact on reducing congenital CMV infection compared to vaccination of older age

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groups.[12] Elucidating immunological factors associated with vertical transmission of CMV in settings with high maternal seroprevalence might provide insights for developing CMV vaccines.

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DATA AVAILABILITY STATEMENT

Opportunities for collaboration should be directed to the coinvestigator, Diana Valencia (ile9@cdc.gov).

REFERENCES

1. Rawlinson WD, Boppana SB, Fowler KB, et al.Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017;17(6):e177–e188. [PubMed: 28291720]
2. Britt WInfectious diseases of the fetus and newborn7th edition, Elsevier Inc. 2011;706–755. 10.1016/B978-1-4160-6400-8.00023-7
3. Lanzieri TM, Dollard SC, Bialek SR, Grosse SD. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. Int J Infect Dis. 2014;22:44–48. [PubMed: 24631522]
4. Rasanathan JJ, MacCarthy S, Diniz D, Torreele E, Gruskin S. Engaging human rights in the response to the evolving Zika virus epidemic. Am J Public Health. 2017;107(4):525–531. [PubMed: 28207337]
5. Gonzalez M, Tong V, Rodriguez H, et al.Cohort profile: congenital Zika virus infection and child neurodevelopmental outcomes; Zika en embarazadas y ninos (ZEN) cohort study in Colombia. Epidemiol Health. 2020:e2020060. [PubMed: 32882120]
6. Boppana SB. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA. 2010;303(14):1375–1382. [PubMed: 20388893]
7. Squires JB. Ages & stages questionnaires, third edition (ASQ-3): a parent completed child monitoring system. Paul H. Brookes Publishing Co, Inc; 2009.
8. Pontificia Universidad Javeriana, Facultad de Medicina, Departamento de Epidemiología Clínica y Bioestadística. Escala abreviada de desarrollo-3 Bogota, Colombia; 2017. https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/PP/ENT/Escalaabreviada-de-desarrollo-3.pdf
9. Leruez-Ville M, Magny JF, Couderc S, et al.Risk factors for congenital cytomegalovirus infection following primary and nonprimary maternal infection: a prospective neonatal screening study using polymerase chain reaction in saliva. Clin Infect Dis. 2017;65(3):398–404. [PubMed: 28419213]

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10. Lanzieri TM, Dollard SC, Josephson CD, Schmid DS, Bialek SR. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. Pediatrics. 2013;131(6):e1937–e1945. [PubMed: 23713111]

11. Boucoiran I, Mayer BT, Krantz EM, et al.Nonprimary maternal cytomegalovirus infection after viral shedding in infants. Pediatr Infect Dis J. 2018;37(7):627–631. [PubMed: 29889809]

12. Lanzieri TM, Gastanaduy PA, Gambhir M, Plotkin SA. Review of mathematical models of vaccination for preventing congenital cytomegalovirus infection. J Infect Dis. 2020;221(Suppl_1):S86–S93. [PubMed: 32134475]

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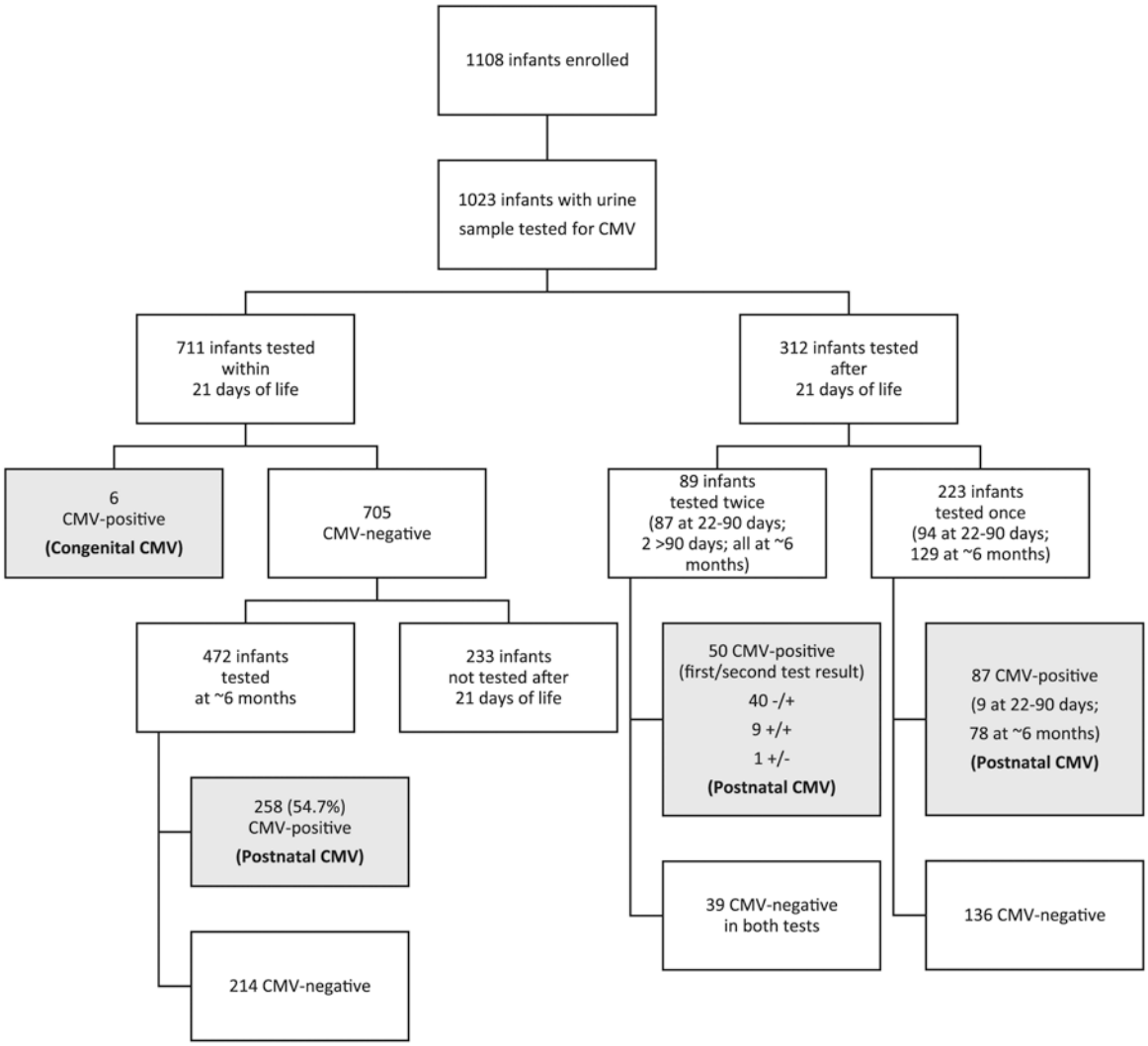

FIGURE 1.

Cytomegalovirus (CMV) testing, congenital and postnatal infection among infants enrolled in the ZEN study

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TABLE 1

Demographic characteristics of pregnant women enrolled in ZEN by Cytomegalovirus Immunoglobulin G antibodies status at enrollment

	All tested ***N*** **=1501** ***n*** **(%)**	**IgG-positive** ***N*** **=1473** ***n*** **(%)**	**IgG-negative**[a] ***N*** **= 28**	***p*** **Value**[b]
≥25 years of age	717 (47.8)	709 (48.1)	8 (28.6)	.04
≥1 previous live birth	757 (50.8)	749 (51.2)	8 (28.6)	.02
≥1 child living in household	1078 (72.8)	1064 (73.2)	14 (51.9)	.01
Married or living with partner	1299 (86.8)	1277 (86.9)	22 (81.5)	.39
Secondary level of education or less	968 (64.6)	955 (65.0)	13 (46.4)	.04
Lowest household socioeconomic stratum	715 (50.5)	705 (50.7)	10 (37.0)	.16
Job involving contact with body fluids	77/1483 (5.2)	76/1455 (5.2)	1/28 (3.6)	1.00
Reported regularly caring for any children <5 years of age[c]	277/619 (44.8)	274/609 (45.0)	3/10 (30.0)	.52
Reported contact with saliva and body fluids of those young childre[c,d]	172/273 (63.0)	170/270 (63.0)	2/3 (66.7)	1.00

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; ZEN, Zika en Embarazadas y Niños.

[a]Includes indeterminate results ($n = 4$).

[b]Comparison of proportions between CMV IgG-positive and -negative, using χ^2 or Fisher's exact test.

[c]Collected at follow-up beginning on September 17, 2017. Data collected before this date did not include this information.

[d]Among those women who reported regularly caring for any children less than 5 years of age.