

Seroprevalence of cytomegalovirus over the last 2 decades (2001–2020): A retrospective data analysis from a single laboratory in Singapore

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Dear Editor,

Cytomegalovirus (CMV) is ubiquitous and infects human of all ages, where it remains latent after primary infection and can reactivate upon various triggers.¹ Reactivated CMV may cause complications and end organ damages in immunocompromised hosts, leading to increased morbidity and mortality.² In addition, the presence of actively replicating CMV during pregnancy can result in congenital sequelae, a leading cause of nongenetic sensorineural hearing loss in children.³ Despite the potential harm, few women of childbearing age in Singapore are aware of this risk.⁴

Worldwide CMV seroprevalence is estimated at 83%, but could vary between 44–100% in different regions depending on the socioeconomic status of the population.^{5,6} With rapid advances in the economy and living standards in Singapore,⁷ a decrease in CMV seroprevalence is expected, as observed in countries with high socioeconomic status. However, little is known regarding this trend over the past decades.

To fill this gap, a retrospective data analysis from a single laboratory was performed on Singapore citizens and permanent residents who had CMV Immunoglobulin G (IgG) result between 2001 and 2020 (Supplementary Material). Only the first result from individuals were included in the analysis. The associations of CMV seroprevalence with age, gender, ethnicity and year of test performed were tested by multivariate logistic regression analysis. Age and year of test were modelled as continuous variables and ordinal variables in separate regression analyses. When categorised into ordinal variables, the year of test performed was stratified into 2 time periods of 10-year intervals: Period 1 (2001–2010) and Period 2 (2011–2020), and the age at time of test was categorised into 6 age groups: 2–14, 15–24, 25–34, 34–44, 45–54, and ≥55 years. Ethnicity was grouped into Chinese, Malays, Indians and Others. Categorical variables were compared using Fisher's Exact test and multiple comparisons were corrected using

the Benjamini-Hochberg false discovery rate method. All analyses were done with R version 4.2.2 (R Core Team 2023).

Results from a total of 16,985 unique individuals aged 2–101 years were included in the multivariate regression analysis (Supplementary Table S1). While CMV seropositivity increased with age (adjusted odds ratio [AOR], 1.082; 95% confidence interval [CI] 1.078–1.085), seroprevalence decreased significantly over 2 decades from a peak of 87.9% (2002) to 73.7% (2020) (Fig. 1A; AOR, 0.951; 95% CI 0.944–0.959). Women were less likely to be seropositive than men (AOR, 0.880; 95% CI 0.802–0.955); Malays (AOR, 2.646; 95% CI 2.351–2.981), Indians (AOR, 1.592; 95% CI 1.367–1.858) and other ethnic groups (AOR, 1.843; 95% CI 1.553–2.195) had higher seropositivity than Chinese.

A significant interaction in multivariate logistic regression was found between age and year of test performed ($P < 0.001$), and to ease further analysis, these variables were categorised as ordinal variables into 6 age groups and 2 time periods respectively (Supplementary Table S1). When stratified by 2 time periods, the seroprevalence was observed to decrease significantly for age groups ≥25 years in Period 2 for both genders (Figs. 1B–C). However, the rates of change in seropositivity were different between sexes. Females reached higher seropositivity at an earlier age group (15–24 years) compared to males, while the largest decline observed for males was in the 25–34 age group but between 35–44 for females (Figs. 1B–1C).

Between the 2 time periods, the seropositivity for Chinese adults ≥25 years decreased significantly. The Malays also experienced a decline in seropositivity across most age groups, with a significant decrease (10%) in the 25–34 age group. Although not statistically significant, the seropositivity for Indians similarly decreased in Period 2. In contrast, other ethnic groups did not show significant changes across the 2 time periods (Supplementary Figs. 1A–D).

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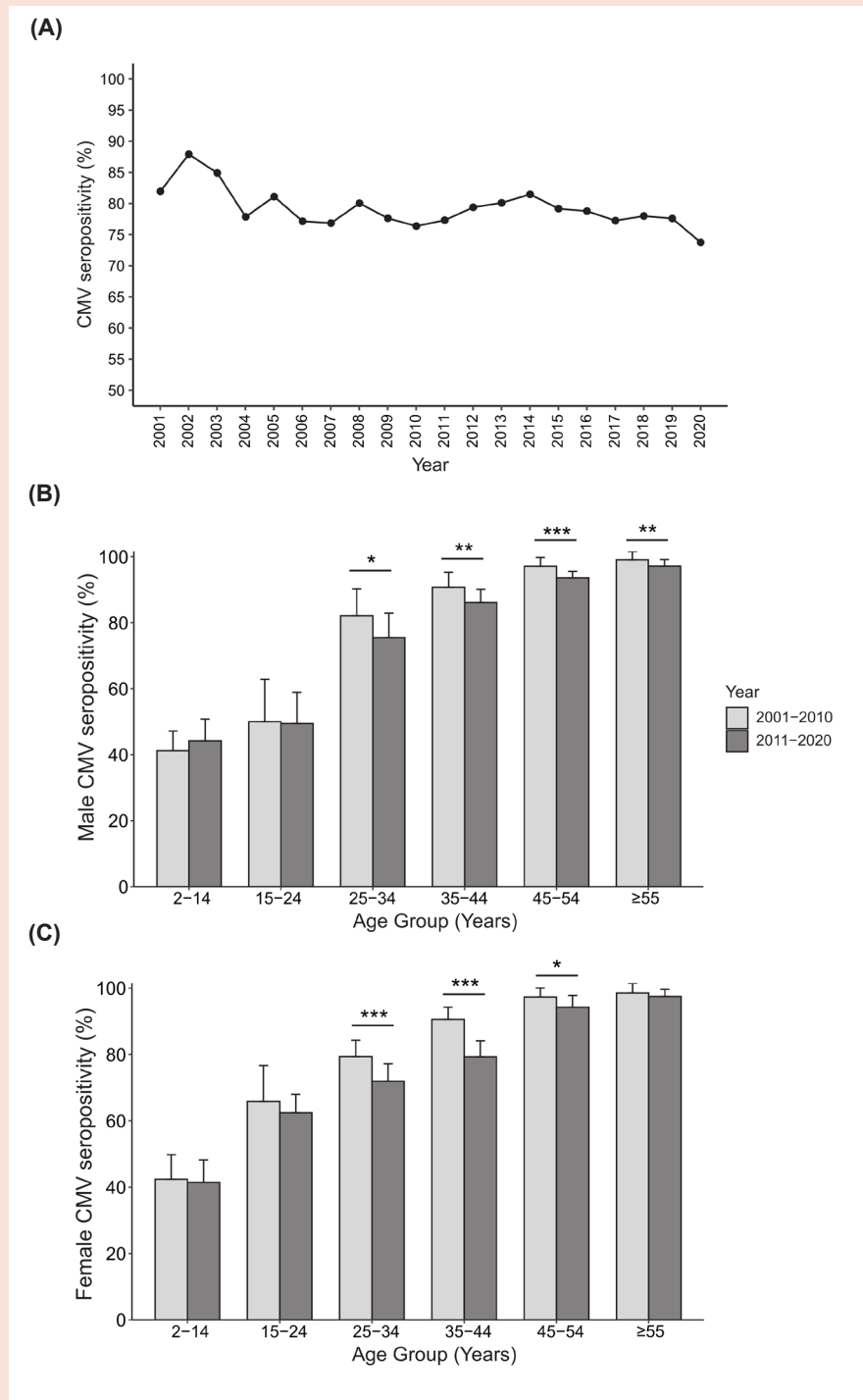
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Fig. 1. Changes in cytomegalovirus (CMV) seroprevalence (A) overall trend over 20 years, (B) male and (C) female by age group over the 2 time periods.



* $P < 0.02$, ** $P < 0.01$, *** $P < 0.001$. Error bars represent standard deviations (SDs).

To correlate the observed change of CMV seroprevalence trend with the socioeconomic status of residents, we extracted data from the Singapore Census of Population surveys.⁸⁻¹¹ The household median incomes of residents doubled from SGD3638 in 2000 to SGD7744 in 2020. Education levels improved considerably, while the proportion of singles has increased every decade

from 2000–2020; in fact, the Chinese had the highest proportion of singles among the ethnic groups. In addition, the average number of children born had decreased for all ethnicities over the past 2 decades. These changes in demographic characteristics and socioeconomic statistics of Singapore residents together with our seroprevalence data are consistent with studies that

demonstrated CMV seroprevalence decreases as countries become more developed.^{5,6}

The significant decrease in CMV seropositivity in females of childbearing age observed in the recent decade in Singapore translates to an increasing proportion of women who are at risk of primary CMV infection during pregnancy. CMV screening is currently not part of routine antenatal care; coupled with the low awareness in the local context, this means that education on CMV transmission and preventive hygiene behaviours is of utmost importance for expectant mothers.⁴

The risk of CMV disease in organ transplant patients is dependent on the serostatus of the donor and recipient, with the highest risk for complications occurring in seropositive donor (D+)/seronegative recipient (R-). Imlay et al. found a significant increase in the proportion of CMV D+/R-mismatch in solid organ transplants that resulted from a disproportionate increase in R- and a smaller corresponding change in D+ over a period of 20 years.¹² More studies would be needed to determine if the decrease in CMV seropositivity locally may result in a similar increase in the number of high-risk CMV D+/R- mismatch, which may have an impact in risk management for organ transplant patients.

Admittedly, the data from this study originate from clinical samples sent by clinicians for various reasons including clinical investigation or as part of screening protocols prior to certain management, which may result in bias in our data set. Nonetheless, indications for testing have not changed, hence the information presented over the past 2 decades remain comparable.

Although still in development, CMV vaccine has been proposed as a preventive measure in the CMV-naïve to prevent primary infection or offer to boost immunity for those already exposed. Our study showed that approximately 42% of the population were already infected with CMV by the age of 15 years; therefore the optimal age for vaccination should be considered at a much earlier age in life for maximum effectiveness. Until an effective vaccine is available, continuous monitoring of changes in seroprevalence is essential to predict the impact of CMV in pregnancies, organ transplant patients and in those who are severely immunosuppressed.

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Declaration

The authors declare no conflicts of interest.

Ethics approval

Institutional review board application and informed consent were not required for this study under the SingHealth Institutional rules for research using unidentifiable data.

Data availability

Aggregated data can be shared on reasonable request to the corresponding author, conditional on ethical vetting.

Keywords: cytomegalovirus, epidemiology, infectious diseases, public health, socioeconomics, statistics

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