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Title: Congenital cytomegalovirus infection : disease burden and screening tools : towards newborn screening

Date: 2012-03-29

Chapter 4

The paradox of maternal immunity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model

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Submitted for publication

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Abstract

Background

Maternal immunity to cytomegalovirus (CMV) provides substantial protection against severe congenital CMV disease. Paradoxically, the prevalence of congenital CMV infection increases with CMV seroprevalence in the underlying population.

Objective

To quantify the contribution of non-primary maternal CMV infection on the disease burden of congenital CMV as a function of the seroprevalence in the population.

Methods

A population-based prediction model was developed and applied for a wide range of CMV seroprevalence. Main outcome measures were: the estimated proportion of children with congenital CMV and CMV-related sequelae attributable to non-primary maternal infection, with CMV seroprevalence in the population as independent variable, and the risk for preconceptionally seropositive pregnant women of having a congenitally-infected newborn, compared to this risk for seronegative pregnant women, as a function of the seroprevalence.

Results

Both the proportion of newborns with congenital CMV infection and the proportion of newborns with sequelae, attributable to non-primary maternal infections increased with CMV seroprevalence in the underlying population. These proportions ranged up to 96% (95%CI 88-99%) and 89% (95%CI 26-97%), respectively, in populations with seroprevalence of 95%.

Furthermore, seropositive pregnant women were found to be at higher risk of having a congenitally infected newborn than seronegative pregnant women, for all population CMV seroprevalence values. In contrast, seropositive pregnant women were at lower risk of having a newborn with sequelae related to congenital CMV than seronegative pregnant women.

Conclusions

Our data stress the impact of non-primary congenital CMV infection on the disease burden of congenital CMV, among all (sub)populations. Awareness of the risk for seropositive women of having a newborn with CMV-related sequelae will have significant consequences for preventive strategies including hygiene counseling, maternal serological screening, and immunization studies.

Background

Congenital cytomegalovirus (CMV) infection is an important public health problem with approximately 7 in 1,000 newborns affected.¹ Approximately one in five congenitally infected infants will suffer from long-term neurological sequelae, with hearing impairment being encountered most frequently.² Primary maternal CMV infection during pregnancy is transmitted to the fetus in 32 percent of the cases, whereas the transmission risk in CMV seropositive women is about 30-fold lower.¹ Moreover, severe symptoms at birth and long-term sequelae are seen more frequently among congenitally infected newborns from preconceptionally CMV seronegative than seropositive women², indicating that acquired maternal immune response provides substantial protection against harmful infection in the newborn. Thus, preventive measures for congenital CMV have mainly been focused on preconceptionally seronegative women.

Paradoxically, a positive correlation between the birth prevalence of congenital CMV and CMV seroprevalence in the underlying population has been found, with birth prevalence ranging from 0.3% to 2% or higher in (sub)populations with CMV seroprevalence of 30% to 98%.^{1;3;4} Recent calculations addressed the contribution of non-primary maternal CMV infections to the number of congenital CMV infections in the United States⁵ and demonstrated their non-negligible impact. The precise effect of the CMV seroprevalence in the underlying population on the proportion of congenitally infected children with sequelae born to seropositive mothers is largely unknown.

To quantify the contribution of non-primary maternal CMV infection on the disease burden of congenital CMV as a function of the seroprevalence in the population, a prediction model was developed, and applied for a wide range CMV seroprevalence.

Methods

A population-based prediction model was developed, estimating the proportion of children with congenital CMV infection and CMV-related sequelae for non-primary and for primary maternal infection, with seroprevalence in the underlying population as an independent variable. After development, the model was applied for a wide range of CMV seroprevalence.

Model development

The proportion of children with congenital CMV infection and CMV-related sequelae in a population, as a function of the seroprevalence, was estimated as the sum of the proportion of newborns with congenital CMV infection and CMV-related sequelae from seropositive women and from seronegative women (Figure 1). The risk of seropositive pregnant women of having a newborn with congenital CMV infection was composed of the maternal-to-fetal transmission rate in seropositive women. The risk of having a newborn with congenital CMV infection and CMV-related sequelae for seronegative women was composed of the product of the rate of seroconversion during pregnancy and the maternal-to-fetal transmission rate after primary maternal infection. Parameters in this model were based on sero-survey data in the literature, and were estimated as follows.

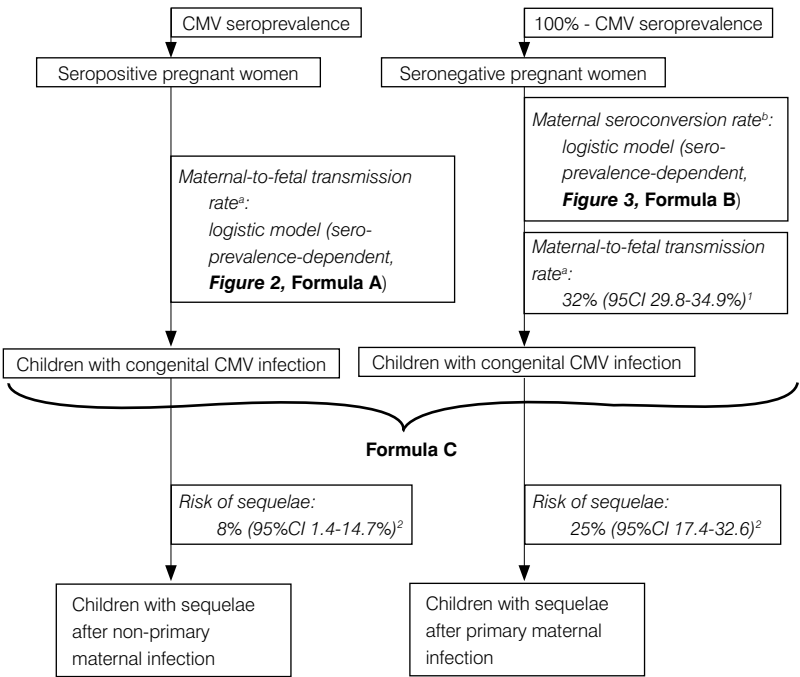


Figure 1 Flow diagram summarizing the model used in this study, estimating the number of children with congenital CMV and CMV-related sequelae, as a function of the seroprevalence in the underlying population, classified by maternal preconceptional CMV IgG seroimmune status.
^a; per pregnancy, ^b; per year

Maternal-to-fetal transmission rate in seropositive women

The maternal-to-fetal transmission rate in seropositive women, as a function of the seroprevalence in the underlying population, was estimated by performing an analysis of the raw data from reports on the CMV birth prevalence among preconceptionally CMV IgG seropositive women⁶⁻¹², listed in a meta-analysis by Kenneson et al.¹ We combined these birth prevalence data with CMV seroprevalence data from the original reports. Only reports with seroprevalence data representative for the underlying population were included (N=7, Figure 2).⁶⁻¹² We fitted a logistic regression model on these data-points (curved line) and included random effects to account for heterogeneity between the studies, computing

$$P(\text{CMV newborn} \mid \text{seropos. pregnancy}) = \frac{1}{1 + \exp(6.15 - 2.44 \times \text{seroprevalence})}$$

(Formula A)

In this logistic regression model, CMV seroprevalence was a predictor of the birth prevalence among newborns from seropositive mothers ($p = .067$, χ^2 test, two-sided).

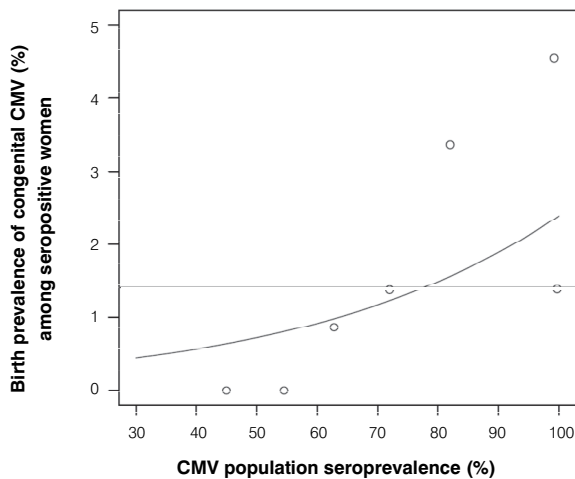


Figure 2 Birth prevalence of congenital CMV among preconceptionally CMV IgG seropositive women (%), as a function of CMV seroprevalence in the underlying population, for each study group.⁶⁻¹² The curved line is our logistic regression fit. Each circle represents a study group, previously listed by Kenneson et al.¹

Maternal seroconversion rate

To quantify the effect of CMV seroprevalence in the underlying population on the seroconversion rate during pregnancy, we fitted a logistic regression model on the combined raw data of the studies listed in meta-analysis by Hyde et al¹³ and Wang et al⁵ (Figure 3). Hyde et al¹³ analysed studies with data on annual CMV seroconversion rates among pregnant women combined with CMV seroprevalence in the study population (N=24 data points).^{10-12;14-32} Wang et al⁵ reported data on annual CMV seroconversion rates combined with CMV seroprevalence data among several ethnic subgroups in the United States (N=12), extracted from Colugnati et al.³³ We fitted a logistic regression model on these data-points (curved line) and included random effects to account for heterogeneity between the studies, computing

$$P(\text{Maternal seroconversion}) = \frac{1}{1 + \exp(6.54 - 3.83 \times \text{seroprevalence})}$$

(Formula B)

In this logistic regression model, CMV seroprevalence was a significant predictor of the birth prevalence among newborns from seronegative mothers ($p < .0001$, χ^2 test, two-sided).

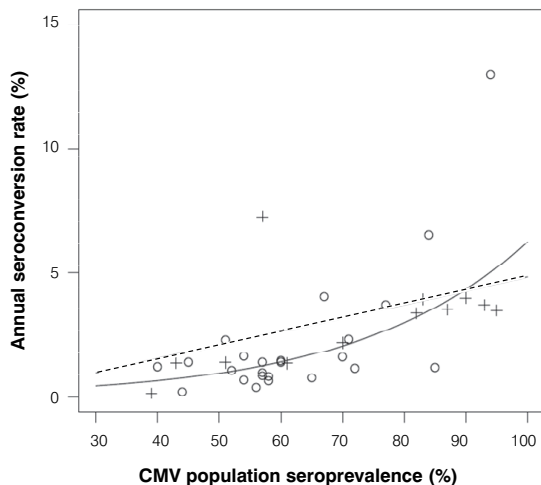


Figure 3 Annual seroconversion rates (%) among seronegative pregnant women, as a function of CMV seroprevalence in the underlying population, for each study group. The curved line is our logistic regression fit, the straight line represents the linear fit of Hyde et al.¹³ Circles represent data from studies reported by Hyde et al¹³, crosses represent data from subpopulations reported by Wang et al⁵.

Maternal-to-fetal transmission rate

The maternal-to-fetal transmission rate following seroconversion was estimated in a previous meta-analysis by Kenneson et al¹ as 32% per pregnancy (95% confidence interval (CI) 29.8%-34.9%).

Overall proportion of congenital CMV

The overall proportion of children with congenital CMV in a population, as a function of the seroprevalence, was the sum of the proportion of newborns with congenital CMV from non-primary and from primary maternal infections, including the proportion of seropositives and seronegatives in the population (seroprevalence and 1-seroprevalence, respectively), resulting in

$$P(\text{CMV newborn} | \text{population}) = \frac{\text{seroprevalence}}{1 + \exp(6.15 - 2.44 \times \text{seroprevalence})} + \frac{0.32 \times (1 - \text{seroprevalence})}{1 + \exp(6.54 - 3.83 \times \text{seroprevalence})}$$

(Formula C)

Risk of sequelae related to congenital CMV

The risk of having a newborn with sequelae related to congenital CMV as a function of the seroprevalence was estimated by supplementing the model with the risk of sequelae following non-primary and primary maternal infection (8% and 25%, respectively²). Congenital CMV-related sequelae were defined as sensorineural hearing loss, IQ ≤ 70 , chorioretinitis, microcephaly, seizures, paresis or paralysis, and death.²

Model application

To quantify the effect of the CMV seroprevalence in the underlying population on the contribution of non-primary maternal infection, the developed model was applied for a wide range of (worldwide present) CMV seroprevalence (30-95%). Outcome measures were the number and proportion newborns with congenital CMV and CMV-related sequelae, and the relative risk for seropositive women.

Newborns with congenital CMV

For CMV seroprevalence 30-95%, the number of children with congenital CMV per 10,000 births for non-primary infection was estimated ($10,000 \times \text{seroprevalence} \times \text{Formula A}$) and for primary infection ($10,000 \times (1 - \text{seroprevalence}) \times \text{Formula B} \times 0.32$).

Additionally, for CMV seroprevalence 30-95%, the proportion (%) of children with congenital CMV attributable to non-primary and primary maternal infection,

relative to the total number of children with congenital CMV was estimated ($\frac{\text{Seroprevalence} \times \text{Formula A}}{\text{Formula C}}$ and $\frac{(1 - \text{Seroprevalence}) \times \text{Formula B} \times 0.32}{\text{Formula C}}$, respectively).

Sequelae related to congenital CMV

The number and proportion of children with sequelae attributable to non-primary and primary infection, for CMV seroprevalence 30-95%, was estimated by supplementing the estimates of the number and proportion of newborns with the risk on sequelae described above.

Relative risk for seropositive women

For CMV seroprevalence 30-95%, the risk (relative risk, or risk ratio, RR) for preconceptionally seropositive pregnant women of having a newborn with congenital CMV and CMV-related sequelae estimated, relative to this risk for seronegative pregnant women ($\frac{\text{Formula A}}{\text{Formula B} \times 0.32}$ and $\frac{\text{Formula A} \times 0.08}{\text{Formula B} \times 0.32 \times 0.25}$, respectively).

Sensitivity analysis

Simultaneous 95% confidence intervals (CI) were computed using Monte Carlo simulations³⁴ (10,000 runs) in which all parameters (maternal-to-fetal transmission rate for seropositive and for seronegative women, maternal-to-fetal transmission rate, and risk on sequelae after non-primary and primary maternal infection) were varied simultaneously. Single-point estimates were selected for each parameter from the respective probability distributions for each evaluation run. 95% CIs, incorporated the uncertainty surrounding each variable.

All statistical analysis were conducted using R (version 2.11.1).

Results

Model application

Newborns with congenital CMV

The estimated number and proportion of newborns with congenital CMV attributable to non-primary and for primary maternal infections, for CMV seroprevalence 30-95% in the underlying population, is shown in Figures 4 and 5.

For example, in a population with 50% CMV seroprevalence, 36 newborns with congenital CMV per 10,000 births were estimated to be attributable to non-primary infections (Figure 4A) and 15 newborns with congenital CMV were attributable to primary infections (Figure 4B). This results in a birth prevalence of congenital CMV of

51 per 10,000 births. The proportion of congenital CMV attributable to non-primary infections in that population is 70% (36 per 10,000 / 51 per 10,000 births) (Figure 5A). The estimated number of newborns with congenital CMV attributable to non-primary maternal infections increased with CMV seroprevalence, and ranged from 13 (95%CI 1-54) to 202 (95%CI 82-345) per 10,000 births for seroprevalence of 30% to 95% (Figure 4A). In contrast, the number of newborns with congenital CMV attributable to primary maternal infections ranged from 10 (95%CI 4-16) to 8 (95%CI 4-13) per 10,000 births for seroprevalence of 30% to 95% (Figure 4B). The proportion of newborns with congenital CMV attributable to non-primary maternal infections increased with CMV seroprevalence, and ranged from 57% (95%CI 24-85%) to 96% (95%CI 88-99%) in populations with CMV seroprevalence of 30% to 95% (Figure 5A).

Sequelae related to congenital CMV

In a similar way, the estimated number and proportion of newborns with sequelae related to congenital CMV (including sensorineural hearing loss) for CMV seroprevalence 30-95% in the underlying population are shown in Figures 4C/D and 5B.

For example, in a population with 50% CMV seroprevalence, 43% of the congenital CMV infections with sequelae were attributable to non-primary maternal infections (3 infected newborns born to seropositive women per 10,000 births, out of in total 7 congenitally infected newborns per 10,000 births).

Both the number and proportion of congenitally infected children with CMV-related sequelae attributable to non-primary maternal infections increased with CMV seroprevalence in the underlying population. The estimated number of children with sequelae attributable to non-primary infections ranged from 1 (95%CI 0-4) to 16 (95%CI 0-37) per 10,000 births in populations with CMV seroprevalence of 30% to 95%(Figure 4C). In contrast, the number of children with sequelae attributable to primary infections ranged from 3 (95%CI 1-5) to 2 (95%CI 1-4) per 10,000 births in populations with CMV seroprevalence of 30% to 95%(Figure 4D).

The proportion of congenital infections with sequelae attributable to non-primary infections ranged from 29% (95%CI 2-70%) to 89% (95%CI 26-97%) in populations with CMV seroprevalence of 30% to 95% (Figure 5B). Non-primary CMV infections were estimated to account for the majority of children with CMV-related sequelae among populations with seroprevalence values of 63% and higher.

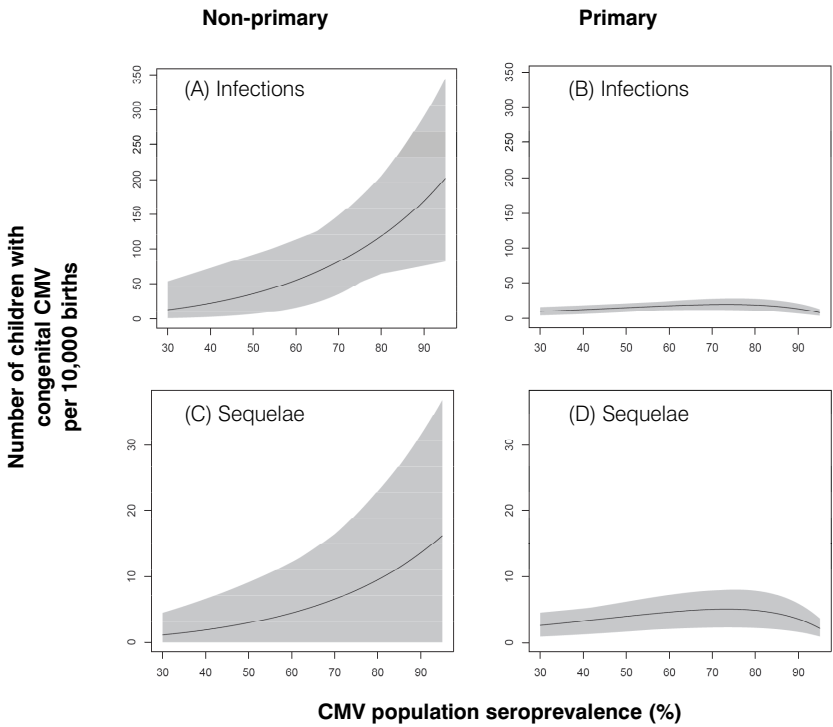


Figure 4 A/B: The estimated number of newborns with congenital CMV per 10,000 births, as a function of the CMV seroprevalence in the underlying population, classified by non-primary (A) and primary maternal infection (B). C/D: The estimated number of children with congenital CMV-related sequelae per 10,000 births, as a function of the CMV seroprevalence in the underlying population, classified by non-primary (C) and primary maternal infection (D). Sequelae include sensorineural hearing loss, $\text{IQ} \leq 70$, chorioretinitis, microcephaly, seizures, paresis and paralysis, and death.² Grey zones represent 95% CIs.

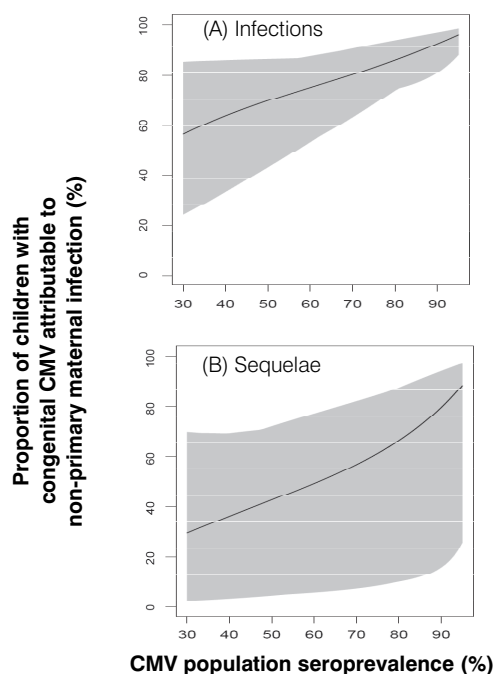


Figure 5 Estimated proportion (%) of children with congenital CMV (A) and CMV-related sequelae (B) born to seropositive mothers, relative to the total number of children with congenital CMV and CMV-related sequelae respectively, as a function of the seroprevalence in the underlying population.

Relative risk for seropositive women

The estimated risk for preconceptionally seropositive women of having a newborn with congenital CMV and CMV-related sequelae, compared to this risk for seronegative pregnant women (relative risk, RR), is shown in Figure 6. E.g., in a population with 50% seroprevalence, the relative risk for seropositive women of having newborn with congenital CMV was 2.3 (absolute risk for seropositive women / absolute risk for seronegative women in that population, 0.72% / 0.31%).

For all CMV seroprevalence values, seropositive women were at higher risk of having a congenitally-infected newborn than seronegative women ($RR > 1$), with a relative risk of 3.0 (95%CI 0.7-27) to 1.3 (95%CI 0.6-3.5) in populations with CMV seroprevalence of 30% to 95% (absolute risks of 0.44% / 0.15% to absolute risks of 2.12% / 1.67%). In contrast, the risk of having a child with sequelae related to congenital CMV was lower for seropositive women ($RR < 1$), for all seroprevalence values. This relative risk ranged from 0.97 (95%CI 0.06-12) to 0.41 (95%CI 0.05-1.80) in populations with CMV seroprevalence of 30% to 95% (absolute risk of 0.04% / 0.04% to absolute risks of 0.17% / 0.42%). This is similar to a 1.0 to 2.5 times higher relative risk for seronegative women compared to seropositive women.

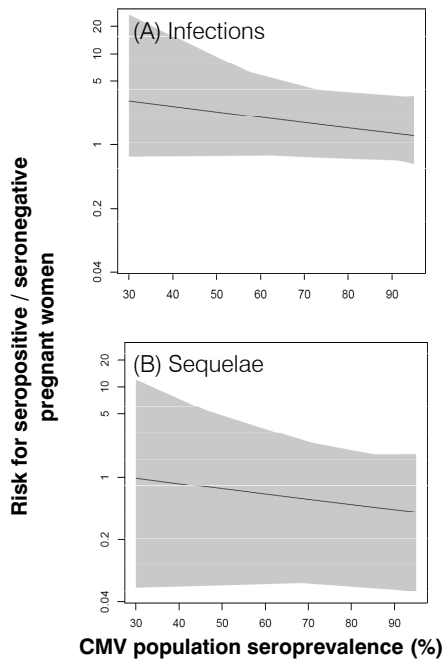


Figure 6 The estimated risk (RR) for preconceptually seropositive pregnant women of having a child with congenital CMV (dotted line) and CMV-related sequelae (continuous line), relative to this risk for seronegative pregnant women, as a function of the seroprevalence.

Discussion

Using our model, we found that both the number and the proportion of newborns with congenital CMV infection attributable to non-primary maternal infections increased with CMV seroprevalence in the underlying population. Importantly, both the number and proportion of newborns with sequelae attributable to non-primary maternal infections was also highest in highly seroprevalent populations. Furthermore, seroimmune pregnant women were found to be at higher risk of having a congenitally infected newborn than seronegative pregnant women, for all population CMV seroprevalence values. This relative risk was up to three times higher among seroimmune pregnant women in populations with low CMV seroprevalence values, and decreased with CMV seroprevalence in the population. In contrast, seropositive pregnant women were at lower risk of having a newborn with sequelae than seronegative pregnant women.

Our findings are supported by earlier findings⁷ and recent calculations on the absolute number of congenital CMV infections in the United States attributable to non-primary maternal infections.⁵ Additional to these reports, our model predicted the contribution of non-primary infections for a wide range of CMV seroprevalence, and took into account an exponential effect of CMV seroprevalence on both the maternal-to-fetal transmission rate and the seroconversion rate. Furthermore, we added the risk for sequelae to these population-based estimates.

Parameters used in our model were based on data from previous studies listed in recent and extensive meta-analysis, and robustness of the parameters was assessed in our sensitivity analysis. It must be noted that the estimated proportion of newborns had wide 95%CI, resulting from the denominator (total congenital infections), combined with the crude estimate of the risk for sequelae, and should therefore be interpreted with care.

It would be of interest to quantify the contribution of non-primary CMV infection on different sequelae separately, since it may well be that sequelae associated with primary infection are more severe than sequelae associated with non-primary infection.² However, outcomes from studies assessing e.g. hearing impairment following non-primary maternal infections vary widely^{2,4,35}, and render it difficult to produce reliable estimates on the risk on these different sequelae to date. A complicating factor might be that the severity of disease, including hearing loss, following primary infections may vary with gestational age at infection.^{36,37} More detailed studies are needed to calculate the exact impact of non-primary maternal infections on the different sequelae separately, as a function of the seroprevalence.

The apparent contradiction of maternal immunity as a risk factor for congenital CMV can be understood as follows. Once infected, previously seronegative pregnant women are at much higher risk of transmitting CMV to their fetuses compared to preconceptionally seropositive pregnant women. However, it is also necessary to include the risk of actually acquiring an infection. If this risk is also taken into account, seropositive pregnant women are at higher risk of having a congenitally infected newborn compared to preconceptionally seronegative pregnant women. The risk of re-infection or reactivation in seropositive pregnant women outweighs the combined risks of the risk of acquisition and transmission in seronegative pregnant women. Recent serological studies assessing strain-specific CMV antibody responses have shown that maternal re-infection with a new strain is a major source of congenital infection in seroimmune women, with re-infection occurring in 8% of the seroimmune pregnancies.³⁸ The circulation of CMV or the force of infection appeared to be highest in highly seroprevalent populations, based on age-specific seroprevalence data.^{33,39} Differences in acquisition rates between high and low seroprevalent (sub)populations seem plausible given their difference in first exposure, and are likely based on environmental and behavioral differences.

Our data stress the relevance of non-primary maternal congenital CMV infection for the disease burden of congenital CMV, among all (sub)populations. Awareness of the risk for seroimmune pregnant women of having a congenitally infected and neurologically disabled newborn will have significant consequences for preventive strategies to reduce the disease burden of congenital CMV. Preventive measures such as hygienic behavior should be advised for both seronegative and seroimmune pregnant women. In that case, prenatal maternal serological screening will be futile as long as no adequate intervention is available. Awareness of the fact that CMV seroimmunity is only partially protective for congenital infection raises questions on the role of re-infections with new strains and reactivations of latent virus in seroimmune pregnant women. Passive and active immunization efforts will be challenged since the induction of a specific CMV immune response may not fully protect against fetal infection and disease, and an immunological correlate of full protection is lacking. A CMV glycoprotein B vaccine boosted immunity in CMV seropositive women⁴⁰, however a potential effect on maternal to fetal transmission rate and congenital CMV disease remains to be tested. In short, awareness of the paradox of maternal seroimmunity as a risk factor for congenital infection as addressed in this study will have significant consequences for preventive strategies including hygiene counseling, maternal serological screening, and immunization studies.

Acknowledgment

We thank Friedo W. Dekker (Dept. of Clinical Epidemiology, LUMC, Leiden, the Netherlands) for critically reading the manuscript.

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