Breast Milk–Acquired Cytomegalovirus Infection and Disease in VLBW and Premature Infants

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**KEY WORDS**
breast milk, cytomegalovirus, premature infant, very low birth weight infant, sepsis-like syndrome

**ABBREVIATIONS**
CI—confidence interval
CMV—cytomegalovirus
SLS—sepsis-like syndrome
VLBW—very low birth weight

Dr Lanzieri conceptualized and designed the study, reviewed the literature and carried out the analyses and interpretation of data, and drafted the initial manuscript; Dr Dollard assisted with conceptualizing the systematic review and interpreting the findings of the systematic review and meta-analysis, and critically revised the manuscript; Dr Josephson assisted with interpreting the findings of the systematic review and meta-analysis and critically revised the manuscript; Dr Schmid assisted with conceptualizing the systematic review, interpreting the findings of the systematic review and meta-analysis, and critically revised the manuscript; Dr Bialek conceptualized and designed the study, interpreted the findings of the systematic review and meta-analysis, and critically revised the manuscript; and all authors approved the final manuscript as submitted.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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**abstract**

**BACKGROUND:** Very low birth weight (VLBW) and premature infants are at risk for developing postnatal cytomegalovirus (CMV) disease, including CMV-related sepsis-like syndrome (CMV-SLS) for which in the United States are lacking.

**METHODS:** We performed a systematic review and meta-analysis to estimate the pooled proportions (and 95% confidence intervals) of VLBW and premature infants born to CMV-seropositive women with breast milk–acquired CMV infection and CMV-SLS. We combined these proportions with population-based rates of CMV seropositivity, breast milk feeding, VLBW, and prematurity to estimate annual rates of breast milk–acquired CMV infection and CMV-SLS in the United States.

**RESULTS:** In our meta-analysis, among 299 infants fed untreated breast milk, we estimated 19% (11%–32%) acquired CMV infection and 4% (2%–7%) developed CMV-SLS. Assuming these proportions, we estimated a rate of breast milk–acquired CMV infection among VLBW and premature infants in the United States of 6.5% (3.7%–10.9%) and 1.4% (0.7%–2.4%) of CMV-SLS, corresponding to 600 infants with CMV-SLS in 2008. Among 212 infants fed frozen breast milk, our meta-analysis proportions were 13% (7%–24%) for infection and 5% (2%–12%) for CMV-SLS, yielding slightly lower rates of breast milk–acquired CMV infection (4.4%; 2.4%–8.2%) but similar rates of CMV-SLS (1.7%; 0.7%–4.1%).

**CONCLUSIONS:** Breast milk–acquired CMV infection presenting with CMV-SLS is relatively rare. Prospective studies to better define the burden of disease are needed to refine guidelines for feeding breast milk from CMV-seropositive mothers to VLBW and premature infants.

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Cytomegalovirus (CMV) may be transmitted in utero as a result of primary maternal infection or recurrent infection resulting from reinfection with a new CMV strain or reactivation of latent virus. CMV may also be acquired perinatally via exposure to infected maternal genital secretions during delivery, or postnately by blood transfusion or infected breast milk. CMV disease caused by postnatally acquired infection is uncommon in full-term infants, presumably because of protection from passive transfer of maternal antibodies that occur mostly in the third trimester, and the infant’s more mature immune system. However, infants born at <32 weeks’ gestational age or with a birth weight <1500 g may be at higher risk of developing symptomatic postnatal CMV disease, characterized by hepatopathy, thrombocytopenia, neutropenia, petechiae, respiratory distress syndrome, and sepsis-like syndrome.

Breastfeeding is a common route for CMV transmission, particularly in populations with high CMV seroprevalence and high rates of breastfeeding. CMV is commonly excreted in breast milk from seropositive women, beginning during the first week postpartum, peaking at 4 to 8 weeks after delivery, and declining steadily thereafter. Infectious virus and CMV DNA and RNA have been isolated from cell-associated and whey fractions in the breast milk of 40% to 97% of CMV-associated and whey fractions in the RNA have been isolated from cell-infected virus and CMV DNA and RNA have been isolated from cell lines, expert opinions, multiple reports from the same population, and acquired CMV infection postnatally.

We conducted a systematic review and meta-analysis of studies reporting on postnatal CMV infection and disease presumably acquired via consumption of breast milk among very low birth weight (VLBW) and premature infants born to CMV-seropositive women but uninfected at birth. We applied the results of our meta-analysis to US population-based data to estimate the annual rates in the United States of 3 outcomes: breast milk–acquired CMV infection, CMV-related symptoms, and CMV-related sepsis-like syndrome (CMV-SLS).

METHODS

Systematic Review

Studies published in English, French, Spanish, or Portuguese with no restriction on publication date were identified by searching Web of Science, PubMed, OVID/Medline, and Embase databases, using the following keywords and variations: breast feeding or breast milk, premature or preterm, low birth weight or very low birth weight infants, cytomegalovirus or CMV, postnatal CMV infection, breast milk–acquired CMV infection. We included original studies providing data on postnatal CMV infection in VLBW and premature infants born to CMV-seropositive mothers, presumably acquired via consumption of untreated, frozen, or pasteurized breast milk. We also included additional studies found in the references of studies identified during the literature search that were not among our search results. We excluded reviews, guidelines, expert opinions, multiple reports from the same authors reporting results from the same population, studies of non-VLBW infants, and case reports.

We reviewed each study for the following information: assessment of maternal CMV serological status; infant inclusion criteria (weight and gestational age at birth); infant exclusion criteria (methods for diagnosing congenital CMV infection); methods for diagnosing postnatal CMV infection among infants; breast milk handling process (pasteurization, freezing, no treatment); numbers of infants who acquired postnatal CMV infection and developed CMV-related symptoms or CMV-SLS born to and fed breast milk from CMV-seropositive mothers; infants’ birth weight and corrected gestational age at onset of CMV viruria; measures taken to prevent or identify CMV transmission from blood transfusion; and administration of prophylactic immunoglobulin (Ig). The risk of bias of individual studies was assessed by evaluating the study population (inclusion and exclusion criteria) and possible CMV transmission by means other than breast milk (eg, blood transfusion).

Meta-analysis

We included studies that reported the number of infants born to CMV-seropositive mothers, defined by assessment of maternal serological status, who were uninfected at birth (ie, congenital CMV infection was excluded) and acquired CMV infection postnatally. Congenital CMV infection was defined as a positive viral culture, shell vial assay or CMV-DNA test in cord blood or urine within the first 3 weeks of life. Postnatal CMV infection was defined as a positive viral culture, shell vial assay, or CMV-DNA test in urine not earlier than after 2 weeks of life when previous results were negative. We defined CMV-related symptoms as any of the following: neutropenia, thrombocytopenia, petechiae, hepatopathy, hyperbilirubinemia, elevated liver enzymes, jaundice, or CMV pneumonia; and CMV-SLS as sepsis-like symptoms, such as...
bradycardia, apnea, or respiratory deterioration, in the absence of bacterial infection and coincident with CMV viruria.

We grouped studies or subgroups within studies by infants who were fed (1) untreated breast milk; (2) frozen breast milk; or (3) combinations of untreated, frozen, or pasteurized breast milk, or unspecified. We ran separate meta-analyses for each of these 3 groups and estimated the pooled proportions (and 95% confidence intervals [CIs]) of infants born to CMV-seropositive mothers who acquired CMV infection, developed CMV-related symptoms, or CMV-SLS. We used random effects (DerSimonian-Laird) models for the meta-analyses, which accounts for heterogeneity across studies by minimizing 2 sources of variance in measuring the true prevalence: within-study errors and variation across studies. We calculated the $I^2$ statistic to assess the heterogeneity across the studies. To assess the robustness of the meta-analysis results, we performed a sensitivity analysis that included only the studies that attempted to rule out CMV infection acquired through transfused blood products and studies that attempted to prevent such transmission by using CMV seronegative or leukocyte-reduced blood products. All meta-analyses were done using Comprehensive Meta-Analysis version 2.2.064 (Biostat, Englewood, NJ).

**Estimated Rates of Breast Milk–Acquired CMV Infection and Disease in the United States**

To estimate annual rates of breast milk–acquired CMV infection, CMV-related symptoms, and CMV-SLS in the United States, we used the pooled estimated proportions of these 3 outcomes from our meta-analyses with population-based data, which accounted for differences in CMV seropositivity, breast milk feeding, and VLBW and prematurity rates by maternal age and race/ethnicity in the United States. We used the following formula: $Z_{i} = (1 - \alpha)\beta P_{i}$ weighted by the proportion of VLBW and premature infants by maternal age and race/ethnicity, where $\alpha$ is the birth prevalence of congenital CMV infection by maternal age and race/ethnicity, $\beta$ is the age- and race/ethnicity-specific CMV seropositivity proportion among women, $\mu$ is the breast milk feeding rate, and $P_{i}$ is the meta-analysis pooled estimated proportions (and 95% CI) for each of the 3 outcomes stated previously, for infants fed (1) untreated breast milk, (2) frozen breast milk; or (3) combinations of untreated, frozen, or pasteurized breast milk or unspecified. For US estimates of congenital CMV birth prevalence and CMV seropositivity among women, we used published data based on the third US National Health and Nutrition Examination Survey. For breast milk feeding rates, we used published data on breast milk feeding from the California Perinatal Quality Care Collaborative, which includes data on >90% of NICUs in California. Because rates of breast milk feeding stratified by maternal age and race/ethnicity together were not available, we had to develop 2 separate models. Model 1 accounted for breast milk feeding rates by maternal race/ethnicity and model 2, by maternal age. We then applied each of our estimated rates to the number of US infants born annually with birth weight <1500 g and gestational age <32 weeks, based on 2008 national vital statistics data.

**RESULTS**

**Systematic Review**

Of a total of 67 unique citations from 1980 to 2011, 50 (78%) were excluded. Excluded citations included 13 case reports; 12 reviews, guidelines, or expert opinions; 10 studies assessing prevalence of perinatal infection or CMV transmission in non-VLBW infants; 6 reports from overlapping populations; and 9 studies unrelated to the scope of this review, including animal models and laboratory studies. The 17 studies included in this review were published from 2001 to 2011 (Table 1). Nine studies were conducted in Europe (Germany, Italy, France, United Kingdom, and Sweden), 4 in Asia (Japan and Taiwan), 2 in North America (Canada and United States), 1 in South America (Brazil), and 1 in the Middle East (Israel). All studies assessed maternal serological status by detection of CMV antibodies at delivery or up to 1 week postpartum. Mothers were tested for IgG and IgM antibodies in 9 studies and for IgG antibodies in 4 studies. 4 studies did not report which serological tests were performed.

Studies varied regarding infant inclusion criteria, more commonly specifying a birth weight cutoff of <1500 g (7 studies) or gestational age <32 weeks (6 studies) (Table 1). Infants with congenital CMV infection were excluded in all studies based on positive viral culture or CMV-DNA test in cord blood or urine within the first 3 weeks of life. Among infants who were uninfected at birth, postnatal CMV infection was determined through collection of infants’ urine weekly, biweekly, or monthly until 8 to 12 weeks of age, and analysis by polymerase chain reaction or shell vial assay. Of the 17 studies, 5 included infants fed with untreated breast milk, 6 included infants fed breast milk that was frozen at temperatures of $18^\circ C$ to $-20^\circ C$ for >24 hours or 72 hours, 5 included infants fed untreated breast milk in combination with frozen breast milk and/or pasteurized breast milk from donors, and in 1 study it was unclear whether the infants were given untreated or treated milk.
<table>
<thead>
<tr>
<th>Study, by Year of Publication, Country</th>
<th>Methods: Inclusion Criteria</th>
<th>Infants Fed Breast Milk From CMV-Seropositive Mothers</th>
<th>Infants With Breast Milk-Acquired CMV Infection</th>
<th>Infants With CMV-Related Symptoms&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Infants With CMV-SLS&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>Hämpechrt, 2001, Germany&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Birth Weight, g, Gestational Age, wk</td>
<td>Infants Fed Study, by Year of Publication, Country</td>
<td>$n$</td>
<td>$n$ (%)</td>
<td>Onset of CMV Viruria</td>
</tr>
<tr>
<td>Mussi-Pinhata, 2004, Brazil (Subgroup)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>$&lt; 1500$ or $&lt; 32$</td>
<td>90</td>
<td>33 (37)</td>
<td>55.5 (27–120)</td>
<td>34.5 (28.3–47.1)</td>
</tr>
<tr>
<td>Meier, 2005, Germany&lt;sup&gt;9&lt;/sup&gt;</td>
<td>$≤ 2010$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>21</td>
<td>5 (24)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Miron, 2005, Israel&lt;sup&gt;10&lt;/sup&gt;</td>
<td>$&lt; 1500$ or $&lt; 32$</td>
<td>7</td>
<td>1 (14)</td>
<td>53</td>
<td>36.8</td>
</tr>
<tr>
<td>Croly-Labordette, 2006, France&lt;sup&gt;11&lt;/sup&gt;</td>
<td>$&lt; 1500$ and $&lt; 32$</td>
<td>62</td>
<td>9 (15)</td>
<td>51 (35–80)</td>
<td>36.1 (31–41.4)</td>
</tr>
<tr>
<td>Capretti, 2009, Italy&lt;sup&gt;12&lt;/sup&gt;</td>
<td>$&lt; 1200$ or $&lt; 34$</td>
<td>34</td>
<td>3 (9)</td>
<td>54 (42–84)</td>
<td>33.3 (33.1–39.7)</td>
</tr>
<tr>
<td>Jim, 2004, Taiwan&lt;sup&gt;13&lt;/sup&gt;</td>
<td>$&lt; 1500$ and $&lt; 35$</td>
<td>40</td>
<td>6 (15)</td>
<td>77° (21–168)</td>
<td>NA</td>
</tr>
<tr>
<td>Lee, 2007, United States&lt;sup&gt;14&lt;/sup&gt;</td>
<td>$&lt; 1500$ or $&lt; 32$</td>
<td>23</td>
<td>2 (9)</td>
<td>40.5 (37–44)</td>
<td>33.1 (29.3–33.1)</td>
</tr>
<tr>
<td>Jim, 2009, Taiwan&lt;sup&gt;15&lt;/sup&gt;</td>
<td>$&lt; 1500$ and $&lt; 35$</td>
<td>23</td>
<td>8 (35)</td>
<td>63° (SD = 2.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Buxmann, 2009, Germany&lt;sup&gt;16&lt;/sup&gt;</td>
<td>$&lt; 1710$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35</td>
<td>5 (14)</td>
<td>73 (43–89)</td>
<td>35.7 (32–39.6)</td>
</tr>
<tr>
<td>Chiavarini, 2011, Italy&lt;sup&gt;17&lt;/sup&gt;</td>
<td>$&lt; 2000$ or $&lt; 32$</td>
<td>57</td>
<td>1 (2)</td>
<td>47</td>
<td>35.1</td>
</tr>
<tr>
<td>Overall (n)</td>
<td>$&lt; 1200$ or $&lt; 33$</td>
<td>212</td>
<td>26</td>
<td>77</td>
<td>19 (11–32)</td>
</tr>
<tr>
<td>Pooled proportion from meta-analysis, % (95% CI)</td>
<td>$&lt; 1200$ or $&lt; 33$</td>
<td>77</td>
<td>29</td>
<td>50</td>
<td>4 (2–77)</td>
</tr>
<tr>
<td>Combined</td>
<td>$&lt; 1200$ or $&lt; 33$</td>
<td>13</td>
<td>8</td>
<td>37</td>
<td>67</td>
</tr>
<tr>
<td>Mosca, 2001, Italy&lt;sup&gt;18&lt;/sup&gt;</td>
<td>$≤ 1380$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>30</td>
<td>5 (17)</td>
<td>34 (NA)</td>
<td>NA</td>
</tr>
<tr>
<td>Sharland, 2002, United Kingdom&lt;sup&gt;19&lt;/sup&gt;</td>
<td>$&lt; 32$</td>
<td>18</td>
<td>1 (6)</td>
<td>62</td>
<td>32.9</td>
</tr>
<tr>
<td>Mussi-Pinhata, 2004, Brazil (subgroup)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>$&lt; 1500$ or $&lt; 34$</td>
<td>46</td>
<td>8 (17)</td>
<td>75 (32–140)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Doctor, 2005, Canada&lt;sup&gt;20&lt;/sup&gt;</td>
<td>$&lt; 1000$ or $&lt; 28$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>61</td>
<td>4 (7)</td>
<td>48–72</td>
<td>NA</td>
</tr>
<tr>
<td>Omarsdottir, 2007, Sweden&lt;sup&gt;21&lt;/sup&gt;</td>
<td>$≤ 1166$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7</td>
<td>2 (28)</td>
<td>34–46</td>
<td>31.3 (29.1–33.4)</td>
</tr>
<tr>
<td>Hayashi, 2011, Japan&lt;sup&gt;22&lt;/sup&gt;</td>
<td>$&lt; 1000$ or $&lt; 28$</td>
<td>22</td>
<td>1 (5)</td>
<td>70</td>
<td>36.7</td>
</tr>
<tr>
<td>Overall (n)</td>
<td>$&lt; 1000$ or $&lt; 28$</td>
<td>184</td>
<td>21</td>
<td>4</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pooled proportion from meta-analysis, % (95% CI)</td>
<td>$&lt; 1000$ or $&lt; 28$</td>
<td>3 (1–8)</td>
<td>3 (1–7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA, not available.</td>
<td></td>
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<tr>
<td>&lt;sup&gt;a&lt;/sup&gt;CMV-related symptoms defined as any of the following: neutropenia, thrombocytopenia, petechiae, hepatopathy, hyperbilirubinemia, elevated liver enzymes, jaundice, or CMV pneumonia.</td>
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<tr>
<td>&lt;sup&gt;b&lt;/sup&gt;CMV-SLS defined as sepsis-like symptoms, such as bradycardia, apnea, or respiratory deterioration, in the absence of bacterial infection and coincident with CMV viruria.</td>
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<tr>
<td>&lt;sup&gt;c&lt;/sup&gt;The observed upper end of the birth weight and/or gestational age shown for studies that used only 1 criterion or none.</td>
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<tr>
<td>&lt;sup&gt;d&lt;/sup&gt;Median and range reported for all study infants, not just those shown in this category of breast milk.</td>
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</table>
Overall, 695 infants born to and fed breast milk from CMV-seropositive mothers were identified in the 17 studies, with a median of 38 infants per study (range: 7–90) (Table 1). The reported proportions of infants with breast milk–acquired CMV infection varied from 2% to 37%; those who developed CMV-related symptoms and CMV-SLS varied from 0% to 10% to 14%, respectively.

The median time to first detection or onset of CMV viruria was 50 days (range: 27–120) among the 42 infants in the 8 studies that reported individual data. The study by Jim et al had the widest range in the time to first detection of CMV viruria, 21 to 168 days. In 11 studies, corrected gestational age at onset of CMV viruria was reported or could be calculated: among 45 infants with breast milk–acquired CMV infection, 34 (75%) had onset of CMV viruria between 28 and 37 weeks corrected age and 11 (25%) at age >37 weeks. Among 19 infants who developed CMV-SLS, 8 (32%) had onset of CMV viruria at <32 weeks corrected age, 4 (21%) between 33 and 36 weeks, and 9 at unknown corrected age.

Three of 17 studies attempted to determine CMV viral load in breast milk and its association with transmission. In the study by Yamasuda et al., the maximum viral load in breast milk from mothers of 12 uninfected infants was higher than that from mothers of 3 infected infants. The study by Jim et al. found that at weeks postpartum, viral load in breast milk from mothers of 8 infected infants was significantly higher than that of mothers of 15 uninfected infants. The study by Omarsdottir et al. found only 2 infected infants among 7 included. The numbers were too small to assess a possible association between viral load in breast milk and either transmission or disease.

Fourteen of the 17 studies included information on the use of blood products, but most did not present data on the number of infants who received blood products. We found that the number of transfusions can be high: Hayashi et al. reported that 20 of 27 infants (22 born to CMV-seropositive mothers and 5 to CMV-seronegative mothers) required a median of 2 (range = 1–8) red blood cell transfusions, and 1 infant required a platelet transfusion. One of the 17 studies excluded infants who had received transfusion of blood products. In 10 studies, investigators reported the measures used to prevent CMV transmission from transfused blood products in their institutions, which included transfusion of CMV-IgG seronegative blood products in 5 studies, use of leukocyte-depleted blood products in 5 studies, and both in 1 study. In 3 studies, actual samples of blood products administered to infants were tested as part of the study for CMV-DNA and all were negative. In 1 study, γ-irradiated blood of unknown CMV status was used, although this method does not inactivate CMV and may even increase CMV replication in latently infected cells. Three studies did not mention any attempt to prevent or identify CMV transmission through transfused blood products. In 2 studies, infants were prophylactically treated with intravenous Ig.

Meta-analysis

Among the 695 infants, 299 were fed untreated breast milk, 212 infants were fed frozen breast milk, and 184 were fed combinations of untreated, frozen, or pasteurized breast milk or unspecified. Among infants who were fed untreated breast milk, 19% (95% CI 11%–32%) acquired CMV infection, 10% (95% CI 5%–17%) developed CMV-related symptoms and 4% (95% CI 2%–7%) developed CMV-SLS. Among infants who were fed frozen breast milk, 13% (95% CI 7%–24%) acquired CMV infection, 7% (95% CI 3%–14%) developed CMV-related symptoms, and 5% (95% CI 2%–12%) developed CMV-SLS. In the 1 available US study included in the meta-analysis, a lower proportion of infants born to CMV-seropositive mothers who received frozen breast milk acquired infection (9%) and developed CMV-related symptoms (4%), estimates that are within our observed ranges, none had CMV-SLS. Among infants who were fed combinations of untreated and frozen or pasteurized breast milk or nonspecified, 13% (95% CI 7%–20%) acquired CMV infection, 3% (95% CI 1%–8%) developed CMV-related symptoms, and 3% (95% CI 1%–7%) developed CMV-SLS. The I² values for each of the meta-analyses for CMV infection and CMV-related symptoms varied widely, indicating considerable heterogeneity of the studies, but was low for CMV-SLS (Table 1).

Results of the sensitivity analysis limited to the 13 studies that ruled out CMV infection through transfused blood products or that attempted to prevent such by using CMV seronegative or leukocyte-reduced blood products yielded results with CIs that overlapped with those from the meta-analysis that included all studies (online Supplemental Information).

Estimated Rates of Breast Milk–Acquired CMV Infection and Disease in the United States, 2008

We combined the results of the meta-analysis with US population-based data (online Supplemental Information) to derive estimates of breast milk–acquired CMV infection and disease in the United States. Adjusting for breast milk feeding rates by maternal race/ethnicity, our estimated rates from model 1 assuming the meta-analysis results for the group of infants fed untreated milk were 6.5% (95% CI 3.7%–10.9%) for breast milk–acquired CMV infection, 3.4% (95% CI 1.7%–5.8%) for...
CMV-related symptoms, and 1.4% (95% CI 0.7%–2.4%) for CMV-SLS (Table 2). These correspond to ~2800 infants with breast milk–acquired CMV infection, 1500 with CMV-related symptoms, and 800 with CMV-SLS in the United States in 2008, as a result of exposure to untreated breast milk (Fig 1). Point estimates for rates of breast milk–acquired CMV infection and CMV-related symptoms were lower assuming the meta-analysis results for the group of infants fed frozen milk, but the confidence limits overlapped the point estimates for the group fed untreated milk. Based on these estimates, 1900, 1000, and 700 infants acquired CMV infection, and developed CMV-related symptoms and CMV-SLS in the United States in 2008, as a result of exposure to frozen breast milk. Rates of breast milk–acquired CMV infection assuming the meta-analysis results for the group of infants fed combinations of untreated, frozen, or pasteurized milk or infants fed combinations of untreated and CMV-SLS were lower. These corresponded to an estimated 1900 infants with breast milk–acquired CMV infection, 400 with CMV-related symptoms, and 400 with CMV-SLS in 2008. Point estimates for the 3 outcomes based on model 2 adjusted for breast milk feeding rates by maternal age were slightly higher than those from model 1.

### DISCUSSION

According to our estimates, 0.3% to 4.5% of VLBW and premature infants in the United States may develop CMV-SLS from breast milk–acquired CMV infection, resulting in up to ~2000 affected VLBW and premature infants in 2008. If all VLBW and premature infants were fed fresh breast milk, as recently recommended by the American Academy of Pediatrics,18 we estimate the rate of CMV-SLS from breast milk–acquired CMV infection would be ~2.5% (95% CI 1.3%–4.4%). Although breast milk provides many benefits to VLBW and premature infants, those fed breast milk from CMV-seropositive mothers are at risk for postnatal CMV infection, in a minority of whom CMV-SLS may result, which has been associated with longer hospitalizations during infancy.9,13,28,33

Our understanding of the degree to which freezing breast milk is effective for reducing CMV infection and disease in VLBW and premature infants is incomplete. Although freezing breast milk is known to decrease viral titer, it has not been shown to reliably eliminate CMV completely.34,35 Our meta-analysis suggests that the risk of breast milk–acquired CMV infection is lower if infants are fed frozen breast milk compared with untreated breast milk, but the risk of developing CMV-SLS appears to be similar in both groups, a finding that persisted after exclusion of studies that failed to fully rule out CMV transmission from blood transfusion.13–15,25 Nonetheless, some caveats need to be considered. Many of the studies we identified in the literature review had small numbers of participants or lacked control groups (ie, did not directly compare feeding of untreated versus treated breast milk). Most of the studies were conducted in other countries, where clinical practice, infection control measures, and transmission patterns might be different from those in the United States. Although some studies did not fully control for other sources of postnatal CMV infection, such as transfusion of blood products, based on our sensitivity analysis, this did not affect the direction of our findings. Also, the effectiveness of freezing to inactivate CMV may vary by storage temperature and length of time frozen; there were differences in freezing practices across studies included in our meta-analysis. Accurate categorization of exposure to untreated breast milk can be challenging; it is possible that some infants categorized as having received frozen milk had some exposures to untreated milk. These and other factors contributed to the lack of precision in our estimates for CMV infection and disease among infants who received untreated versus frozen breast milk.

Our review highlights the need for more robust studies of breast milk–acquired CMV infection and disease, particularly in the United States. The 1 US study included in the meta-analyses was conducted in a hospital in California.

### TABLE 2

<table>
<thead>
<tr>
<th>Breast Milk</th>
<th>Breast Milk–Acquired CMV Infection % (95% CI)</th>
<th>CMV-Related Symptomsa % (95% CI)</th>
<th>CMV-SLSb % (95% CI)</th>
</tr>
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<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Untreated</td>
<td>6.5 (3.7–10.9)</td>
<td>3.4 (1.7–5.8)</td>
<td>1.4 (0.7–2.4)</td>
</tr>
<tr>
<td>Frozen</td>
<td>4.4 (2.4–6.2)</td>
<td>2.4 (1.0–4.8)</td>
<td>1.7 (0.7–4.1)</td>
</tr>
<tr>
<td>Mix</td>
<td>4.4 (2.4–6.8)</td>
<td>1.0 (0.3–2.7)</td>
<td>1.0 (0.3–2.4)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>7.2 (4.1–12.0)</td>
<td>3.8 (1.9–6.4)</td>
<td>1.5 (0.8–2.6)</td>
</tr>
<tr>
<td>Frozen</td>
<td>4.9 (2.9–7.0)</td>
<td>2.6 (1.1–5.3)</td>
<td>1.9 (0.8–4.5)</td>
</tr>
<tr>
<td>Mix</td>
<td>4.9 (2.6–7.5)</td>
<td>1.1 (0.4–3.0)</td>
<td>1.1 (0.4–2.6)</td>
</tr>
</tbody>
</table>

a CMV-related symptoms defined as any of the following: neutropenia, thrombocytopenia, petechiae, hepatopathy, hyperbilirubinemia, elevated liver enzymes, jaundice, or CMV pneumonia.

b CMV-SLS defined as sepsis-like symptoms, such as bradycardia, apnea, or respiratory deterioration, in the absence of bacterial infection and coincident with CMV viruria.
where maternal milk is frozen at 20°C for at least 24 hours before feeding and fresh breast milk is not allowed until the infant is able to feed at the breast. Among 23 VLBW and premature infants who had CMV-seropositive mothers, 2 (9%) acquired CMV infection and 1 (4%) developed CMV-related symptoms coincident with the first positive test, but none had CMV-SLS.27 In contrast, in a US study excluded from our review because it did not report data on the number of infants fed breast milk from CMV-seropositive mothers, investigators found a 15% (5/33) rate of CMV-SLS among infants with birth weight <1100 g and gestational age <28 weeks,36 which was much higher than our final estimates (1.0%–2.6%). In that study, all infected infants were fed untreated breast milk and had onset of CMV viremia or viruria between 35 and 60 days of life, corresponding to 30.4 to 33.7 weeks corrected age for gestation. It is possible that the population in the study we excluded, composed of extremely premature infants with early postnatal virus transmission, was at higher risk of developing CMV-SLS.37 These 2 studies also suggest that current practices regarding use of breast milk in NICUs in the United States may vary substantially across NICUs.

To estimate annual rates of breast milk–acquired CMV infection and disease in the United States, we combined the results of the meta-analysis with US population-based data. The meta-analysis included data from studies conducted in different countries, but restricted to infants born to CMV-seropositive mothers. Rates of CMV excretion in breast milk may not differ substantially among CMV-seropositive women across populations; however, detection rates could vary depending on laboratory methods used across studies to detect virolactia (17%–58% with viral culture)11,13,14 or DNAlactia (67%–97% for polymerase chain reaction),8,9,12–14,16,17 timing of sample collection, and storage. Nonetheless, rates of breast milk–acquired CMV infection and disease may vary widely across populations depending on population-specific rates of CMV seropositivity, breast milk feeding, VLBW, and prematurity. Among the data we used to estimate these rates for the United States, the breast milk feeding rates likely contribute the most uncertainty, because they vary depending on the medical condition of the infant (ie, infants with serious medical conditions are less likely to be fed breast milk)23,38,39 and sociodemographic factors, such as maternal race/ethnicity, age, education level, and family income.40 In addition, little is known about breast milk handling and feeding practices for VLBW and premature infants or infection control policies in place to prevent CMV transmission in US NICUs. Monitoring these practices nationally is critical for understanding the burden of postnatal CMV disease among VLBW and premature infants.

Although an assessment of risk factors for CMV infection and disease was not a goal of our systematic review, we found some valuable data. Most infants who developed CMV-SLS from breast milk–acquired CMV infection had onset of CMV viruria before 32 weeks corrected gestational age. The study by Maschmann et al,37 which comprised the same population as the study by Hamprecht et al8 included in our review, found that lower birth weight and early CMV infection had onset of CMV viruria before 32 weeks corrected gestational age. The study by Maschmann et al,37 which comprised the same population as the study by Hamprecht et al8 included in our review, found that lower birth weight and early CMV infection had onset of CMV viruria before 32 weeks corrected gestational age. The study by Maschmann et al,37 which comprised the same population as the study by Hamprecht et al8 included in our review, found that lower birth weight and early CMV infection had onset of CMV viruria before 32 weeks corrected gestational age.
providing substantial nutritional and breast milk is the optimal food for these infants.

Breast milk from CMV-seropositive mothers to mature infants, breast milk feeding is prolonged viral excretion in breast milk, and higher milk whey viral loads. These may suggest that treating breast milk from CMV-seropositive mothers would be necessary only until the infant reaches a certain age or birth weight, after which the risk of symptomatic disease decreases. A better understanding of risk factors for CMV-SLS in VLBW and premature infants may help refining guidelines for feeding breast milk from CMV-seropositive mothers to these infants.

Breast milk is the optimal food for infants, including premature infants, providing substantial nutritional and immunologic benefits. Among premature infants, breast milk feeding is associated with improved neurodevelopmental outcomes and a lower risk of retinopathy of prematurity, infections, and necrotizing enterocolitis. These benefits appear to outweigh the risks of severe disease from breast milk–acquired CMV infection in the neonatal period, which has not been definitively associated with the delayed development or sensorineural hearing loss seen with congenital CMV infection. However, long-term follow-up data on the effects of postnatal CMV infection are limited, with only a small number of infants studied into childhood. One recent study found that the cognitive and motor function scores of VLBW infants with breast milk–acquired CMV infection were within normal ranges when examined at school age but not as high as those of the controls (VLBW infants without CMV infection). More studies are needed to better describe risk factors for severe postnatal CMV disease and long-term neurodevelopmental outcomes. Data from these kinds of studies would be important to support or further refine future guidelines on breast milk feeding of VLBW and premature infants born to CMV-seropositive mothers, and will help health care providers and parents make decisions weighing the risk of CMV transmission and the benefits of breast milk.

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REFERENCES

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stalled migration.12,13 This should have read: “Whereas the exact mechanism causing the hyperadhesiveness of the integrins is not known, the symptoms bear resemblance to mice expressing constitutively active LFA-1 in which excessive adhesion prevents leukocytes from entering injured tissues and, when tested in vitro, causes increased adhesion and stalled migration.”15,16

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An error occurred in the article by Lanzieri et al, titled “Breast Milk-Acquired Cytomegalovirus Infection and Disease in VLBW and Premature Infants” published in the June 2013 issue of Pediatrics (2013;131[6]:e1937–e1945; originally published online May 27, 2013; doi:10.1542/peds.2013-0076). On page e1937, in the abstract, on line 3–4, this reads: “including CMV-related sepsis-like syndrome (CMV-SLS) for which in the United States are lacking.” This should have read: “including CMV-related sepsis-like syndrome (CMV-SLS), for which estimates in the United States are lacking.”

doi:10.1542/peds.2014-0217