

Author's response to reviews

Title: Washing our hands of the congenital cytomegalovirus disease epidemic

Authors:

Michael J Cannon (mcannon@cdc.gov)

Katherine FINN Davis (kdavis9@emory.edu)

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Author's response to reviews: see over

Cannon and Davis, Reply to Reviewers

Note: Reviewer comments are in bold, our responses are in plain text. All reviewer comments are addressed below but Reviewer 1's comments are reorganized and grouped according to topic.

Reviewer 1: Edward Mocarski

Many of this reviewer's comments take the form of general criticisms that are difficult either to address or rebut, for example:

“Overall, the manuscript is a reasonably good public health piece, but is written more for the lay audience than a medical or informed public health audience. As a review, there are a number of aspects that are not particularly well focused and make it less useful overall.”

“As an abstract for a review, this needs better organization and focus.”

“The integration of existing information is quite a problem throughout the text.”

“As the manuscript stands, there are too many inconsistencies to consider it complete and too little new information or perspective to consider it appropriate for a public health journal.”

We address the specific criticisms below.

“The manuscript by Cannon and Davis is intended to present a debate but amounts to a less-than-up- to-date review and perspective on the field.”

“Many references are too old to be appropriate, particularly when referring to the inability to treat CMV infection.”

The motivation for writing this article came from reading *recent* articles that provided mixed messages about congenital CMV prevention. We quoted from a sample of those articles (Discussion, 2nd paragraph) which encouraged behavioral changes but were skeptical that they would work. These mixed messages have the effect of discouraging widespread implementation of behavioral interventions. We submitted our article in the “Debate” category because we believe that, given the current state of knowledge, these mixed messages are inappropriate.

The criticism that our article is a less-than-up- to-date review is hard to understand. Half of the articles we cited were from the last five years, and many of the older citations were from key epidemiologic studies of the 1980's and 1990's. The one sentence that discusses the treatment of CMV infection cites two articles from 2003.

The "CMV and congenital disease" section is intended to convey some primary information, but amounts to a reflection on some literature and a challenge to advocate hand washing for control fo CMV transmission. This section is insufficient and is dwarfed by the following Discussion section, suggesting that the entire text should be re-organized into a proper review that makes a case for public health changes, which are really not debatable in principle but may be hard to enact in practice.”

“The manuscript by Cannon and Davis is intended to present a debate but amounts to a less-than-up- to-date review and perspective on the field. Overall, the manuscript is a reasonably good public health piece, but is written more for the lay audience than a medical or informed public health audience.”

“If the authors reorganize the manuscript to be a proper review, starting with a focus on the impact of hand washing on infectious diseases through the ages and finishing with a summary of the current status of CMV infection and transmission, the work may gain in scholarship. They might spend more time on the practical benefits and difficulty in implimenting handwashing in this context.”

We appreciate these comments but think that our intent was misunderstood. Our intent was to argue that the scholarly articles that have presented a nuanced and conservative view of congenital CMV prevention have had the unintended consequence of discouraging a vigorous public health prevention message. We argue that allowing this unfortunate situation to continue is akin to “washing our hands of the congenital CMV disease epidemic”. Whether one agrees with our point of view or not, our intent was to debate this issue, not to present a comprehensive review of congenital CMV. For this reason the section on “CMV and congenital CMV disease” was short and the “Discussion” section was long. We agree with the reviewer that a review of handwashing interventions and their implementation would be useful. Although we feel further discussion is beyond the scope of our article, in response to his suggestion we added the following sentence:

- Preventing CMV infection through hygienic practices, 4th paragraph—“An in-depth review of the literature would be useful for determining the key factors associated with the success of these and other community interventions.”

“The current emphasis on lack of evidence that handwashing works to control transmission is actually in contrast to reports in 1996 and 2004 from Stuart Adler and his group. While the 1996 paper is referenced in the body of the manuscript, the tone in the abstract does not accurately reflect current knowledge.”

The reviewer is mistaken on this point. We do not emphasize in the Abstract that there is a lack of evidence that handwashing works to control transmission of CMV. Instead, we state that there is widespread agreement that prevention “measures are likely to be efficacious”, but there are still “concerns about effectiveness” (as evidenced by the recent examples we cite in the body of the article). The idea that the Adler studies have removed these concerns is not accurate. The two reports by Adler and colleagues, both of which we cite and discuss in the body of the article, are the best available data on the effectiveness of handwashing interventions for preventing CMV infection. However, while the 1996 study provided encouraging evidence, it lacked the power to make definitive conclusions about effectiveness, and thus led some to conclude that the intervention failed (e.g., Griffiths, *Semin Neonatol* 2002; 7:293-299). It was also difficult to draw definitive conclusions from the 2004 study, since the intervention had no effect overall but appeared to have been beneficial among a subgroup of pregnant women.

There are places where "a number of experts" is stated without saying who the experts are. This gives the manuscript the tone of a health brochure rather than review.

It appears that the reviewer overlooked our references to who the experts are. It is true that in the Abstract we stated without citation that “Experts agree that such measures are likely to be efficacious...”, since we did not wish to include citations in the abstract. However, in the text we could find only 2 places that fit the reviewer’s description, and these places already had citations:

- Discussion, 2nd paragraph, sentence beginning with “A number of experts...” has 6 citations at the end of the sentence and then goes on to reference the consensus in the ACOG guidelines.
- Discussion, 2nd paragraph, sentence beginning with “A number of authors...” is followed by 4 separate citations throughout the sentence.

Abstract refers only to literature and not to any new information.

Our article synthesizes existing information to allow us to argue for a stronger educational effort to prevent CMV transmission. The Abstract provides the necessary background and outlines the argument. We do not understand the need for new information in a debate article and so it is not clear to us how this reviewer would like the Abstract to be modified.

Everywhere in the manuscript that gives a number associated with CMV infection or disease, it is critical to include the modifier "estimated" because the information has only been gathered in small populations and these numbers have been used to estimate incidence in the population.

We agree that care must be taken when extrapolating estimates to the entire population, and data on congenital CMV incidence and sequelae come from limited geographical regions. In most instances we used the terms “estimated”, “approximately”, or “about”, or used a numerical range (e.g., 10%-15%) to communicate the uncertainty. In the several sentences that did not have such modifiers, we made the requested changes (in italics).

- Abstract, line 1—“Each year in the United States, *an estimated* 40,000 children are born with congenital cytomegalovirus (CMV) infection, causing an estimated 400 deaths and leaving *approximately* 8000 children with permanent disabilities...”
- Background, 2nd paragraph—“Each year in the United States, *an estimated* 40,000 children are born with congenital cytomegalovirus (CMV) infection, causing an estimated 400 deaths and leaving *approximately* 8000 children with permanent disabilities...”
- Discussion, last paragraph—“...each year in the United States, *hundreds of* children will die and *thousands of* others will swell the ranks...”

Reviewer 2: Robert Pass

Major Compulsory Revisions

1. It is important to address the question of what proportion of congenital CMV disease could be prevented if the measures recommended were immediately put into practice and followed by 100% of the target population. In addressing this question there are two key considerations: 1) What proportion of congenital CMV infection results from child to mother transmission as opposed to other routes, such as sexual transmission? 2) What is the estimated effectiveness of the hygienic measures proposed?

We agree that it is important to address the potential effect of CMV prevention measures and have added the following sentence that includes this important insight:

- Next steps, next-to-last paragraph, 2nd sentence—“These trials will be important for quantifying the effectiveness of the proposed hygienic practices and for assessing the proportion of CMV infections that result from child-to-mother transmission as opposed to other routes, such as sexual transmission.”

Unfortunately, there are currently no reliable data on either of the two considerations that the reviewer describes. Addressing this question at this point in time would be pure speculation; a proper treatment would require modeling with a number of assumptions that would be difficult to

evaluate without further data. Therefore, we feel that this sort of analysis is beyond the scope of our article. Furthermore, the results from such an analysis would not change our main messages: 1) Women have a right to know about CMV prevention; and 2) Trials are needed to identify effective interventions.

2. Clarify the message on identify of the target population. Is it only pregnant women? It seems logical to include all women of childbearing potential. What about spouses? What about preventing child to child transmission in day care centers and other settings?

We agree that the educational message should apply to all women of childbearing potential. To make this clear, we made several changes shown below (changes in italics).

- Preventing CMV infection through hygienic practices, next-to-last paragraph, 1st sentence—“*Although all women of childbearing age deserve to be informed about CMV, interventions for preventing CMV transmission are most likely to be effective for pregnant women, who tend to be highly motivated, often changing behavior to protect the health of their developing fetuses.*”
- Next steps, 1st paragraph, next-to-last sentence—“*CMV educational messages should emphasize hygienic practices as a precaution for all women who are pregnant or planning to become pregnant, and reasonable but not extreme measures for minimizing interactions with young children.*”
- Figure Legends, Figure 3—“*Hygienic practices to reduce risk of CMV infection for women who are pregnant or planning to become pregnant.*”

To address prevention of transmission via other routes we added the following sentence:

- Next steps, 1st paragraph, last line—“*Once effective hand-hygiene messages are identified, more ambitious goals might also be considered, such as prevention of sexual transmission or transmission between children in daycare.*”

We recognize that in this article we chose to focus on prevention of only one of several modes of CMV transmission. To clarify our restricted focus we also modified the following sentence (changes in italics):

- Discussion, end of 1st paragraph—“*In contrast, insufficient emphasis has been given to preventing CMV infection in pregnant women. While women may be infected via several routes, the remainder of this article focuses on preventing transmission via the important child-to-mother route, by encouraging hygienic practices such as frequent handwashing.*”

Minor Essential Revisions

~~1. When stating estimates of congenital CMV disease, it is better to give a range based on best data available in the literature.~~

We agree, and for this reason many of our numbers are reported as ranges. In response to Reviewer 1, we included additional modifiers to emphasize that such numbers were estimates and approximations. Having done this, we feel it is reasonable to use the estimates cited in the Institute of Medicine report for the numbers of CMV infection and disease shown in the Abstract and Background.

2. The legend for figure 3 indicates that these recommendations are for pregnant women. What about women who might become pregnant? If this is going to be a public health recommendation, you should have a clear message as to who should employ the recommended practices.

This point was already addressed in response to Major Revision 2.

3. The parachute analogy is overly dramatic and perhaps out of place in this debate. The parachute protects from exposure to a risk that is limited to a few seconds, for a very limited group of persons for whom the outcome without a parachute is undisputed. Some might suggest that what you are recommending is more akin to suggesting that passengers on commercial airliners wear parachutes in transit.

As long as approximately 9000 U.S. children each year continue to be permanently and seriously disabled by a potentially preventable disease, we feel that a little drama is appropriate. The congenital CMV situation more closely resembles the parachute analogy than the commercial airliner analogy. There are not 9000 people in the U.S. who die or become permanently disabled in commercial airline accidents nor would we have reason to expect parachutes to be of use in a commercial airline crash. For CMV, on the other hand, there is a substantial public health burden and good reason to believe that interventions could significantly reduce it. The parachute analogy is not intended to mirror the CMV situation precisely. It is simply a powerful demonstration of the key point we wish to convey (stated in the next-to-last paragraph of the article), "...under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions."

Discretionary Revisions (which the author can choose to ignore)

Suggestions for improvement

1. Tighten the focus. It is not necessary to include references for the achievements that have been made in preventing infectious diseases by vaccination. This is public knowledge. You could shorten the section on congenital CMV disease and biology of CMV infection as well. State the hypothesis or recommended course of action right off and then discuss the rationale.

We agree that such achievements are public knowledge, but they provide an important contrast between the situations for different diseases. Because the article is aimed at an audience that may be unfamiliar with some of the issues relating to congenital CMV, we also feel that the three paragraphs in the section "CMV and congenital CMV disease" are necessary.

2. It is contradictory to state that there is agreement on the action that needs to be taken and then cite several references (later in same paragraph which starts on p. 7) which conclude that nothing can be done to prevent transmission of CMV.

We agree that it is contradictory; we are simply describing the current mixed message found in the literature.

3. Perhaps you should mention the possibility of CMV contamination of the environment. Cleaning of the environment is not mentioned in the list in Figure 3.

We address this briefly in Figure 3, which says to avoid contact with environmental objects such as cups, plates, towels, etc. In response to this suggestion we added the following to Figure 3:

- Figure 3—"Clean toys, countertops and other surfaces that come in contact with urine or saliva."

4. What about fathers? Should they also employ hygienic practices if the spouse is or will become pregnant? What about child to father to spouse transmission?

See previous comments.