Author's response to reviews

**Title:** Increased seroprevalence of IgG-class antibodies against cytomegalovirus, parvovirus B19, and varicella-zoster virus in women working in child day care

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**Version:** 2  **Date:** 27 March 2012

**Author's response to reviews:** see over
Dear Dr Furuno,

Thank you for your message of 1st February 2012 with the feedback of the reviewers and the invitation to prepare a revised version of the manuscript. We have carefully considered the comments of the reviewers and have revised the manuscript accordingly. Please find below a point-by-point reply to the comments made by the reviewers. We have changed the title to “Increased seroprevalence of IgG-class antibodies against cytomegalovirus, parvovirus B19, and varicella-zoster virus in women working in child day care”. We hope that these changes meet with your approval and that the manuscript is now acceptable for publication in BMC Public Health.

Sincerely, on behalf of the co-authors,

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Reviewer's report

Title: Occupational risk for cytomegalovirus, parvovirus B19, and varicella-zoster virus in women working in child day care

Version: 1 Date: 15 January 2012
Reviewer: Jennifer S. Albrecht

Reviewer's report:

Major Compulsory Revisions

1. The DCW data set contains data that are clustered, i.e. women were sampled from the same day care centres. However, it appears that clustering was not taken into account in the analysis, leading to an underestimation of the standard errors of the odds ratios. These data should be reanalyzed using a technique that will account for clustering (see below).

   We have re-analysed the data, this time taking clustering into account (see Methods section).

2. The data from the general female population was collected using frequency stratification. Turks and Moroccans were oversampled. This stratification must be accounted for in the analysis so that the sampled population is representative of the target population. If the authors have done so, they should indicate this in the methods.

   We acknowledge that the sample used is not representative for the Amsterdam general female population. This study compares seroprevalence of CMV, Parvovirus B19 and VZV in a sample of women working in child day care (DCW) and in a sample of women not working in day care. Although the sample from the general population is not representative for the general population due to the oversampling of certain groups, this has been addressed in the statistical analysis.

3. Because the prevalence of seropositivity (of CMV, B19 and VZV) is greater than 10%, odds ratios will overestimate the prevalence ratios. An analysis using a log binomial regression model with the day care centre id as the clustering variable would provide more precise estimates of the prevalence ratios and their standard errors.

   We agree. We have re-analysed the data, this time taking clustering into account using a log binomial regression model. (See the Methods and Results section).

4. A cross sectional study can’t establish risk because there is no temporal link. All references (including title) to the occupational risk of infection should be replaced with wording that discusses the increased prevalence of seropositivity among DCW, accounting for confounders. While this increase in seropositivity could be due to working as a DCW, it could also be due to unmeasured confounding.
The authors agree that an occupational risk cannot be concluded from cross-sectional data, We also agree that odds ratios often are misinterpreted as risk ratios (or mistaken for it). We understand the possible confusion caused by the title. To avoid misunderstandings we have adapted parts of the text; in the new version of the manuscript we present prevalence ratios, and have changed the title to: “Increased seroprevalence of IgG-class antibodies against cytomegalovirus, parvovirus B19, and varicella-zoster virus in women working in child day care”.

Minor Essential Revisions

1. The methods section should include more information on the sampling scheme used in the cross-sectional study on the general female population, the methods used in obtaining target population estimates for that study, the methods used for accounting for clustering in the DCW set, and the methods used for the selection of the final regression model.

As various earlier research papers have been published based on the data of the Amsterdam Health Monitor 2004, using the same procedures, the authors decided not to include all details, but to refer to other publications instead.*

In the methods section, the description of the statistical analysis has been re-written to include the methods used to account for clustering in the DCW set, and those used to build the final regression model.


An English description of the details on the Amsterdam Health Monitor 2004 can be found in chapter three of the thesis of Joanne Ujcic-Voortman, available from:
2. The citation for the original study on the DCW is missing. Were the authors responsible for that study?

The data from the DCW survey and its outcomes are described in this manuscript.

3. The DCW data set includes information on women aged 16-44 while the other study contains information on women aged 18-44. Can the authors comment on the lack of inclusion of information on the women aged 16-18?

In the cross-sectional population-based health survey (the Amsterdam Health Monitor) only adults ≥ 18 years were included. Among the DCW there were four participants aged 17 and one participant aged 16.

4. On page 12, the authors should limit themselves to commenting on what the data indicate.

We have re-written this part of the discussion.

5. In the Discussion, the authors should indicate that it is not possible to establish risk in a cross-sectional study. This is the largest limitation of the study, yet it is not mentioned.

We addressed this issue at point 4 of Major Compulsory Revisions. To avoid misunderstandings we have re-written parts of the text; in the new manuscript we present prevalence ratios, and have changed the title.

8. Also in the Discussion, the authors state that the ‘sampling data of the populations differed’ but it is not clear how they differed. Please provide a more detailed explanation.

In Table 1 as well as in the Results section we give a detailed description of how the two populations differed. The authors are aware of the opportunity for confounding. In the multivariable regression models we aimed to adjust for this. However, it is always possible that such adjustment is not complete. In the Discussion this is mentioned as a limitation, together with the probability that important unmeasured confounders were not reported and so could not be adjusted for.

9. The authors state that the DCW are at risk of infection with CMV, but these results suggest that they are at decreased risk of infection because they have increased immunity.
CMV seropositivity does not imply immunity. Nevertheless, from other research it is known that the risk of congenital infection is highest for children of CMV seronegative women. In the Introduction this is discussed: “Primary CMV infection results in life-long latent infection, and although congenital infection after reactivation and re-infection with a different CMV strain may occur, the risk of congenital infection is highest for seronegative women”. In the Discussion this is also addressed. “Whilst the same risk could not be proven for DCW born outside Europe (because of their high background seropositivity), they probably have a similar occupational risk of (re-)infection to their Dutch and European colleagues.”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests

Reviewer’s report II

Title: Occupational risk for cytomegalovirus, parvovirus B19, and varicella-zoster virus in women working in child day care

Version: 1 Date: 27 January 2012

Reviewer: Sheila Dollard

Reviewer’s report:
The authors tested sera from 242 day care workers (DCW) and a comparison group of 298 non-DCW for antibody to CMV, VZV and parvovirus B19 to assess whether working in day care is an occupational risk for infection of these viruses. Based on differences in IgG seroprevalence, they concluded that that working in a child day care centre poses a significant risk for CMV and B19 infection. Several other associations between demographic characteristics and infection were reported. The main weakness of the paper is the lack of multivariable analyses which is especially necessary with the highly dissimilar comparison group in this study. The Amsterdam population (comparison group) was substantially demographically different from the day care workers (DCW) in every variable measured (Table 1). For example, Characteristics such as age, having children, and number of children highly correlate with each other and need to be examined independently. The following are the most interesting and clear results that should be the focus of a much shorter paper: (1) independent association between CMV infection and European DCW, (2) independent association between B19 infection and DCW, (3) and the similar positivity of B19 between ethnicities in contrast to CMV and VZV. In the case of VZV, that is established by other studies and not as much in this study.

Major revisions:
1. Results for VZV are the weakest and can be reduced substantially. All sera were tested for antibodies to CMV and B19 with a single test. In contrast, VZV antibodies were measured in the DCW and the Amsterdam groups using different serology tests which may well have performed differently and contributed to the relatively small difference in high VZV prevalence in the 2 groups (100%, 94%). Moreover, no logistic regression analysis was possible to control for obvious confounders of age and ethnicity. Thus, the authors cannot conclude that higher prevalence among DCW was due to exposure to children. Results with these limitations mentioned can be summarized briefly as text and Table 4 can be eliminated.

We revised the section according your advice and deleted table 4.

2. Figure 1 shows higher CMV seroprevalence by country of birth which is well established as the authors note. Many studies have shown that CMV seroprevalence increases with age, as observed with all human herpes viruses. Ref 11 provided by the authors, Staras et al., 2008, examined children and should be replaced with Staras et al., 2006 CID, which examined a large population sample of women of child-bearing age and showed a strong association between CMV seroprevalence and age. Lack of increase with age and decrease between some age groups shown in Fig 1 likely reflect demographic heterogeneity in sample and small sample size. Fig 1 can thus be eliminated or this contradiction with the expected result and the literature can be included in the discussion.

We revised the section according to your advice and deleted figure 1.

Minor revision on CMV serology testing: “Women with dubious and positive results were considered immune.” Need to replace ‘dubious’ with a term that is clear.

We have replaced the word ‘dubious’ with ‘equivocal’.

Optional revision: The authors may consider noting in the Discussion similar infectious fluids for B19 (respiratory droplets) and CMV (saliva) and overlapping transmission routes in a day care setting that could be possibly be reduced by the same precaution measures.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: no competing interests