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High Prevalence of Asymptomatic CMV Shedding in Healthy Children Attending the Minnesota State Fair

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Abstract

Background: Young children in the household are a known risk factor for maternal CMV infection and consequently, congenital infection in infants. However, little is known about viral shedding in pre-school aged children.

Objectives: To estimate the prevalence of CMV DNA shedding and CMV antibodies among healthy children and their mothers.

Study Design: A study of children ages 0 through 5 years was undertaken at the 2019 Minnesota State Fair. Children and their mothers were assessed for CMV shedding by procurement of a saliva swab for CMV PCR testing. An optional finger-stick for capillary blood was used to assess CMV antibodies.

Results: A total of 109 children and 85 mothers were enrolled. The prevalence of CMV saliva shedding among children (mean age 3.1 years, SE=0.16) and their mothers was 12/109 (11.0%) and 1/85 (1.2%), respectively. The prevalence of CMV DNA among children peaked at 3 years of age (26%) while the mean viral load was greatest at one-year of age (236,693 IU/mL). CMV IgG antibodies among those who agreed to a finger-stick were detected in 16/35 mothers (45.7%) and 0/7 children (0%). Mothers of children aged 5 years or greater had the highest seroprevalence (61.5%).

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Conflict of Interest

The authors have no conflicts of interest to declare.

Conclusions: The prevalence of CMV salivary shedding in this unselected sample of young children was approximately 11.0%. The overall maternal seroprevalence in our sample was <50%, suggesting these women are at risk for acquisition of a primary CMV infection in subsequent pregnancies.

Keywords

Cytomegalovirus (CMV); Asymptomatic shedding; CMV PCR; Congenital CMV

Background

Cytomegalovirus (CMV) is the most prevalent congenital infection in the U.S. occurring in 0.5–2.0% of all live births [1–4]. Between 15–20% of these infants will have a permanent deficit, including microcephaly, mental disability, and sensorineural hearing loss (SNHL) [5,6]. Transmission of CMV during pregnancy can occur either through primary infection in a seronegative woman, or through reinfection [7]. It is estimated that 2.3% of all pregnant women acquire a primary CMV infection annually in the U.S. [8] and among these women there is a 40–60% risk of transmission to the fetus [9]. This is in contrast to CMV infections in women with preconception immunity, in which congenital transmission occurs in 1–2% of pregnancies [9], usually due to reinfection with new strains of virus or less commonly, reactivation of latent virus. The risk of transmission is therefore clearly much higher in primary CMV infections occurring during pregnancy and, although controversial [10], the risk of neonatal disability is believed to be higher than for recurrent infections [11]. Identifying those sources of viral shedding that place women at risk for CMV infection is an important public health measure that can lead to improved outcomes for newborns.

Transmission of CMV occurs by contact with infectious secretions, such as saliva or urine [12]. Toddlers enrolled in group daycare have a high prevalence of CMV shedding [13,14] and pose a risk for acquisition for women of childbearing age. CMV infections are typically asymptomatic so individuals are unlikely to be aware they are shedding virus[15]. While infants and toddlers may continue shedding virus for a year or more, little is known about viral shedding in older children[2,13,16]. Therefore, to address this area of knowledge deficit, we aimed to estimate the prevalence of CMV DNA among healthy children aged 0–5 years and their mothers at the 2019 Minnesota State Fair.

Materials and Methods

Study Population and Participant Recruitment

Study participants included children aged 0 through 5 years and their mothers with primary residence in Minnesota. Participant enrollment occurred over a 3-day period (August 26–27, 31) at the 2019 Minnesota State Fair. The University of Minnesota (UMN) has an existing research facility on the fairgrounds, the Driven to Discover (D2D) building [17]. The D2D building represents a unique opportunity to survey a wider cross-section of Minnesotans from every county and region in the state. In 2019, over 27,700 fairgoers participated in 55 research studies.

Collection of Questionnaires and Biospecimens

Parents completed a demographic/history questionnaire through a REDCap instrument on an iPad. Demographic information (month and year of birth, gender, race, ethnicity) was collected for each participating child in a family. Information was also collected on daycare attendance and breastfeeding history to identify potential risk factors associated with CMV acquisition in young children.

Upon completion of the survey, study staff collected a buccal sample using a FLOQSwab (COPAN Diagnostics, California, USA) from children and participating mothers to test for the presence of CMV DNA. Swabs were placed in between the cheek and jaw and rotated for 5 seconds on each side then placed in tubes for transport to the laboratory, where they were air-dried and then stored at room temperature until PCR could be performed. An optional finger-stick to collect a minimum of 50 μL of blood in an BD microtainer tube containing EDTA to test for CMV IgG and IgM antibodies was also offered to children and mothers. All samples were refrigerated before transportation to the central laboratory (cmv.umn.edu) for subsequent processing and testing.

Sample Processing and Detection of CMV

For serological assay, the OnSite™ CMV IgG/IgM Rapid Test (CTK Biotech, Poway, California, USA) kit was utilized, following the manufacturer's protocol. Briefly, the test is a lateral flow chromatographic immunoassay, containing CMV antigens conjugated with colloidal gold. A nitrocellulose strip contains two test lines and one control line. The test lines are pre-coated with anti-human IgG and IgM for the detection of anti-CMV IgG and IgM antibodies, respectively. A total of 10 lμ of the whole blood sample was added to the sample well along with 2 drops of sample diluent. The sample was allowed to migrate for ten minutes with results read and interpreted according to the manufacturer's specifications.

Quantitative real-time PCR (qPCR) was performed as described elsewhere [18]. Briefly, hydration of the dried swab was performed using 300 μl of QuantaBio Extracta® incubated at 95 °C for 30 minutes in a thermomixer with low agitation. Tubes were then chilled to 4 °C and centrifuged briefly. The eluate was used directly for qPCR or stored at −80 °C until PCR testing. For qPCR, 5 μl of eluate was used in a reaction volume of 25 μl. Primers and probes for the CMV UL83 gene were utilized [19] and qPCR conditions were carried out as previously described [20], using the LightCycler 96 PCR System (Roche). qPCR was run in duplicate and specimens were considered positive if 2 of 2 replicates were positive or if 3 of 4 replicates were positive for samples tested twice. For calculating viral load (copies per milliliter of saliva), the volume of saliva eluted from the swab was estimated to be 75 μl based on previous studies [21]. The results are expressed as International Units (IU) based on the World Health Organization International CMV Standard [22].

Statistical Analysis

Descriptive analyses of the prevalence of CMV DNA and CMV antibodies by demographic characteristics were computed for children and their mothers. Children who did not give a swab sample or who had missing data on age were excluded from analysis. CMV status was compared by demographic characteristics with Fisher exact test for categorical variables

and analysis of variance for continuous variables. Cohen's Kappa statistic was calculated for concordance between siblings for CMV DNA detection. All statistical analyses were conducted using Stata/IC, version 15.1 (StataCorp LP, College Station, Texas). Figures were generated using GraphPad Prism, version 9.0 (GraphPad Software, La Jolla, California).

Ethical Considerations

This study was reviewed and approved by the UMN Institutional Review Board. Written and informed consent was obtained by participating mothers aged 18 years or older and from legal guardians of children 5 years and under.

Results

A total of 91 families, consisting of 117 children and 85 mothers (six mothers chose not to participate, but allowed samples to be collected on their children) were enrolled during the 3-day study period at the Minnesota State Fair. Of the 117 children, 5 did not have a swab sample and 3 did not provide an age, leaving 109 who had complete demographic and sample data and were included in the final analysis (Figure 1). The mean age of the enrolled children was 3.1 years (standard error [SE] = 0.15). The study population characteristics by age group are shown in Table 1. Overall, 86 (78.9%) of children represented the oldest or only eligible child in a family enrolled, and 23 (21.1%) were the younger sibling. Children enrolled were slightly more likely to be female (53.2%) and were predominantly white (78.9%). Eighty-nine percent of children were breastfed (97/109) (mean duration= 9.6 months, SE = 0.6) and 74.3% (81/109) attended daycare (mean duration= 28.7 months, SE=2.1).

Detection of CMV Among Children

Overall, 12 of the 109 children (11.0%) tested positive for CMV DNA in their saliva (Table 2). The mean CMV viral load was 83,091 IU/mL (SE=77,626). Children who were CMV positive were predominantly male (58.3%) and an older or only sibling (66.7%). The mean age among those with detectable CMV DNA was 2.5 years (SE=0.31) compared to 3.1 years (SE=1.6) among those negative.

There were no significant differences in the distribution of CMV DNA prevalence by a child's race/ethnicity (p=0.78). Ten of the 12 positive identified as white (83.3%). There was a higher percentage of black children who were shedding (1/4; 25.0%), in contrast to white children (10/86; 11.6%) or Latino children (1/11; 9.1%) (p=0.78).

Of the children who had detectable CMV DNA, 100% (12/12) were breastfed, compared to 86.7% (85/97) of children who tested negative (p=0.35). Ten of the 81 children (12.3%) who attended group daycare were shedding compared to 2/28 who did not attend (7.1%) (p=0.45). Overall, a higher percentage of children who tested positive (10/12; 83.3%) attended group daycare than those who were not shedding (71/97; 73.2%) (p=0.73).

Seven children (6.4%) agreed to an optional finger-stick to test for CMV antibodies. One of the seven (14.3%) had detectable IgG antibodies, indicating past infection. However, this child did not have detectable CMV DNA in saliva. None of the children had CMV

IgM antibodies, indicative of primary infection. One of the seven children (14.3%) was shedding CMV DNA in saliva; however, this child did not have detectable CMV IgG or IgM antibodies.

Detection of CMV Among Mothers

Of the 85 mothers who agreed to a buccal swab, only 1 (1.2%) was shedding CMV (Figure 2A). Thirty-five (41.2%) agreed to the additional finger-stick for the detection of CMV antibodies and 16 (45.7%) were CMV IgG positive. No mothers had indication of acute CMV infection by the presence of IgM antibodies. Among the thirty-five mothers with serology data, we examined the prevalence of CMV DNA among their children (Figure 2B). The prevalence of saliva shedding among children whose mothers were CMV IgG positive was 1/20 (5.0%) compared to 1/21 (4.8%) for children of seronegative mothers (p=1.0). For the remaining ten children who were shedding CMV in saliva, no serology data was available for their corresponding mothers.

Prevalence of CMV Antibodies Among Mothers by Child's Age

To examine the prevalence of CMV in relation to child's age, we plotted the prevalence of CMV DNA and mean viral load (IU/mL) among children and the seroprevalence of CMV IgG antibodies among mothers against the children's ages (Figure 3). The prevalence of CMV DNA among children peaked at 3 years of age (26.3%) while the mean viral load was greatest at one year of age (236,693.3 IU/mL). Children ≤3 years, overall, appeared more likely to be shedding than older children but this difference was not statistically significant (p=0.76). Mothers of children aged 1- and 5- years had 57.1% and 61.5% seroprevalence, respectively.

Concordance of CMV Shedding Among Siblings

We assessed the concordance of CMV shedding among the 23 sibling pairs in our study (Figure 4). Only one of the 23 sibling pairs (1/23; 4.3%) included both children shedding. Overall, there was 82.6% agreement in CMV shedding between siblings (Kappa =0.25; p=0.102), indicating siblings often had the same result but this finding was not statistically significant.

We had antibody data from the mothers of eight sibling pairs (8/23; 34.5%). Of those eight households, all children were CMV DNA negative while half of the mothers (4/8) were CMV IgG seropositive.

Discussion

Our study of CMV shedding and seroprevalence among healthy children and their mothers produced several important findings that implicate children as a source for maternal infections. First, the prevalence of CMV shedding among healthy young children is understudied; many studies have measured CMV shedding, however, these studies have been limited to children attending group daycare or congenitally infected infants. Second, the prevalence of CMV shedding appears to vary by age, with children ≤3 years more likely to have detectable CMV DNA in their saliva (p=0.76) while the highest viral load was found in

infants one-year of age (236,693.3 IU/mL). Lastly, mothers were less likely to be shedding despite having a higher CMV seroprevalence.

Overall, we detected CMV DNA shedding in 11% of children aged 0–5 years of age who attended the Minnesota State Fair. Our finding is consistent with the prevalence reported by Stowell et al., who also found a CMV shedding rate of approximately 11% in saliva samples of healthy children without controlling for serostatus [23]. However, Stowell et al. reported maternal CMV shedding in 21% of mothers, which is in contrast to our finding of only 1.2%. One difference between these results is Stowell et al. only included mothers of children who screened CMV-seropositive while we included mothers of all children screened. Thus, it is expected that Stowell et al. would see a higher maternal shedding prevalence. CMV shedding prevalence in college-aged seropositive women has been reported between 2.0% and 10.4% [24]. A limitation of our study is that we did not collect data for serostatus on all mothers enrolled, thus we cannot make a direct comparison. We did not find a detectable difference in the prevalence of CMV shedding in children whose mothers were CMV seropositive versus seronegative. The prevalence of salivary shedding among children whose mothers were CMV IgG positive was 1/20 (5.0%) compared to 1/21 (4.8%) for children of seronegative mothers (p=1.0).

CMV shedding among children who attend group daycare ranges between 23–41%, depending on the sample type (urine, serum, or saliva) and age of the child [25]. In our study, the prevalence of CMV shedding among children who attended group daycare was 10/81 (12.3%) compared to 2/28 (7.1%) of children who never attended. CMV oral shedding in previous studies in U.S group daycare settings have been primarily limited to children ≤48 months, in which shedding prevalence decreased with age. Indeed, shedding rates in daycare settings have been reported as the highest within the first 2 years of age (6–80% prevalence) and decline to 0–16% among 2–6 year-olds [15,26–29]. As our study was cross-sectional, we would expect with repeated sampling to have more children shed at other points in time.

The age-specific prevalence of CMV shedding, regardless of daycare exposure, is variable. Two studies documented that viral oral shedding occurs most in children under 12 months [30,31] while more have reported that it occurs most frequently between ages 2 and 3 [27,32–34]. When stratified by age, we found the prevalence varied between 0–26.3%, with a peak prevalence among 3-year-olds. However, one-year old children had the highest mean CMV viral IU/mL (236,693.3 IU/mL) of all age groups. Therefore, children aged 1–3 years may be a key risk for maternal transmission due to both high prevalence and high viral load.

Strengths of our study include the unique opportunity to access a large sample of Minnesota residents for a cross-sectional investigation of CMV shedding. The 2019 Minnesota State Fair saw the highest attendance record to-date and had the second highest state fair attendance in the nation [35]. Limitations of our study include the inherent shortcomings of a cross-sectional design; our data represents a single point-in-time and cannot fully capture the cyclical nature of CMV shedding. Additionally, we did not collect serology data on all participants. Thus, we cannot make conclusions as to CMV shedding as it pertains to seropositive children and mothers. Lastly, the serologic assay used to detect CMV antibodies

(OnSite™ CMV IgG/IgM Rapid Test) is not an FDA approved serodiagnostic test and can only be used for research purposes.

In conclusion, the results from this cross-sectional study demonstrate that healthy children shed CMV at a higher prevalence than their mothers and shedding is variable by age. Additionally, maternal seroprevalence in our sample was <50%, suggesting these women are at risk for acquisition of a primary CMV infection in subsequent pregnancies. Our results raise the possibility of conducting additional seroepidemiologic studies in healthy young children to better characterize the prevalence of CMV infection.

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Highlights

- The prevalence of asymptomatic CMV saliva shedding in children 0–5 years was 11.0%
- Prevalence of CMV saliva shedding was greatest among 3-year-olds (26.0%)
- CMV saliva shedding prevalence was low among mothers (1.2%)
- Overall maternal seroprevalence was <50% suggesting risk for primary CMV infection

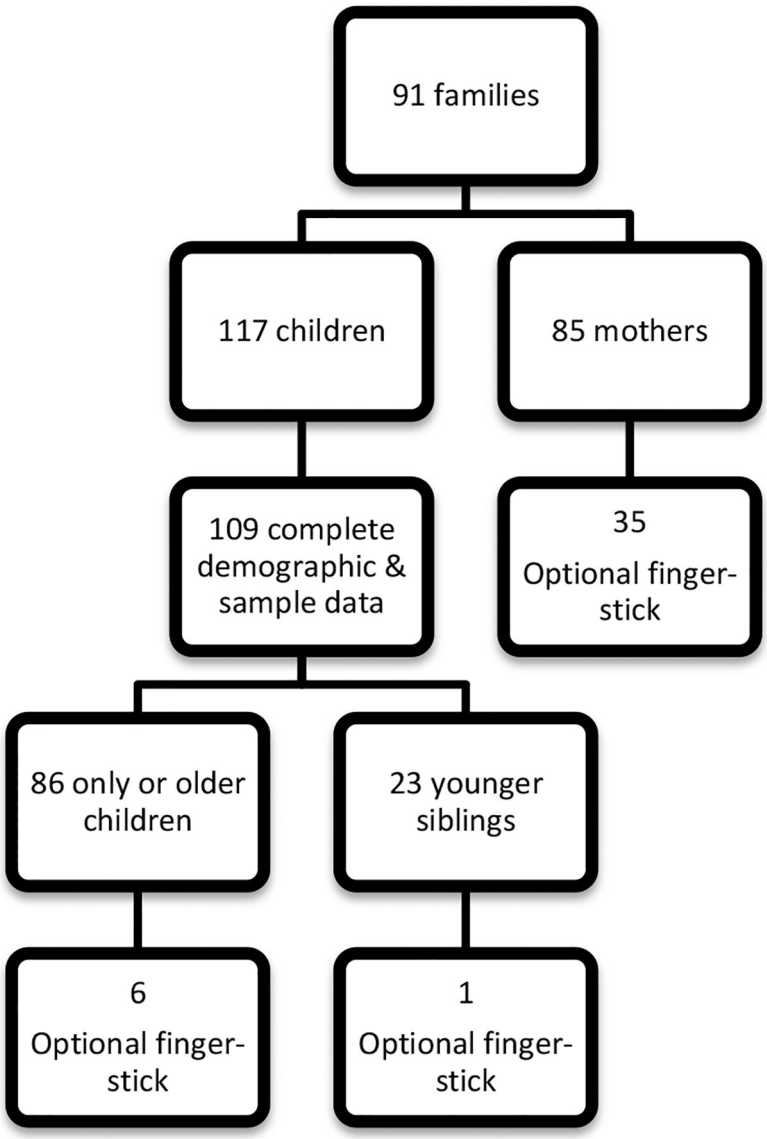

Figure 1: Flow diagram of study enrollment.

91 families participated in the study consisting of 117 children and 85 mothers. Mothers were not required to participate with their children. Children complete demographic and sample data were included in the final analysis (n=109). Thirty-five mothers (41.2%) and 7 children (6.4%) agreed to the optional finger-stick to collect capillary blood.

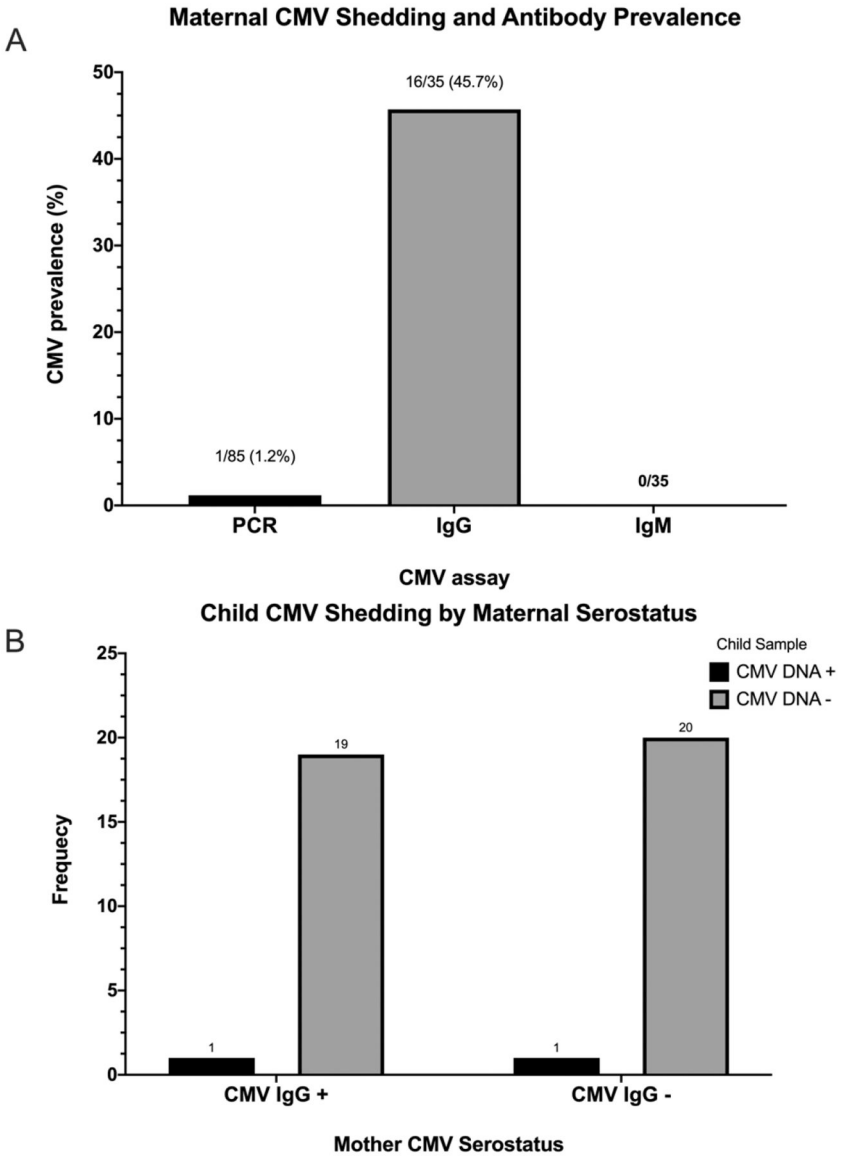

Figure 2:

A) Maternal CMV saliva shedding and antibody prevalence. CMV DNA was detected in 1/85 (1.2%) of swab samples from participating mothers. Thirty-five mothers agreed to provide a finger-stick to test for anti-CMV IgG and IgM antibodies. Of these 35 mothers, 16 (45.7%) tested positive for CMV IgG antibodies and none had detectable CMV IgM antibodies (0/35). **B) Child CMV saliva shedding prevalence by maternal CMV serostatus.** Of the 35 mothers who had a documented CMV serostatus, 6 mothers had two children (17.1%) and 29 (82.9%) had one child tested for CMV shedding in saliva. The prevalence of CMV DNA in saliva samples among children whose mothers were CMV IgG positive was 1/20 (5.0%) compared to 1/21 (4.8%) for children of seronegative mothers (p=1.0).

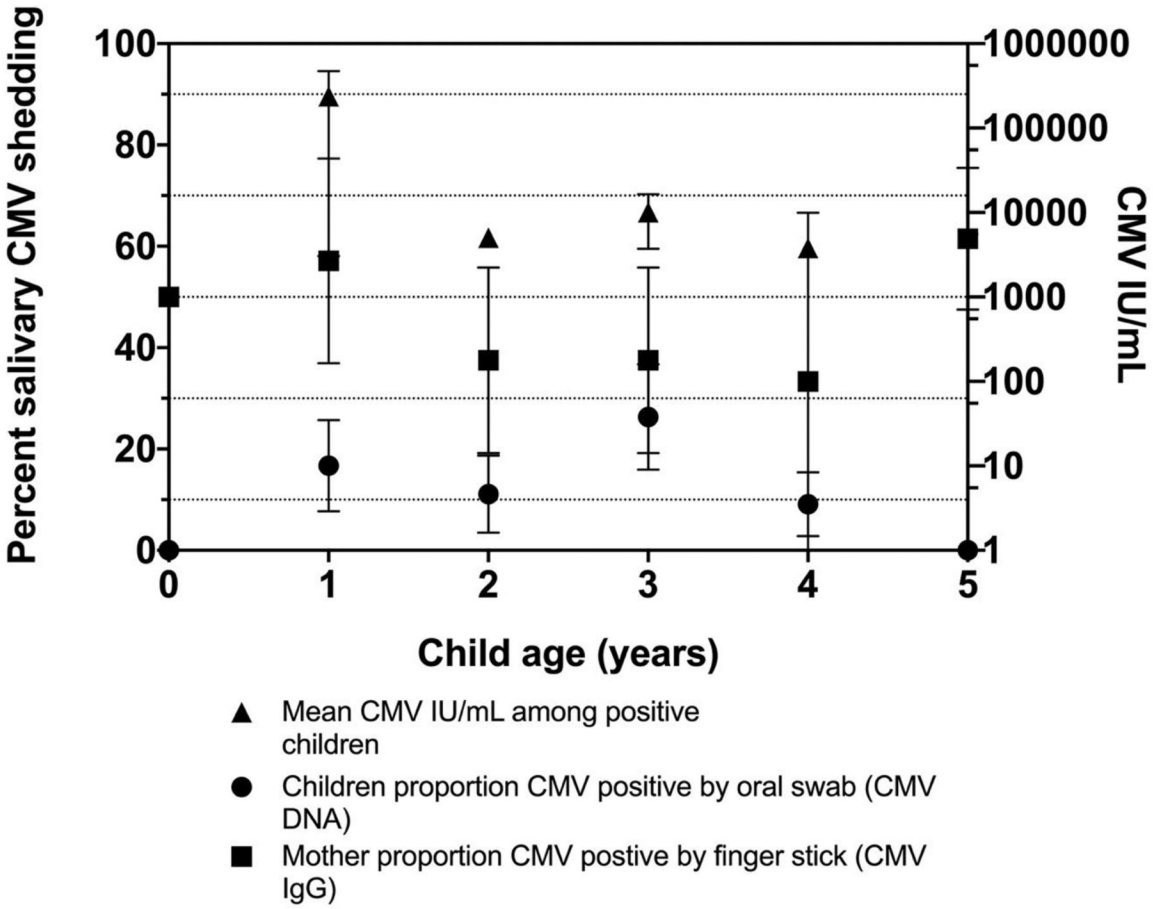

Figure 3: CMV prevalence of children and mothers by child's age.

The proportion of children shedding CMV in saliva is shown in solid circles. Mean CMV IU/mL among children are shown in triangles. The percentage of mothers that were CMV IgG positive is shown in solid squares and plotted against their child's age. Mothers who had more than one child in the study are reflected in more than one age category.

		Younger Sibling		
		POS	**NEG**	**TOTAL**
Older Sibling	**POS**	1	1	2
	NEG	3	18	21
	TOTAL	4	19	23

Kappa: 0.25 (SE = 0.19)

Agreement: 82.6%

p = 0.102

Figure 4: Concordance of CMV DNA Detection in Siblings.

CMV DNA status was compared in 23 siblings. Cohen's Kappa statistic and percent agreement was calculated for concordance of CMV prevalence.

Table 1:

Study population characteristics by age group

		Age group (years)					
Characteristics	**All Children**	**0**	**1**	**2**	**3**	**4**	**5**
n (%)	109	5 (4.6%)	18 (16.5%)	18 (16.5%)	19 (17.4%)	22 (20.2%)	27 (24.8%)
Birth order (%)							
Older/Only	86 (78.9%)	4 (80.0%)	12 (66.7%)	13 (72.2%)	12 (63.2%)	19 (86.4%)	26 (96.3%)
Younger	23 (21.1%)	1 (20.0%)	6 (33.3%)	5 (27.8%)	7 (36.8%)	3 (13.6%)	1 (3.7%)
Gender (%)							
Female	58 (53.2%)	4 (80.0%)	8 (44.4%)	11 (61.1%)	8 (42.1%)	13 (59.1%)	14 (51.9%)
Male	51 (46.8%)	1 (20.0%)	10 (55.6%)	7 (38.9%)	11 (57.9%)	9 (40.9%)	13 (48.1%)
Race/ethnicity (%)							
White	86 (78.9%)	5 (100%)	15 (83.3%)	18 (100%)	12 (63.2%)	18 (81.8%)	18 (66.7%)
Black	4 (3.7%)	0	1 (5.6%)	0	1 (5.3%)	1 (4.6%)	1 (3.7%)
Hispanic/Latino	11 (10.1%)	0	1 (5.6%)	0	3 (15.8%)	1 (4.6%)	6 (22.2%)
Asian	6 (5.5%)	0	0	0	3 (15.8%)	1 (4.6%)	2 (7.4%)
American Indian/Alaskan Native	2 (1.8%)	0	1 (5.6%)	0	0	1 (4.6%)	0
Breastfed (%)							
Yes	97 (89.0%)	5 (100%)	15 (83.3%)	17 (94.4%)	17 (89.5%)	21 (95.5%)	22 (81.5%)
No	12 (11.0%)	0	3 (16.7%)	1 (5.6%)	2 (10.5%)	1 (4.6%)	5 (18.5%)
Mean time breastfed, months (SE)	9.6 (0.6)	5.7 (1.8)	9.5 (1.2)	10.1 (1.3)	9.2 (1.3)	10.8 (1.5)	8.7 (1.1)
Daycare attendance (%)							
Yes	81 (74.3%)	0	8 (44.4%)	14 (77.8%)	17 (89.5%)	17 (77.3%)	25 (92.6%)
No	28 (25.7%)	5 (100%)	10 (55.6%)	4 (22.2%)	2 (10.5%)	5 (22.7%)	2 (7.4%)
Mean time in daycare, months (SE)	28.7 (2.1)	-	11.0 (3.1)	14.9 (1.9)	25.7 (3.4)	36.3 (3.3)	39.8 (4.5)

Table 2:

Detection of CMV DNA by qPCR in children's swab samples

	PCR		
Characteristic	**CMV +**	**CMV −**	**p value[a]**
n (%)	12 (11.0%)	97 (89.0%)	
Mean CMV IU/mL (SE)	83,091 (77,626)	-	
Female (%)	5 (41.7%)	53 (54.6%)	0.4
Mean age (SE)	2.5 (0.31)	3.1 (1.6)	0.19
Birth order (%)			0.28
Older	8 (66.7%)	78 (80.4%)	
Younger	4 (33.3%)	19 (19.6%)	
Race/ethnicity (%)			0.78
White	10 (83.3%)	76 (78.4%)	
Black	1 (8.3%)	3 (3.1%)	
Hispanic/Latino	1 (8.3%)	10 (10.3%)	
Asian	0	6 (6.2%)	
American Indian/Alaskan Native	0	2 (2.1%)	
Breastfed (%)	12 (100%)	85 (87.6%)	0.35
Breastfed duration, months (SE)[b]	10.6 (1.5)	9.4 (0.62)	0.51
Daycare attendance (%)	10 (83.3%)	71 (73.2%)	0.73
Daycare enrollment, months (SE)[b]	23.4 (5.5)	29.3 (2.3)	0.42

[a] P value of $p<0.05$ considered significant. Comparisons made using Fisher exact test for categorical variables and one-way analysis of variance for continuous variables.

[b] Duration of breastfeeding for those breastfed; duration of daycare for those who attended.