A White Paper:
Rationale for Targeted Screening for CMV Affected Newborns

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Background

- Congenital CMV is a common cause of infant morbidity, childhood hearing loss and other significant neurodevelopmental problems
- Identification of CMV can lead to improved outcomes in neurologic, developmental, and hearing outcomes
- Screening for CMV is practical and inexpensive
- CMV is a treatable cause of childhood hearing loss if identified early, with a potential for significant savings of societal health care and educational dollars

What is Cytomegalovirus?

CMV is virus in the herpesvirus family with a high prevalence in the United States. By age 5, nearly 1 in 3 children has been infected. By age 40, nearly half of all adults have been infected, most with no signs or symptoms. It is transmitted by direct contact with body fluids. If acquired after birth, there are few, if any symptoms or consequences. If a mother newly acquires a CMV infection during pregnancy, the infection can be passed through the placenta to the developing baby.

How common is congenital CMV?

- Congenital cytomegalovirus affects 20,000-40,000 infant births per year in the United States and 1 million infant births globally. This equates to an incidence of approximately 1 per every 200 births in the United States.
- The incidence of congenital CMV is higher than any currently screened disease within the newborn screening protocol. Newborns are screened for many other diseases that are far less prevalent than congenital CMV; including cystic fibrosis (1 in 3500 births), congenital hypothyroidism (1 in 4,000 births), sickle cell anemia (1 in 375 African American infants) and severe combined immunodeficiency (1 in 75,000 births).
- The rate of congenital CMV is higher in African Americans and individuals with lower socioeconomic status reflecting a disease of health disparity nationally.
CMV is the most common viral cause of birth defects. To place this in perspective, between February 1, 2017 and June 1, 2018, there were 4199 live-born infants suspected of congenital Zika reported in the United States. Of these, 203 (14%) were reported to have a Zika-associated birth defect or a neurodevelopmental abnormality possibly associated with congenital Zika. In the United States, the highest total cases of congenital Rubella occurred in 1969 when 57,686 cases were reported. Therefore, congenital cytomegalovirus is far greater in scope and prevalence than congenital Zika virus and similar in scope and prevalence to that of the congenital Rubella epidemic in 1969.

Congenital CMV is the most common cause of non-hereditary hearing loss and is responsible for hearing loss in 1 in 5 hearing-impaired children with no other known risk factor or cause and 1 in 10 hearing-impaired children overall.

How does cytomegalovirus affect newborns?

- Most infants with congenital Cytomegalovirus are asymptomatic at birth with only 10% showing symptoms such as anemia, jaundice, enlarged spleen and liver, small size for gestational age, small head circumference, lethargy and seizure. Brain imaging frequently shows calcifications and other abnormalities in these children.
- Congenital CMV is associated with long-term neurodevelopmental disabilities including sensorineural hearing loss, cerebral palsy, intellectual disability, visual impairment, lack of coordination and seizures. Approximately 140 deaths occur per year as a result of congenital cytomegalovirus and 500,500 cases of long-term deficits result from this congenital infection.
- Ultimately, disabilities occur in 15-20% of newborns with congenital CMV. Of the infants symptomatic congenital CMV, it can be predicted that 32.8% will also have or develop hearing loss; and of those who do not have symptoms, 9.9% will have or will develop hearing loss. Some studies report much greater risk of hearing loss, up to 65% of children with symptomatic CMV and up to 23% of children affected by asymptomatic CMV.
- Of children with congenital CMV, 70-80% will demonstrate profound hearing loss while 20-30% demonstrate unilateral or milder to more moderate form of hearing loss.
- Hearing loss related to congenital CMV may not be present at birth, but rather delayed in onset, in which case it would be missed by newborn hearing screening. The hearing loss may fluctuate or progress during childhood.
- It is estimated that 2% of children with asymptomatic congenital CMV develop hearing loss severe enough to meet cochlear implantation candidacy criteria.

How is congenital CMV detected?

- Signs of CMV may be detected on ultrasound during pregnancy such as placental thickening, intrauterine growth retardation, enlarged liver or spleen, ascites (fluid accumulation in the belly), small head circumference, and intracranial calcifications.
- Pregnant women can be screened for CMV. If they have not been previously infected they should practice precautions. If they have had a recent infection, the babies progress should be monitored and amniocentesis may be performed to make the diagnosis of CMV infection.
- While infants with symptomatic CMV may be detected and confirmed, infants with asymptomatic CMV at risk for hearing loss may be missed.
- The diagnosis can be established within the first 3 weeks of life by detecting CMV in urine or saliva. After 3 weeks of age, it is more difficult to confirm an in-utero infection, because of the high prevalence of CMV and possibility of a postnatally acquired infection, which would not be
clinically important. Detection of CMV in urine or saliva in conjunction with detection of CMV from the newborn dried blood spot may confirm a congenital infection.

What are the benefits of detecting congenital CMV in newborns with hearing loss?

- A positive diagnosis identifies the etiology of hearing loss in a large proportion of what would otherwise be idiopathic and would reduce the need for other unnecessary tests such as genetic testing, lab investigation, and EKG.
- A positive diagnosis would identify the infants at risk of progressive hearing loss who would be targeted for close audiologic monitoring, which would be especially relevant to the infants with congenital CMV who had normal newborn hearing screens but remain at risk of developing hearing loss.
- Early identification of CMV-related hearing loss provides an opportunity for antiviral therapy.
- Hearing-targeted CMV testing would identify a majority of CMV-related hearing loss that occurs in the neonatal period but may miss children with congenital asymptomatic CMV who passed the newborn hearing screen but remain at risk of delayed hearing loss or other complications. 7

Congenital CMV is a potentially treatable cause of childhood hearing loss.

- Treatment with gancyclovir or valgancyclovir may stabilize or improve mild and moderate hearing loss in a significant number of infants. 8, 9, 10, 11, 12, 13
- Several clinical trials are currently underway to evaluate the effectiveness of valgancyclovir on hearing loss in infants with asymptomatic CMV

Costs

- The estimated cost of cytomegalovirus is approximately $4 billion per year in the United States alone including the medical burden and societal costs.
- Additionally, it is estimated that sensorineural hearing loss costs an individual approximately $1.4 million over the course of a lifetime due to the reduction in gainful employment and educational opportunities as a result of hearing deficit.
- For example, in Virginia the cost for cytomegalovirus screening ranges from $10-50 per individual and is similar to the cost of all current newborn screening protocols.
- If antiviral treatment is successful in reducing the hearing loss and avoiding the need for cochlear implantation for just one infant per year, public savings would offset public costs of screening and treatment. 14, 15

Legislative actions

- Currently Virginia, Connecticut, Iowa16, New York17, and Utah18 mandate newborns who fail their newborn hearing screening to be tested for congenital cytomegalovirus, while Illinois requires cytomegalovirus testing to be offered to parents of children who fail their newborn hearing screening. Numerous other states have either proposed or drafted legislation regarding congenital Cytomegalovirus testing.19 Screening must be offered per Illinois mandates.20
- Currently, awareness of Cytomegalovirus is estimated at only 14% of women compared to 98% awareness for HIV/AIDS and 97% for Down syndrome and 83% for fetal alcohol syndrome.
Consensus Statements

- Major birthing hospitals in the United States have recognized the importance of identifying CMV in newborns with hearing loss and provide hearing-targeted CMV screening including University of Colorado Hospital Birth Center, Kaiser Permanente, Cincinnati Children’s Hospital, Boston Children’s Hospital, and Texas Children’s Hospital. In addition, Sentara Leigh Hospital and Sentara Norfolk General Hospital in Virginia offer hearing-targeted CMV testing.

- A consensus report from the International Congenital Cytomegalovirus Recommendations Group was recently published in the UK medical journal, the Lancet. The report, entitled “Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy”, is the result of an international consensus meeting held in Brisbane, Australia at the 5th International Congenital Cytomegalovirus Conference.
  - “Consideration must be given to universal neonatal screening for cytomegalovirus to facilitate early detection and intervention for sensorineural hearing loss and developmental delay, where appropriate.”
  - “The group agreed that education and prevention strategies for mothers were beneficial, and that recommendations will need continual updating as further data become available.”

- AAP Task Force on Improving Newborn Hearing Screening, Diagnosis, and Intervention does not support the concept of performing the very first newborn hearing screening test in the medical home rather than at the hospital or birthing center due to concerns that decreased emphasis on screening the “captive audience” will result in higher rate of newborns lost to follow-up. “The hospital-based institutional commitment to equipment calibration and oversight by qualified audiologists in the hospital setting allow for a quality standard that may be difficult to duplicate when screening is performed in the medical office setting.” Similarly, the best place to ensure timely and routine CMV testing is in the birth hospital.

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1 https://www.cdc.gov/cmv/congenital-infection.html
3 https://www.cdc.gov/mmwr/volumes/67/wr/mm6731e1.htm?s_cid=mm6731e1_w
5 https://www.uptodate.com/contents/congenital-cytomegalovirus-infection-clinical-features-and-diagnosis


https://le.utah.gov/xcode/Title26/Chapter10/26-10-S10.html?v=C26-10-S10_1800010118000101

https://www.nationalcmv.org/cmv-research/advocacy
