

# Who Actually Gains from Nationwide New Born Diagnosis for Cerebral Cytomegalovirus Illness?

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## Editorial

Congenital hypothyroidism (0.25–0.5 per 1000) and sensorineural hearing loss (SNHL, 1.1/1000 neonates) are less common than congenital cytomegalovirus (cCMV) infection, which has a higher reported prevalence of 6/1000 newborns [1-3]. Similar to the range of SNHL severities found in newborn hearing screens, which range from mild unilateral loss to bilateral profound hearing loss, cCMV also presents with a wide range of outcomes, such as varying degrees of SNHL loss, visual impairment, developmental delay, and cognitive impairments [4]. Children that are affected may also not show many symptoms. The diagnosis of cCMV infection may only be made within a specific timeframe, which makes it distinct from other infections. It will become impossible to differentiate between congenital and postnatal infections after 3–4 weeks, as the former typically does not result in negative consequences to hearing, vision, or development. The use of polymerase chain reaction with dried blood spots obtained at or soon after birth for screening of metabolic diseases is the only way to address this diagnostic conundrum in the absence of newborn CMV screening, despite the fact that Ross et al. have demonstrated that this method has low sensitivity and specificity for identifying cCMV [5,6]. Which kids will benefit from cCMV screening universally? Of the

25488 children with cCMV, only 3262 (12.8%) were symptomatic at birth, according to estimates made by Cannon et al [1]. Only 815 of them would have a clinical diagnosis of cCMV at delivery. These kids will not gain anything from screening. Additionally, it was shown by Dollard et al. that 8.10 cCMV babies had a 12.7% symptom rate [7]. Regretfully, a systematic method for diagnosing symptomatic cCMV at birth does not exist. Not one of the symptoms is unique to cCMV; instead, there are several that are related to the brain (microcephaly, seizures), growth (intrauterine growth retardation [IUGR]), haematological and systemic involvement (petechia, jaundice, anaemia, splenomegaly, hepatomegaly), and respiratory infection (pneumonia). The amount of symptoms that require cCMV study in the various clinical contexts affects clinical diagnosis as well. Dollard et al. ruled out IUGR, a sign that infected newborns frequently experience [7]. However, Rivera et al. demonstrated that IUGR was a separate risk factor for congenital or late-onset hearing loss in cases of symptomatic cCMV infection [8]. In order to identify a symptomatic disease and recruit participants for the valgancyclovir therapy of cCMV trial, Kimberlin et al. took into account at least one or more of a set of symptoms [9]. It follows that a large number of kids with vague or minimal symptoms would not receive a diagnosis. According to Cannon et al., 87.2 percent of cCMV are asymptomatic at birth and would go undiagnosed if universal screening wasn't implemented, and 75% of children with symptomatic cCMV are not clinically diagnosed as CMV at birth.

## Sensorineural Hearing loss

Kennedy et al. came to the conclusion that newborn CMV screening would be beneficial for these children because their research demonstrated that children diagnosed prior to this age had considerably higher receptive and expressive language scores than those diagnosed later. Between the ages of 9 and 24 months, 256 (1%) children were identified as having hearing loss [11]. They came to the conclusion that SNHL would be detected earlier than if CMV had gone undiagnosed, and that newborn screening would therefore also help this group [12] using

data from the pre-new born hearing screening era, when only 18% of children were diagnosed before the age of 2 years.

Is it possible to identify newborns with SNHL who would benefit from antiviral treatment through newborn screening? Children with SNHL and CNS involvement participated in the first phase III randomised control trial of Ganciclovir therapy, which demonstrated improvement in hearing outcomes after six months of treatment [13]. Given the high probability of a clinical diagnosis in the context of CNS involvement, newborn screening may not be beneficial for this group. Infants having one symptom at least, possibly more, were included in a later trial by Kimberlin et al. using valganciclovir [9]. One of the symptoms may have been hearing loss alone. This work opens the prospect of treating isolated SNHL, even if the authors later stated that children with only SNHL without additional clinical evidence of symptomatic disease were not enrolled in substantial numbers [14]. 75% of symptomatic newborns (2447 infants, or 9.6% of the entire cohort) did not receive a cCMV diagnosis, according to research by Cannon et al. [1]. Hence, treatment may have been beneficial for the 2447 symptomatic but undiagnosed cCMV infants (14.5 percent of all infants with cCMV) and the 1245 asymptomatic but SNHL at birth children, as Kimberlin et al. demonstrated that a 6-month course improved hearing outcomes at 12 and 24 months in comparison to a 6-week course.

### Developmental and cognitive difficulties

According to Cannon et al., 763 (or 3% of all cCMV children) of the 815 symptomatic children who were clinically confirmed as having the disease experienced developmental delay or cognitive impairment [1]. These kids will not gain anything from screening. 574 (2.3%) of the 2447 symptomatic children who did not receive a cCMV diagnosis experienced these issues. In comparison to a 6-week period, Kimberlin et al. demonstrated that a 6-month course of treatment increased the neurodevelopmental scores on the Bayley -III at 24 months in symptomatic infants with at least one symptom [9]. As a result, these kids who would have benefited from treatment may have benefited from screening. These issues were also present in 1045 youngsters (4.1%) who were asymptomatic. It is possible that some of these kids had congenital hearing loss, in which case antiviral therapy would have been necessary. The incidence of these problems is the same in controls and asymptomatic cCMV [15]. The potential advantages of universal screening for these kids stem from the clinical recommendation, as well as potential legal mandate, of close developmental follow-up for

high-risk kids from the American Academy of Paediatrics [16, 17]. Therefore, there's a good chance that developmental issues will be noticed and treated sooner rather than later if they go undiagnosed. The diagnostic process may take far less time for impacted children who show up later on with developmental delay and/or cognitive delay than it would for children who do not have a previous diagnosis. A youngster with cCMV is not likely to experience any of these issues. Later pregnancies won't raise the risk of genetic issues. Having a diagnosis is also likely to improve prognosis. However, given the absence of a developmental follow-up framework for CMV, whether symptomatic or not, the advantages of newborn screening might not be as clear for this particular set of infants.

### Economic considerations

Any programme aimed at universal screening must take cost into account. Screening programmes have the potential to reduce severe to profound hearing loss by 4.2-13%, with a direct cost of \$10.86 per screened infant. Gantt et al. based their findings on the assumption that the benefits of screening stem from early identification of postnatal hearing loss and antiviral therapy for affected newborns to reduce hearing loss [18]. According to their estimates, the lifetime expenses of a child with severe or profound hearing loss come to almost US\$ 1.2 million. Overall, they came to the conclusion that screening newborns for cCMV is justified because it is typically linked to cost savings or is cost neutral when considering net public spending. With about 40,000 new cases reported annually, the estimated yearly cost of cCMV in the US is currently higher than \$3 billion [19]. While acknowledging the drawbacks and moral dilemmas associated with newborn screening generally, universal newborn CMV screening offers notable benefits, chief among which is the decrease in the incidence of SNHL [20]. Determining whether treating isolated and late-onset SNHL is beneficial is crucial. The significance of universal screening will increase if this treatment window can be established.

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