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

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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.

Keywords

Cytomegalovirus; Congenital infection; Prevalence; Developing countries

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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.

Methods

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

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). Six studies were published after the year 2000, four in the 1990s, and one in 1978. The duration of enrollment for the studies varied from 3 months to 6 years. Four were cross-sectional studies and seven were cohort studies.

The number of newborns tested for congenital CMV infection varied from 317 to 12 195; seven out of 11 studies had <1000 newborns tested. Three of the 11 studies excluded some

categories of ill newborns from screening: the study from Gambia excluded newborns that were preterm or had serious congenital deficits; the study from Taiwan screened only newborns who were ‘essentially healthy’ at birth; and the study from Mexico was limited to newborns from the well-baby nursery. Clinical specimens were collected within 3 days of birth in nine studies and within 1 or 2 weeks of birth in the remaining studies. Five studies relied exclusively on PCR for the detection of CMV. Our quality assessment indicated a high risk of bias for all studies except for the Yamamoto study from Brazil.[26]

The birth prevalence of congenital CMV infection varied from 0.6% in Panama to 6.1% in China (Table 1). The I^2 value was 95%, indicating considerable heterogeneity across the studies, therefore we did not combine the studies to estimate an average birth prevalence of congenital CMV infection.

Criteria used to define infected newborns as symptomatic varied across studies. All newborns with congenital CMV infection received a physical examination at birth. More thorough assessment with head imaging, audiological, ophthalmological, and/or neurological examinations was performed in three studies.[22,26,28] The proportion of newborns with congenital CMV infection classified as symptomatic at birth in studies with >15 infected newborns varied from 0% in four of the studies[19,21,24,27] to 29% in the Weirich study from Brazil.[25] Studies conducted in Mexico and Gambia that excluded some categories of ill infants reported 8–11% of infected newborns had symptomatic infection.[20,27] The Yamamoto study from Brazil included a precise case definition of symptomatic congenital CMV disease based on the presence of at least one of the following: petechiae, cholestatic jaundice (conjugated bilirubin level>2 mg/dl), hepatosplenomegaly, purpura, microcephaly, seizures, chorioretinitis, or abnormal cranial computerized tomography (CT) findings.[26] In that study, 12 (10%) of 121 newborns with congenital CMV infection were classified as symptomatic, three of whom had only abnormal cranial CT findings. However, the proportion of symptomatic infants would have increased to 22% if intrauterine growth restriction had also been included as a criterion of symptomatic congenital CMV disease, which it often is.

All studies reported maternal seroprevalence ≥90%, except the study from Panama in which maternal seroprevalence was 84%; mothers were tested directly for CMV IgG antibody in five studies.[20,21,23,25,28] Among six studies that reported maternal demographic information, mothers of infected newborns were younger[20,21,24,25,27] and more likely to be primigravidae or primiparae[20,24,27,28] than mothers of uninfected newborns. In the study from India, the median number of children among mothers of infected newborns was one (range one to two) compared to two (range one to six) among mothers of uninfected newborns.[23] In contrast, the study from Ivory Coast reported similar distributions of maternal age and parity for newborns with and without congenital CMV infection.[19]

Discussion

Our systematic review of the literature on congenital CMV infection in developing countries identified 11 population-based studies using laboratory methods that are established as reliable for identifying congenital CMV infection. The CMV birth rates ranged from 0.6% to

6.1%, which is higher than the range of 0.2–2.0% (average of 0.65%) most often reported for developed countries,[7,8] although the extent to which the selected studies are representative of other developing countries is not known. More studies are needed to understand the burden of disease associated with congenital CMV infection in these populations and how it may be affected by other prevalent conditions such as HIV infection, malnutrition, and malaria.

We found substantial variability across studies in the criteria used to define symptomatic congenital CMV infection, which is the main recognized predictor of permanent sequelae from CMV infection.[8] Based on data from developed countries, an estimated 40–58% of newborns with symptomatic congenital CMV infection at birth will have permanent neurodevelopmental disabilities.[8] Of studies we reviewed that had at least 15 infants with congenital CMV infection, the proportion classified as symptomatic was 0–29%, which is similar to estimates of 5–20% from studies in developed countries.[8] Some of the criteria used to identify symptomatic CMV infection may be problematic when applied to developing countries. For example, intrauterine growth retardation is often associated with congenital CMV,[2,29,30] but it is more common and less specific to CMV in developing countries given its association with maternal socioeconomic and nutritional factors, chronic diseases, and the use of drugs.[31] Abnormal cranial CT findings are associated with congenital CMV infection and long-term sequelae,[32] but CT scans cannot be performed routinely in limited-resource settings, and infants with congenital CMV infection presenting with central nervous system involvement may be more likely to remain undiagnosed in the newborn period.

Conditions for specimen collection, processing, and testing can be suboptimal in developing countries and cause laboratory results to be less accurate. Two reports with the highest rates of congenital CMV infection (5.4% in Gambia[20] and 6.1% in China[10]) relied exclusively on PCR methods. Other reports using PCR that did not meet our inclusion criteria reported higher CMV birth prevalences of 10–20%. Due to the extreme sensitivity of diagnostic PCR, false-positive results can occur in laboratories that do not have extensive expertise and quality control[33] and may result in artificially high estimates of CMV birth prevalence. High quality diagnostics also rely on specimen transport and storage at cold temperatures that are harder to maintain in areas with weaker infrastructure and inconsistent power supplies.

Findings from the countries included in our review are not necessarily representative of that country or region. The results from Gambia and Ivory Coast may not be generalizable to other regions in Africa with significantly different HIV prevalence, since CMV is more readily transmitted in the setting of HIV infection.[34,35] Also, five of the studies were conducted two decades or longer ago and it is likely that living conditions have since changed. High seroprevalence is associated with lower socioeconomic status and crowding, which may have increased or decreased in some regions, altering patterns of CMV infection. This is especially true with very large, socioeconomically dynamic countries like China, India, and Brazil, where birth prevalences may vary substantially from region to region and by sociodemographic characteristics. A study from 1985 by Pannuti et al.[36] screened two groups of approximately 500 newborns for CMV by viral culture with results similar to other studies. The Pannuti study was not included in our analysis to avoid over-

representation of any given population, because their sample was from the same region of Brazil as the 2011 study by Yamamoto[26] with 12 195 newborns screened.

CMV seroprevalence in developing countries is generally over 90% by adolescence and over 95% by early adulthood. Consequently most cases of congenital CMV infection result from non-primary maternal infection. By comparison, the CMV seroprevalence among 12–40-year-olds is 40–60% in the USA,[37] where both primary and non-primary maternal infection contribute substantially to congenital CMV infection.[4] Distinguishing congenital CMV infections due to primary vs. non-primary maternal infection from one another is not easily done. Studying congenital CMV infection in regions with very high seroprevalence presents the opportunity to study outcomes in a population in which those are likely due almost entirely to non-primary infection. A meta-analysis by de Vries et al. reported that the pooled risk of hearing loss from seven studies conducted in Europe and the Americas was similar following primary or non-primary maternal CMV infection.[6] In a study from Brazil, the frequency of hearing loss was reported to be 33% (1/3) following primary infection, 15% following non-primary infection (6/40), and 7% (3/42) for indeterminate infections.[26] Overall, 6% of 85 infected infants followed up for at least 12 months were diagnosed with bilateral moderate to profound sensorineural hearing loss.[26] The findings from Brazil suggest that the frequency of bilateral moderate to profound sensorineural hearing loss is similar to or higher than in high-income countries (3–5%),[38] despite a shorter length of follow-up in the Brazilian study. In general, data on the association of non-primary infections with outcomes of congenital CMV infection are lacking.

CMV-associated sequelae could potentially be augmented by other perinatal conditions common in developing countries, such as malnutrition, malaria, and other infections, especially HIV. These factors contribute to higher rates of prematurity and intrauterine growth restriction, which have an impact on neonatal mortality and long-term morbidity.[39] The study from Gambia included in our review found that the prevalence of congenital CMV infection was three-fold higher among infants born to mothers who had acute placental malaria infection.[20] Studies have shown that maternal HIV infection may increase the risk of vertical transmission of CMV, symptomatic disease, and long-term sequelae in infected infants, thus high HIV prevalence increases the overall burden of congenital CMV infection.[34,35,40,41] In addition, adolescent pregnancy is more common in many developing countries and young maternal age is an established risk factor for congenital CMV infection. In this review, the association with young maternal age was present in five of six studies that recorded maternal age.

Our review has several limitations, the main one being the small number of papers that have been published on this subject. We observed a wide prevalence range across countries (0.6% in Panama[28] to 6.1% in China[10]) that could have resulted as much from different methods as from true differences in population prevalence. We made every attempt to identify studies that applied unselected or random screening of newborns, but many studies lacked clear descriptions of their study populations. Three of 11 studies either excluded infants who were ‘seriously ill’ or limited screening to the well-baby nursery, which could have caused an underestimate of CMV birth prevalence in those studies.

In conclusion, developing countries have some of the world's largest populations and highest birth rates, thus the aggregate number of children born with congenital CMV infection in these regions is likely to be enormous. Most congenital CMV infection in developing countries results from non-primary maternal infection, which is less understood as a cause of congenital CMV disease than primary maternal infection. The potential for vaccines and behavioral interventions[42] to reduce non-primary infection and the associated burden of disease is unknown. There is especially a need for research on the potential for other health stresses in developing countries to augment mortality and morbidity of congenital CMV infection. Studies that test unselected populations of newborns for CMV using established methods, and that evaluate the infants at birth and for at least a few years after birth, may not be feasible in many developing countries, but could be a goal if and when resources become available. At the present time no effective interventions to interrupt the transmission of congenital CMV can be recommended for such populations, however, clinicians should be aware of both the ubiquity and risk of CMV infection in pregnancy.

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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] Culture was used as confirmatory test.