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Review Article

A Pooled Estimate of the Global Prevalence of Congenital CMV and Clinical Sequelae at Birth in the Last 10 Years

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ABSTRACT

Background/Objectives: Polymerase chain reaction (PCR) of cytomegalovirus (CMV) in saliva, urine, plasma and dried blood spots (DBS) are newer forms of detecting congenital CMV (cCMV), while CMV culture of saliva or urine have been considered the standard method. Many studies from various countries have screened large numbers of newborns for cCMV in the last 10 years using PCR techniques. The objective of this study is to compile these studies to give an updated pooled global prevalence of cCMV, and to estimate the prevalence of detectable abnormalities caused by CMV at birth.
Method: By reviewing studies using PCR of CMV DNA as a screening method of populations of all newborn infants for cCMV, this study estimates the global prevalence of cCMV and the percentage of infants with clinical sequelae evident at birth, within the last ten years.
Results: Fifteen articles published from 2007 to 2017, using PCR techniques for cCMV detection, give a global prevalence of all newborns with cCMV as 0.47% (95% CI, 0.44-0.50%), with the percentage of symptomatic cCMV as 13%. A meta-analysis of the fifteen prevalences, gives a pooled prevalence of cCMV as 0.46%(95%CI: 0.43-0.49%).
Conclusion: The global prevalence of cCMV is seemingly decreasing, though the percentage of cases of cCMV with symptoms at birth is relatively unchanged.
Keywords: Cytomegalovirus, congenital, prevalence, meta-analysis, review, CMV

INTRODUCTION

Cytomegalovirus (CMV) is the most common congenital viral infection in many populations throughout the world. CMV does not yet have a vaccine and can be vertically transmitted to the fetus during both primary infections and recurrent infections. Congenital CMV can cause fetal sequelae of poor growth, pancytopenia, microcephaly, thrombocytopenia, hepatosplenomegaly, icterus, petechiae, neurological impairment, hearing deficit, intracranial calcifications and even death. A review of studies from 1966 to 2006 estimated the global prevalence of congenital CMV (cCMV) as 0.64%, a prevalence based on wide-scale screening of newborns for CMV using culturing techniques. This study also estimated approximately 11% of infants with cCMV have clinical abnormalities detected at birth. [1]

Within these last ten years, newer means of detecting cCMV have become available and are more commonly used. Polymerase chain reaction (PCR) of CMV in saliva, urine, plasma and dried blood spots (DBS) are newer forms of detecting cCMV, while CMV culture of saliva or urine have been considered the standard method. PCR of saliva and urine are comparable, if not superior to, cultures of saliva and urine; while PCR of DBS may be comparable or inferior. Using wet or dry saliva samples, or urine specimens, the sensitivity of the detection of CMV DNA by PCR ranges 97-100%, and 95-100%, respectively. [2-5] In 2010, within the CMV

and Hearing Multicenter Screening (CHIMES) study, PCR of DBS had an overall sensitivity <35%. The authors concluded PCR of DBS is unsuitable for screening infants for CMV. [6] In 2015, a meta-analysis of PCR of DBS showed an overall sensitivity of 84.4%. [7] Even with the results of the meta-analysis, controversy exists regarding the suitability of DBS in the detection of CMV, especially as many infants with congenital CMV may not be viremic at birth. [6] With regards to PCR detection of CMV DNA, saliva and urine samples are preferred for their sensitivities, [8] while DBS are preferred for their universal collection and ability to be tested after years of storage. [9]

Some precaution is warranted when collecting salivary samples as there could be contamination by maternal milk. Though CMV is rarely detected in milk before two weeks postpartum, [10] saliva samples are often collected >30 minutes to 1 hour after last breastfeeding to decrease the chance of contamination by breast milk. [11-13] To reduce the theoretical concern of contamination by breast milk in regards to salivary samples, the contamination by vaginal secretions of any sample shortly after birth, or the possibility that blood samples may miss infants with cCMV not viremic at birth, some studies repeat or run a confirmation test. [2,11]

Many studies from various countries have screened large numbers of newborns for CMV in the last 10 years. PCR detection of CMV DNA in saliva, urine, plasma, and DBS is a common means of testing. Not all studies follow-up with a confirmatory test, yet others confirm with multiple tests. This study compiles studies using PCR of CMV DNA as a screening method to update the estimate of the global prevalence of congenital CMV and its clinical sequelae.

MATERIALS AND METHODS

MEDLINE/PubMed was searched for the following: *CMV* or *cytomegalovirus*, *prevalence*, *neonate* or *vertical transmission*; and limited to the English language. Studies had to include whole populations of neonates screened en masse, and not selectively screen neonates for any reason such as maternal symptoms, findings on ultrasound, prematurity or HIV. Studies could not exclude any infants from screening for any particular reason. Studies could not be case series or reviews. Studies had to begin screening after 2006. If a more recent study included the same population as a prior study, but expanded the number or regions screened, then only the later study was included. [2,3,6,14] Over 500 articles were screened by a single reviewer. If an article was chosen, similar articles and its references were also scanned for possible contributions. A total of fifteen articles were compiled representing ten countries on four continents. The means of detecting CMV had to be PCR of DNA in saliva, urine, plasma or dried blood spots (DBS). CMV culture of saliva or urine could be used in tandem or for confirmation. Five of the articles only screened infants with one method. The remaining ten articles used two or more methods of CMV detection on either all infants, or only infants with a positive screen to confirm the initial positive test. This current review article did not account for sensitivities of the detection method used. All CMV infections had to be considered congenital/vertical by the authors and not neonatal/postnatal infections. As such, all initial testing had to be collected in the first three weeks after birth. The National Congenital CMV Disease Registry defines symptomatic cCMV as having any of the following: petechiae, purpura, small for gestational age, hepatomegaly, splenomegaly, jaundice, bilirubin greater than three milligrams per deciliter, platelets less than 75,000 per millimeter cubed, alanine transaminase greater than 100 units per liter, neurologic abnormalities, microcephaly, intracranial calcifications, hearing impairment, or chorioretinitis. [15] As articles may not disclose all infant data, symptomatic cCMV was per the authors' conclusions to be symptomatic at birth. With each study, the

percent of symptomatic infants with cCMV was listed as concluded in the study.

Statistical Methods:

The global birth prevalence of cCMV was calculated as the total infants testing positive for CMV divided by the total infants screened in all studies, with a 95% confidence interval. A meta-analysis of prevalence giving a pooled prevalence and 95% confidence interval was also calculated using the inverse variance method with the double arcsine transformation for proportions closer to zero. [16] The prevalence of infants symptomatic with cCMV at birth only included studies giving such estimates and was calculated by the total symptomatic infants at birth divided by the total number of positive cCMV cases at birth, with a 95% confidence interval.

RESULTS

Fifteen articles were used to calculate the birth prevalence of cCMV. These articles screened all live born infants for congenital CMV using PCR for detection during a period of time after 2006. The range of the prevalence of cCMV per live birth is 0.14% to 3.8%. Cases of cCMV from all fifteen articles total 955 (0.47%; 95% CI: 0.44-0.50%) out of 205,000 newborns tested.Using the inverse variance method with double arcsine transformation, [16] a meta-analysis of the fifteen prevalences, gives a pooled prevalence of cCMV as 0.46%, 95%CI: .43-.49%.Twelve of the fifteen articles give data on symptomatic cCMV cases; three articles are missing data on symptomatic infants at birth and are excluded in all symptomatic cCMV calculations. [9,17,18] The percentage of infants with symptomatic cCMV at birth ranges 0% to 50%. Newborn infants with symptomatic cCMV total 95 (12.93%; 95% CI: 10.70-15.55%) of 735 cases of cCMV. These calculations use each article's given percentage of symptomatic cases. All articles are summarized in Table 1 and Figure 1.

Table 1, Prevalence of Congenital CMV at Birth, Studies Using PCR for CMV Detection

COUNTRY YEAR PUBLISHED	NEONATES TESTED/ INCLUDED	CMV POSITIVE (%) PREVALENCE	SALIVA PCR	URINE PCR	DBS or Plasma PCR	URINE CULTURE	SEQUELA AT BIRTH (%)
USA 2017 [14]	99945	443 (0.44%)	+		+		40 (9.0%)
China 2017 [11]	10933	75 (0.69%)	+		+		0 (0%)
Japan 2016 [19]	6348	32 (0.50%)		+	+		16 (50%)
Netherlands 2016 [9]	31484	156 (0.50%)			+		--
Iran 2016 [20]	1617	8 (0.49%)		+			3 (37.5%)
Turkey 2015 [12]	944	18 (1.91%)	+	+	+		0(0%)
Nigeria 2015 [21]	263	10 (3.8%)	+				2 (20%)
Israel 2014 [8]	9845	47 (0.48%)	+	+		+	10 of 46 evaluated at birth (22%)
Iran 2013 [13]	620	2 (0.32%)	+	+			0 (0%)
Israel 2013 [22]	8105	22 (0.27%)			+	+	2 (9.1%)
Slovenia 2012 [23]	2841	4 (0.14%)		+	+		0 (0%)
Japan 2011 [24]	21272	66 (0.31%)		+	+	+	20 (30.3%)
Netherlands 2011 [17]	6433	35 (0.54%)			+		--
USA 2010 [18]	3927	28 (0.71%)			+		--
India 2008 [25]	423	9 (2.1%)	+	+			2 (22.2%)

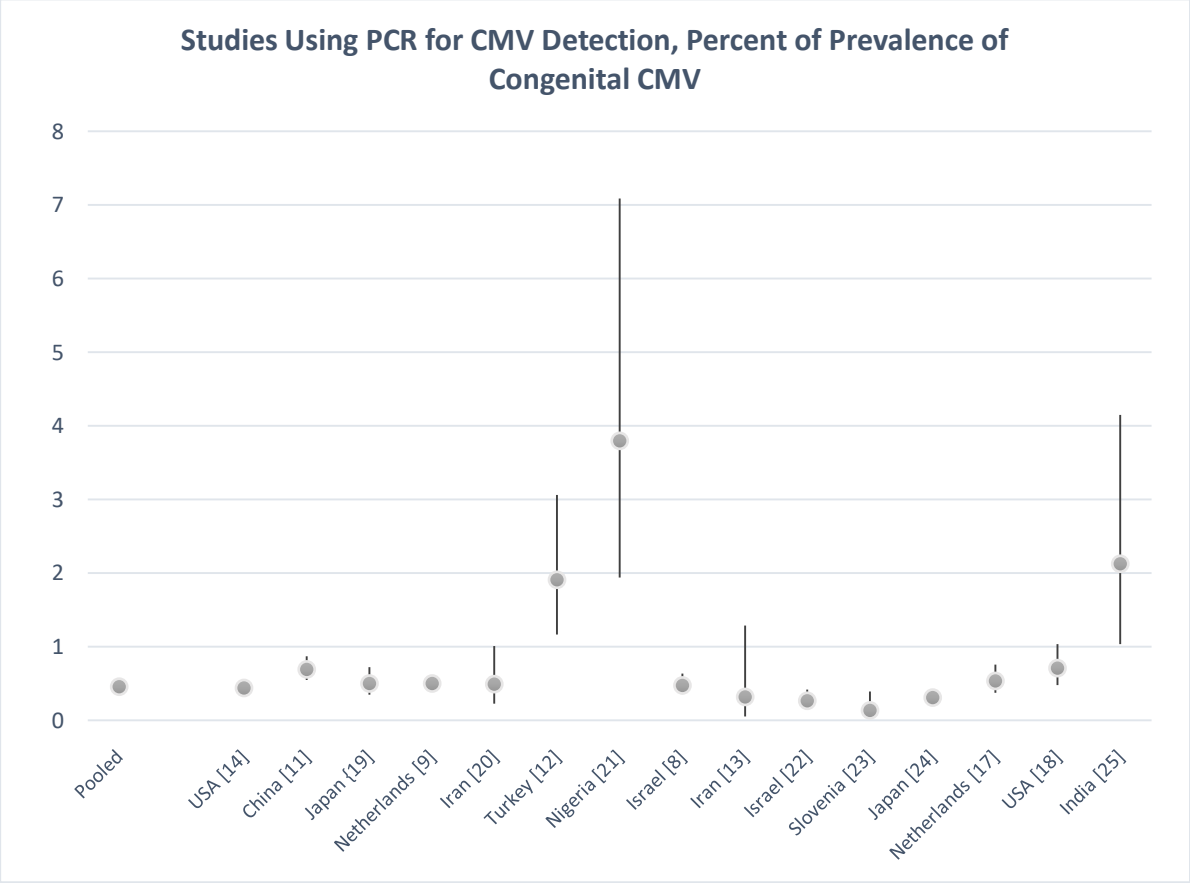

Figure 1.

DISCUSSION

The overall global birth prevalence of cCMV is 0.47% (95% CI: 0.44-0.50%), with a range of 0.14% to 3.8%, based on articles all using PCR techniques for the detection of CMV. This incorporated fifteen studies, published from 2007 to 2017, on study populations starting no earlier than 2006. The meta-analysis of these fifteen prevalences, gives a pooled global birth prevalence of cCMV as 0.46%(95%CI: 0.43-0.49%). A prior study by Kenneson and Cannon looked at similar studies dated 1966 to 2006, and found a global birth prevalence of 0.64% (95%CI: 0.60-0.69%), with a range of 0% to 13.6%. Kenneson and Canon based their estimate on 27 articles using viral cultures of saliva or urine. [1] Using the same meta-analysis method [16] on these 27 articles, gives a pooled global birth prevalence of cCMV as 0.60% (95% CI: 0.56-0.64%). This may signify the global prevalence of congenital CMV is decreasing, but cannot be completely ascertained as the regions of populations studied and methods of testing would have to be identical. As described in the background, the sensitivities of detection of cCMV by PCR in various specimens are comparable to sensitivities of cultures, perhaps with the exception of DBS. This study did not attempt to control for varied techniques. Excluding five articles with only one testing method, the global prevalence of cCMV is 0.45% (95% CI: 0.42-0.48%). All three articles using only DBS for testing are excluded in this estimate which is not significantly different.

In order to verify a global reduction in the prevalence of cCMV, identical populations would need to be examined. Using the Kenneson and Cannon paper as reference, five countries have studies in common with this paper. Most notably they report twelve papers from the USA with a range of prevalence of 0.44-6.2%; of 49960 infants tested, 471 tested positive for cCMV (0.94%; 95% CI: 0.86-1.03%). Compare

this to the two studies here with a range of 0.44-0.71%; of 103,872 infants, 471 tested positive for cCMV (0.45%; 95% CI: 0.41-0.49%). Given many of the states listed in their papers are states represented in the more recent CHIMES study, this is a fair comparison. China has one paper in both reviews with a ~1996 prevalence of 1.8% (95% CI: 1.1-2.9%; 18 of 1000 infants tested), to a 2017 prevalence of 0.69% (95% CI: 0.54-0.86%; 75 of 10933 infants tested). Japan has two papers in both reviews with corresponding pre/post 2006 prevalences of 0.33% (95% CI: 0.24-0.45%; 41 of 12548 infants), and 0.35% (95% CI: 0.29-0.43%; 98 of 27620 infants). Israel has two papers testing infants' urine for CMV culture and CMV DNA by PCR in 1998-1999, with a prevalence of 0.7% (95% CI: 0.42-1.17%; 14 of 2000 infants); compared to this post 2006 prevalence of 0.38% (95% CI: 0.30-0.48%, 69 of 17950 infants). Of these countries, three of the four have a drop in prevalence of cCMV.

The global prevalence of cCMV relies heavily on the amount of infants tested within the various countries. Of these fifteen articles, India [24] had a prevalence of 2.1% and Nigeria [21] a prevalence of 3.8%. Had more infants been tested in regions with higher prevalences, the overall global prevalence of cCMV would increase. Within the Kenneson and Cannon review, Gambia had the highest prevalence of 13.6%, and a study from the USA had the second highest prevalence of 6.2%. [1] The global regions involved in testing influence the prevalence of cCMV, yet overall, the mix of countries represented by testing for cCMV has not changed much as countries with higher national revenue and scientific endowments continue to make up most of the testing.

This study estimates symptomatic cases of cCMV at 12.93% (95% CI: 10.70-15.55%), and the Kenneson and Canon study yielded an estimate of 11%. [1] In both reviews, the percentages of symptomatic cases are likely underestimated as limited by the varied definitions of symptomatic cases. Though the National Congenital CMV Disease Registry defines symptomatic cCMV, [15] studies vary in their definitions, and often limit symptomatic cases by either not including lesser findings [20,21,24] or not including findings with no statistical variation from those of infants without cCMV. [11] The study from Turkey only lists that there were no symptomatic cases, but does not list criteria. [12] Several studies do not comment about any neuroimaging. [12,13,21] If the study shows a lower prevalence of cCMV, they also often show fewer infants with symptoms, and the authors often conclude the cost to disease ratio does not warrant universal testing. [12,13,23] If the study lists symptoms of cCMV cases at birth, often more symptomatic cases could fulfill the definition given by National Congenital CMV Disease Registry, [15] as in four studies within these fifteen: The first study from the USA lists an additional 19 infants with confirmed abnormal hearing tests at birth; this might expand their number of symptomatic infants at birth from 40 (9.0%) to 59 (13.3%). [14] The study from China records abnormalities in infants with cCMV as five with IUGR, one with "weak muscular force," two with jaundice, and two with abnormal hearing tests. It is not reported whether this accounts for ten separate infants, or less if a single infant had multiple findings. This set then represents five to ten infants, using five (6.7%) conservatively. [11] In one study from Iran, in addition to the three infants deemed symptomatic by the authors, another three had abnormal brain imaging by ultrasound with calcifications, one of these infants also had neutropenia, and the other two of these infants had palpable spleens. With this data, six of eight (75%) could be considered symptomatic at birth. [20] The study from Nigeria reports another three infants as having jaundice which could increase symptomatic cCMV from two (20%) to five (50%). [21] Given these possible inclusions of infants with symptomatic cCMV, the theoretical maximum of symptomatic cases

of cCMV is 125 (17.01%; 95% CI: 14.47-19.90%) of 735 cases of cCMV.

CONCLUSION

Given ten years of broad population screenings of new borns for cCMV with PCR methods, this study shows a slightly decreased global prevalence of cCMV, 0.47%. The percentage of symptomatic cases is unchanged at almost 13%, and is subjective due to differing case definitions.

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