

# Screening for Congenital Cytomegalovirus (CMV) Infection and Hearing Loss as an Adjunct to EHDI Programs

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# CMV and EHDI

- **Early Hearing Detection and Intervention (EHDI) is more than just newborn hearing screening**
- **Many children with late-onset or progressive hearing losses are not detected by newborn hearing screening**
- **Congenital CMV is leading cause of late-onset hearing loss**
- **Screening for congenital CMV could lead to earlier detection of late-onset hearing losses**



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# Overview

- **Background on congenital CMV**
- **CMV and hearing loss**
  - **Prevalence of hearing loss**
  - **Attributable fraction of hearing loss**
- **Methods to screen for congenital CMV**



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# Cytomegalovirus (CMV) infection

- **CMV is spread through bodily fluids, e.g. saliva**
  - Main exposure is young children
- **Majority seropositive for CMV**
  - NHANES III data (Staras, 1996)
  - Seropositivity 36% at 6-11 years, 91% at 80+ years
  - Overall seropositivity ages 6+ is 59%
    - Non-Hispanic white 51%
    - Non-Hispanic black 76%
    - Mexican-American 82%



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# Congenital CMV

- Overall prevalence of congenital CMV 0.4% to 1.2% of newborn infants
  - Most common perinatal infectious disease
  - Varies by SES and ethnicity
- Transmission depends on CMV status of mother
  - Primary infection in seronegative women
    - High risk of transmission
  - Recurrent infection in seropositive women
    - Lower risk of transmission



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# Congenital CMV Sequelae

- About 10-15% have symptoms at birth, although often not detected
  - Perhaps 50% develop sequelae
    - Mental retardation, hearing loss, visual impairment, etc.
    - Multiple impairments common
- Asymptomatic infants also at risk
  - About 10-15% develop sequelae, mostly hearing loss (Dollard, 2007)



# CMV and Hearing Loss

- **Sensorineural hearing loss (SNHL) occurs in 10-15% of children overall according to systematic review (Dollard et al., 2007)**
  - **11% of children without symptoms at birth**
  - **35% of children with symptoms at birth**
- **Many losses are progressive or late-onset**



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# Laterality and Level of Hearing Loss in Congenital CMV

- **How many children have bilateral SNHL?**
  - 9.3%, or 60% of those with CMV (Dahle, 2000)
  - 3.5%, or 34% of those with CMV (Ross, 2006)
  - 94% of those with CMV (Ogawa, 2007)
- **Moderate to profound bilateral SNHL**
  - 5% with bilateral SNHL at 50 dB (Hicks, 1993)



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# Late-Onset HL in Congenital CMV

- **Fraction of SNHL detectable at birth**
  - **1/3 in UAB study at 20 dB threshold (Fowler, 1999)**
    - 5.2% SNHL detected at birth
    - 15.4% SNHL at age 6 years
  - **1/2 in UAB study at 30 dB threshold (Fowler, 1999)**
    - 3.9% SNHL detected at birth
    - 8.3% SNHL detected at 6 years



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# Moderate-Profound Bilateral SNHL and CMV

- At least 30,000 infants born with congenital CMV in US (0.7% of 4.1 million)
- 3,000 to 5,000 have SNHL (10-15%)
- 1,000 to 3,000 have bilateral SNHL  $\geq 20$  dB (34-60%)
- 500 to 2,700 have bilateral SNHL  $\geq 40$  dB (50-90% of those with bilateral HL)



# CMV-Attributable Fraction of SNHL

- **What fraction of permanent hearing loss in children is due to congenital CMV?**
  - Most studies report  $<4\%$ , based on symptomatic cases and HL detectable at birth (Morzaria, 2004; Dent, 2004)
  - Some attribute 30% of SNHL to congenital CMV (Fowler, 1995; Barbi, 2003; 2006; Fowler, 2006)
  - Best estimate is 15-20% (see next slides)



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# CMV-Attributable Fraction of SNHL: Empirical Evidence (1)

- **Sweden study (Harris, 1984; Ahlfors, 1999)**
  - According to Harris (1984) 4 of 10 (40%) children with profound bilateral HL had congenital CMV
  - Ahlfors (1999) reported rate of profound bilateral hearing loss 57% as high in complete cohort, implying attributable fraction of 23%
- **Texas study (Ohlms, 1998)**
  - 21 of 118 (18%) children with HL had CMV, apparently based on assay of samples taken after birth but no details provided



# CMV-Attributable Fraction of SNHL: Empirical Evidence (2)

- Italy study (Barbi, 2003)
  - 22 of 130 (17%) children with bilateral HL > 40 dB
    - 9 of 87 (10%) with HL detected soon after birth
    - 13 of 43 (30%) with HL of unknown causes detected >3 months after birth



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# CMV-Attributable Fraction of SNHL: Empirical Evidence (3)

- Japan study (Ogawa, 2007)
  - Families of children with SNHL diagnosed as university clinic asked to bring in dried umbilical cord specimens stored as Japanese custom
  - 10 of 67 (15%) with any SNHL
    - 9 of 55 (16%) with bilateral SNHL at 55 dB threshold
    - 8 of 36 (22%) with profound SNHL (>90 dB)
  - 21 of 67 (31%) with a known genetic risk
    - 9 of 67 (24%) with *GJB2* mutation



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# Implications for EHDI Programs

- **Congenital CMV is a leading cause of hearing loss**
  - Second to *GJB2* (Connexin 26) mutations
  - About 15-20% of all childhood SNHL
- **About half of all HL due to CMV is not detectable by UNHS**
- **Screening for CMV could result in the detection of HLs missed by UNHS**
  - How feasible is detection?



# Potential Methods for Congenital CMV Screening

- Urine or saliva specimens
  - Gold standard for detection
  - Requires hospital laboratory to perform assay
  - No public health infrastructure
- Dried blood spot (DBS) specimens
  - Public health NBS system
  - No specimen collection cost
  - High-throughput laboratories can lower cost
  - Uncertain sensitivity





# Two Methods to Detect CMV in DBS Specimens

- **IgM assay**
  - Presence of CMV-specific IgM antibodies indicates infection with CMV in utero
- **PCR assay**
  - Used to detect viral DNA
  - Genome copy number indicates viral load

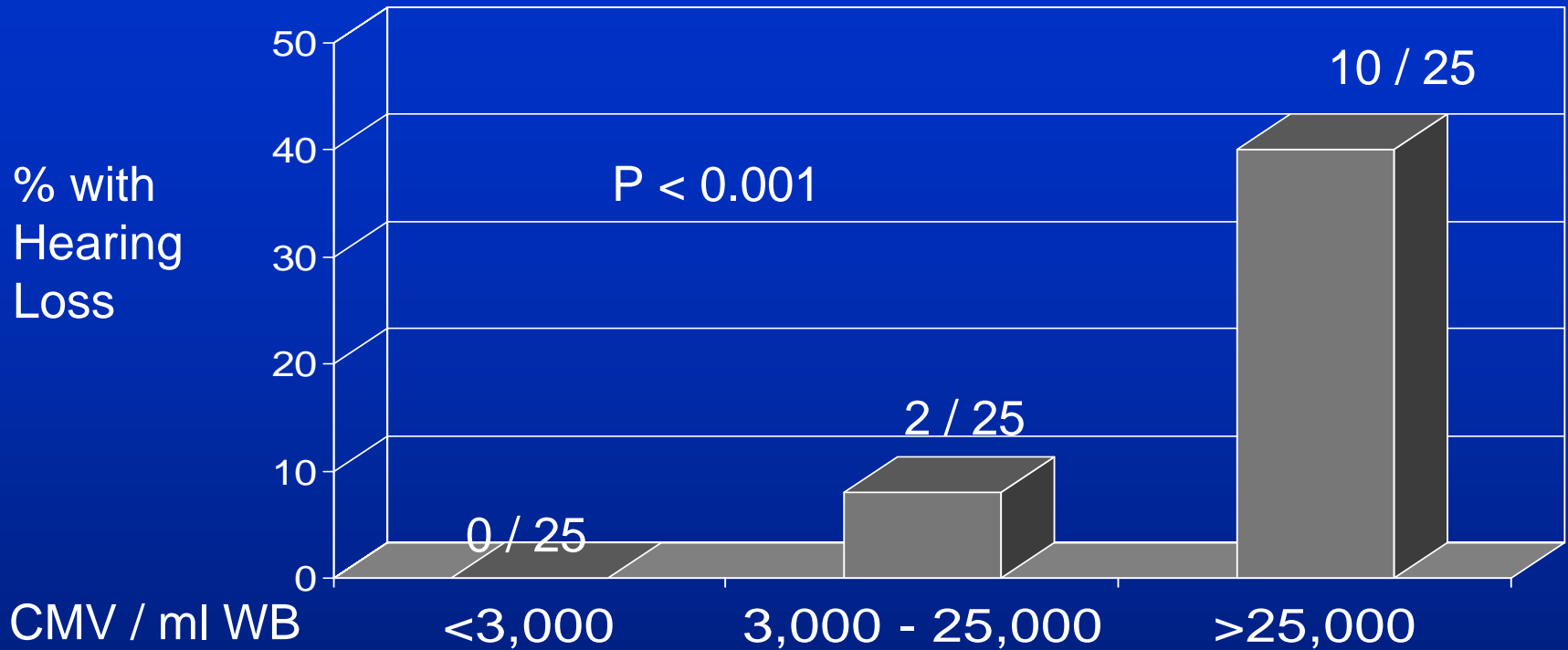


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# CMV Viral Load Associated with Hearing Loss

(Boppana, 2005)



Copies CMV /  
3 mm punch

<10

10-80

>80

Copies CMV /  
PCR reaction

<2

2 - 16

>16



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# Validation of PCR Assay for CMV Viral Load: California-CDC Study

- 5000 Newborn DBS (50% Latino)
- 1.2 cm DBS received per newborn
- 6 mm punch for CMV IgG and limited IgM testing
- 6 mm punch for nucleic acid extraction CMV and PCR
- Partial results indicate high sensitivity of PCR assay, about 1% prevalence



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# Evaluation of CMV Screening Options

- Trade off between sensitivity and cost
  - IgM assay
    - Less sensitive, perhaps 70-80%
    - Less costly, <\$5 per specimen
  - PCR assay
    - Appears highly sensitive
    - Relatively costly, >\$10 per specimen
- More work needed to assess analytical validity



# Utility of CMV Screening

- **EHDI goals**
  - Prompt identification of hearing loss in young children
  - Prompt referral for intervention
    - Early intervention services
    - Amplification or other option
- **Expected benefit of CMV screening**
  - Early identification of children with late-onset or progressive hearing loss
  - Improved language development and school outcomes



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# References (1)

- Ahlfors K, Ivarsson S-A, Harris S. Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. *Scand J Infect Dis* 1999; 31:443-57.
- Barbi M, Binda S, Caroppo S, et al. A wider role for congenital cytomegalovirus infection in sensorineural hearing loss. *Pediatr Infect Dis J*. 2003;22:39-42.
- Barbi M, Binda S, Caroppo S, Primache V. Neonatal screening for congenital cytomegalovirus infection and hearing loss. *J Clin Virol*. 2006;35:206-9.
- Boppana SB, Fowler KB, Pass RF, et al. Congenital cytomegalovirus infection: association between virus burden in infancy and hearing loss. *J Pediatr*. 2005;146:817-23.
- Dahle AJ, Fowler KB, Wright JD, et al. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol*. 2000;11:283-90.
- Dent KM, Kenneson A, Palumbos JC, , et al. Methodology of a multistate study of congenital hearing loss: preliminary data from Utah newborn screening. *Am J Med Genet C Semin Med Genet*. 2004;125:28-34.
- Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Under review, 2007.
- Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. 2006;35:226-31.



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## References (2)

- Fowler KB, Pass RF. Cytomegalovirus infection as a cause of hearing loss among children. *Am J Public Health* 1995;85:734-5.
- Harris S, Ahlfors K, Ivarsson S, et al. Congenital cytomegalovirus infection and sensorineural hearing loss. *Ear Hear* 1984;5(6):352-5.
- Hicks T, Fowler K, Richardson M, et al. Congenital cytomegalovirus infection and neonatal auditory screening. *J Pediatr*. 1993;123:779-82.
- Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol*. In press, 2007.
- Morzaria S, Westerberg BD, Kozak FK. Systematic review of the etiology of bilateral sensorineural hearing loss in children. *Int J Pediatr Otorhinolaryngol*. 2004;68:1193-8.
- Ogawa H, Suzutani T, Baba Y, et al. Etiology of severe sensorineural hearing loss in children: independent impact of congenital cytomegalovirus infection and GJB2 mutations. *J Infect Dis*. 2007;195:782-8.
- Ohlms LA, Chen AY, Stewart MG, Franklin DJ. Establishing the etiology of childhood hearing loss. *Otolaryngol Head Neck Surg* 1999;120:159-63.
- Pass RF, Fowler KB, Boppana SB, et al. Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome. *J Clin Virol*. 2006;35:216-20.
- Ross SA, Fowler KB, Ashrith G, et al. Hearing loss in children with congenital cytomegalovirus infection born to mothers with preexisting immunity. *J Pediatr*. 2006;148:332-6.

