Congenital CMV Infection and Hearing Loss

Suresh B. Boppana, MD
University of Alabama School of Medicine
Birmingham, Alabama

Disclosures

- Received one time consulting fee as a member of the GSK CMV Vaccine Advisory Board
- Do not intend to discuss unlabeled or commercial products other than issues related to treatment of congenital CMV infection

Outline

- Historical perspective
- Background
- CMV-related hearing loss
  - Natural history of CMV-related hearing loss
  - Risk factors for CMV-associated SNHL
    - Symptomatic congenital CMV infection
    - Maternal Immunity
  - Pathogenesis of CMV-related SNHL
- Interim results from the CHIMES Study

Historical Perspective

1904 Ribbert described protozoan like cells in organs of an infant with presumed cong. Syphilis
1921 Goodpasture and Talbot hypothesized that the swollen cells (cytomegalia) were host cells injured by a virus
1926 The term salivary gland virus was used to describe infectious agents present in the salivary glands of guinea pigs
1952 Cytomegalic Inclusion Disease (CID) as a clinical entity was described
1954 Smith successfully propagated the mouse SGV
1955 Isolation and propagation of a new virus by three independent groups; Smith, Rowe, and Weller
1956 Weller first isolated the virus from an infant with CID
1960 The name “Cytomegalovirus” was proposed by Weller
1962 First published report of virologic and clinical findings in CID by Weller
Consequences of congenital infections

Sensorineural Hearing Loss 15%
- Bilateral Hearing Loss 9%
- IQ ≤ 70 10%
- Retinitis 6%
- Cerebral Palsy 5%
- Seizures 5%

Rates of congenital CMV infection from four large newborn screening studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Newborns screened</th>
<th>Rate of congenital CMV infection*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada, 1980</td>
<td>15,212</td>
<td>4.2</td>
</tr>
<tr>
<td>England, 1983</td>
<td>14,200</td>
<td>3.0</td>
</tr>
<tr>
<td>Sweden, 1984</td>
<td>10,328</td>
<td>4.8</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower income</td>
<td>18,343</td>
<td>11.8</td>
</tr>
<tr>
<td>Middle/upper income</td>
<td>11,154</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Per 1,000 live births

Symptomatic congenital CMV infection
Clinical findings

<table>
<thead>
<tr>
<th>Finding</th>
<th>Positive/Total Examined (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>36/106 (34)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>53/106 (50)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>80/106 (75)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>69/103 (67)</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>63/105 (60)</td>
</tr>
<tr>
<td>Purpura</td>
<td>14/105 (13)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>54/102 (53)</td>
</tr>
<tr>
<td>Seizures</td>
<td>7/105 (7)</td>
</tr>
</tbody>
</table>

Congenital CMV Infection - Update 3

Asymptomatic congenital CMV infection

- Historical perspective
- Background
- CMV-related hearing loss
  - Natural history of CMV-related hearing loss
  - Risk factors for CMV-associated SNHL
    - Symptomatic congenital CMV infection
    - Maternal Immunity
  - Pathogenesis of CMV-related SNHL
- Interim results from the CHIMES Study

Outline

CMV related hearing loss

- 1964 Medearis first described deafness in children with CID
- 1969 McCracken, et al. 4/13 surviving infants (31%) had hearing loss; all diagnosed after the first year; 1 at 40 months of age
- 1973 Initial reports of asymptomatic or subclinical congenital CMV infection
- 1974 Reynolds et al., Dahle et al. 4/16 children (25%) with subclinical CMV infection had definite bilateral or unilateral SNHL
Congenital CMV Infection - Update

**CMV related hearing loss**

- Hanshaw, et al. 1976
  5/40 (13%) children with clinically silent or asymptomatic CMV infections had bilateral severe HL
- Stagno, et al. 1977
  7/51 infants (14%) with asymptomatic congenital CMV infection had hearing loss; progressive loss indicated in 1 infant (between 21 to 37 months)
- Dahle, et al. 1979
  Progressive HL observed in 4/12 (33%) of children with congenital CMV infection

**Congenital CMV infection**

- 0.5% to 1.0% of all live births (20,000 to 40,000 infected infants Annually)
  - 85-90% Asymptomatic
  - 10-15% Symptomatic
  - ~10% sensorineural hearing loss
  - 40-60% with sequelae (SNHL, MR, CP)

**CMV-related hearing loss - Summary**

- 22 – 65% Symptomatic children will have hearing loss
- 6-23% Asymptomatic children will have hearing loss
- SNHL following congenital CMV infection may be present at birth or delayed onset
- Variable degree of hearing loss - unilateral high frequency loss to profound bilateral loss
- Frequent progression (> 10 dB deterioration) and fluctuation of hearing loss

**Estimates of Causes of Deafness at Birth and Four Years in the United States**


- In a cohort of ~12,000 children in Sweden who were screened for congenital CMV infection and monitored for hearing outcome:
  - 10/12,000 (0.08%) had bilateral, profound HL
  - 4 with HL due to congenital CMV infection
  - 4 with HL due to genetic causes
  - 2 with HL of unknown etiology

**UAB Longitudinal Study of CMV Related Hearing Loss**

<table>
<thead>
<tr>
<th>Characteristics of Loss</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of children</td>
<td>651</td>
<td>209</td>
</tr>
<tr>
<td>Number with hearing loss</td>
<td>48 (7.4%)</td>
<td>85 (41%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>25 (52%)</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>High frequency loss</td>
<td>23 (48%)</td>
<td>57 (67%)</td>
</tr>
<tr>
<td>(4000 – 8000 Hz)</td>
<td>18 (30%)</td>
<td>11 (13%)</td>
</tr>
</tbody>
</table>

**UAB longitudinal study of CMV related hearing loss**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Asymptomatic (N=651)</th>
<th>Symptomatic (N=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed onset loss</td>
<td>18 (38%)</td>
<td>23 (27%)</td>
</tr>
<tr>
<td>Median age of delayed onset (range)</td>
<td>44 Mo (24-182)</td>
<td>33 Mo (6-197)</td>
</tr>
<tr>
<td>Progressive loss</td>
<td>42 (54%)</td>
<td>46 (54%)</td>
</tr>
<tr>
<td>Median age of progression (range)</td>
<td>51 Mo (3-186)</td>
<td>26 Mo (2-209)</td>
</tr>
</tbody>
</table>


**UAB Longitudinal study of CMV related SNHL Degree of loss**

<table>
<thead>
<tr>
<th>Degree of Loss</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (21 – 45 dB HL)</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>Moderate (46 – 70 dB HL)</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>Severe (71 – 90 dB HL)</td>
<td>17%</td>
<td>31%</td>
</tr>
<tr>
<td>Profound (&gt;90 dB HL)</td>
<td>51%</td>
<td>44%</td>
</tr>
</tbody>
</table>


**Cumulative incidence of SNHL according to age**

<table>
<thead>
<tr>
<th>Age</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – one month</td>
<td>25.5%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Three months</td>
<td>31.4%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Six months</td>
<td>43.1%</td>
<td>67.1%</td>
</tr>
<tr>
<td>Two years</td>
<td>47.1%</td>
<td>82.4%</td>
</tr>
<tr>
<td>Three years</td>
<td>58.8%</td>
<td>88.2%</td>
</tr>
<tr>
<td>Four years</td>
<td>72.5%</td>
<td>89.4%</td>
</tr>
<tr>
<td>Six years</td>
<td>86.6%</td>
<td>95.3%</td>
</tr>
<tr>
<td>Seven – 15 years</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>


**Estimated number of children with CMV-related hearing loss in the U.S.**

- 32,000 (0.8%) infants are born each year in the US with congenital CMV infection
- 3.9% will have HL at birth
- Assume universal hearing screening
- 1,248 children with congenital CMV infection & HL will be identified before hospital discharge
- 0.31 per 1000 children
- 1,408 children with congenital CMV infection born each year will develop hearing loss later
- 0.35 per 1000 children

**What proportion of children with CMV related hearing loss will be detected on newborn hearing screen?**

Risk criteria based neonatal auditory screening was not successful in identifying HL due to congenital CMV infection

Only 17.6% of children with SNHL due to congenital CMV infection were identified by risk criteria based neonatal auditory screening at UAB between 1985-1998

Hicks, et al., 1993
Fowler, unpublished data

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Risk factors for CMV related SNHL

- Symptoms at birth
  - Disseminated infection at birth
  - Neuroimaging abnormalities
  - IUGR
- Virus burden
- Maternal immunity

Clinical impact of congenital CMV infection according to condition at birth

<table>
<thead>
<tr>
<th>Sequela</th>
<th>Symptomatic (10-15%)</th>
<th>Asymptomatic (85-90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>40-60%</td>
<td>7-15%</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>45%</td>
<td>2-10%</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>35%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>15%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

Risk Factors for HL in Symptomatic Infants

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Health Insurance</td>
<td>2.8 (1.4-6.2)</td>
</tr>
<tr>
<td>IUGR</td>
<td>2.2 (1.1-4.9)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>2.8 (1.2-6.0)</td>
</tr>
</tbody>
</table>

Adjusted for: race, insurance status, IUGR, petechiae, HSM, jaundice, microcephaly, seizures, thrombocytopenia & referral status

Rivera, et al., Pediatrics, 2002

Maternal immunity

- Provides significant protection against intrauterine transmission
  - Transmission rate drops from 20-60% in primary infection to 1-2% in non-primary infection
- Lower incidence of SNHL and other sequelae following non-primary infection (Fowler, 1992)
- Protects from transfusion acquired CMV disease in premature infants
- Current vaccine strategies are focused on preventing primary maternal infection

Maternal immunity only provides partial protection

- Congenital CMV infection in consecutive births to same mother
- Congenital infection rates are directly proportional to seroprevalence rates
- More frequent in offspring of low-income, young women

Prevalence of Congenital CMV Infection

<table>
<thead>
<tr>
<th>Location</th>
<th>No. studied</th>
<th>% Congenital CMV infection</th>
<th>Seroprevalence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester, England</td>
<td>9,051</td>
<td>0.24</td>
<td>25</td>
</tr>
<tr>
<td>Aarhus, Denmark</td>
<td>3,060</td>
<td>0.4</td>
<td>69</td>
</tr>
<tr>
<td>Hamilton, Canada</td>
<td>16,212</td>
<td>0.42</td>
<td>44</td>
</tr>
<tr>
<td>Birmingham (upper SES)</td>
<td>8,345</td>
<td>0.6</td>
<td>54</td>
</tr>
<tr>
<td>Birmingham (lower SES)</td>
<td>2,673</td>
<td>1.4</td>
<td>77</td>
</tr>
<tr>
<td>Houston (upper SES)</td>
<td>481</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>Houston, TX (lower SES)</td>
<td>493</td>
<td>1.2</td>
<td>83</td>
</tr>
<tr>
<td>London, England</td>
<td>720</td>
<td>0.69</td>
<td>68</td>
</tr>
<tr>
<td>Abidjan, Ivory Coast</td>
<td>2,032</td>
<td>1.38</td>
<td>100</td>
</tr>
<tr>
<td>Santiago, Chile</td>
<td>118</td>
<td>1.7</td>
<td>98</td>
</tr>
<tr>
<td>Ribeirão Preto, Brazil</td>
<td>8,047</td>
<td>1.1</td>
<td>98</td>
</tr>
<tr>
<td>Ballabgarh, India</td>
<td>423</td>
<td>2.1</td>
<td>99</td>
</tr>
<tr>
<td>Sukuta, The Gambia</td>
<td>741</td>
<td>5.4</td>
<td>95</td>
</tr>
</tbody>
</table>

Symptomatic infection following non-primary maternal infection

- A study of 246 congenitally infected children between 1991 and 1997:
  - Of the 47 symptomatic infants, 8 were born to immune mothers and 8 were born following primary maternal CMV infection
- These results suggested:
  - Symptomatic infection follows non-primary maternal infection more often than has been thought
  - Newborn disease is not milder
- Is the outcome in these children different?

Boppana et al., Pediatrics 1999

Hearing loss following non-primary maternal infection

- 300 children with congenital CMV were identified between 1980 and 2000
- Maternal infection classified by serology
- Audiologic evaluations done at 3-8 wks, 6, 12, 18, 24, 30 mo and annually

Ross et al., J Pediatr, 2006

Type of maternal infection and hearing loss

- 300 Study Children
- 124 Non-Primary Infection
- 176 Primary Infection
- 13 (10%) Hearing Loss
- 19 (11%) Hearing Loss

p=0.56

Ross et al., J Pediatr, 2006

Type of maternal infection and hearing loss

<table>
<thead>
<tr>
<th>Hearing loss characteristic</th>
<th>Non-Primary (N=19)</th>
<th>Primary (N=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>23%</td>
<td>42%</td>
<td>0.36</td>
</tr>
<tr>
<td>Delayed</td>
<td>31%</td>
<td>53%</td>
<td>0.29</td>
</tr>
<tr>
<td>Progressive</td>
<td>15%</td>
<td>63%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hi-Frequency</td>
<td>36%</td>
<td>19%</td>
<td>0.42</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>31%</td>
<td>43%</td>
<td>0.72</td>
</tr>
<tr>
<td>Severe/Profound</td>
<td>23%</td>
<td>63%</td>
<td>0.04</td>
</tr>
<tr>
<td>Age of Hearing Loss Diagnosis (mo)</td>
<td>39 (±53)</td>
<td>13 (±21)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>7 (0-182)</td>
<td>5 (0-76)</td>
<td>0.16</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ross et al., J Pediatr, 2006
Conclusions

- Rate of hearing loss similar in children born following primary and non-primary maternal infection
- Hearing loss is less severe and less likely to progress in the non-primary group
- Maternal immunity seems to provide some but not complete protection against damaging fetal infection

Birth Prevalence of Congenital CMV Infection in Ribeirão Preto, Brazil

- 7484 mothers
- 8047 infants
- 87 (1.08%) infants with congenital CMV (95% CI: 0.86-1.33)

Demographic Characteristics

<table>
<thead>
<tr>
<th>Finding</th>
<th>CMV-infected (n=87)</th>
<th>CMV-uninfected (n=7960)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (yrs)</td>
<td>25.6 ± 6.7</td>
<td>23.9 ± 7.1</td>
<td>0.023</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>407 (51.1)</td>
<td>54 (62.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Twin infants (%)</td>
<td>370 (46)</td>
<td>10 (11.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean birth weight</td>
<td>2893 ± 709</td>
<td>2671 ± 724</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>37.9 ± 2.7</td>
<td>37.7 ± 2.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Gestational age &lt;37 wks (%)</td>
<td>1442 (18.1)</td>
<td>23 (26.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>SGA (%)</td>
<td>852 (10.7)</td>
<td>21 (24.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Newborn Findings

<table>
<thead>
<tr>
<th>Finding</th>
<th>Positive/total examined (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice (direct bilirubin &gt;2 mg/dL)</td>
<td>4/87 (4.6)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>4/87 (4.6)</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>4/87 (4.6)</td>
</tr>
<tr>
<td>Purpura</td>
<td>2/87 (2.3)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>0/85 (0.0)</td>
</tr>
<tr>
<td>Seizures</td>
<td>1/87 (1.1)</td>
</tr>
<tr>
<td>Cranial CT scan abnormalities</td>
<td>3/79 (3.8)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100,000/mmc3)</td>
<td>4/41 (10.0)</td>
</tr>
<tr>
<td>Elevated ALT or AST (&gt;130 IU/L)</td>
<td>4/20 (20.0)</td>
</tr>
<tr>
<td>At least one clinical abnormality</td>
<td>7/87 (8.1)</td>
</tr>
</tbody>
</table>

Sensorineural Hearing Loss in 58 Infants

- Tested at a median age of 21 mo (3-63 mo)

 sources of non-primary maternal infection

- Reactivation of persistent/latent infection?
- Reinfection by new strain of virus?
  - Water recognized antigenic diversity of CMVs
  - Children in day care
  - STD clinic attendees
  - Immuno compromised hosts
  - Transplant recipients and HIV infected patients
- Congenital infection
  - Arav-Boger et al. JID, 2002; 186: 1057
  - Congenital infection rates vary with SES
Table 3. Comparison of Strain-Specific Antibody Responses against Glycoprotein H in Serial Serum Samples from Mothers with Preconceptional Immunity against CMV, According to Whether Their Infants Had Congenital CMV Infection.

<table>
<thead>
<tr>
<th>Acquired by New</th>
<th>Mothers with</th>
<th>Mothers of</th>
<th>N</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Response</td>
<td>Infection</td>
<td>Uninfected</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (62)</td>
<td>4 (13)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (38)</td>
<td>26 (87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 for the comparison with the mothers of infected infants.

Maternal reinfection and congenital CMV infection - Conclusions

- Reinfection may be associated with intrauterine transmission and severe fetal infection
- Reinfections may occur more often in populations with increased CMV exposure
- Strain-dependent immunity may have a protective role

Unresolved issues

- The exact frequency of reinfection in healthy people is not known
- Significance of reinfection
- Other factors associated with intrauterine transmission in women with preexisting immunity
- The role of strain-specific immunity

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- CHIMES Study – Interim findings

CMV related hearing loss
Pathology and pathogenesis

- Limited human temporal bone studies
  - Virus replication or the presence of viral antigens in structures of inner ear
    • CMV can readily infect epithelium of inner ear
  - Lack of significant inflammatory infiltrates
    • Delayed host immune response?
    • Delayed infection of inner ear?
**Pathogenesis of hearing loss**

- Animal studies (guinea pig model)
  - Disseminated fetal infection
  - CMV antigens in epithelium and neural cells of inner ear
  - ~28% of infected animals with abnormal auditory function
  - Intact immune function is required for developing hearing loss

**Neonatal MCMV Infection Model Cochlear Whole Mount**

**Representative ABR tracings from 3 month old MCMV infected and age-matched uninfected control animals**

**Hearing loss in mice infected neonatally with MCMV**

**Neonatal MCMV Infection Model Summary**

- BALB/c mice, infected peripherally with MCMV at birth, develop systemic infection followed by dissemination to the CNS
- Infected animals demonstrate significant, but variable hearing loss (half of ears have an abnormal ABR at 3 months)
- Hearing loss appears to be progressive

**Pathogenesis of CMV related hearing loss**

- Both human and animal studies support a model that includes virus infection and host inflammatory responses leading to both acute (viral mediated) and chronic (virus and host derived) damage
- Other:
  - Host factors
    - Genetic susceptibility
    - Stage of differentiation
  - Virologic determinants
    - Tissue tropism
    - Virulence factors
    - Genetic polymorphisms
Uncertainties and gaps in knowledge

- Exact contribution of CMV in newborn and early childhood hearing loss
  - Few population based studies and lack of studies in different population groups
- Better methods to screen newborns
- Predictors of hearing loss in asymptomatic infection
- Understanding of the pathogenesis
  - Host factors: Immune response, genetic susceptibility
  - Virologic determinants: Tropism, polymorphisms
- Better predictors of outcome

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CHIMES Study

Overall Objectives
- Define the long-term audiologic outcome in children with congenital CMV infection
- Determine the clinical validity and utility of CMV screening:
  - in the detection of hearing impairment in the newborn
  - In the prediction of hearing impairment with onset during infancy or in the early years of life

Study Population:
Between March 2007 and March 2009, 43,557 infants born at seven medical centers in different geographic regions of the United States were enrolled in the NIDCD CHIMES study.

Study hospitals included:
- University Hospital, Birmingham, AL
- Mississippi Medical Center, Jackson, MS
- Saint Peter's University Hospital, New Brunswick, NJ
- Carolinas Medical Center, Charlotte, NC
- Good Samaritan Hospital, Cincinnati, OH
- Magee Women's Hospital, Pittsburgh, PA
- Parkland Hospital, Dallas, TX.

The study population reflects the underlying newborn population of the respective medical centers.

Overall prevalence of congenital CMV infection

0.51% (95% CI, 0.44 – 0.58)
### Congenital CMV Infection Prevalence

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiracial</td>
<td>0.9% (0.4 – 1.8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.08% (0.01 – 0.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>1.1% (0.9 – 1.3%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.3% (0.2 – 0.4%)</td>
</tr>
<tr>
<td>White, Non Hispanic</td>
<td>0.3% (0.2 – 0.4%)</td>
</tr>
</tbody>
</table>

**NIDCD Multicenter CHIMES Study**

### Comparison of Saliva and DBS Results

<table>
<thead>
<tr>
<th>DBS PCR</th>
<th>Saliva DEAFF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>P</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>59</td>
<td>20322</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>20332</td>
</tr>
</tbody>
</table>

Total positive: 124 (saliva, DBS or both)

### DBS PCR Results

- **Sensitivity:** 48.3% (38.8–57.8)
- **Specificity:** 99.9% (99.9–100)
- **PPV:** 84.6% (73.4–92.4)

### Comparison of DEAFF and PCR Results

<table>
<thead>
<tr>
<th>Saliva PCR</th>
<th>Saliva DEAFF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>0</td>
<td>17644</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>17652</td>
</tr>
</tbody>
</table>

Total positive: 93 (DEAFF, PCR, or both)

### Saliva PCR in Newborn CMV Screening

- **Sensitivity:** 100% (95.8 - 100)
- **Specificity:** 99.9% (99.8 - 99.9)
- **PPV:** 91.4% (83.8 - 96.2)
- **NPV:** 99.6% (99.5 - 99.7)

### CHIMES study – Interim findings

- Race, ethnicity and maternal age contribute to differences in the prevalence of congenital CMV infection in the United States.
- Black infants & multiracial infants have an increased risk of congenital CMV infection.
- Hispanic infants have a lower rate of congenital CMV infection than white non Hispanic infants.
- Offspring of young women < 20 years have the highest prevalence of congenital CMV infection.
- DBS PCR has unacceptably low sensitivity
- Saliva PCR has excellent sensitivity and specificity
Recap

- Congenital CMV infection is a leading cause of hearing loss in children in both developed and developing world
- CMV-related hearing is often progressive and can appear later during childhood
- Preexisting maternal immunity only provides partial protection
- Predictors of hearing loss in asymptomatic congenital CMV infection are not known
- Pathogenesis is not well understood
Primary Endpoint
Treatment Effect on Hearing Outcome (6 months)

<table>
<thead>
<tr>
<th>Biologic Assessment</th>
<th>Functional Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>100%</td>
</tr>
<tr>
<td>Na Treatment</td>
<td>56%</td>
</tr>
</tbody>
</table>

P < 0.0001 (unadjusted)
P < 0.0001 (adjusted)

Ganciclovir No Treatment

Biologic Assessment
- Others
- Worse

Functional Assessment
- Others
- Worse

Treatment Effect on Hearing Outcome (≥ 1 yr)

<table>
<thead>
<tr>
<th>Biologic Assessment</th>
<th>Functional Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>52%</td>
</tr>
<tr>
<td>Na Treatment</td>
<td>79%</td>
</tr>
</tbody>
</table>

P = 0.0460 (unadjusted)
P = 0.0158 (adjusted)

Ganciclovir No Treatment

Biologic Assessment
- Others
- Improved +
- No Change
(Nor → Nor)

Functional Assessment
- Others
- Improved +
- No Change
(Nor → Nor)

Conclusions

- Ganciclovir therapy both improves hearing (or maintains normal hearing) and prevents hearing deterioration at 6 months
- Ganciclovir therapy may produce a functional effect on prevention of hearing deterioration at ≥ 1 year
- Two-thirds of ganciclovir-treated patients developed significant neutropenia
- Potential for bias introduced in number of non-evaluable patients