

Outcomes of a targeted congenital cytomegalovirus infection screening approach among infants born ≥ 35 weeks gestation

Dear Editor,

Cytomegalovirus (CMV) is a common cause of congenital viral infection. The estimated incidence of congenital CMV (CCMV) is about 1–6% worldwide, although reliable estimates from Singapore and surrounding countries are unavailable.^{1,2} Previous local serologic studies among pregnant women reported high rates of CMV seropositivity ($>80\%$),³ highlighting the possible high burden of CCMV. With the establishment of oral valganciclovir as an effective treatment for infants with CCMV, prompt diagnosis and treatment of infants with symptomatic disease is important to reduce the risk of moderate to severe sensorineural hearing loss (SNHL) and neurodevelopmental impairment.⁴ We report the findings of a targeted CCMV screening approach using failed newborn hearing screen (NHS) or small-for-gestational-age (SGA) status as triggers for screening among infants born ≥ 35 weeks gestation.

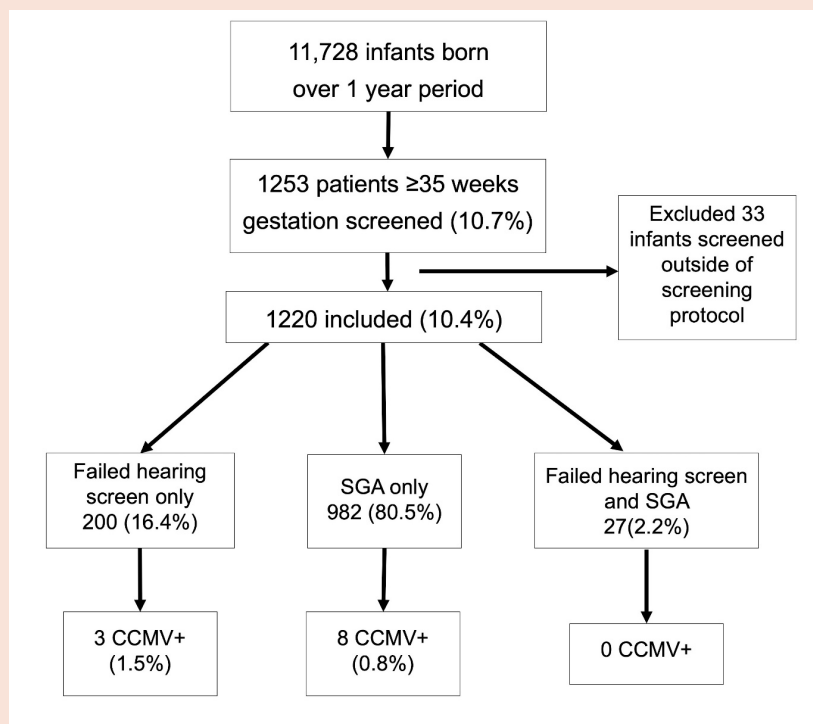
We performed a retrospective evaluation of targeted CCMV screening programme from 1 April 2022 to 31 March 2023 at KK Women's & Children's Hospital, a tertiary-level perinatal centre in Singapore with approximately 12,000 deliveries

annually. Our screening strategy recommended CMV screening by urine polymerase chain reaction (PCR) for all infants born ≥ 35 weeks gestation who failed NHS prior to initial discharge and/or were born SGA (Supplementary Fig. S1). Hearing screen is routinely performed for all newborns using automated auditory brainstem response testing. SGA was defined as birthweight <10 th percentile based on local growth charts.⁵ Urine sample for CMV was collected <21 days of life.

Descriptive analysis was performed with proportions presented with percentages and median expressed with interquartile ranges (IQRs). Data were analysed using SPSS Statistics v23.0 (IBM Corp, US). This study protocol received an exemption from the SingHealth Centralised Institutional Review Board (Reference No: 2023/2345).

Over the 1-year period of our screening protocol, 1220/11,728 infants (10.4%) were screened (Fig. 1). A total of 200 (16.4%) infants were screened for failing NHS, 982 (80.5%) due to SGA, and 27 (2.2%) had both indications (Fig. 1). Eleven infants (0.9%) were diagnosed with CCMV—3/200 (1.5%) NHS failure and 8/982

Fig. 1. The proportion of infants screened and confirmed with congenital cytomegalovirus infection according to indications of the screening programme.



CCMV: congenital cytomegalovirus; SGA: small for gestational age

(0.8%) SGA. There were 2 additional CCMV cases that were detected outside the screening protocol—1 infant born to a mother with non-primary CMV infection during pregnancy and another was screened after her SGA twin was positive.

The mothers of affected infants had a median age of 30.5 years (IQR 29.5–31.5), were predominantly multigravida (69.2%) and majority delivered via vaginal route (61.5%). The affected infants were predominantly female (9/13, 69.2%) with a median testing age of 2 days (Supplementary Table S1). Quantitative blood CMV PCR testing was performed on 11 patients—7/11 (63.6%) had detectable CMV copies when tested as part of the initial workup within <3 weeks of life (range from <500 copies/mL to 780,000 copies/mL) (Supplementary Table S2). All patients had normal initial ophthalmologic examination, and 3 had non-specific findings on cranial ultrasound (2 [15.4%] with thalamostriate vasculopathy, 1 [7.7%] with germinal matrix haemorrhage). Two of the 3 infants with initial failed NHS prior to discharge were started on valganciclovir treatment for CCMV at days 24 and 27 of life. They failed subsequent hearing tests at 2–3 months of life.

Based on our targeted screening strategy, we determined the incidence of CCMV among our group of high-risk infants to be 0.9%. This incidence is higher than the reported estimated pooled incidence of 0.67% (95% confidence interval [CI] 0.54–0.83%) from countries with universal screening of newborns.² Our rates were also about twice the estimated pooled prevalence of 0.48% (95% CI 0.40–0.59%) from 54 high-income countries.² The difference in the rates is very likely due to the targeted approach of our screening programme which sampled a high risk group and constitutes only 10% of the annual birth cohort.

While targeted screening using failed NHS provides a practical approach for the identification of infants with CCMV, this strategy may miss a large group of infected infants without hearing loss after birth. CCMV-associated hearing loss can occur later in childhood—up to 50% of infants with CCMV who passed their NHS can go on to develop SNHL by 3.5 years of age.⁶ In a large prospective study involving 99,945 newborns, a hearing screen-based strategy detected 57% of all infants with CCMV-related SNHL but missed 43% of infected infants without hearing loss.⁷ In this study, the proportion of CCMV among infants in the well-infant nursery with hearing loss prior to discharge was 2.8%. Screening infants with confirmed permanent neurological hearing loss through subsequent detailed audiological testing has been

shown to increase the CMV detection rate—up to 5.9% of the infants tested.⁸ However, this strategy leads to inability for timely testing for CCMV (by 21 days, a prerequisite for confirmation of CCMV) and a missed opportunity for treatment and counselling for this congenital infection.

The indication of screening infants who are SGA is based on the established link between intrauterine growth restriction and congenital infections, such as CMV. Older studies have reported significant association between CCMV and SGA status, although subsequent studies have shown conflicting data.⁹ SGA status continues to be a trigger for considering CMV screening in our setting and hence, it was adopted as an indication to supplement the NHS in our screening strategy. While none of the SGA infants had evidence of hearing loss after birth, 4/8 had detectable CMV copies in their blood, which may highlight their continued risk for long-term sequelae.¹⁰

These data are limited by small sample size in a single institution, limited range of clinical indicators included and short follow-up period (1 year). All infants with CCMV are currently being followed-up by a multidisciplinary team to ensure the early detection of any long-term complications, and treatment is commenced in timely manner if it is required. These initial data from this screening programme provides important information on the burden of CCMV and the potential clinical benefit of targeted screening programme in Singapore. This information would also facilitate the assessment of cost-effectiveness of this targeted screening approach when compared to a universal screening strategy in order to provide valuable insights prior to deploying any such approaches.

Ethics approval

This study protocol was reviewed and granted an exemption from full review by the SingHealth Centralised Institutional Review Board (Reference No: 2023/2345).

Conflict of Interest

The authors declare no conflicts of interest.

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Data availability statement

Data are available upon reasonable request from the corresponding author.

Keywords: congenital, cytomegalovirus infection, hearing loss, infant, infectious disease, neonatology, small for gestational age

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