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Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries ☆☆

Tatiana M. Lanzieri [a], Sheila C. Dollard [a,*], Stephanie R. Bialek [a], Scott D. Grosse [b]

[a] National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[b] National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

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SUMMARY

Background: Congenital cytomegalovirus (CMV) infection is the leading infectious cause of congenital hearing loss and neurodevelopmental disability in developed countries. Information on congenital CMV infection in developing countries appears to be lacking.
Methods: We conducted a systematic literature review to identify studies from developing countries with population-based samples of at least 300 infants that used laboratory methods established as reliable for the diagnosis of congenital CMV infection.
Results: Most studies were excluded due to biased samples or inadequate diagnostic methods; consequently the search identified just 11 studies that were from Africa, Asia, and Latin America. The number of newborns tested ranged from 317 to 12 195. Maternal CMV seroprevalence ranged from 84% to 100%. CMV birth prevalence varied from 0.6% to 6.1%. CMV-associated impairments were not documented in most studies.
Conclusions: Birth prevalence ranges were higher than for Europe and North America, as expected based on the higher maternal CMV seroprevalence. With very limited data available on sequelae, the disease burden of congenital CMV in developing countries remains largely unknown at this time.

1. Introduction

Human cytomegalovirus (CMV) is a member of the herpesvirus family and one of the most ubiquitous viruses in humans. Congenital CMV infection occurs when virus from the mother crosses the placenta and infects the immunologically immature fetus. The consequences or sequelae of congenital CMV infection include fetal death, infant death, and neurological and sensory impairments.[1,2] During pregnancy, women may have either a primary (first) CMV infection or non-primary infection, in which a previously infected woman experiences reactivation of a latent virus or re-infection with a new viral strain. The frequency of vertical transmission and severity of the outcome is reported to be much greater for primary maternal infection;[3] however, non-primary infection is more common than primary infections and thus likely contributes more total cases of congenital CMV infection and related disability.[4–6]

The prevalence of congenital CMV infection has been reported to vary from approximately 0.2% to 2% (average 0.65%), with higher overall rates in countries with higher maternal seroprevalence.[7,8] Most of these estimates come from studies conducted in Europe, the USA, and Japan. In developing countries, the reported prevalence of congenital CMV infection varies substantially, both within and between countries, with some reported prevalences as high as 6–14%.[9,10] Higher birth prevalences combined with additional stresses on infant health in developing countries could augment disability from congenital CMV infection. We conducted a systematic review of the literature to identify population-based studies from developing countries that evaluated congenital CMV infection birth prevalence, and where available sequelae, using methods that are considered reliable for the evaluation of congenital CMV infection.

2. Methods

We identified studies published prior to May 2013 that reported the birth prevalence of congenital CMV infection by

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* Corresponding author.
E-mail address: sdollard@cdc.gov (S.C. Dollard).

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searching PubMed/MEDLINE, Embase/Ovid, LILACS, SciELO, BioMed Central, and CABDirect databases using the keywords CMV, HCMV, cytomegalovirus, human cytomegalovirus, congenital, infant, neonate, newborn, incidence, and prevalence, with no restrictions on language. We restricted the search to articles from countries in Africa, the Americas, Caribbean Region, Central America, Latin America, South America, Asia, Atlantic Islands, and Indian Ocean Islands. We excluded articles from the USA, Canada, Japan, Australia, and Europe, and articles focused on HIV infection. Articles were flagged if the title or abstract indicated that the study reported the birth prevalence of congenital CMV infection in countries classified as developing by the International Monetary Fund.[11] Two studies were included that were from countries currently not categorized as developing, but which were considered developing when the studies were conducted (Taiwan 1996; Republic of Korea 1992).[11] We also reviewed citations in the articles from our search to identify any additional relevant articles not captured by the database searches. We reviewed titles and abstracts from the resulting group of citations and selected articles that reported the birth prevalence of CMV.

Among selected articles, we reviewed the full text to identify studies meeting the following criteria: original peer-reviewed studies with either a cohort or cross-sectional design, a population-based sample of at least 300 newborns, diagnosis of congenital CMV infection by detection of virus by culture or viral DNA by PCR from infant urine or saliva collected within 3 weeks of birth.[12,13]

We excluded studies using CMV IgM-based screening because of the low sensitivity of IgM for the detection of congenital infection[14,15] and highly variable performance among commercial tests.[16,17] In the case of multiple reports from the same authors with overlapping study dates, we included the most recent or most comprehensive report. We excluded studies limited to maternal populations with an elevated risk of transmitting congenital CMV infection, such as mothers with recent primary CMV infection or HIV infection. We also excluded studies with infant populations selected for clinical signs of congenital CMV infection or hospitalization in neonatal intensive care units.

For each of the studies that met the above criteria we extracted the following information: maternal demographics and CMV seroprevalence; methods used for CMV newborn screening (types of clinical specimen, time to specimen collection following birth, laboratory methods); number of newborns tested for and positive for congenital CMV infection; number of congenitally infected newborns who were symptomatic at birth, as assessed by the individual studies since criteria for defining symptomatic congenital CMV disease varied across studies and in some studies was not defined. The quality of individual studies was assessed by evaluating sample size, risk of bias in the study population, and the laboratory methods. We calculated the confidence intervals for the birth prevalence estimates and, to assess the heterogeneity across the studies, we calculated the I^2 statistic, which indicates the proportion of total variation across studies that is due to heterogeneity (e.g., likely to arise from true differences in prevalence, study quality, inclusion criteria, laboratory methods) rather than chance.[18] Analyses were performed using Comprehensive Meta Analysis Version 2.2.064 (Biostat, Englewood, NJ, USA).

3. Results

Of a total of 564 citations identified, 84 met criteria for full-text assessment, of which 11 met criteria for inclusion in this review. Of the 73 studies excluded after full-text assessment, 55 (46%) had a sample size less than 300 newborns, 52 (44%) had biased populations that over-represented mothers with primary CMV infection or symptomatic newborns, and 34 (29%) used exclusively CMV IgM-based screening; 44 (71%) were excluded for more than one of the above reasons. Of the 11 studies included in this review, two were conducted in Africa (Ivory Coast[19] and Gambia[20]), four in Asia (Korea,[21] Taiwan,[22] China,[10] and India[23]), and five in Latin America (Chile,[24] Brazil,[25,26] Mexico,[27] and Panama[28]) (Table 1).

Table 1
Summary of methods and results from studies assessing birth prevalence of congenital CMV infection in developing countries

First author and year of publication	Country and time period	Maternal seroprevalence	Newborn screening			Number of newborns with congenital CMV (%)		
			Clinical specimens	Laboratory methods	Tested	Infected		Symptomatic
						n	Prevalence, % (95% CI)	
Schopfer 1978[19]	Ivory Coast -	100%	Urine	Culture	2032	28	1.4 (1.0–2.0)	0 (0)
van der Sande 2007[20]	Gambia[a] 2002–2005	100%[b]	Urine	PCR	741	40	5.4 (4.0–7.3)	3 (8)
Sohn 1992[21]	Korea 1989–1991	96%[b]	Urine and cord blood	Culture	514	6	1.2 (0.5–2.6)	0 (0)
Tsai 1996[22]	Taiwan[a] -	90%	Urine	Culture, PCR	1000	18	1.8 (1.1–2.8)	2 (11)
Zhang 2007[10]	China 1997–2000	92–99%	Urine	PCR	1159	71	6.1 (4.9–7.7)	17 (24)
Dar 2008[23]	India -	99%[b]	Saliva, urine[c]	PCR	423	9	2.1 (1.1–4.0)	1 (11)
Luchsinger 1996[24]	Chile 1989–1994	98%	Urine and saliva	Culture, PCR	658	12	1.8 (1.0–3.2)	0 (0)
Weirich 1997[25]	Brazil 1994–1995	90%[b]	Saliva	Culture	663	21	3.2 (2.1–4.8)	6 (29)
Yamamoto 2011[26]	Brazil 2003–2009	96%	Urine and/or saliva	PCR, culture[c]	12 195	121	1.0 (0.8–1.2)	12 (10)
Noyola 2003[27]	Mexico[a] 2001	92%	Saliva	Culture	560	5	0.9 (0.4–2.1)	0 (0)
Estripeaut 2007[28]	Panama 2003–2004	84%[b]	Urine	PCR	317	2	0.6 (0.2–2.5)	1 (50)

CMV, cytomegalovirus; CI, confidence interval.
[a] Studies that were conducted in well-baby nurseries or excluded severely ill newborns.
[b] Mothers tested as part of the study.
[c] Indicates specimen or method used for confirmation.