Author’s response to reviews

Title: Laboratory Testing and Diagnostic Coding for Cytomegalovirus among Privately Insured Infants in the United States: a Retrospective Study using Administrative Claims Data

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Author’s response to reviews: see over
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Dr. Irene Pala  
Executive Editor  
*BMC Pediatrics*

Dear Dr. Irene Pala,

We would like to thank you for reviewing this article (Manuscript #: 1544900826955228, “Laboratory Testing and Diagnostic Coding for Cytomegalovirus among Privately Insured Infants in the United States: a Retrospective Study using Administrative Claims Data), and considering the article for inclusion in *BMC Pediatrics*. We would like to thank the journal and the reviewers for their thoughtful evaluation of this manuscript. Reviewers #1 and #2 did not have any specific comments to address. Below are responses to comments from the 4 other reviewers.

**Reviewer 3: Sheetal Manicklal**

1. The sensitivity of this approach of analyzing a claims database is not known and cannot be ascertained from the design of this study.

   *Authors’ response: We agree with this comment and have indicated in the manuscript that future research is needed to examine the sensitivity of using a claims database for surveillance for CMV: “Finally, we were unable to validate the sensitivity and specificity of codes for CMV testing and diagnosis using medical claims. In the future, it would be useful to conduct a validation study of coding to enhance the interpretability of claims data for CMV testing and diagnostic coding.” [Discussion; Page 10, Lines 9-11]*

2. Most of the clinical findings are non-specific and in the absence of laboratory confirmatory data (gold standard for diagnosis) linked to the codes, it is not known whether infants may have been misclassified or have had other conditions/diseases with similar clinical findings.

   *Authors’ response: We agree with the reviewer’s comment. We have indicated in the methods that we were unable to confirm CMV infection using laboratory testing because we did not have laboratory test results: “… we did not include laboratory confirmation of CMV infection because laboratory testing results were not available in the MarketScan database” [Methods; Page 5, Lines 19-20]. In addition, we have added the following to the Discussion: “We were only able to identify infants with a diagnostic code for CMV infection, but were unable to confirm congenital CMV infection without access to laboratory test results or medical record review.” [Discussion; Page 9, Lines 18-20].*
3. The fact that there was a tenfold difference between the observed rate of symptomatic infection using claims data and the expected rate is unlikely to be explained mainly on the basis of the characteristics of the population or low awareness among clinicians, and suggests the claims data is highly insensitive for ascertaining actual prevalence and disease burden. This is further supported by the fact that the claims data shows more than 100,000 infants had symptoms suggestive of congenital CMV but a lab test was only associated with around 200 of them.

Authors’ response: We agree that a claims database is not able to capture the vast majority of congenital CMV cases because most cases are not diagnosed in the absence of newborn screening for CMV. However, in the absence of other sources for national surveillance for CMV in the United States, data from healthcare claims may still be useful for surveillance to monitor trends in CMV testing and diagnostic coding for CMV disease. We have edited this in the Discussion: “Although healthcare claims databases are not sensitive enough to identify all symptomatic congenital CMV infections in the United States, they may be useful for surveillance to monitor trends in testing practices and diagnostic coding for congenital CMV disease in the absence of national surveillance for congenital CMV infection or disease.”

[Discussion; Page 9, Lines 7-10]

4. Although one can conclude based on the findings that the rates of CMV-specific testing in infants is very low, it is impossible to determine the causes for this.

Authors’ response: We agree with the reviewer’s comment that we would be unable to determine the cause for low rates of CMV-specific testing using this healthcare claims database.

5. The conclusion that low rates of CMV testing suggests gaps in knowledge and/or awareness is purely speculative. Given the limitations of the study and perhaps the low sensitivity of this approach, it is equally possible that the findings indicate flaws in the study design and that the objectives of the study are not achievable by the analysis of such databases rather than gaps in knowledge/awareness. Therefore, the authors should revise the conclusion section of the abstract and the discussion.

Authors’ response: The objective of the study was to determine rates of coding for CMV diagnosis and testing among insured infants less than one month of age in the United States using a large national healthcare claims database [Background; Page 4, Line 22–Page 5, Line 2]. We found that the rates of coding for CMV diagnosis and testing in this population were low. As the reviewer points out, we can only speculate on the reasons for the low rates of coding for CMV diagnosis and testing in this claims database. We have added limitations of the healthcare claims database in the Discussion sections; please see responses to Reviewer’s 2nd and 3rd comments. We have also edited the conclusion section of the abstract to indicate limitations of the claims database: “Although claims databases presumably do not capture all diagnosed CMV cases or CMV-specific testing, healthcare claims are a potential source for surveillance and monitoring practices of CMV-specific testing and diagnostic coding for CMV among infants” [Abstract; Page 3, Lines 19-21].
6. The authors suggest validation of the claims data but the findings of this study suggest that it is unlikely that claims data could be shown to be valid for clinical activities. Therefore, this approach would have to be coupled with ongoing prospective monitoring of the quality of data.

Authors’ response: We agree that the claims data would not be used for clinical activities, but rather for surveillance. We have clarified this in the Discussion: “Although healthcare claims databases are not sensitive enough to identify all symptomatic congenital CMV infections in the United States, they may be useful for surveillance…” [Discussion; Page 9; Lines 7-9]

7. As the authors have pointed out, the increased practice of bundling of services may have led to incomplete coding. Therefore, not all laboratory tests may have been coded separately for billing.

The authors have pointed out the need for further research but they have not proposed how to address this issue. Only prospective studies will provide data on the true disease burden. The apparent problems with using claims data as a surveillance method serves to strengthen the case for routine national virologic screening of newborns, and this should be highlighted.

Authors’ response: We agree with the reviewer’s comment and have included that laboratory tests may have been missed because of bundling of services [Discussion; Page 9, Line 23-Page 10, Line 2]. A validation study to compare claims and medical records would help to determine the accuracy of coding for CMV laboratory tests and diagnoses. In addition, it would help to determine the proportion of CMV-specific tests that are missed due to bundling of services. Since CMV testing is not a routine test performed, we believe that a majority of CMV tests are likely not bundled as part of routine services.

As mentioned in response to the reviewer’s comment # 5, although a claims database would not identify all congenital CMV cases, it can still be useful as a surveillance tool to monitor trends in diagnosis of CMV and laboratory testing. National surveillance for congenital CMV will be useful for understanding the epidemiology of congenital CMV in the United States. To determine whether health care claims can be used for a surveillance tool, future research would need to be conducted to validate healthcare claims data as mentioned in the Discussion: “In the future, it would be useful to conduct a validation study of coding to enhance the interpretability of claims data for CMV testing and diagnostic coding.” [Discussion; Page 10; Lines 10-11]. Other future research needed include: “Further investigation of the low prevalence of diagnosed symptomatic congenital CMV disease detected in this population merits further research to understand the true burden and spectrum of congenital CMV disease in this population, the extent to which symptomatic congenital CMV disease may go undiagnosed, and the validity of medical claims data for identifying this condition whether claims data could be an adequate source for surveillance to monitor trends in CMV testing and diagnostic coding in the United States.” [Discussion; Page 10; Lines 16-21]

Reviewer 4: Liliane Grangeot-Keros

1. Among the 17 infants with a code for CMV disease and 5 with a code for both CMV infection and CMV disease, only 7 had a code for CMV-specific testing! Can the authors please explain how the ICD-9-CM code defines CMV disease?
Authors’ response: We would only be able to identify those with a diagnostic code for CMV using these claims data. We would not be able to confirm CMV infection because of lack of laboratory test results and medical record review. We have clarified this as a limitation: “We were only able to identify infants with a diagnostic code for CMV infection, but were unable to confirm congenital CMV infection without access to laboratory test results or medical record review.” [Discussion; Page 9, Lines 18-20].

2. It is said that 101 (44%) had a code for serologic testing (CMV IgG, IgM, or EIA). Code for EIA is indicated in the Appendix, but codes for IgG and IgM are missing. In addition, which class of antibody is supposed to be detected by EIA (IgG, or IgM, or both)?
Authors’ response: We have updated the Appendix to indicate the code for CMV IgG and CMV IgM [Appendix Table 1; Page 20]. Unfortunately, the current procedural code (CPT) for EIA does not differentiate between IgG and IgM.

3. Page 7, lines 1-2: the fact that the authors give the number/percent of IgM and IgG testing enforces the idea that there is a specific code for these classes of antibodies even if these codes are not mentioned (see above).
Authors’ response: We have edited the Appendix according to reviewer’s comment. Please see response to the reviewer’s 2nd comment. [Appendix Table 1; Page 20]

4. Page 7, lines 4-5: it is written: "Most infants with a code for CMV-specific testing (187/229; 82%) had # 1 codes for a potentially CMV-associated condition [Table 1], while fewer of those with only non-specific viral or molecular testing (599/1091; 55%) did. It does not seem that the data of the second part of the sentence are shown in a Table: the text would be more understandable if the data of non-specific viral or molecular testing were shown (also see the first paragraph of Results).
Authors’ response: As suggested by the reviewer, we have added data on infants with non-specific testing to Table 1 [Pages 14-16].

Reviewer 5: Klaus Hamprecht

1. Can the authors exclude any bias using the national healthcare claims of privately insured infants by generating epidemiological data via the commercial MarketScan database? In “Methods” on page 5 (study definitions) the authors state, that the MarketScan database does not include laboratory testing results.

Author response: We agree that the MarketScan Commercial databases are not reflective of the entire US population since they primarily include those with employer-sponsored insurance. Age and sex distributions in those databases are comparable to the US population with employer-sponsored insurance, but there is no information on race in MarketScan Commercial databases. Other research has shown that populations with employer-sponsored insurance tend to include a higher proportion of high-income and white populations relative to people with either public insurance or no health insurance. For example, one published analysis of the MarketScan Commercial and Medicaid databases found that the frequency of sickle cell disease (SCD) among children was 1 in 850 in the Medicaid sample and 1 in 4,800 in the Commercial sample. The overall prevalence of SCD among children in the US is probably between 1 in 2,000 and 1 in 2,500. An all-payers claims database could accurately
represent the population of a given state, and several states are in the process of setting up such databases.

We have included in the discussion: “An additional factor that might help account for the low frequency of diagnoses of congenital CMV in the present study is the selective nature of the MarketScan population, which represents individuals with employer-sponsored health insurance, about 55% of the US population in 2011[11]. People with employer-sponsored insurance are less likely to be low-income or non-white than are uninsured or publicly-insured people [12]. Future work could examine the frequencies of coding for CMV diagnosis and CMV testing rates in the US population with publicly-financed health insurance.” [Discussion; Page 9, Line 11-16]

2. How many potentially cCMV infected infants are excluded using only privately insured patients?

Authors’ response: There were 55% with employer-sponsored insurance in the United States in 2011. Approximately 86% of Americans with private insurance have employer-sponsored insurance and populations in the MarketScan Commercial databases appear representative of the US population with private insurance. Since people with employer-sponsored insurance are less likely to be low-income or non-white than are uninsured or publicly-insured people, the prevalence of cCMV is likely to be substantially lower than among the latter. It would be useful to look at practices of diagnostic coding and testing for CMV in Medicaid populations. We have added this information in the Discussion section. Please see the response to Reviewer’s 1st comment. [Discussion; Page 9, Line 11-16]

3. What influence does this approach have on the selection of ethnical background of the infected infants (white versus Hispanic versus black population)?

Authors’ response: Unfortunately, there is no information on race in MarketScan Commercial databases. Other research has shown that populations with employer-sponsored insurance tend to include a higher proportion of white populations relative to people with either public insurance or no health insurance. We have added this information in the Discussion section. Please see the response to Reviewer’s 1st comment. [Discussion; Page 9, Line 11-16]

4. How the authors comment the potentially biased approach with “CMV specific testing” including the mixed CPT code for CMV IgG, IgM (serology), together DFA or PCR (direct virus detection)? (page 5) Using that approach the authors will get also cCMV-unrelated information using CMV serology, since in context of postnatal CMV and preterm infants it might be of interest, whether the mother is potentially excreting CMV or not. Additionally to exclude cCMV the detection of CMV IgM is not helpful. Indeed, the authors mention the underlying problem and point it out, but the acquired data may misleading, since specific laboratory confirmation is not available.

Authors’ response: We agree that congenital CMV cannot be diagnosed with CMV serology and state this in the background: “Congenital CMV infection is confirmed by detection of
CMV DNA by PCR or CMV by viral culture from urine, saliva, or blood [8].” [Background; Page 4, Lines 17-19]. Due to limitations in this database, we would be unable to confirm congenital CMV cases with laboratory testing; we can only look at frequency of claims for CMV-specific testing, and types of tests performed among infants. Although serological assays are not useful in diagnosing congenital CMV, we were still interested in including this as a type of CMV-specific test to identify the types of CMV-specific tests performed among infants since there is no published information on this in the United States. We have clarified this in the methods: “In order to characterize practices in laboratory testing for CMV, we looked at claims for all types of CMV-specific tests without restricting to laboratory tests used for diagnosing congenital CMV infection.” [Methods; Page 6, Lines 3-5]

5. Table 1: There are given 61 infants with cCMV—either asymptotically or symptomatically infected. Is it conclusive that in only 5 infants (8.2%) thrombocytopenia was found?

Authors’ response: We are certain that 5 infants had diagnostic codes for both congenital CMV and thrombocytopenia. It is possible that we have missed individuals with thrombocytopenia because it was not coded for. We have added the following to the discussion: “Many of the conditions associated with congenital CMV disease, such as jaundice, low birth weight, and hearing loss, are non-specific and have numerous potential underlying etiologies. It is difficult to definitively determine from medical claims data whether these conditions were due to congenital CMV infection but not recognized by providers as being CMV-related, coded to indicate an evaluation rather than diagnosis of CMV, or if an alternative etiology was identified. Some signs of symptomatic congenital CMV infection, such as petechiae and hepatosplenomegaly, are unlikely to be coded in claims data, even if recognized and recorded in the medical record.” [Discussion; Page 10, Lines 2-9]

6. Table 2: Can the authors exclude any bias by correlating “CMV specific testing”, which includes serology (in 44%: abstract, results) and CMV PCR and DFA with CMV-associated conditions? It would be very interesting to see the results of Table 2 via the correlation of only PCR/culture and not CMV serology to the CMV associated conditions.

Authors’ response: We agree that congenital CMV cannot be diagnosed with CMV serology and state this in the background: “Congenital CMV infection is confirmed by detection of CMV DNA by PCR or CMV by viral culture from urine, saliva, or blood [8].” [Background; Page 4, Lines 17-19]. However, we included all types of CMV-specific testing and did not restrict this to only tests to confirm congenital CMV, because we were interested in seeing CMV testing practices occurring in the United States. We have clarified this in the methods. See response to the Reviewer’s 4th comment. [Methods; Page 6, Lines 3-5]

We have provided a supplementary table with data on association between CMV PCR testing and presence/absence of CMV-associated conditions to address the reviewer’s comment. We found that the results when restricted to only those with CMV PCR were similar to the results for all CMV-specific tests. Since, we do not feel that the data alters our conclusion that there are low rates of CMV testing among infants with symptoms suggestive of congenital CMV infection, we are not intending that the table be included in the published manuscript. However, we leave it to the editors to determine if this data should be included in the manuscript.
Reviewer 6: Aparecida Yulie Y Yamamoto

1. The major limitation of this retrospective study is the definition of cases of congenital infection because laboratory testing results were not available in the data source and the authors did not include laboratory confirmation of congenital CMV infection. No standardized diagnosis testing such as viral detection within 3 weeks of life for congenital CMV infection was defined to confirm the diagnosis in infants with a diagnostic code for CMV.

Authors’ response: We agree with the reviewer’s comment that we were unable to confirm congenital CMV infected cases but only able to determine the infants with a diagnostic code for CMV. We clarified this in the Discussion: “We were only able to identify infants with a diagnostic code for CMV infection, but were unable to confirm congenital CMV infection without access to laboratory test results or medical record review.” [Discussion; Page 9, Lines 18-20].

2. The authors should include as CMV-associated conditions some laboratory testing that are usually performed as part of evaluation of the neonate with congenital CMV infection. The rates of CMV-specific tests may increase when both clinical and laboratory findings were included as CMV-associated conditions. Among the laboratory abnormalities, it is well known that elevated liver transaminase levels, direct hyperbilirubinemia and thrombocytopenia can be found in approximately 80% of the symptomatic infants.

Authors’ response: We agree that it may be potentially useful to look at other laboratory tests commonly performed among symptomatic congenital CMV-infected infants. However, since we do not have the laboratory results available and the majority of these tests performed on infants suspected to have congenital CMV infection (e.g., tests for liver transaminase, hyperbilirubinemia, thrombocytopenia) are not specific for CMV-infection, this may not provide additional information to describe these infants with a diagnostic code for CMV. In the future, this would be potentially useful to include in studies to validate claims data in instances when laboratory results would be available.

3. In the first paragraph, line 1, page 6, the authors described that the 368,266 infants were less than 1 year of age. In page 7, they reported the diagnosis of hearing loss in 542 infants with #3 visits within the 1st year of life. However, in the Methods section, the authors reported that they analyzed medical claims from infants who were less than 30 days of age. Please clarify.

Authors’ response: Our study cohort consisted of infants who were <1 month of age, and the majority of analyses were restricted to claims within the 1st month of life. However, hearing loss is a common symptom of infants with congenital CMV infection, but may not be detectable within the 1st month of life. For this reason, we looked at claims for hearing loss within 1 year of life. As suggested by the reviewer, we have clarified this in the methods: “We restricted our analyses for rates of claims for CMV-specific testing, and diagnostic coding for CMV and CMV-associated conditions to claims within 30 days of the newborn code. Hearing loss is also a common symptom of CMV infection,[2] although it may not be diagnosed in the newborn period. To examine diagnostic coding for hearing loss, we examined claims within the 1st year of the newborn code. A diagnosis of hearing loss was defined as ≥3 medical encounters with a hearing loss code since the work-up for a diagnosis for hearing loss
in infancy often requires >2 medical evaluations.” [Methods; Page 6, Lines 5-11] We have also corrected this typo in the results: “Among the 368,266 infants ≤1 month of age…” [Results, Page 6, Line 23].

4. Table 1. According to previous published reports, petechiae, jaundice and hepatosplenomegaly are the most frequent manifestations in symptomatic congenital infection, being present in about 75 -80% of infected infants.

In the Table 1, a code for petechiae was present in 1,650 (0.5%) of all infants; however, among 229 infants with CMV-specific testing, only 1 (0.4%) infant with petechiae was tested and only 1 (1.6%) among 61 infants with code for congenital or CMV disease was noted to have petechiae as CMV associated condition. It is likely that the proportion of infants with petechiae was greatly underestimated. In addition, as showed in the Table 1, hepatomegaly and splenomegaly were not found as CMV-associated condition in any infant with a diagnosis code for CMV.

The low frequencies of various clinical abnormalities seen commonly in symptomatic congenital CMV infection may be explained by incomplete medical claims coding.

In addition, 24/61(39%) of infants with the diagnostic code for congenital CMV infection had none of the 11 CMV-associated conditions. In the absence of routine neonatal screening for congenital CMV infection, it would be of interest to verify if other CMV-associated findings were present in these 24 infants.

Authors’ response: We identified these 11 CMV-associated conditions based on published literature of clinical symptoms of congenital CMV cases symptomatic at birth from several references [See References # 5-7]. All clinical symptoms identified in these publications were included in this analysis, with the exception of hypotonia and lethargy. None of these 24 infants with a diagnostic code for CMV who did not have one of the CMV-associated conditions had a diagnostic code for hypotonia (ICD-9 791.3) or lethargy (ICD-9 780.79). We have added additional information regarding selection of these 11 CMV-associated conditions in the methods: “CMV-associated conditions, identified by ICD-9-CM codes listed in Appendix Table 1, were defined as 11 conditions included in previously published definitions of symptomatic congenital CMV [5-7] present in the newborn period (within the first month of birth).” [Methods; Page 5, Lines 21-23]

We agree that some of these CMV-associated conditions may not have been coded for in this claims database. These are claims submitted for reimbursement, so it is possible that these 24 infants had one of these 11 CMV-associated conditions, but codes were not included on the claims if they were non-reimbursable. We have added the following to the Discussion: “Many of the conditions associated with congenital CMV disease, such as jaundice, low birth weight, and hearing loss, are non-specific and have numerous potential underlying etiologies. It is difficult to definitively determine from medical claims data whether these conditions were due to congenital CMV infection but not recognized by providers as being CMV-related, coded to indicate an evaluation rather than diagnosis of CMV, or if an alternative etiology was identified. Some signs of symptomatic congenital CMV infection, such as petechiae and hepatosplenomegaly, are unlikely to be coded in claims data, even if recognized and recorded in the medical record.” [Discussion; Page 10, Lines 2-9]
5. Table 2: Considering that phenylketonuria, hypothyroidism, galactosemia, and hemoglobinopathies testings are performed as standard routine care for all infants, it was no clear why only 38,344 (10.4%) among 368,266 infants were tested. These results reinforce the insensivity of claims data to identify the majority of diagnoses and laboratory tests reported in medical records. As commented by the authors, “In the absence of national surveillance for congenital CMV infection or disease further investigation should be done to determine whether claims data could be an adequate data source for monitoring trends in diagnosed congenital CMV disease”, claims data could not be an adequate data source and the quality of the data is the greatest concern.

Authors’ response: We agree with the reviewer that there are limitations to using claims data. In particular, the low frequency of codes for disorders detected by newborn screening reflects the fact that claims data are only intended to capture tests ordered individually for a patient and not public health newborn screening tests performed in central laboratories. When an infant screens positive and is evaluated to determine whether the child had a condition, the ICD-9 code for the follow-up evaluation will be recorded. Because CMV is not included in routine newborn screening panels, the lack of newborn screening test records is not related to the low frequency of CMV test codes. Although the MarketScan database may not capture all CMV-specific lab tests performed or all infants diagnosed with congenital CMV, it may provide useful data on trends in laboratory testing practices and diagnostic coding for congenital CMV among infants.

Please do not hesitate to contact me if you need any further questions. Thank you again for considering our manuscript for publication in BMC Pediatrics.

Sincerely Yours,

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