Author's response to reviews

Title: Cytomegalovirus Infections among African-Americans

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Author's response to reviews: see over
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RE: Manuscript 1232628475184542

Dear Editors:

Thank you agreeing to consider a revision of the above referenced manuscript. The reviewers’ comments very insightful helpful and we considered them carefully and responded to each.

Reviewer: Rawlinson

General comments:

1. The reviewer is correct. The term infection can mean either incidence or prevalence. Since we measured prevalence we agree that we should be precise in the text and as such have changed “infection rates” to “CMV seroprevalence rates” wherever appropriate in the text.

2. There reviewer is correct when he states subjects were seeking medical consultation and as such this may have introduced selection bias. To make this clear to the reader’s we have revised the discussion on page 8 to read:

First, our subject sample may not be representative of the population of African-Americans residing in Richmond, VA or elsewhere especially since we selected subjects seeking medical consultation.

Essential revisions:

1. Obtaining blood and urine was beyond the scope this study for several reasons. First, obtaining blood would have severely restricted our ability to recruit subjects, especially young children, and this would have introduced additional selection bias. We had nearly 100% participation by only having to obtain saliva. Second, the initial aim of the study was to determine the ages of CMV acquisition. Since were measuring seroprevalence, few if any subjects would have been expected to have viremia which only persists for a few weeks or months after a primary CMV infection. Third, the costs of these assays were beyond our means.

2. The ethics approvals have added on page 5:

This study was approved by the Virginia Commonwealth University Institutional Review Board. Informed written consent or assent was obtained from all subjects and
studies were conducted in accordance with human experimentation guidelines of the US Department of Health and Human Services.

3. There were only four families with incomes >$80,000 and family incomes for all groups were not associated with seroprevalence rates. The independent variables plus age are all listed in Table 1 and figure 1 and these should be clear to the majority of readers.

Minor revisions:

1. One page 3 we added the number of families recruited from each type of pediatric practice.

2. On page 4, 20° has been changed to -20°

3. On page 3 we state that: “Serum neutralizing titers in seropositive sera are > 1:256.” Further the seroprevalence rates we observed for adults were nearly identical to those observed in several other studies that used sera. Hence it is very unlikely that by using saliva we underestimated the true seroprevalence rates due to low titers. A statement to this effect could be added to the discussion. We will do this if the editor prefers.

4. On page 9 we address the age related quadratic trend in figure 1:

   We observed a decline in the seropositivity rate with age for African-American adults between 40 and 45 years of age. The significance, if any, of this observation is uncertain. This decline was not due to reduced antibody levels in saliva associated with aging since antibody titers to CMV persist for life and actually increased throughout adulthood with highest levels in the elderly [11]. Although this decline may represent another cohort of older African-Americans with lower infection rates, the number of subjects in this age range was low and thus the 95% confidence intervals were wide and as shown in figure 1, the 95% confidence intervals overlapped.

5. The reviewer requests that we remove tables 2-4, however the second reviewer has requested we add another table. The tables are simple 2x2 contingency tables which are easy to comprehend and require less space then a text description. We prefer to leave them, unless the editor feels otherwise.

6. As noted above the term seroprevalence is now used rather than infection.

7. Our data do not concern ethnicity but rather race. We unaware of any data for the African race in Europe, although this is definitely an interesting question. In previous studies European Caucasians have about the same rates of seropositivity as do American Caucasians.

8. This comment conflicts with number 4 above. In comment 4 the reviewer asked for expanded discussion on the decline in seropositivity rates with age and this comment suggests it be removed. We are happy to remove this part of the discussion, however, see no obvious problem with retaining it since some readers may ask what we think it means.

9. We agree with the reviewer that sibling-to-sibling transmission was not directly proven. Therefore we revised the discussion on page 10 to read:
The second novel observation from our study was that sibling-to-sibling transmission may have been the primary mode of CMV acquisition among African-American children and adolescents.

Reviewer: Grangeot-Keros

1. Under study population the number of subjects has been added.

2. To avoid confusion we deleted reference to the 113 adults (113 is correct) who participated from the first paragraph in the results section. Note that the second paragraph under results reads:

   The average age of the 103 adults who reported their age was 33 years (range 19 to 53 years, SD = 8.75).

   Thus 113 adults participated but only 103 reported their age. Thus should clarify the numbers in figure 1.

3. We could present the data for the association between index children and their mothers but the more meaningful data are in table 2, which are for all children for each mother.

4. For figure 1 we do have sufficient numbers to represent seropositivity by year. If the editor requests we can add another two figures to the paper, one for adults and one for children. These two can’t be displayed side-by-side, as we have done with the histogram in figure 1, because of the large difference between adults and children. Thus to reduce the number of figures to one, we presented the histogram rather than a year-by-year depiction of the seropositivity by age.

   The reference to Table 2 when discussing age has been corrected.

5. Yes, the number of children attending day care was too low to take into account and we have revised the discussion to read:

   In the current study only 19 children reported day care attendance. Children not in day care probably spend more time at home with their siblings than occurs for children attending day care. Since child-to-child transmission of CMV requires prolonged and frequent contact; the association of seroprevalence rates among African-American siblings, most of whom received home care, may represent sibling-to-sibling transmission.

6. The reviewer is correct about the need to now test Caucasian children. However when we began the study our aim was simply to “perform a study among African-American-American children and adolescents to determine the possible sources of infection. We did not anticipate the low seroprevalence rate we observed. Because this is an important point we have therefore revised to discussion on page 8 to now read:

   Ours is the first recent study to determine CMV seroprevalence rates for the current generation of lower socioeconomic African American children and adolescents. We did not measure the seroprevalence rates in age-matched Caucasians, however, the low rates we observed for lower socioeconomic African
American children and adolescents were nearly identical to the low seroprevalence rates reported for Caucasians children and adolescents measured for the entire US population between 1988 and 1994 and for Caucasian children measured in Houston Texas in the late 1980s [2, 4]. In contrast, in these studies the seroprevalence rates for African-American children were significantly higher than age-matched Caucasians. Thus our data suggest the current generation of African-American and Caucasian children will have similar CMV seroprevalence rates.

7. The SES abbreviation has been deleted.

One new reference has been added.

Once again, thank you for consideration of this report. We would be happy to consider any further revisions you suggest.

Sincerely,

Stuart Adler