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Research article

Time dependent risk of cytomegalovirus infection in Japan

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Abstract: Cytomegalovirus (CMV), a major cause of congenital infections, has high morbidity and mortality rates associated with it. However, a decline in the proportion of anti-CMV antibody-positive individuals has been observed. The present study aimed to quantify the time-dependent transmission dynamics of CMV infection in Japan by analysing the seroepidemiological datasets for pregnant women collected from five cord blood banks from 1996 to 2009. By employing a mathematical model and using the maternal age distribution of child births from the census data, we computed the seroprevalence among the pregnant Japanese women as a function of time. A decreasing trend was observed for the force of infection, i.e. the rate at which susceptible individuals are infected, which decreased from 0.04 to 0.03 (/year) over the period from 1996 to 2009. While the total number of births has steadily declined in Japan over time, the estimated number of live births at risk of CMV infection has increased over time. Our data reveal that in 2009 in Japan, at least 0.3 million women may have been at risk of contracting a CMV infection during the perinatal period. Moreover, about 2,726 congenital CMV infections were expected to have occurred in 2009. The average age at infection has already reached the child bearing age, and it must be noted that the age at infection can be elevated even more, reaching close to 30 years old which is the ongoing mean age at child delivery. It must be remembered that, if vaccine can become one of the options for the control of CMV in the future, the vaccination can lead to further elevation of age at infection, which may coincide with further elevation of mothers' age of delivery in Japan.

Keywords: cytomegalovirus; mathematical modeling; congenital (intrauterine) infection; force of infection; age at infection

1. Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus and Betaherpesvirinae member [1]. Infections with CMV occur mainly during infancy or adolescence and a substantial fraction of those infections are asymptomatic and, as observed with infections with other herpesviruses, latent infection can continue over a person's lifetime [1]. The infection can sometimes cause infectious mononucleosis and hepatitis, even among immunocompetent individuals [1]. Premature babies and patients with primary immunodeficiency disease who have just undergone transplantation or have acquired immunodeficiency syndrome (AIDS) are particularly susceptible to viral reactivation, which can trigger opportunistic infections such as retinitis, pneumonia, hepatitis and myocarditis [1].

Once CMV infection or reactivation occurs in a pregnant woman, the virus is transferred from the mother to the foetus through the placenta with a high probability, resulting in congenital CMV infection. It has been estimated that 1–4% of antibody-negative pregnant women experience their first CMV infection during pregnancy and that 33–40% of infections in those seronegative women involve their foetus [2]. Some of these foetal infections (10–15%) are clinically relevant, as revealed by low birth weight, premature birth, jaundice, purple skin splotches and/or a rash, hepatosplenomegaly and thrombocytopenia [2]. Moreover, 90% of clinically relevant congenital CMV infections and 10–15% of asymptomatic congenital infections involve sequelae (after effects) that include neurological abnormalities such as hearing loss, mental retardation and visual disability [2,3]. Hearing loss is especially common with CMV infections, accounting for at least 15% of all severe hearing losses [3].

The frequency of post-infection disability attributable to congenital CMV infection is estimated to be 10 among 10,000 live births in Japan [4–6], a rate comparable to the frequency of trisomy 21 (i.e. Down's syndrome), which is estimated at 9.6 per 10,000. Nevertheless, the infection is mostly asymptomatic, meaning that timely laboratory testing for it is considered difficult to be practiced, and few methods exist that can confirm the causality of any apparent disability as originating from CMV infection. Thus, it is believed that a substantial number of CMV-associated disabilities are overlooked. Considering that the transmission of CMV is potentially associated with socioeconomic status [7], epidemiological monitoring of the frequency of infection with it and its variations as a function of time due to time-varying economic climate is of utmost importance.

Recently, a decline in the observed proportion of people who are CMV antibody-positive has been highlighted in several countries including Japan [4,5,8–11]. This decline implies that the risk of congenital infection has possibly been increasing among women of around child bearing age. That is, paradoxically, the decline in the force of infection offers an opportunity for pregnant women, who were supposed to have been already immune in the past, to experience primary infection during pregnancy due to reduced frequency of infection in childhood. To obtain more information on this, the present study aimed to quantify the time-dependent transmission dynamics of CMV infection in Japan, by analysing the seroepidemiological datasets available for pregnant women.

2. Materials and method

2.1. Epidemiological data

The present study rests on the published seroepidemiological data collected from 1996 to 2009

in Japan [4]. The prevalence of anti-CMV IgG antibodies was assayed using serum samples from five cord blood banks in Sapporo, Tokyo, Osaka/Kyoto, Okayama and Fukuoka. Among the pregnant women who agreed to store cord blood in advance of their delivery or operation, maternal serum samples were also obtained and those maternal samples were examined for antibody prevalence. From 1996 to 2007, the particle agglutination method was employed to measure anti-CMV IgG antibodies, except in Kyoto and Sapporo where the enzyme immunoassay (EIA) method was employed until 2002 after which it was replaced by the microparticle EIA in 2003 to 2007. Then, in 2008 and 2009, all sites employed the chemiluminescence EIA method. In total, 22,100 serum samples were examined [4]. Individual age of sampled mothers was not available. However, we have an access to mothers' age at delivery from the census for the entire Japan in every year. Thus, in addition to the seroprevalence data, we also extracted the maternal age distribution for child births from 1996 to 2009 from the Vital Statistics of Japan (published by the Ministry of Health, Labour and Welfare, Japan) [12].

2.2. Mathematical model

The observed seropositive fraction represents maternal antibody data as a function of time. Here, we employed a mathematical model to capture the time-dependent transmission dynamics of CMV from the seroprevalence data. Let $S(a,t)$ be the fraction of susceptible individuals at age a and year t. Assuming that everyone is born susceptible to CMV and discarding maternal antibodies, we have the boundary condition $S(0,t) = 1$ for any t. Using the force of infection, i.e. the rate at which susceptible individuals experience infection, that depends on age a and year t, $\lambda(a,t)$, the susceptible individuals are reduced, i.e.,

$$\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial t}\right) S(a,t) = -\lambda(a,t)S(a,t) \tag{1}$$

The force of infection is usually modelled as what it depends on the prevalence of infection in the population. We do not decompose the force of infection, but assume that the force of infection can vary with time and age. Namely, we assume that the force of infection is separable into age- and time-components, and moreover, that the force of infection is age-independent as is assumed in the tuberculosis model [13], i.e.,

$$\lambda(a,t) = f(a)\lambda(t), \tag{2}$$

and moreover,

$$\lambda(0,t-a) = \lambda(a,t-a) = \lambda(t-a) \tag{3}$$

Namely, $\lambda(a,t) = \lambda(t)$. Integrating both sides of (1), we obtain

$$S(a,t) = S(0,t-a)\exp\left(-\int_{t-a}^{t}\lambda(s)\,ds\right) = \exp\left(-\int_{t-a}^{t}\lambda(s)\,ds\right) \tag{4}$$

Parametrically modelling $\lambda(t)$ as an exponentially decreasing function with year t, i.e., $\lambda(t) = \lambda_0 exp(-\beta t)$, we have

$$S(a,t) = \exp\left(-\int_{t-a}^{t}\lambda_0 exp(-\beta s)\,ds\right), \tag{5}$$

where λ_0 and β are the parameters to be estimated. Let $b(a,t)$ be the relative frequency of live births as a function of age a in year t. The expected seropositivity is modelled as

$$p(t) = \int_0^\infty b(a,t)\{1 - S(a,t)\}\, da, \tag{6}$$

in year t.

To quantify the force of infection, we employed a likelihood-based approach. Given that there were m_t positive women among the total of serum samples drawn from n_t women in year t, the likelihood function to estimate parameter θ was modelled as

$$L(\theta: \boldsymbol{n}, \boldsymbol{m}) = \prod_{t=1996}^{2009} \binom{n_t}{m_t} p(t)^{m_t} \big(1 - p(t)\big)^{n_t - m_t} \tag{7}$$

The 95% confidence intervals (CI) of estimated parameters were computed using the profile likelihood. The 95% CI of model predictions was computed by using the parametric bootstrap, employing the covariance matrix and randomly resampling parameters from a multivariate normal distribution. Not only the entire Japan estimate, but the force of infection was estimated by the geographic location of the cord blood bank.

Once unknown parameters are estimated, we calculated the mothers at risk of infection in year t by

$$B(t) \int_0^\infty b(a,t) S(a,t)\, da, \tag{8}$$

where $B(t)$ represent the total number of live births in year t. Similarly, we calculated the expected number of live births with CMV infection, $q(t)$, by

$$q(t) = B(t) \int_0^\infty b(a,t) S(a,t) \left\{1 - \exp\left(-\int_{t-\theta}^{t} \lambda_0 exp(-\beta s)\, ds\right)\right\} da, \tag{9}$$

where θ is the gestational age at risk of congenital CMV infection during the period of one year, which we assumed at 16/52.

3. Results

From a total of 22,100 samples, 16,191 were revealed to be positive, with the sample proportion positive estimated at 73.3% (95% CI: 72.7, 73.8). As a function of time, the highest proportion of positive was estimated at 82.5% in 1996, and the lowest was 70.3% in 2004. Figure 1A shows the observed sample proportion as a function of time. By linearly regressing the sample proportion by year, the seropositive fraction has decreased every year by 0.7% ($p < 0.001$).

$\lambda(t) = \lambda_0 exp(-\beta t)$, the assumed parametric function for the force of infection, approximately captured the observed time trend for the seropositive fraction (Figure 1A). λ_0 was estimated at 0.15 (95% CI: 0.10, 0.20), and the exponential decrease rate β was 0.024 (95% CI: 0.017, 0.030). Figure 1B shows the reconstructed force (hazard) of infection among susceptible individuals by year. A decreasing trend was observed in the estimated force of infection, and a decrease of 0.04 to 0.03 (/year) was observed over the period from 1996 to 2009. In a stationary population, a decline indicates that the average age at infection is elevated from 1/0.04 = 25.0 years to 1/0.03 = 33.3 years

during the study period.

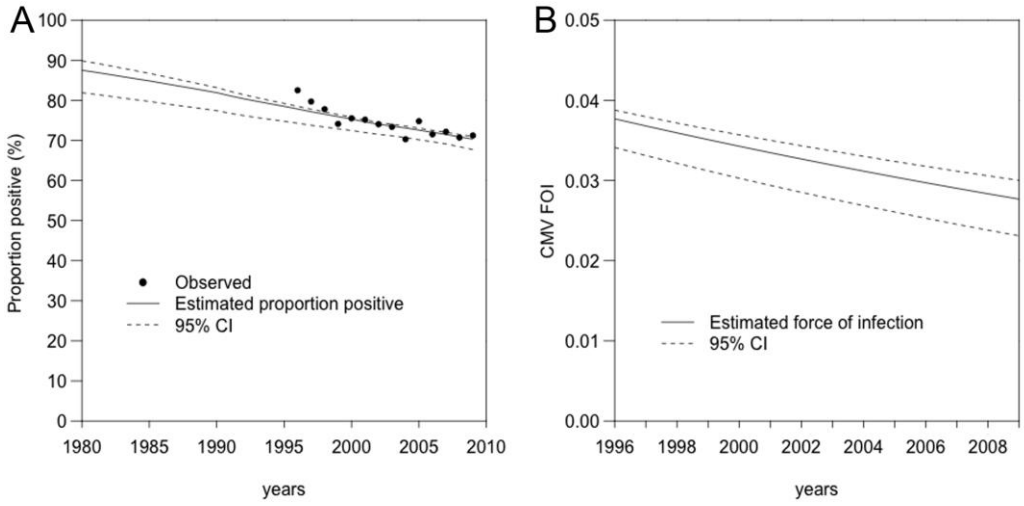

Figure 1. Seroepidemiological trends in anti-cytomegalovirus (CMV) antibodies among pregnant women in Japan over time. A. Observed (dot) and estimated (line) proportion pregnant women positive for cytomegalovirus (CMV)-IgG antibodies in Japan. Black dots represent the observed proportions from 1996 to 2009. The solid line represents the estimated proportion from 1980 to 2009, with the upper and lower 95% confidence intervals shown as dashed lines. B. Estimated force of infection (FOI) for CMV in Japan. The two dashed lines represent the upper and lower 95% confidence intervals as computed by the profile likelihood. CMV FOI (the vertical axis unit) is per year.

Figure 2A shows the age-specific immune fraction for the people by year (i.e., 1980, 1990, 2000 and 2009). A rightwards shift was observed in the age-dependent seroprevalence curve, reflecting a time-dependent decline in the force of infection. From 1980–2009, the median age of infection was elevated from 10.0 years old to 19.7 years old. This delay in infection is also overlaid with a delay in child delivery age, as shown in Figure 2A. From 1980–2009, the mode for the maternal age of live births was elevated from 26 years old to 29 years old. Would this age shift help avoid the increased risk of CMV infection among pregnant women? The answer is no, as shown in Figure 2B. While the total number of births has steadily declined in Japan over time, the estimated number of live births at risk of CMV infection has increased over time. In 1996, the estimated pregnant women at risk of primary infection were estimated at 268,000 persons, and the figure continuously increased over time. In 2009, at least 0.3 million women were considered to have been at risk of CMV infection during the perinatal period. The estimated total number of congenital CMV infection events was 3,124 in 1996, and the estimate has decreased over time to 2,726 in 2009 due mainly to natural decline in the total number of live births.

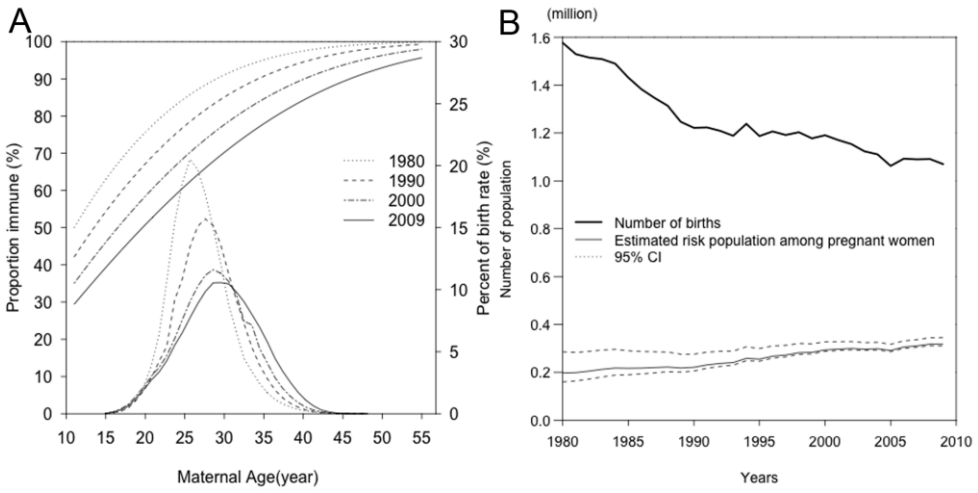

Figure 2. Estimated populations at risk of CMV infection in Japan. A. Comparison of the age-specific frequency of live births and age-dependent proportion of immune individuals. Using the time-dependent force of infection mathematical modelling described in the Methods section, the immune fraction was computed for the years 1980, 1990, 2000 and 2009. B. Comparison of the time trends between the total number of live births (bold line) and the number of live births at risk of contracting a CMV infection. The solid line represents the maximum-likelihood estimate, and the dashed lines represent the lower and upper 95% confidence intervals, (CIs) as computed by the bootstrap method.

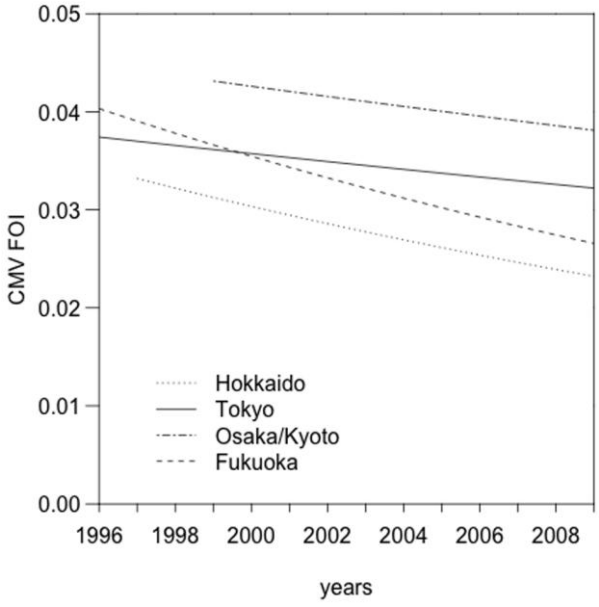

Figure 3. Force of infection (FOI) comparison for CMV in multiple Japanese cities from 1996 to 2009. The maximum-likelihood estimates for Hokkaido, Tokyo, Osaka/Kyoto and Fukuoka are compared. CMV FOI (the vertical axis unit) is per year.

Figure 3 compares the time-dependent patterns of the estimated force of infection against the different geographic locations of the cord blood banks in Japan. While a time-dependent decline was evident in Hokkaido and Fukuoka, the rate of decline in the force of infection was slower in Tokyo. Depending on the geographic location, the estimate was observed to vary widely. Although the rate of decline was not significantly different among four different geographic regions, the increased range for the force of infection in 2009, as compared with those in earlier years, implies that geographic heterogeneity is likely to have increased.

4. Discussion

The present study examined the time trend for the force of infection with CMV in Japan by analysing the seroprevalence survey data from pregnant women as a function of time. By employing a mathematical model and using the maternal age distribution of child births from Japanese vital statistics, we computed the seropositivity (i.e. probability of being seropositive) among pregnant women by year. By fitting the computed probability to the observed seropositive data, we have shown that the observed decline in the proportion of CMV-positive pregnant women mirrors the steadily declining force of infection over time.

To the best of our knowledge, the present study is the first to objectively show that the force of infection for CMV has declined over time in Japan. It is noteworthy that the estimate was obtained using the data from blood samples from pregnant women only. Numerous published epidemiological study results have indicated that the seroepidemiological characteristics of CMV have changed over time and age (e.g. studies in the USA [9] and China [10], and a mathematical modelling study that also explored the risk of infection at the population level in Brazil [8]). A possible age shift for CMV infection has also been discussed in some modelling studies [8,10], including those whose focus was on future vaccination against the disease [8,14–16]. Our study results augment the literature by showing that the age at which CMV infection is acquired has been naturally elevating over time, a trend that we were able to successfully reconstruct using the data for serum samples from the pregnant women alone. The exact reasons for the decline remain unexplored, but considering that CMV is transmitted through direct contact and via environment, reduced physical contact over time and improved hygienic conditions can be possible speculations to explain the observed phenomena. Although regional variations were just reflective of sampling error, slower decline in Tokyo compared with other three cities is in line with the notion of improved hygiene: Tokyo has already been urbanized for the long time compared with other cities.

We have focused on the fact that the age at child delivery has increased over time while a monotonic decline in the total number of live births also occurred [17]. Despite the declining birth rate, we have shown that the age of infection with CMV has been increasing over time, and the population size for women at risk of CMV infection has also increased over time. In fact, as many as 0.3 million births in Japan each year will contain babies who are susceptible to CMV infection during the perinatal period, indicating the importance of continuously monitoring the age of infection in relation to the childbearing age of women. The average age at infection has already reached the child bearing age, and it must be noted that the age at infection can be elevated even more, reaching close to 30 years old which is the ongoing mean age at child delivery. It must be remembered that, if vaccine can become one of the options for the control of CMV in the future, the vaccination can lead to further elevation of age at infection. Such elevation may coincide with further elevation of

mothers' age of delivery in Japan.

Our study was not free of limitations. First, we employed an age-independent assumption for the force of infection, which was necessary because the empirical data did not provide any information for the age element. At least, we adjusted the age-dependent frequency of childbirth explicitly, because, in this context, age has been considered to be an important element for regulating the transmission dynamics of CMV [18]. Continual monitoring of pregnant women and stratifying them into multiple age groups would allow for a more accurate estimation to be made in any future studies. Second, an exponential model alone was employed to parametrically capture the time trend for the force of infection. As shown in Figure 1A, we were not able to gain any additional insight (e.g., more detailed parametric functions) from the data for the time dependence element. Observation for a longer time period is called for. Third, the anti-CMV IgG assay results rested on different laboratory testing procedures from 1996–2007, but we analysed the data collectively, because we did not identify any considerable differences in the observed seroprevalence values from the different testing methods. However, as part of the sensitivity analysis, we were able to examine the geographic heterogeneity element in the force of infection. Fourth, fixed cut-offs used by serological assay might have resulted in underascertainment of seropositive individuals. As already indicated, the fixed cut-off could sacrifice specificity, while sensitivity is ensured to be high [19].

Considering that a natural decline in the force of infection was observed, future studies should ideally explore the impact of introducing mass vaccination into children and women only targeted vaccination policies on the resulting outcome of overall infections and congenital CMV infections, as explored already elsewhere in different settings for both CMV [14–16] and other infectious diseases [20–23]. Reconstructing the time- and age-specific patterns for immune individuals in the population would be a step in the right direction towards designing an object-oriented vaccination program [24–27].

5. Conclusion

The present study analysed the seroprevalence survey data from pregnant women as a function of time, computing the seropositivity among pregnant women by year. By fitting the computed probability to the observed seropositive data, we have shown that the observed decline in the proportion of CMV-positive pregnant women mirrors the steadily declining force of infection over time. Due to the elevated age at infection, pregnant women are exposed to high risk of congenital CMV infections in Japan. Vaccine development is anticipated, but if it is planned for the entire country, the present study recommends close monitoring of the seropositivity over time to avoid artificial increase in congenital infections.

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Conflict of interest

All authors declare there are no conflict in this paper.

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