March 27, 2019

DR. JOSEPH A. BOCCHINNI, JR., M.D., CHAIRMAN

Advisory Committee on Heritable Disorders in Newborns and Children
5600 Fishers Lane, Room 18W68
Rockville, MD 20857

Dear Dr. Bocchini:

The National CMV Foundation (NCMVF) is honored and excited to submit this nomination for congenital cytomegalovirus (CMV) to be considered for inclusion on the recommended universal screening panel (RUSP). We submit this nomination on behalf of all children infected with congenital CMV, their families, and a multi-disciplinary team of experts representing CMV research, clinical practice, public health, industry, and advocacy.

The National CMV Foundation (NCMVF) is a 501(c)(3) public non-profit organization dedicated to educating women of childbearing age about congenital CMV. Our purpose is to prevent CMV infection in women of childbearing age, by:

- Empowering women, parents, families and local community networks through grassroots engagement to facilitate conversation and champion the cause.
- Delivering consistent, clear messaging and evidence-based data that aids in prevention, educates the public and increases its understanding of congenital CMV.
- Influencing CMV research priorities regarding CMV prevention, treatment and intervention.
- Advocating for a CMV vaccine.

The accomplishment of these priorities will be possible due to the work and support of the communities represented by this diverse nominating team and will come to fruition much more quickly when each newborn is screened for congenital CMV.

NCMVF is the only organization in the United States dedicated to promoting awareness, providing access to resources, and sharing prevention information to eliminate congenital CMV. We are a grassroots organization that relies on peer to peer fundraising from within the community to fund our programs. Since 2014, we have committed $75,000 to research awards and $160,000 to public health awareness grants and educational efforts. NCMVF engages with an audience of over 16,000 Facebook followers, nearly 2,000 Twitter followers, and over 1,000 Instagram fans. We are active with closed online communities, such as CMV Mommies (3,000 members) and the National CMV State Advocacy Group (40 members) plus another 268,200 individuals within peer to peer or parent support member groups.
closely aligned with CMV-related outcomes and especially, the NCMVF mission. Our website has an average of 25,000 monthly unique visitors, and many of our educational materials are offered digitally for download or social sharing. Several fliers and documents have been cobranded and are circulating within a dozen state departments of health as the go-to resource on CMV prevention and counseling.

NCMVF board members, staff, and volunteers dedicate thousands of hours in support of our work, representing all 50 states and several countries. We amplify our reach and impact through strategic alliances and our stakeholder networks. Our parent advocates organize awareness and fundraising events, speak at non-profit, public health, and clinical conferences, and attend like-minded workshops and meetings annually. In 2018 alone, we were able to reach in-person audiences of more than 3,000 state health professionals, healthcare providers, and influencers across the nation.

The team listed on the enclosure assembled and reviewed this nomination. The compiled materials and data demonstrate the readiness of the field to implement newborn screening for CMV. The attached nomination form and supporting evidence show the need for early identification of congenital CMV, the availability of validated laboratory tests, the availability of a continuum of treatments including antiviral treatments and early intervention services provided based on established delays or an indication of the high likelihood of delays.

We look forward to working with the committee, your staff, and the review groups and are dedicated to responding to any inquiries and providing any necessary information to ensure the nomination is reviewed.

With Gratitude,

Kristen Spytek  
President and CEO  
National CMV Foundation

Sara Menlove Doutre  
Chair, Scientific Advisory Committee  
National CMV Foundation

Janelle Greenlee  
Chair, RUSP Nomination Team  
National CMV Foundation
Enclosures:

- RUSP Nomination Team Membership Nomination Form
- References
- Letters of Support and Completed Conflict of Interest Disclosure Forms from team members
## RUSP Nomination Team Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sara Menlove Doutre</td>
<td>Chair, Scientific Advisory Committee</td>
<td>National CMV Foundation</td>
</tr>
<tr>
<td>Kristen Hutchinson Spytek</td>
<td>President and CEO</td>
<td>National CMV Foundation</td>
</tr>
<tr>
<td>Suresh B. Boppana, MD</td>
<td>Hugh Dillon, MD Endowed Professor of Pediatrics</td>
<td>University of Alabama Birmingham</td>
</tr>
<tr>
<td>Marcia Fort</td>
<td>Past President, Directors of Speech and Hearing Programs in State Health and Welfare Agencies</td>
<td></td>
</tr>
<tr>
<td>Karen B. Fowler, DrPH</td>
<td>Professor</td>
<td>University of Alabama Birmingham</td>
</tr>
<tr>
<td>David W. Kimberlin, MD</td>
<td>Co-Director, Division of Pediatric Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td>Stanley A Plotkin</td>
<td>Professor Emeritus of Pediatrics, University of Pennsylvania</td>
<td></td>
</tr>
<tr>
<td>Pablo J. Sánchez, M.D.</td>
<td>Professor of Pediatrics</td>
<td></td>
</tr>
<tr>
<td>Karl R. White, Ph.D.</td>
<td>Director, National Center for Hearing Assessment and Management</td>
<td></td>
</tr>
<tr>
<td>Janelle Greenlee</td>
<td>Chair, RUSP Nomination Team</td>
<td>National CMV Foundation</td>
</tr>
<tr>
<td>Roy D. Baynes, MD, PhD</td>
<td>Senior Vice President &amp; Head Global Clinical Development, Chief Medical Officer</td>
<td>Merck</td>
</tr>
<tr>
<td>Gail J. Demmler Harrison, MD</td>
<td>Professor Pediatrics</td>
<td></td>
</tr>
<tr>
<td>William C. Gruber, M.D., FAAP, FIDSA</td>
<td>Senior Vice President, Vaccine Clinical Research and Development</td>
<td>Pfizer, Inc.</td>
</tr>
<tr>
<td>Kathrin U. Jansen, PhD</td>
<td>Senior Vice President and Head, Vaccine Research and Development</td>
<td>Pfizer, Inc.</td>
</tr>
<tr>
<td>Adrin Nazarian</td>
<td>Assembly Member</td>
<td></td>
</tr>
<tr>
<td>Shannon A. Ross, MD</td>
<td>Associate Professor</td>
<td></td>
</tr>
<tr>
<td>Mark R. Schleiss, MD</td>
<td>American Legion and Auxiliary Heart Research Foundation Professor, Division of Pediatric Infectious Diseases and Immunology</td>
<td></td>
</tr>
<tr>
<td>Karl R. White, Ph.D.</td>
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<td></td>
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<tr>
<td></td>
<td>Professor of Psychology</td>
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<tr>
<td></td>
<td>Utah State University</td>
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</tbody>
</table>
ACHDNC Form for Nomination of a Condition for Inclusion in the Uniform Screening Panel

**NAME OF NOMINATOR AND ORGANIZATION**
(include professional degrees)

<table>
<thead>
<tr>
<th>National CMV Foundation</th>
<th>Advocacy Organization</th>
</tr>
</thead>
</table>

**CO-SPONSORING ORGANIZATIONS**
(include professional degrees)

<table>
<thead>
<tr>
<th>NCMVF RUSP Nomination team (see enclosure for membership list)</th>
<th>Advocates, Public Health Professionals, Researchers, Subject Matter Experts, Legislator, and Clinicians (see enclosure for individual affiliations)</th>
</tr>
</thead>
</table>

*Note: Please reference each statement/answer with the corresponding reference number listed in Section III – Key References.*

**SECTION I – CONDITION INFORMATION AND TREATMENT**

**SECTION I, PART A**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>STATEMENT</th>
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<tbody>
<tr>
<td>Nominated Condition</td>
<td>Congenital Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>Type of Disorder</td>
<td>Congenital viral infection</td>
</tr>
<tr>
<td>Screening Method</td>
<td>Saliva PCR</td>
</tr>
<tr>
<td>Gene</td>
<td>NA</td>
</tr>
<tr>
<td>Locus</td>
<td>Include ClinVar link if applicable. NA</td>
</tr>
<tr>
<td>OMIM or other names for condition</td>
<td>Include Genetics Home Reference link if applicable. NA</td>
</tr>
<tr>
<td>Case Definition</td>
<td>A definite case of congenital cytomegalovirus is a child from whom cytomegalovirus was detected in the first three weeks of life from urine, blood, saliva or any tissue taken at biopsy.</td>
</tr>
</tbody>
</table>

Definitions of congenital cytomegalovirus infection and disease:

**Moderately to severely symptomatic congenital cytomegalovirus disease**

- Multiple manifestations attributable to congenital cytomegalovirus infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or
cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of cytomegalovirus DNA in cerebrospinal fluid.

**Mildly symptomatic congenital cytomegalovirus disease**  
- Might occur with one or two isolated manifestations of congenital cytomegalovirus infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation.

**Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss**  
- No apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss (≥21 decibels).

**Asymptomatic congenital cytomegalovirus infection**  
- No apparent abnormalities to suggest congenital cytomegalovirus disease, and normal hearing.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Determined by what method(s): pilot screening or clinical identification?</th>
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<tbody>
<tr>
<td></td>
<td>In developed countries including the United States, congenital cytomegalovirus is estimated to occur in ~5 to 7 per 1000 live births.²,³ A recent multi-center, hospital based study screening of 100,332 newborn infants for congenital cytomegalovirus and the overall prevalence was 4.5 per 1000 live births.⁴</td>
</tr>
<tr>
<td></td>
<td>Approximately 10% of infants with congenital cytomegalovirus will have clinical findings at birth (symptomatic infection). The vast majority of infected infants (~90%), however, will have no clinical manifestations present during the newborn period (asymptomatic infection). Approximately 40% to 60% of symptomatic infants will manifest permanent sequelae, with sensorineural hearing loss (SNHL) being the most common, followed by cognitive impairment, retinitis, and cerebral palsy. Asymptomatic infants are also at risk for CMV-related disabilities, and ~10% to 15% of asymptomatic infants will develop SNHL.² In the United States, disabilities from symptomatic and asymptomatic congenital cytomegalovirus infection are more common in children than other more recognized diseases such as Down syndrome, fetal alcohol syndrome, or spina bifida.²-⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing of Clinical Onset</th>
<th>Relevance of the timing of newborn screening to onset of clinical manifestations.</th>
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<tbody>
<tr>
<td></td>
<td>Congenital CMV can only be diagnosed with testing for cytomegalovirus in saliva, urine, or both within the first 3 weeks of life. After this time, diagnostic tests do not distinguish congenital from postnatal cytomegalovirus infection in babies.</td>
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<tr>
<td></td>
<td>Approximately, 10% of infected newborns will be symptomatic at birth and 50% of those will develop disabilities. Among the 90% asymptomatic infants, at least 10% will develop disabilities or disorders due to congenital CMV later.⁵-⁷</td>
</tr>
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</table>

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<thead>
<tr>
<th>Severity of Disease</th>
<th>Morbidity, disability, mortality, spectrum of severity.</th>
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<tr>
<td></td>
<td>The severity of long-term adverse outcomes varies substantially, from minimal deficits with unilateral mild sensorineural hearing loss, to major neurodevelopmental complications and death for a minority of neonates.²-⁵ Although universal newborn hearing screening, which is now done in many developed countries, successfully</td>
</tr>
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</table>
detects many neonates with congenital hearing impairment at birth, only 57% of infants who will eventually develop hearing loss due to congenital cytomegalovirus are identified by the newborn hearing screening.\textsuperscript{6,7} In addition, nearly 10% of initially asymptomatic cytomegalovirus-infected neonates develop hearing loss later, at which point the capacity for cytomegalovirus diagnosis and opportunities for early intervention are lost or substantially reduced.

SECTION I, PART B

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>STATEMENT</th>
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</thead>
<tbody>
<tr>
<td>Modality</td>
<td>Drug(s), diet, replacement therapy, transplant, other. Include information re regulatory status of treatment.</td>
</tr>
</tbody>
</table>

As established by the international consensus group (2017), consideration should be given to universal cytomegalovirus screening to enable identification of infants with congenital cytomegalovirus infection, facilitating early detection and intervention for sensorineural hearing loss during critical stages of speech and language development and other developmental delays when appropriate.\textsuperscript{1,8} Early intervention including targeted monitoring for hearing loss and other delays will reduce the impact of hearing loss and other developmental disabilities.\textsuperscript{10}

Among currently available antivirals, intravenous ganciclovir and oral valganciclovir have been studied for the treatment of infants with congenital cytomegalovirus infection.\textsuperscript{11-15} Results from a randomized placebo-controlled trial showed statistically significant benefit of valganciclovir treatment in symptomatic neonates.\textsuperscript{12}

**Recommended treatment regimen and monitoring of the congenitally cytomegalovirus-infected neonate\textsuperscript{1}**

**Who to treat**
- Neonates with moderately to severely symptomatic congenital cytomegalovirus disease.

**When to treat**
- Within the first month of life.

**What to treat with**
- Oral valganciclovir 16 mg/kg per dose orally, twice a day.

**How long to treat**
- Treatment duration for the goal of improving audiological or developmental outcomes should not exceed 6 months.

**Monitoring during treatment**
- Absolute neutrophil counts should be followed weekly for 6 weeks, then at week 8, then monthly for the duration of therapy.
- Levels of transaminases should be followed monthly throughout therapy.

**Follow up**
- An ophthalmological examination should be done early in the course of treatment, with follow-up eye examinations as suggested by the ophthalmologist.
- Audiological testing should be done at 6-month intervals for the first 3 years of life, and annually thereafter through adolescence (ages 10–19).
- Developmental assessments beginning at the first year of life might be helpful in some children with symptomatic congenital cytomegalovirus disease and should be employed on a case-by-case basis.
<table>
<thead>
<tr>
<th>Urgency</th>
<th>How soon after birth must treatment be initiated to be effective?</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Congenital cytomegalovirus infection can only be confirmed if tested in the first three weeks of life.</td>
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<td></td>
<td>For children with hearing loss, the Joint Committee on Infant Hearing recommends diagnosis by three months of life and early intervention before six months of life. The committee identified CMV infection as a risk factor indicating a need for early and more frequent assessments. Because 43% of infants who will eventually have sensorineural hearing loss due to congenital cytomegalovirus will pass the newborn hearing screening, universal cytomegalovirus screening is the best method to identify those infants to ensure ongoing assessments and appropriate early intervention.</td>
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<td></td>
<td>Antiviral therapy has been shown to be effective when treatment begins within the first month of life.</td>
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<table>
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<tr>
<th>Efficacy (Benefits)</th>
<th>Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence.</th>
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<tbody>
<tr>
<td></td>
<td>The benefits of early detection and intervention for congenital cytomegalovirus-associated hearing loss are expected to be similar to those seen in children with hearing loss from other causes.</td>
</tr>
<tr>
<td></td>
<td>Among currently available antivirals, intravenous ganciclovir and oral valganciclovir have been studied for the treatment of infants with congenital cytomegalovirus infection. A phase 3 randomized clinical trial assessed the outcome of ganciclovir treatment in symptomatic congenital cytomegalovirus infected neonates with neurological deficits. This study had a large number of children who could not be evaluated for the primary endpoint because of loss to follow-up, but still found that ganciclovir treatment might have prevented hearing deterioration at 6 months and less than 1 year of life. Additional analyses of this trial suggested that ganciclovir might also improve neurodevelopmental outcome. Case reports and pilot observational studies provided additional evidence that ganciclovir treatment improves or prevents hearing loss in infants with symptomatic congenital cytomegalovirus infection. Results from a randomized placebo controlled trial showed statistically significant benefit of valganciclovir treatment in symptomatic neonates. All symptomatic cytomegalovirus infected neonates received valganciclovir for 6 weeks, and were then randomized to placebo or valganciclovir treatment. Neonates receiving 6 months of valganciclovir had a 2-6-times increased likelihood of improved total hearing at 24 months than those who received only 6 weeks of valganciclovir treatment. Neurodevelopmental outcomes were also improved with longer duration of therapy. Valganciclovir treatment was associated with neutropenia, although the incidence was markedly lower than previously observed with intravenous ganciclovir. Valganciclovir treatment for 6 months is recommended for congenitally infected neonates with moderately to severely symptomatic disease.</td>
</tr>
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</table>

### Availability

Limits of availability?

Early intervention programs are available in all states. IDEA Part C at 34 CFR §303.21 (https://www.ecfr.gov/cgi-bin/text-idx?SID=0cb09a7ab9d5e161aa67b872d0d57873&m=true&node=se34.2.303_121&rgn=div8) provides a definition of infant or toddler with a disability that includes a list of conditions that may indicate a high probability of resulting in a developmental delay and thus establish eligibility for early intervention services. 34 CFR §303.21(a)(2)(ii) lists congenital infections as one of those conditions. In most states, congenital cytomegalovirus is a diagnosis that may be used to establish eligibility for services under the clause for diagnosed conditions. Hearing loss is an eligible diagnosis in all states.

Currently, antiviral therapy has been recommended only for infants with symptomatic infection.

### Potential Harms of Treatment

Potential medical or other ill effects from treatment

Children with asymptomatic and mildly symptomatic infections will benefit from monitoring for hearing function and early intervention services which are not associated with potential harms.

Because of noteworthy toxicities of cytomegalovirus antivirals, consideration of their use in congenitally infected neonates must balance known risks (such as neutropenia) and possible risks (eg, gonadal dysgenesis, carcinogenicity) with potential benefits.11-15

The international consensus group1 recommended that valganciclovir treatment for 6 months should only be for congenitally infected neonates with moderately to severely symptomatic disease as defined in the case definition section of this form. Neonates with asymptomatic congenital cytomegalovirus infection should not be given antiviral therapy. Neonates with mildly symptomatic congenital cytomegalovirus infection should not routinely be given antiviral therapy.

### SECTION II – EVIDENCE-BASED INFORMATION

For a nominated condition to be considered there are 3 core requirements:

1. Validation of the laboratory test (see Section II, Part A)
2. Widely available confirmatory testing with a sensitive and specific diagnostic test (see Section II, Part B)
3. A prospective population based pilot study (see Section II, Part C)
## SECTION II, PART A

<table>
<thead>
<tr>
<th><strong>TEST</strong></th>
<th><strong>STATEMENT</strong></th>
</tr>
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</table>
| **Screening test(s) to be used** | Description of the high-volume method, instrumentation and if available as part of multi-analyte platform.  

The diagnosis of congenital cytomegalovirus-infected neonates should include real-time PCR of saliva, urine, or both within the first 3 weeks of life, with saliva as the preferred sample.\(^1\)  

Real-time PCR of newborn saliva specimens without the need for DNA extraction, which can be scaled up for high throughput capacity. Real-time PCR equipment is needed. However, many states now provide SCID screening by real-time PCR, so PCR equipment may already be available in some states. |

| **Modality of Screening** | (Dried blood spot, physical or physiologic assessment, other)  

Detection of CMV DNA in newborn saliva specimens by real-time PCR  

A large prospective study reported that real-time PCR analysis of dried blood spots had low sensitivity for newborn cytomegalovirus testing.\(^16\) Results from a 2015 study\(^17\) that included testing of a small number of dried blood spots spiked with blood specimens from transplant recipients showed that DNA yield from dried blood spots was improved by using different extraction methods; however, the sensitivity of these methods in identifying infants with congenital cytomegalovirus has not been evaluated in screening of unselected neonates.  

The same prospective multicenter study reported that real-time PCR of saliva showed high sensitivity (>97%) and specificity (99%) for detecting congenital cytomegalovirus infection.\(^18\)  

The 2017 consensus group\(^1\) concluded that the diagnosis of congenital cytomegalovirus infection in neonates should include real-time PCR of saliva, urine, or both, as soon as possible after birth but within the first 3 weeks of life, with saliva as the preferred sample. |

| **Does the screening algorithm include a second tier test? If so, what type of test and availability?** | (Dried blood spot, physical or physiologic assessment, other)  

Similar to other newborn screening assays, a positive cytomegalovirus screening result should be confirmed by testing a subsequent sample (either saliva or urine) collected within the first 3 weeks of life. Testing for cytomegalovirus in saliva, urine, or both, as early as possible, appears optimal since diagnostic tests do not distinguish congenital from postnatal cytomegalovirus infection in newborn babies older than 3 weeks of age, who might have acquired the virus at birth or through breastmilk. Obtaining a saliva sample at least 1 hour after breastfeeding to avoid potential contamination with cytomegalovirus from breastmilk has been proposed. However, utilizing published nationally representative CMV seroprevalence and breastfeeding rates, the false positive rates of saliva CMV PCR assay were shown be very low, ranging from 0.03% in white Hispanic infants to 0.14% in white non-Hispanic infants. These findings suggest that saliva PCR results are unlikely to be significantly influenced by breastfeeding. |
<p>| The second test can be done either by PCP or public health authorities. |   |</p>
<table>
<thead>
<tr>
<th>TEST</th>
<th>STATEMENT</th>
</tr>
</thead>
</table>
| **Clinical Validation** | Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.  
In a multicenter study, 34,989 infants were screened for CMV by testing saliva specimens with a real-time PCR assay and the standard rapid culture method. One hundred and seventy seven (5 per 1000 live births) infants tested positive and subsequently confirmed to have congenital CMV infection. The sensitivity and specificity of saliva real-time PCR assay were 97.4% and 99.9%, respectively. The positive and negative predictive values were 90.2% and 99.9%, respectively. The false positive rate (1-specificity) was 0.1%. |
| **Analytical Validation** | Limit of detection/quantitation, detection rate, reportable range of test results, reference range. Include regulatory status of test, information about reference samples and controls required for testing and availability of or potential for external quality assurance system, e.g., QC and PT for both screening and confirmatory tests.  
The limit of detection for real-time PCR assay of saliva samples is 200 IU/mL of sample as determined with the use of international reference standards. |
| **Considerations of Screening and Diagnostic Testing** | False positives, carrier detection, invasiveness of method, other.  
False positive rates. The real-time PCR of newborn saliva samples was shown to be highly sensitive (>97%) and specific (99.9%). The false positive rates were very low (0.1%). The collection of saliva specimens is simple and non-invasive. Avoiding the need for DNA extraction further simplifies the method. Saliva real-time PCR assay was further modified to use dried saliva swabs (without the need for transport media and refrigeration) simplifying specimen storage and transport. The collection of saliva and urine samples is not invasive. |
| **Potential Secondary Findings** | Detection or suggestion of other disorders. |

**SECTION II, PART B**

<table>
<thead>
<tr>
<th>CONFIRMATORY TESTING</th>
<th>STATEMENT</th>
</tr>
</thead>
</table>
| Clinical and Analytical Validity | Quantitative or qualitative? Include sensitivity, specificity, etc.  
The sensitivity and specificity of confirmatory testing is similar to the screening method. |
| Type of test and/or sample matrix (blood, radiology, urine, tissue sample, biophysical test) | Saliva or Urine PCR can be collected at point of care via an oral swab or urine bag. |
Is test FDA cleared/approved

Include availability information, sole source manufacturer, etc.
Yes; no sole source manufacturer. The test is offered by commercial diagnostic laboratories including ARUP and hospital laboratories.

List all CLIA certified labs offering testing in the US

Link to GeneTests and Genetic Test Reference if applicable.
There are both commercially available CLIA certified laboratories and CLIA certified hospital-based laboratories that provide saliva or urine PCR testing for congenital CMV infection. Most commercial and hospital laboratories offer this test under CPT code 87496.

SECTION II, PART C

<table>
<thead>
<tr>
<th>POPULATION-BASED PILOT STUDY</th>
<th>STATEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of Prospective Pilot</td>
<td>Universal hospital-based screening at the University of Alabama at Birmingham Hospital (1980-1997). Contact for more information and data: Karen Fowler - 205-996-7791 - <a href="mailto:kowler@uab.edu">kowler@uab.edu</a></td>
</tr>
<tr>
<td></td>
<td>Hospital-based testing was conducted at 7 US sites led by the University of Alabama at Birmingham through the NIDCD CHIMES study.(^4) Contact for more information and data: Karen Fowler - 205-996-7791 - <a href="mailto:kowler@uab.edu">kowler@uab.edu</a></td>
</tr>
<tr>
<td></td>
<td>Utah began population-based testing in 2013. The State of Utah, by law, tests all infants who fail their newborn hearing screening tests for congenital CMV.(^20) Other states including Connecticut and Illinois also test infants who fail their newborn hearing screening. Contact for more information and data: Stephanie Browning McVicar - 801-581-6343 - <a href="mailto:smcvicar@utah.gov">smcvicar@utah.gov</a>. See attached presentation (Boetger, McVicar) from 2018 CMV Public Health and Policy Conference. Numbers provided in this form are for 7/1/13 to 12/31/17. Additional data may be available during the review of this nomination from an ongoing universal screening study at the University of Minnesota. Contact for more information and data: Mark Schleiss - 612-626-9913 - <a href="mailto:schleiss@umn.edu">schleiss@umn.edu</a></td>
</tr>
<tr>
<td>Number of Newborns Screened</td>
<td>University of Alabama at Birmingham Hospital (1980-2000): 38,031 CHIMES: 100,332 State of Utah: 968</td>
</tr>
<tr>
<td>Number of Screen Positive Results</td>
<td>Positive by primary test vs. 2(^{nd}) tier test if applicable. University of Alabama at Birmingham Hospital: 464 CHIMES Study (7 hospitals in different regions of US): 497 State of Utah: 40</td>
</tr>
</tbody>
</table>
| False Positive Rate; False Negative Rate (if known) | False positive by primary test vs. 2\(^{nd}\) tier test if applicable. University of Alabama at Birmingham Hospital: Not available CHIMES Study (7 hospitals in different regions of US): 0.05%false positive rate State of Utah: 9 (majority were in first six months when recommendation to wait 60
mins after nursing was in place, reduced after changing to >120 minute wait time); no false negatives reported.

<table>
<thead>
<tr>
<th>Number of Infants Confirmed with Diagnosis</th>
<th>How is diagnosis confirmed [clinical, biochemical, molecular]?</th>
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<tbody>
<tr>
<td></td>
<td>Diagnosed with congenital CMV infection:</td>
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<tr>
<td></td>
<td>University of Alabama at Birmingham Hospital: 422 infants confirmed CMV positive with second urine or saliva specimen; 42 infants, including 3 infants who died, were unavailable for further diagnostic confirmation.</td>
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<tr>
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<td>CHIMES Study (7 hospitals in different regions of US): 391 infants confirmed CMV positive with second urine or saliva specimen; 35 infants were CMV negative on further testing; 13 had indeterminate positive screening results that were not confirmed; 58 infants including 3 deaths were not available for further diagnosis confirmation.</td>
</tr>
<tr>
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<td>State of Utah: 27</td>
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<tr>
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<td>Diagnosed with disabilities or disorders due to the congenital CMV infection:</td>
</tr>
<tr>
<td></td>
<td>University of Alabama at Birmingham Hospital: 116 infants</td>
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**SECTION III – KEY REFERENCES**

**LIST OF REFERENCES**

Limited to 20 references from scientific journals to support statements in Sections I-IV. For sources based on un/non-published data, references may be written statements from clinicians, researchers, and/or investigators.

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Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

William D Rawlinson, Suresh B Boppana, Karen B Fowler, David W Kimberlin, Tiziana Lazzarotto, Sophie Alain, Kate Daly, Sara Doutré, Laura Gibson, Michelle L Giles, Janelle Greenlee, Stuart T Hamilton, Gail J Harrison, Lisa Hui, Cheryl A Jones, Pamela Palasanthiran, Mark R Schleiss, Antonia W Shand, Wendy J van Zuylen

Congenital cytomegalovirus is the most frequent, yet under-recognised, infectious cause of newborn malformation in developed countries. Despite its clinical and public health importance, questions remain regarding the best diagnostic methods for identifying maternal and neonatal infection, and regarding optimal prevention and therapeutic strategies for infected mothers and neonates. The absence of guidelines impairs global efforts to decrease the effect of congenital cytomegalovirus. Data in the literature suggest that congenital cytomegalovirus infection remains a research priority, but data are yet to be translated into clinical practice. An informal International Congenital Cytomegalovirus Recommendations Group was convened in 2015 to address these questions and to provide recommendations for prevention, diagnosis, and treatment. On the basis of consensus discussions and a review of the literature, we do not support universal screening of mothers and the routine use of cytomegalovirus immunoglobulin for prophylaxis or treatment of infected mothers. However, treatment guidelines for infected neonates were recommended. 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.

**Introduction**

Many adverse fetal and neonatal outcomes have been prevented since the introduction of maternal screening for infectious diseases during pregnancy, and since the institution of routine rubella vaccination of women of reproductive age. In stark contrast, congenital cytomegalovirus infection remains largely unrecognised in the developed and developing world.1 This is despite congenital cytomegalovirus now being the major infectious cause of sensorineural hearing loss and neurodevelopmental abnormalities in infants born in developed countries,2 and second only to cerebral palsy in all causes of serious malformation in many parts of the world. The prevalence of congenital cytomegalovirus has been reported as 0·2% to 2·0% (average of 0·64%) of pregnancies.3 Many factors contribute to congenital cytomegalovirus mortality and morbidity, including the limited awareness of clinicians and parents about infection during pregnancy, low levels of routine testing of neonates at risk, the absence of maternal or neonatal screening programmes, the limited efficacy and toxicity of current treatments, and the absence of licensed vaccines. In part, because of these limitations, congenital cytomegalovirus and preventive measures for acquiring cytomegalovirus during pregnancy are not routinely or consistently discussed with pregnant women or women attempting conception. However, with evidence for efficacy of preventive actions,4 efficacy of early intervention for children with sensorineural hearing loss,5 evolving antiviral treatments, and recent availability of candidate vaccines for pregnant women and neonates,6 there is an emerging consensus that more attention must be directed to this infection by clinicians’7 researchers, and communities. In some states of the USA, legislation requires cytomegalovirus education as part of routine antenatal care.8–10

To assist with clinical care, an informal International Congenital Cytomegalovirus Recommendations Group was convened as part of the 5th International Congenital Cytomegalovirus conference on April 19, 2015, to review and grade available evidence, and to draft recommendations that could be used to guide congenital cytomegalovirus diagnosis, prevention, and therapy. The International Congenital Cytomegalovirus Recommendations Group addressed whether pregnant women should be screened to aid diagnosis of maternal cytomegalovirus infection, and also addressed methods for diagnosis of maternal or fetal cytomegalovirus infection. Suggestions about who should be educated about congenital cytomegalovirus infections, and preventive measures for maternal cytomegalovirus infection, were considered. Whether cytomegalovirus hyperimmunoglobulin or antiviral therapy could be used routinely to prevent or treat congenital cytomegalovirus infection during pregnancy was discussed. Neonatal screening and the important questions of whether to treat infected neonates, and what form this therapy should consist of, were also addressed.

**Methods to provide global recommendations on cytomegalovirus prevention, diagnosis, and treatment**

Expert clinicians, opinion leaders for congenital cytomegalovirus, researchers with expertise in congenital cytomegalovirus infection, and representatives of the congenital cytomegalovirus community from Europe, the USA, and Australia were identified and invited to a
Panel 1: Key findings and recommendations

Diagnosis
- If maternal primary cytomegalovirus infection is diagnosed or fetal infection is suspected, referral to a clinician with experience in the diagnosis and management of fetal cytomegalovirus infection is recommended.
- Cytomegalovirus serology tests (cytomegalovirus-specific IgG, IgM, and IgG avidity) should be offered when a pregnant woman develops an illness with influenza-like symptoms (typically fever, fatigue, and headache) not attributable to another specific infection, or when imaging findings (ultrasound or the less frequently used MRI) are suggestive of fetal cytomegalovirus infection.
- For cytomegalovirus-seronegative pregnant women, the diagnostic assessment of primary cytomegalovirus infection should include the detection of cytomegalovirus-specific IgM in serum. When the immune status before pregnancy is unknown, the diagnosis of maternal primary cytomegalovirus infection should be on the basis of the detection of both cytomegalovirus IgM and cytomegalovirus IgG antibodies of low-to-moderate avidity.
- A confirmed diagnosis of fetal cytomegalovirus infection can be made after 20–21 weeks of gestation, and at least 6 weeks from the time of maternal infection, by testing amniotic fluid for cytomegalovirus using nucleic acid test assays such as real-time PCR.
- The diagnosis of congenital cytomegalovirus-infected neonates should include real-time PCR of saliva, urine, or both within the first 3 weeks of life, with saliva as the preferred sample.
- Consideration should be given to universal neonatal cytomegalovirus screening to enable early detection of congenital cytomegalovirus-infected infants allowing early intervention for sensorineural hearing loss and developmental delay where appropriate. However, universal screening of all pregnant women to assist in the diagnosis of primary cytomegalovirus infection is currently not recommended.

Prevention
- All pregnant women and health-care providers should be educated about congenital cytomegalovirus infection and preventive measures.
- Cytomegalovirus hyperimmunoglobulin should not be routinely administered to pregnant women with primary cytomegalovirus infection to prevent fetal cytomegalovirus infection.
- Routine antiviral therapy to prevent congenital cytomegalovirus infection during pregnancy is not recommended.

Therapy
- Cytomegalovirus hyperimmunoglobulin treatment should not be routinely administered for fetal cytomegalovirus infection.
- Routine antiviral therapy to treat fetal cytomegalovirus infection during pregnancy is not recommended.
- Valganciclovir treatment for 6 months is only recommended for congenitally infected neonates with moderately to severely symptomatic disease.
- Antiviral therapy should not be administered to neonates with asymptomatic congenital cytomegalovirus infections.
- Antiviral therapy is not routinely recommended for asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss, or for neonates with mildly symptomatic congenital cytomegalovirus infection.

Screening for maternal cytomegalovirus infection
Universal cytomegalovirus screening of pregnant women is not recommended by national public health bodies in any country. However, selective testing of pregnant women for congenital cytomegalovirus, from lists of plenary speakers at international conferences, and from availability to attend the workshop and thereafter in drafting the recommendations. The International Congenital Cytomegalovirus Recommendations Group clearly could not embody all clinicians and researchers with expertise in congenital cytomegalovirus, but it did comprise internationally recognised experts with published expertise within diagnosis, prevention, and therapy.

The group first formulated which specific issues should be addressed (appendix) and assessed these before the workshop by reviewing the scientific literature. A systematic review of prevention and treatment of congenital cytomegalovirus infection was also undertaken before the workshop to ensure current published, and unpublished views were expressed in an unbiased manner. The use of a systematic review, combined with consensus meeting and discussion was on the basis of similar projects.

Recommendations were formulated after discussion and scientific evidence was graded (appendix). The quality of evidence on which recommendations were based was scored using the Oxford Centre for Evidence Based Medicine (OCEBM) levels of evidence. These are defined as: level 1, evidence from at least one properly randomised controlled trial; level 2a, controlled trials without randomisation; level 2b, cohort or case-control analytical studies; level 2c, multiple time series or uncontrolled experiments (including data on new therapies that were not collected in a randomised fashion); and level 3, evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. These recommendations then underwent a panel vote, with consensus declared if 100% of the group agreed to a recommendation. After the workshop, a draft document was distributed among the members of the group, with 4 weeks allowed for responses, all of which were collated to finalise the document of consensus recommendations.

The key findings of this workshop are summarised in panel 1. The definitions of congenital cytomegalovirus infection and disease used in this document were those previously used, with minor adjustments based on discussions of the group (panel 2), to provide retrospective comparability. The final document was reviewed by all authors, by other internationally recognised authors with obstetric, paediatric, infectious diseases, and virology expertise who were unable to participate in the original workshop or publication, and was sent to all members of the Australian and New Zealand Paediatric Infectious Diseases Group for comment.

Review
women is done as part of population-based studies, and by some clinicians independently of formal screening programmes in parts of Europe, Israel, Australia, and the USA.23–25

One proposed approach to reducing the incidence of congenital cytomegalovirus infection is universal cytomegalovirus screening of pregnant women to assist diagnosis of primary infection.20 Primary maternal cytomegalovirus infection has been associated with the highest individual risk of in-utero transmission and clinical consequences for the fetus.20 Several studies have used serological screening (cytomegalovirus-specific IgG testing) to identify those seronegative pregnant women with a higher risk of seroconversion.20–22 The results of studies showed that providing these women with advice regarding appropriate precautions to reduce their risk might prevent primary maternal cytomegalovirus infection. However, universal screening of all pregnant women to identify those who are cytomegalovirus-seronegative is not recommended as part of routine antenatal screening in any country known to the expert group. This arises from health-economical, practical, and jurisdictional reasons, and because congenital cytomegalovirus infection can occur in infants born to women who were cytomegalovirus-seropositive before pregnancy (non-primary maternal cytomegalovirus infection).20–22 Estimates suggest that more than two-thirds (about 75%) of all congenital cytomegalovirus cases in the USA (and by implication in other developed countries) occur in infants born to women with non-primary cytomegalovirus infection, presumably due to reactivation of latent virus, reinfection with a new cytomegalovirus strain, or both.20,23,24 Additionally, increasing evidence shows that the risk of symptomatic infection, especially that resulting in hearing loss, is similar after maternal primary or non-primary cytomegalovirus infection.1,15–16 Data from nationwide registries for congenital cytomegalovirus (such as those in France and the USA) could assist further investigation of this risk and the effect of maternal primary and non-primary cytomegalovirus infection.

The members of the group did not recommend universal screening of pregnant women to diagnose primary cytomegalovirus infection (on the basis of level 2b evidence).

Diagnosis of maternal cytomegalovirus infection
When maternal primary cytomegalovirus infection is clinically suspected, then cytomegalovirus testing can assist in determining the risk of transmission to the fetus. The diagnosis of maternal primary cytomegalovirus infection cannot be made on the basis of clinical symptoms alone, because these are non-specific (typically fever, fatigue, and headache), and 25–50% of mothers have no symptoms.20–21 When maternal primary cytomegalovirus infection is suspected, diagnostic testing should include detection of de-novo cytomegalovirus-specific IgG in the serum of previously seronegative pregnant women (seroconversion). In practice, the diagnosis by seroconversion alone is rarely achieved because of the frequent absence of an appropriate baseline cytomegalovirus-specific IgG negative sample. However, comparison with stored pre-pregnancy or early pregnancy serum, where available, is ideal.

When cytomegalovirus immune status before pregnancy is unknown, isolated detection of cytomegalovirus IgG avidity (maturity) or detection of specific IgM antibodies are inadequate single measures to diagnose maternal primary infection.27–30 However, the concurrent use of both measures improves identification of primary infection,31 with the detection of cytomegalovirus IgM antibodies and low–moderate cytomegalovirus IgG avidity serving as good indicators of recent primary infection.32 When these antibodies are detected using validated assays,30 particularly before 12–16 weeks of gestation, they indicate a higher risk for symptomatic congenital infection.33,34 Consensus recommendations from the group were that cytomegalovirus serology tests (for cytomegalovirus-specific IgG, IgM, and IgG avidity) should be offered when a pregnant woman develops an illness with influenza-like symptoms (typically fever, fatigue, and headache) not attributable to another specific infection, or when imaging findings (ultrasound or MRI) are suggestive of congenital cytomegalovirus infection.

Panel 2: Definitions of congenital cytomegalovirus infection and disease

Mildly symptomatic congenital cytomegalovirus disease

- Might occur with one or two isolated manifestations of congenital cytomegalovirus infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation

Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss

- No apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss ($\geq$21 decibels)

Asymptomatic congenital cytomegalovirus infection

- No apparent abnormalities to suggest congenital cytomegalovirus disease, and normal hearing

Definitions as published by Kimberlin and colleagues,1 with minor emendation from discussions of the International Congenital Cytomegalovirus Recommendations Group.
suggesive of fetal cytomegalovirus infection (level 3 evidence). For cytomegalovirus-seronegative pregnant women, the diagnostic assessment of primary cytomegalovirus infection should include the detection of cytomegalovirus-specific IgG in serum (level 2b evidence). When the immune status before pregnancy is unknown, the diagnosis of maternal primary cytomegalovirus infection should be based on the detection of both cytomegalovirus IgM and low–moderate avidity cytomegalovirus IgG antibodies (level 2b evidence).

Prenatal diagnosis of fetal cytomegalovirus infection

Prenatal diagnosis of fetal cytomegalovirus infection can be made via testing of amniotic fluid for cytomegalovirus by amniocentesis, since the virus is excreted into the amniotic fluid through fetal urine. An amniocentesis for cytomegalovirus can be recommended in two situations: when there is maternal primary cytomegalovirus infection during pregnancy, or when there are abnormalities on ultrasound that are compatible with fetal cytomegalovirus infection. There is a low risk of miscarriage associated with amniocentesis, with a population-based study suggesting minimal or no increased rates of miscarriage in women who underwent amniocentesis by a fetal medicine expert. Amniocentesis for cytomegalovirus achieves the best sensitivity after 20–21 weeks’ gestation, once fetal urination is well established, and at least 6 weeks from the time of maternal cytomegalovirus infection. The sensitivity of amniocentesis before 20 weeks can be as low as 45%, but it might be warranted in certain circumstances, particularly when ethical and practical difficulties limit management options after 21 weeks of gestation. The use of amniocentesis for the diagnosis of fetal infection has been tested in a number of studies. The presence of cytomegalovirus can be detected using PCR, other nucleic acid test assays, or virus culture. Most studies confirm that nucleic acid test assays such as real-time PCR are the most sensitive methods for the detection of cytomegalovirus in amniotic fluid. If cytomegalovirus is detected in the amniotic fluid, fetal infection is confirmed. Perinatal outcome following confirmed fetal cytomegalovirus infection ranges from healthy asymptomatic livebirth to stillbirth or postnatal survival with severe disability. Several methods have been investigated to predict the perinatal outcome of fetal infection, including prenatal ultrasound and fetal MRI.

Prevention of maternal cytomegalovirus infection during pregnancy

Prevention of maternal cytomegalovirus infection through vaccination has been tested in a phase 2 trial of a recombinant glycoprotein B vaccine in seronegative women, which showed 50% efficacy for maternal seroconversion. However, waning immunity was observed, which questions the long-term efficacy of this vaccine formulation. A randomised, double-blind, placebo-controlled phase 2 study testing this glycoprotein B vaccine in cytomegalovirus-negative adolescent girls produced similar results, with 45% efficacy for seroconversion after two doses. Several cytomegalovirus vaccines are under development and completion of several clinical trials is anticipated between 2017 and 2019 (ClinicalTrials.gov trial registry numbers NCT02594566, NCT02396134, NCT02506933, and NCT01877655). A particular risk factor for maternal cytomegalovirus infection is close contact with children younger than 2 years of age, since cytomegalovirus excretion in saliva and urine can continue for months or years in young children. Children can shed high levels of cytomegalovirus, and frequently acquire cytomegalovirus from other children, including those attending daycare. Therefore, hygienic and behavioural interventions (panel 3) have been investigated to prevent cytomegalovirus infection in pregnant women.

Results from two cluster randomised trials and one single-group study showed that behavioural measures that reduce contact with bodily fluids from young children reduced cytomegalovirus seroconversion in pregnant women. These trials probably have selection and detection biases, and control data are missing in the single-group study. However, a more recent interventional and observational controlled trial has provided further evidence that a prevention strategy based on provision of information to pregnant women at risk for cytomegalovirus infection is effective. In a 2015 study by Revelo and colleagues, pregnant women in the prospective intervention group received the same information and behavioural instructions as mothers in the 1996 study by Adler and colleagues, with the exception of using gloves and avoiding co-sleeping with the infant. Seroconversion occurred in four (1.2%) of 331 pregnant women in the intervention group, at a lower rate compared with 24 (7.6%) of 315 in the comparator, non-instructed group (absolute risk reduction [Δ]=6–4% [95% CI 3.2–9.6]; p<0.001 [exact value not reported]).
Adler and colleagues\(^6\) described that all (n=106) mothers reported these behavioural interventions as being done easily, indicating that this approach was not difficult to implement. However, results from seven studies\(^8\)-\(^14\) have shown that a large proportion (61·0% to 87·5%) of pregnant women are unaware and uninformedit about congenital cytomegalovirus infection, and the results of four studies\(^6\)-\(^9\) suggested that health-care providers, such as doctors, obstetricians, and midwives, do not possess sufficient knowledge of this infection.

The consensus recommendations from the group were that health-care providers, including midwives, obstetricians, and paediatricians, should be educated about congenital cytomegalovirus infection and preventive measures (panel 3; level 2b evidence). Given the potential risk of congenital cytomegalovirus in all pregnancies, albeit at low risk in the individual cytomegalovirus-seropositive woman,\(^1,19\) all pregnant women should be educated about congenital cytomegalovirus infections and preventive measures (level 2b evidence). The group also concluded that research is needed to identify the education content and methods that are most effective in preventing cytomegalovirus infection in pregnant women. Educational resources should be developed and used locally, and preferably shared online.

**Prevention of vertical transmission of cytomegalovirus infection**

Passive immunisation with cytomegalovirus hyperimmunoglobulin has been investigated as a potential means to prevent cytomegalovirus transmission to the fetus in pregnant women with primary cytomegalovirus infection. Four studies evaluated the efficacy of hyperimmunoglobulin treatment to prevent fetal cytomegalovirus infection. Although a non-randomised controlled phase 1 and 2 study,\(^9\) a double-blinded, randomised placebo-controlled study,\(^10\) and two observational studies\(^11\)-\(^13\) report some evidence of benefit and a trend towards efficacy of hyperimmunoglobulin, the results from these studies are inconsistent and not definitive, which could be related to suboptimal doses used or the application interval.\(^3\) No serious adverse events due to hyperimmunoglobulin therapy were reported in the three non-randomised studies.\(^11\)-\(^13\) Results from a randomised trial\(^14\) showed no significant benefit for treatment, but reported obstetric complications (preterm delivery, preeclampsia, and fetal growth restriction) in seven (13%) of 53 women in the group receiving hyperimmunoglobulin, compared with one (2%) of 51 women in the placebo group (p=0·06). At least one randomised clinical trial is underway (NCT01376778), which might clarify the role for prophylactic hyperimmunoglobulin treatment.

The benefits and harms of antiviral drugs used to prevent vertical transmission in pregnant women are being studied in one randomised, phase 2, double-blinded clinical trial that is planned to evaluate the efficacy of valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy (NCT02351102). The results of this trial might provide much-needed evidence for antiviral safety and efficacy in the prevention of congenital cytomegalovirus acquisition during pregnancy.

The group recommended that hyperimmunoglobulin should not be routinely administered to pregnant women with primary cytomegalovirus infection for prevention of congenital cytomegalovirus, on the basis of insufficient evidence (level 2c evidence). If such patients are treated, their data should be tracked to contribute to understanding of the safety of this approach. Routine antiviral therapy to prevent congenital cytomegalovirus infection during pregnancy is also not recommended, on the basis of insufficient current evidence (level 3 evidence).

**Treatment of the cytomegalovirus-infected fetus during pregnancy**

Treatment options for fetal cytomegalovirus infection during pregnancy to prevent or reduce the severity of fetal cytomegalovirus-associated symptoms are limited. Management options of the infected fetus include therapy with cytomegalovirus hyperimmunoglobulin or antiviral drugs. However, because there is insufficient evidence for the efficacy of antiviral drugs, they should currently all be regarded as investigational, and therefore should not be used outside of a clinical trial setting.\(^14\)

Evidence for potential efficacy of hyperimmunoglobulin treatment to reduce disease from congenital cytomegalovirus has been reported in four prospective and two retrospective studies, each treating between three and 31 pregnant women diagnosed prenatally with congenital cytomegalovirus infection.\(^15\)-\(^18\) Nigro and colleagues\(^19\) observed that pregnant women with cytomegalovirus-positive amniotic fluid, treated with 200 U/kg of hyperimmunoglobulin intravenously, gave birth to infants with a reduced rate of symptomatic disease (one [3%] of 31) compared with women who declined hyperimmunoglobulin treatment (seven [50%] of 14). A partly
randomised case-control study by Visentin and colleagues reported that fewer infants had poor outcomes (such as sensorineural hearing loss) at 1 year of age when the mother was treated with 200 U/kg hyperimmunoglobulin intravenously at 20–24 weeks’ gestation (four of 31 [13%]), compared with infants from untreated mothers (16 of 37 [43%]). However, the findings of these studies are not definitive because of the small number of women treated with hyperimmunoglobulin, and other methodological issues, as reviewed previously.

Antiviral drugs such as ganciclovir, the oral pro-drug valganciclovir, foscarnet, and cidofovir have been used extensively to treat cytomegalovirus in immunocompromised patients. However, foscarnet and cidofovir are unsuitable therapeutics during pregnancy because of nephrotoxicity and potential carcinogenicity, with minimal safety or efficacy data in pregnancy. Additionally, there are limited safety and efficacy data for ganciclovir and valganciclovir in pregnancy, with four case reports describing ganciclovir use in pregnancy for transplant recipients and in a woman with HIV/AIDS without teratogenic effects. Ganciclovir is not recommended for use in pregnancy because of reported risks of gonadal dysgenesis in animal studies, and the inability to monitor for fetal toxicities, including neutropenia. Ganciclovir, valganciclovir, foscarnet, and cidofovir are currently classified by the US Food and Drug Administration (FDA) as category C.

Aiclovir and the oral pro-drug valaciclovir have been used as prophylaxis for cytomegalovirus infection in transplant recipients and patients with HIV/AIDS. The premise for use in pregnancy is that although they have weak activity against cytomegalovirus, they have very low rates of adverse effects in pregnancy on the basis of two small observational studies and one large registry-based study managed by the drug manufacturer. A subsequent registry-based study provided additional evidence that aciclovir, valaciclovir, and famciclovir are not teratogenic. Results from a pilot observational study by Jacquemard and colleagues showed that oral valaciclovir was tolerated by pregnant women with confirmed fetal cytomegalovirus infection and might decrease viral load in fetal blood, without clear improvement in fetal outcome, possibly due to the small sample size or lack of efficacy. One non-randomised, single group assignment phase 2 clinical trial evaluated the efficacy of valaciclovir in treatment of confirmed fetal cytomegalovirus infection in 41 women with 43 moderately symptomatic congenital cytomegalovirus-infected fetuses. Mothers were treated with 8 g/day oral valaciclovir, analysed using Simon’s optimal two-stage design, whereby valaciclovir was assumed to have a positive effect if at least 31 of 43 neonates were asymptomatic at birth. In total, 34 of 43 neonates were born asymptomatic, which suggests efficacy of valaciclovir treatment, although these findings are not conclusive due to the design of the study, and the small number of valaciclovir-treated women to date. Further evaluation of the use of aciclovir, valaciclovir, and famciclovir (FDA category B) is of interest. However, they cannot be recommended routinely because current data on antiviral efficacy and safety profiles during pregnancy are limited.

The consensus recommendations from the group were that antenatal cytomegalovirus hyperimmunoglobulin should not be routinely recommended as therapy for fetal cytomegalovirus infection (level 2b evidence). If such patients are treated, their data should be tracked to contribute to the overall understanding of the safety of such an approach. Routine antiviral therapy to prevent or treat congenital cytomegalovirus infection during pregnancy is also not recommended, on the basis of insufficient evidence for safety and effectiveness of antiviral drugs on clinical outcomes (level 2c evidence).

**Neonatal cytomegalovirus screening**

Congenital cytomegalovirus-infected neonates might be asymptomatic or symptomatic at birth (panel 2). The severity of long-term adverse outcomes varies substantially, from minimal deficits with unilateral sensorineural hearing loss, to major neurodevelopmental complications and death for a minority of neonates. Universal newborn hearing screening, which is now done in many developed countries, successfully detects many neonates with congenital hearing impairment at birth. However, nearly 10% of initially asymptomatic cytomegalovirus-infected neonates later develop hearing loss, at which point the capacity for cytomegalovirus diagnosis and opportunities for early intervention are lost or substantially reduced.

Studies reviewed by Cannon and colleagues reported evidence that cytomegalovirus screening of all neonates could significantly improve the outcome of those infected with cytomegalovirus with delayed hearing loss. It is well established that infants with an early diagnosis of hearing loss develop better receptive and expressive language with improved cognitive function than do infants with a later diagnosis. Therefore, targeted cytomegalovirus screening of newborn infants (eg, testing of infants who fail newborn hearing screening) and cytomegalovirus screening of all neonates has been the focus of investigations over the past few years. A 2015 cost–benefit analysis reported a net public benefit for targeted cytomegalovirus testing of neonates with hearing loss. A separate cost-effectiveness analysis based on data derived from large prospective cohorts reported that both universal and targeted newborn cytomegalovirus screening were cost-saving. Additional prospective studies and cost-effectiveness studies would further inform any recommendation regarding universal or targeted cytomegalovirus testing of neonates.

The group recommended that consideration should be given to universal neonatal cytomegalovirus screening to enable early detection of congenital cytomegalovirus-infected infants, facilitating early detection and intervention for sensorineural hearing loss and
developmental delay where appropriate (level 2b evidence).

Diagnosis of the cytomegalovirus infected neonate

A large prospective study reported that real-time PCR analysis of dried blood spots had low sensitivity for newborn cytomegalovirus testing. Results from a 2015 study that included testing of a small number of dried blood spots spiked with blood specimens from transplant recipients showed that DNA yield from dried blood spots was improved by using different extraction methods; however, the sensitivity of these methods in identifying infants with congenital cytomegalovirus has not been evaluated in screening of unselected neonates. Yamamoto and colleagues showed that both urine and saliva are reliable specimens for neonatal cytomegalovirus screening using PCR, and a prospective multicentre study reported that real-time PCR of saliva showed high sensitivity (>97%) and specificity (99%) for detecting congenital cytomegalovirus infection. Similar to other newborn screening assays, a positive cytomegalovirus screening result should be confirmed by testing a subsequent sample (either saliva or urine) collected within the first 3 weeks of life. Testing for cytomegalovirus in saliva, urine, or both, as early as possible, appears optimal since diagnostic tests do not distinguish congenital from postnatal cytomegalovirus infection in newborn babies older than 3 weeks of age, who might have acquired the virus at birth or through breastfeeding. Obtaining a saliva sample at least 1 hour after breastfeeding to avoid potential contamination with cytomegalovirus from breastmilk has been practised and described.

The consensus recommendations from the group were that the diagnosis of congenital cytomegalovirus infection in neonates should include real-time PCR of saliva, urine, or both, as soon as possible after birth but within the first 3 weeks of life, with saliva as the preferred sample (level 2b evidence).

Treatment of congenitally cytomegalovirus infected neonates

Because of noteworthy toxicities of cytomegalovirus antivirals, consideration of their use in congenitally infected neonates must balance known risks (such as neutropenia) and possible risks (eg, gonadal dysgenesis, carcinogenicity) with potential benefits. Among currently available antivirals, intravenous ganciclovir and oral valganciclovir have been studied for the treatment of infants with congenital cytomegalovirus infection. Results from a phase 2 trial published in 1997, comparing 8 mg/kg and 12 mg/kg daily doses for 6 weeks, showed that ganciclovir treatment significantly improved or stabilised hearing in five (16%) of 30 infected infants with a daily dose of 12 mg/kg. A subsequent phase 3 randomised clinical trial assessed the outcome of ganciclovir treatment in symptomatic congenital cytomegalovirus-infected neonates with neurological deficits. This study had a large number of children who could not be evaluated for the primary endpoint because of loss to follow-up, but still found that ganciclovir treatment might have prevented hearing deterioration at 6 months and less than 1 year of life. However, this study also observed an association of ganciclovir treatment with neutropenia. Additional analyses of this trial suggested that ganciclovir might also improve neurodevelopmental outcome. Two case reports and two pilot observational studies provided additional evidence that ganciclovir treatment improves or prevents hearing loss in infants with symptomatic congenital cytomegalovirus infection.

Evidence that oral valganciclovir improves or preserves hearing in infants with symptomatic congenital cytomegalovirus infection has been reported in three case studies. More recently, results from a randomised placebo-controlled trial showed statistically significant benefit of valganciclovir treatment in symptomatic neonates. All symptomatic cytomegalovirus-infected neonates received valganciclovir for

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Panel 4: Recommended treatment regimen and monitoring of the congenitally cytomegalovirus-infected neonate

**Who to treat**
- Neonates with moderately to severely symptomatic congenital cytomegalovirus disease

**When to treat**
- Within the first month of life

**What to treat with**
- Oral valganciclovir 16 mg/kg per dose orally, twice a day

**How long to treat**
- Treatment duration for the goal of improving audiological or developmental outcomes should not exceed 6 months

**Monitoring during treatment**
- Absolute neutrophil counts should be followed weekly for 6 weeks, then at week 8, then monthly for the duration of therapy
- Levels of transaminases should be followed monthly throughout therapy

**Follow up**
- An ophthalmological examination should be done early in the course of treatment, with follow-up eye examinations as suggested by the ophthalmologist
- Audiological testing should be done at 6-month intervals for the first 3 years of life, and annually thereafter through adolescence (ages 10–19)
- Developmental assessments beginning at the first year of life might be helpful in some children with symptomatic congenital cytomegalovirus disease, and should be employed on a case-by-case basis
A randomised efficacy study is planned to evaluate the randomised, controlled trial of valganciclovir therapy in initiation of antiviral therapy beyond the first month of life as of 2016, recruiting participants for a phase 2 clinical trial is investigating whether early treatment with oral valganciclovir of infants up to 12 weeks of age with congenital cytomegalovirus infection and sensorineural hearing loss can prevent progression of hearing loss (NCT01649869). A randomised efficacy study was planned to evaluate the benefit of antiviral treatment with valganciclovir on hearing and balance in children aged 6 months to 12 years with congenital cytomegalovirus (NCT02606266), which might provide evidence to inform treatment options.

The group recommended that valganciclovir treatment for 6 months should only be for congenitally infected neonates with moderately to severely symptomatic disease as defined in panel 2 (level 1 evidence). Neonates with asymptomatic congenital cytomegalovirus infection should not be given antiviral therapy (level 3 evidence). Neonates with mildly symptomatic congenital cytomegalovirus infection should not routinely be given antiviral therapy (level 3 evidence). If such patients are treated on a case-by-case basis, their data should be accumulated to contribute to the overall understanding of the safety of such an approach. Antiviral therapy is not routinely recommended for congenital cytomegalovirus infection with isolated sensorineural hearing loss and otherwise asymptomatic, based on insufficient evidence (level 3 evidence). If such patients are treated, their data should be tracked to contribute to the overall understanding of the safety and efficacy of such an approach.

Conclusions
This Review summarises current data on the efficacy of prevention, the significant improvements in diagnostic capacity globally (particularly in molecular detection and characterisation of infection), and data showing utility of antiviral therapy in some infected neonates. These, and other published data, can now be used to inform jurisdictional policy, and practice, in reducing the global impact of congenital cytomegalovirus.
Alix A.


New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection

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SUMMARY

Congenital CMV is a major cause of neurological and sensory impairment in children. Reliable estimates of the prevalence of permanent sequelae and mortality associated with congenital CMV are needed to guide development of education and prevention programmes and to gauge the financial costs associated with this disease. To calculate such estimates, this review used data solely from studies in which children with congenital CMV were identified through universal screening. Based on 15 studies with a total of 117,986 infants screened, the overall CMV birth prevalence estimate was 0.7%. The percentage of infected children with CMV-specific symptoms at birth was 12.7%. The percentage of symptomatic children with permanent sequelae was 40–58%. The percentage of children without symptoms at birth who developed permanent sequelae was estimated to be 13.5%. The true burden of congenital CMV infection is unclear because data on important outcomes, such as visual impairment, are lacking and follow-up of infected children has been too short to fully identify late-onset sequelae. Therefore, the estimates of permanent sequelae associated with congenital CMV presented here are likely underestimates. Future studies should extend follow-up of CMV-infected children identified through universal screening and include the evaluation of visual impairment. Copyright © 2007 John Wiley & Sons, Ltd.

INTRODUCTION

Human cytomegalovirus is a widely distributed herpesvirus spread through close interpersonal contact with infected bodily fluids, usually saliva, urine, blood or genital secretions. CMV can be transmitted from mother to fetus anytime during gestation and is most likely to cause serious harm to the fetus when the mother experiences a primary CMV infection during pregnancy. Congenital CMV can cause permanent physical sequelae

or impairments that result in disabilities such as hearing loss (HL), visual impairment, and mental retardation; it also raises the risk of infant mortality [1,2]. According to a recent review, between 20,000 and 40,000 children are born with congenital CMV infections in the United States each year; 100–200 die as a consequence of symptomatic infections, and 4000–8000 develop permanent neurological complications that often lead to permanent disabilities [3]. Higher estimates of the burden of congenital CMV in terms of death and disability have also been published [4,5].

Sensorineural hearing loss (SNHL) is the most common symptom of CMV infection among the 10–15% of children with symptoms of infection at birth [6,7]. HL occurs at a lower rate among the 85–90% of infected infants who are asymptomatic at birth; however, because there are many more asymptomatic infants, the majority of cases of SNHL caused by CMV occur in this group.
The frequencies of visual impairment, mental retardation or milder cognitive impairment are less well established and are concentrated among the minority who are symptomatic at birth [8]. Infant mortality has been reported in 10% or more of children who are symptomatic at birth [4,5]; however, one recent review suggested that the mortality rate from symptomatic CMV could be less than 5% [3].

Although several studies have estimated the burden of congenital CMV, the current study is the first systematic review of neurological and sensory sequelae associated with congenital CMV infection. It is also the first review of congenital CMV sequelae to include data from only studies that performed universal screening of all infants born at a given centre or centres. The review does not include studies in which any of the children with CMV were referred to the study based on clinical symptoms, nor does it include reports based on screening subsets of infants at elevated risk for congenital CMV infection. Our purpose is to provide an unbiased estimate of the frequency of permanent sequelae associated with congenital CMV infection to more accurately measure the preventable burden of this disease. To that end, this review presents estimates of the birth prevalence of symptomatic and asymptomatic congenital CMV infections and the probabilities of neurological sequelae in each of these groups.

METHODS
We searched the Medline/OVID database for English-language papers published from 1966 through December 2006 using the subject headings ‘CMV’ or ‘cytomegalovirus’ with the keywords ‘congenital’ or ‘newborn.’ Papers were then restricted to those with any of the following key words: ‘sequelae’, ‘symptoms’, ‘symptomatic’, ‘abnormalities’, ‘impairment’, ‘outcome’, or ‘prognosis’. This search resulted in approximately 450 papers, which we reviewed for the following inclusion criteria: (1) original peer-reviewed papers; (2) study populations from high-income countries, based on per capita income during the study period; (3) sample of 800 or more children; (4) identification of congenital CMV through universal screening in a defined population and (5) detection of CMV based on culture of urine or saliva collected within 3 weeks of birth. In the case of multiple reports from the same authors with overlapping study dates, we chose the most recent or most comprehensive report to avoid counting the same study subjects more than once. Eighteen unique studies met our search criteria for universal screening of a birth cohort. Of these, 15 reported the prevalence of symptoms at birth and 3 studies reported infected children only.

Our criteria were defined to exclude reports likely to over-represent infants with severe sequelae. These include: (1) studies that selected women who experienced primary CMV infection during pregnancy or that identified CMV-infected infants based on elevated umbilical cord blood IgM, which mainly detects primary CMV infection [9]; and (2) reports limited to adolescent maternal populations who, being younger and therefore having a lower CMV seroprevalence, are more likely to experience a primary CMV infection. Reports on primarily populations with low socioeconomic status (SES) were included and identified as such. Reports from studies that screened fewer than 800 infants were excluded because of the instability in estimates of birth prevalence and sequelae.

We use the term ‘symptom’ to describe clinical indications of CMV infection in newborns known as cytomegalovirus inclusion disease (CID), defined as the presence of one or more of the following symptoms: petechiae, jaundice with associated hyperbilirubinemia, hepatosplenomegaly, thrombocytopenia, chorioretinitis, seizures, microcephaly, intracranial calcifications or fetal hydrops. The less severe symptoms are usually transient in newborns. Studies that used alternative or undefined criteria for defining symptomatic infection were not included. Intrauterine growth retardation (IUGR; also referred to as ‘small for gestational age’) has been observed in association with congenital CMV infection but was infrequently reported in the literature and not included as a symptom of infection for this review. It should be noted that many of the signs listed are not specific to CMV or readily apparent and hence symptomatic CMV often goes unrecognised in the absence of systematic attempts to identify it.

We use the term ‘sequelae’ to describe CMV-associated developmental delays or differences in sensory function that appear in infected children over time. The clinical terms used to describe sequelae in the literature and the methods used to measure sequelae were not clearly defined or...
standardised across studies. Therefore, we grouped and simplified sequelae as follows: HL includes both unilateral and bilateral SNHL, but not conductive HL because the latter is usually temporary. Cognitive deficit (CD) includes what was variably referred to as mental retardation, neurological impairment and developmental delay. Many children reported as being mentally retarded were, in fact, too young to have been properly evaluated for mental retardation using standardised tests of cognitive ability. Motor deficit (MD) includes any limitation regarding bodily movement and includes cerebral palsy. Because the congenital CMV literature has rarely employed standardised measures of disability associated with neurological or sensory sequelae, we were not able to calculate the frequencies of developmental disabilities.

RESULTS

Our inclusion criteria, which emphasised studies most likely to have unbiased sampling, excluded the majority of published reports on congenital CMV infection. Table 1 summarises data on symptomatic and asymptomatic CMV infection at birth. Table 2 summarises data on CMV-associated sequelae. Among the 117,986 infants in the 15 studies shown in Table 1 [10–24], 810 (0.7%) were infected with CMV. Five of the studies targeted low-SES populations and had an average infection rate of 1.2% (range 0.9–1.3%). The other 10 studies had populations that were unselected by SES (primarily middle SES) and had a markedly lower average infection rate of 0.39% (range 0.3–0.5%).

Among the 810 CMV-infected infants, 103 (12.7%, range 0.0–25.0%) had symptoms of CMV infection, or CID (Table 1). The percentage of infants with congenital CMV who had symptoms at birth did not vary significantly by average SES.

The first 10 reports listed in Table 2 [10–13,18,20,22,25–27] present the results of evaluations of CMV-infected children for both cognitive and physical impairments to determine the frequency of long-term sequelae. Three of those studies [25–27] were not included in Table 1 because they only reported data on CMV-infected children.

Long-term sequelae in the symptomatic group were typically severe, and children were often affected by both HL and cognitive impairments, although the studies showed marked heterogeneity. Four studies in Table 2 [10,18,22,26] assessed both general development and HL among a total of 19 children with symptomatic CMV infection. Eleven of the 19 children (57.9%) in these studies had long-term sequelae, including one child who subsequently died. The largest study was from Sweden [10] in which 4 of 11 (36.4%) children symptomatic at birth had long-term sequelae. In contrast, three studies that each followed only two or three symptomatic children [18,22,26], found that seven out of eight (87.5%) had long-term sequelae.

Four studies in Table 2 examined either HL only [28,29] or cognitive deficit only [16,23]. Fowler et al. [28] followed 53 surviving children with CID, of whom 19 (35.8%) had measurable HL. This finding is similar to that of Ahlfors et al. [10], who reported that 27.2% of children had HL. The reports by Griffiths et al. [16] and Starr et al. [23] followed a total of three children with CID, two of whom (66.7%) had cognitive deficits.

Mortality among children with CID was not specifically assessed in most reports. Fowler et al. [28] report that among a total of 407 children born with congenital CMV at a Birmingham, Alabama, hospital between 1980 and 1996, two were known to have died in the first few years of life and hence were not included in audiologic follow-up. If both deaths occurred among the children with CID, as appears to have been the case, the death rate in that cohort would be 3.6%.

As expected, the frequency of sequelae among children with asymptomatic infections is lower than that among symptomatic children. The 10 studies in Table 2 that followed CMV-infected children for hearing, cognitive and MDs included a total of 252 children who were asymptomatic at birth, 34 of whom (13.5%) developed long-term sequelae. The percentage of asymptomatic children with one or more sequelae ranged from 0.0 to 23.5%, with a majority of studies reporting long-term sequelae among 8.5–17.9% of asymptomatic infants (Table 2). The sequelae were relatively less severe for the majority of the asymptomatic children; 23 of 34 asymptomatic children with sequelae (67.6%) were evaluated as having isolated HL without other impairment.

The two studies in Table 2 that evaluated HL alone reported this outcome among 47 of 394 (11.9%) children with asymptomatic infections. Among the 10 studies with comprehensive evaluations, 24 of 252 asymptomatic children (9.5%) were
identified with HL. Among the four studies with follow-up of at least 3 years [10,20,22,25], a total of 14 of 131 children asymptomatic at birth (10.7%) were diagnosed with HL.

The two studies in Table 2 that examined only cognitive outcomes reported some degree of cognitive deficit among 2 of 31 (6.5%) children with asymptomatic infections. Among the 10 studies...
that examined a range of outcomes, a total of 10 of 252 (4.0%) surviving children were reported to have cognitive deficits. However, not all of the studies appear to have been equally thorough in ascertaining cognitive impairment. In particular, six studies, with a total of 116 children in the asymptomatic group, did not report a single child with cognitive deficits. Among the remaining four studies [10,11,26,27], 10 of 136 (7.4%) children were reported to have cognitive impairment. The latter percentage is consistent with the 6.5% rate from the two studies that assessed cognitive deficits only [16,23]. Only one study [10] included cases of cognitive impairment and conducted follow-up for HL more than 3 years after birth. That study reported a prevalence of 16.3% of long-term sequelae among the asymptomatic group.

**DISCUSSION**

This review estimated the frequency and nature of sequelae attributable to congenital CMV in order to calculate more precise estimates of the probabilities of sequelae of congenital CMV infection. These probabilities, when combined with a new estimate of the birth prevalence of congenital CMV infection, allow evidence-based estimates

<table>
<thead>
<tr>
<th>First author</th>
<th>Location/ time period</th>
<th># Infec. at birth</th>
<th>Symp./ asymp. followed; duration</th>
<th>Evaluation: HL, CD, MD or All</th>
<th>Symp. at birth later sequel</th>
<th>Symp. w/ sequel (%)</th>
<th>Asymp. at birth later sequel</th>
<th>Asymp. w/ sequel (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al.</td>
<td>Denmark 1979 [11]</td>
<td>12</td>
<td>0/12</td>
<td>All</td>
<td>None with symp.</td>
<td>1 CD</td>
<td>2/12</td>
<td></td>
</tr>
<tr>
<td>Barbi et al.</td>
<td>Italy 1998 [12]</td>
<td>6</td>
<td>0/5</td>
<td>All</td>
<td>None with symp.</td>
<td>1 CD + MD</td>
<td>(16.7)</td>
<td></td>
</tr>
<tr>
<td>Casteels et al.</td>
<td>Belgium 1999 [14]</td>
<td>15</td>
<td>0/12</td>
<td>All</td>
<td>None with symp.</td>
<td>2 HL</td>
<td>2/12</td>
<td></td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>Ohio 1984 [25]</td>
<td>17</td>
<td>0/17</td>
<td>All</td>
<td>None with symp.</td>
<td>4 HL</td>
<td>4/17</td>
<td></td>
</tr>
<tr>
<td>Melish and Hanshaw 1973 [18]</td>
<td>New York 1968–1970</td>
<td>20</td>
<td>2/17</td>
<td>All</td>
<td>1 HL + MD</td>
<td>2/2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Saigal et al.</td>
<td>Canada 1982 [22]</td>
<td>64</td>
<td>3/44</td>
<td>All</td>
<td>1 HL</td>
<td>2/3</td>
<td>6 HL</td>
<td>7/44</td>
</tr>
<tr>
<td>Williamson et al.</td>
<td>Texas 1990 [27]</td>
<td>na</td>
<td>na/28</td>
<td>All</td>
<td>Not followed</td>
<td>1 CD</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>Williamson et al.</td>
<td>Texas 1992 [29]</td>
<td>na</td>
<td>na/59</td>
<td>HL only</td>
<td>Not followed</td>
<td>9 HL</td>
<td>9/59</td>
<td></td>
</tr>
<tr>
<td>Griffiths et al.</td>
<td>London 1991 [16]</td>
<td>9</td>
<td>1/7</td>
<td>CD only</td>
<td>1 CD</td>
<td>1/1</td>
<td>1 CD</td>
<td>1/7</td>
</tr>
<tr>
<td>Starr et al. 1970 [23]</td>
<td>Ohio 1968</td>
<td>26</td>
<td>2/24</td>
<td>CD only</td>
<td>1 CD</td>
<td>2/2</td>
<td>1 CD</td>
<td>1/24</td>
</tr>
</tbody>
</table>

Table 2. Frequency and nature of long-term sequelae associated with congenital CMV*

**DISCUSSION**

This review estimated the frequency and nature of sequelae attributable to congenital CMV in order to calculate more precise estimates of the probabilities of sequelae of congenital CMV infection. These probabilities, when combined with a new estimate of the birth prevalence of congenital CMV infection, allow evidence-based estimates...
of the preventable burden of congenital CMV infections. Reliable estimates of the magnitude of the impact in terms of disease, disability and mortality are necessary to calculate cost estimates for treatment and prevention strategies for congenital CMV infections.

This review found that the overall prevalence of congenital CMV infection in industrialised countries is likely to be 0.6–0.7%. This is consistent with a recent meta-analysis that employed less restrictive inclusion criteria resulting in a wider dispersion of estimates, which reported an average birth prevalence of 0.65% [30]. This is more precise than the range of 0.2–2.5% often cited in the literature [1,12,14]. It is also lower than commonly cited prevalence for the United States of 1.0% that is based on studies with predominantly low-SES subjects. Given that low-SES women are often overrepresented in the literature and were overrepresented in this review, the prevalence of congenital CMV infection in the general population is likely to be lower than the point estimate of 0.7% presented here. The exact prevalence of CMV infection cannot be determined without screening a large, representative sample of newborns using a reliable method of detection.

We found that approximately one in eight (12.7%) infants with congenital CMV infection had symptoms at birth identified as CID. This estimate is within the range of 10–15% that is typically cited. This percentage did not differ appreciably by SES or birth prevalence.

Follow-up of CMV-infected children identified by unselected screening supports the general understanding that infants who are symptomatic at birth are much more likely to experience sequela and that their sequelae are more disabling. The reported prevalence of permanent sequelae among children with CID ranges from 35–100%, but the highest percentages come from studies that each included cognitive deficit/mental retardation. Because children can have both HL and cognitive impairment, the two percentages cannot be added together. The one study that had relatively complete data on both HL and cognitive impairment reported that 16.3% of children with asymptomatic infections at birth were diagnosed with HL, and 6.5% were classified as having some type of cognitive or neurological impairment. Breaking the numbers down by impairment, 11–12% of children with asymptomatic infections at birth had sequelae.

Combining the observed prevalence of long-term sequelae in the larger and possibly more accurate Ahlfors et al. [10] and Fowler et al. [28] studies (36–45%) with the point estimate of 57.9% from Table 2 that considered all studies, we consider 40–58% to be a reasonable estimate of the prevalence of long-term sequelae among surviving children with symptomatic CMV infections.

The prevalence of permanent sequelae from congenital CMV was much lower among children who were asymptomatic at birth. The primary type of sequela was isolated SNHL. This contrasts with children who had symptomatic infections, who tended to have multiple sequelae that included cognitive deficit/mental retardation. Because children can have both HL and cognitive impairment, the two percentages cannot be added together. The one study that had relatively complete data on both HL and cognitive impairment reported that 16.3% of children with asymptomatic infections had one or both sequelae [10], which is in agreement with our overall finding of 13.5% prevalence of sequelae in the asymptomatic infection group (Table 2).

In the studies reviewed, data were insufficient to accurately estimate prevalence of visual impairment and mortality, two important outcomes of congenital CMV. Anderson et al. [32] reported that 58% of 113 symptomatic infants had visual impairments, and Coats et al. [33] reported that 22% of 42 symptomatic infants had visual impairments; both of these study populations, however, had an overrepresentation of...
infants with severe sequelae. One study with a likely unbiased recruitment strategy [10] did not report any visual impairment among 60 infected infants. However, because the study findings made no reference to the outcome of visual exams performed on the children, it is not clear whether there was an absence of observed visual impairments or problems with the measurements or their interpretation.

The frequency of death among symptomatic infants is commonly reported to be 10–30%. A large cohort study from Alabama [3,28] reported a much lower death rate of approximately 4% among the symptomatic group, although it is possible that the true death rate was higher because of loss to follow-up among children who screened positive for CMV. The total rate of mortality among the Alabama cohort of children with congenital CMV detected through screening, including both symptomatic and asymptomatic infections, was 0.5% [28]. A large-scale screening study with complete follow-up would be needed to provide a more reliable estimate of the mortality rate in congenital CMV.

The strength of this review is that it reports findings from only studies that used universal screening, rather than studies that recruited from populations at high risk for congenital CMV. However, this review has two important limitations. First, the inclusion criteria used to eliminate unbiased populations resulted in a relatively small number of studies for review. One implication is that we are missing data on important outcomes. For example, as noted previously, very few studies reviewed included data about visual impairment, a known sequela of congenital CMV infection [32,34,35].

Second, the estimates for permanent sequelae among symptomatic children (40–58%) and asymptomatic children (13.5%) are almost certainly underestimate. Length of follow-up in many of the studies reviewed was 3 years or less. This length of time is insufficient to capture late-onset of HL [31] and results in under-ascertainment of long-term sequelae. Studies of 5–7 years follow-up are needed to gain more accurate estimates of long-term sequelae associated with congenital CMV infection.

It is important to note that, although long-term sequelae occur 3 to 4 times more often among infants with CID than among asymptomatic infants (40–58% vs. 13.5%), and sequelae among symptomatic children are often severe, more children with long-term sequelae from congenital CMV are asymptomatic at birth. In a given cohort of 1000 infants with congenital CMV, approximately 127 have CID. If the death rate among those children is 4%, there will be 5 deaths and 122 survivors with CID, 50–70 of whom will have long-term sequelae. Of the 873 with asymptomatic infections, 118 are projected to have long-term sequelae, constituting approximately two thirds of the total children with sequelae (Table 3).

This review supports previous assessments of the prevalence of permanent sequelae among children with asymptomatic sequelae but differs from previous estimates of long-term sequelae among children with symptomatic infections. In particular, the U.S. Institute of Medicine (2000) estimated that 10% of children with symptomatic infections die and that 100% of survivors experience sequelae, including 90% with severe MR, and the rest with mild MR, vision loss, HL or two or more limitations. In contrast, the report assumed that only

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
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<tbody>
<tr>
<td>Number of Infants</td>
<td>127 (12.7%)</td>
<td>873 (87.3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Survivors</td>
<td>122</td>
<td>873</td>
</tr>
<tr>
<td>Number with Permanent sequelae</td>
<td>50–70 (40–58%)</td>
<td>118 (13.5%)</td>
</tr>
<tr>
<td>Conclusion</td>
<td>17–20% of the 1000 infected infants will have permanent sequelae; 1/3 from the symptomatic group and 2/3 from the asymptomatic group</td>
<td></td>
</tr>
</tbody>
</table>
15% of asymptomatic infants would have some deficit, mostly HL. Although the latter estimate is consistent with the evidence reviewed here, the former estimate is not. In particular, one large study with follow-up to age 7 years has assessed former estimate is not. In particular, one large consistent with the evidence reviewed here, the deficit, mostly HL. Although the latter estimate is
15% of asymptomatic infants would have some 3623 362 S. C. Dollard S. C. Dollard et al. et al. this review.

CONCLUSION
Although several previous studies have estimated the burden of congenital CMV, this report presents probabilities of CMV-associated infant mortality and neurological sequelae based on studies with minimal population bias. Overall, we project that 0.5% of children with congenital CMV die and that 17–20% of surviving children have one or more long-term sequelae. These estimates, which show that congenital CMV infection is associated with a substantial long-term burden and an elevated risk of infant mortality, can be used in the development and evaluation of prevention strategies for this important risk factor for death and developmental disability. To better understand the true burden of congenital CMV, future studies should focus on evaluation of visual impairment and extend follow-up of CMV-infected children, to capture sequelae with delayed onset.

ACKNOWLEDGMENTS
We would like to thank members of the CDC congenital CMV working group for useful input and encouragement regarding this review, especially Michael Cannon, Owen Devine, Aileen Kenneson, Esther Sumartojo, Scott Schmid and the European Congenital Cytomegalovirus Initiative for inviting this review.

REFERENCES
The “Silent” Global Burden of Congenital Cytomegalovirus

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SUMMARY

Human cytomegalovirus (CMV) is a leading cause of congenital infections worldwide. In the developed world, following the virtual elimination of circulating rubella, it is the commonest nongenetic cause of childhood hearing loss and an important cause of neurodevelopmental delay. The seroprevalence of CMV in adults and the incidence of congenital CMV infection are highest in developing countries (1 to 5% of births) and are most likely driven by nonprimary maternal infections. However, reliable estimates of prevalence and outcome from developing countries are not available. This is largely due to the dogma that maternal preexisting seroimmunity virtually eliminates the risk for sequelae. However, recent data demonstrating similar rates of sequelae, especially hearing loss, following primary and nonprimary maternal infection have underscored the importance of congenital CMV infection in resource-poor settings. Although a significant proportion of congenital CMV infections are attributable to maternal primary infection in well-resourced settings, the absence of specific interventions for seronegative mothers and uncertainty about fetal prognosis have discouraged routine maternal antibody screening. Despite these challenges, encouraging results from prototype vaccines have been reported, and the first randomized phase III trials of prenatal interventions and prolonged postnatal antiviral therapy are under way. Successful implementation of strategies to prevent or reduce the burden of congenital CMV infection will require heightened global awareness among clinicians and the general population. In this review, we highlight the global epidemiology of congenital CMV and the implications of growing knowledge in areas of prevention, diagnosis, prognosis, and management for both low (50 to 70%)- and high (>70%)-seroprevalence settings.

INTRODUCTION

Cytomegalovirus (CMV) is highly adapted to its human host. A full appreciation of CMV as a pathogen contributing to morbidity and mortality in a variety of immunocompromised hosts is well established. In contrast, the fact that CMV is also a leading cause of congenital infections worldwide is barely appreciated, as is the socioeconomic impact of CMV as the commonest nongenetic cause of childhood hearing loss in the postrubella era and a significant cause of neurodevelopmental delay (1–4). Indeed, CMV causes more cases of congenital disease than the combination of 29 currently screened conditions in most American states (5) and is more common than several disorders included in newborn screening in European Union countries (6).

The worldwide neglect of this problem is underscored by the continued lack of awareness of congenital CMV among health care workers and the public. The low profile of congenital CMV can be explained by the following factors. First, most maternal and newborn infections are asymptomatic and therefore are not recognized at birth. Second, sequelae from congenital CMV infection are frequently delayed in onset, at which point a retrospective diagnosis is challenging. Third, the dogma that congenitally infected children who are born to women with preexisting antibodies have normal outcomes has led to inattention to congenital CMV in developing countries. Emerging data from highly seropositive populations, which are usually in developing countries,
however, suggest that not only is the rate of congenital CMV infection higher than in developed countries but it is an important cause of hearing loss in resource-limited settings (7, 8). In fact, the higher prevalence of congenital CMV infection in highly seropositive populations coupled with recent hearing outcome data from Brazil suggests that the resource-limited settings may bear the greatest burden of congenital CMV infection (7, 8). However, population-based natural history studies that accurately estimate disease, disability, and mortality burden in resource-limited settings are lacking. Moreover, there are insufficient data about the feasibility of newborn screening and antiviral therapy and the cost of long-term care for affected children in developing countries.

The quest for active and passive immunization strategies that can prevent in utero infection remains an ongoing challenge. High virus diversity and the propensity for infection with multiple different virus strains pose an important biological barrier to the development of effective vaccines (9–13). Moreover, at the population level, the fact that most congenitally infected newborns are born to mothers with preexisting immunity limits the benefit of these approaches (14, 15). Therefore, interventions that can reduce the global burden of disease are presently restricted to behavioral measures (16–18).

In this review, we highlight the global epidemiology of congenital CMV and the implications of growing knowledge in areas of prevention, diagnosis, prognosis, and management for both low (50 to 70%) and high (>70%)-seroprevalence settings.

**BIOLOGY**

CMV is a host-restricted member of the *Herpesviridae* family of viruses (19). Primary infection is characterized by a period of active virus replication with virus shedding in saliva, urine, milk, and genital secretions, a viremic phase, and, in some, an infectious mononucleosis syndrome (19, 20). This is followed by the development of a broad immune response involving all arms of the adaptive immune system, and after several weeks, viral latency is established (19). Latent infection is characterized by either a low level or absence of detectable virus replication with the maintenance of viral genomes as episomes in CD14+ peripheral blood mononuclear cells and CD34+ and CD33+ cells in the bone marrow, which will allow subsequent production of endogenous virus (reactivation) (21, 22). Sequence variability across the large viral genome generates extensive viral strain diversity (genotypes), the biological and clinical significance of which remains unknown (11, 23). In immunocompetent mothers, reactivation of endogenous virus and/or reinfection with new strains occurs periodically, and DNAemia and viruria may be present in both (24).

**EPIDEMIOLOGY AND CLINICAL OUTCOMES**

CMV is a global infection, although significant differences in the seroepidemiology exist between and within countries. CMV acquisition in a population is characterized by an age-dependent rise in seroprevalence, and correlates most closely with socioeconomic level and race (25–29). As a result, up to 50% of women of child-bearing age are seronegative in industrialized countries (25, 30). In this population, CMV acquisition occurs at a rate of 1 to 7% per year (31) and usually follows frequent and prolonged contact with young children (less than 3 years of age) (31–34). By comparison, in resource-poor communities in industrialized countries and in developing countries, CMV is usually acquired very early in life owing to breast milk transmission and crowded living conditions, and far fewer adult women are seronegative (7, 35–41).

The incidence of in utero CMV infection is highly population dependent (Fig. 1) and parallels maternal seroprevalence (Fig. 2), probably due to the fact that seroprevalence rates serve as a marker for the size of the reservoir of viruses. Thus, higher seroprevalence rates lead to an increased chance of either reactivation within a host, reinfection of seropositive hosts (together these constitute nonprimary infection), or primary infection of seronegative hosts within the population. This in turn probably leads to various degrees of maternal viremia and influences the risk for subsequent placental and/or fetal infection (42). In addition, seroprevalence levels in a population may reflect variation in host and environmental factors that also influence the risk of maternal (14, 43) and vertical (27) infection. Therefore, in industrialized countries, where the maternal seroprevalence is relatively low overall, rates of congenital CMV infection average 0.6 to 0.7% of live births (1 in every 100 to 150 newborns) (27, 44). However, even within a geographic region, variable rates of CMV seropositivity in mothers from different racial, ethnic, and socioeconomic backgrounds may translate to distinct epidemiological patterns of congenital infection (26, 27, 29, 45, 46). Similarly, in developing nations with highly seropositive populations, higher rates (1 to 5%) have often been reported (7, 47–51).

Most recent studies report lower transmission rates in early pregnancy (in comparison to later gestation) (52–58), with maternal primary infection leading to infection in 30 to 35% (Fig. 2) of fetuses and nonprimary infection having a transmission rate of 1.4% in study populations predominantly from industrialized countries (1.1 to 1.7%) (27). Data from screened populations indicate that while only one in 10 newborns infected in utero have obvious clinical signs of congenital infection (27, 44, 59), 10% to 15% of those without clinical findings (here referred to as having symptomatic and asymptomatic congenital CMV infection, respectively) develop long-term neurological sequelae (44). Specifically, sensorineural hearing loss (SNHL) occurs in about 35%, cognitive deficits in up to two-thirds, and death in around 4% of children with symptomatic infection. Visual impairment is thought to occur in 22 to 58% (60, 61) of symptomatic infants; however, there are insufficient data for this outcome from unbiased sampling. Far lower rates of sensory and cognitive sequelae have been reported in asymptomatic children. Hearing impairment has been reported in 7% to 10% (44, 62) of such infants, while the risk for cognitive deficits has not been studied systematically and the risk for visual impairment appears to be negligible (61). Overall (symptomatic and asymptomatic infections), permanent childhood hearing impairment is the commonest complication. In developed countries, congenital CMV accounts for 21% and 24% of cases of hearing loss at birth and 4 years of age, respectively (3, 59). Without early detection and prompt rehabilitation, this leads to speech, language, and social impairment in a significant number of children and deployment of continued medical care resources (63–66). Since newborn hearing screening may miss or underestimate hearing loss (the majority of children with CMV-associated SNHL have normal hearing at birth and develop subsequent late-onset hearing loss) and since the hearing loss is frequently progressive (50%), long-term monitoring is necessary (59, 67, 68). The public health impact of hearing loss may be even greater in high-seroprevalence settings where birth rates are sub-
The risk for long-term outcomes appears to be highest in infants born to mothers with primary infection in the first half of pregnancy (54, 55, 69–71). Following first-trimester maternal CMV infections, about a quarter of infants (20 to 25%) who are congenitally infected (Fig. 3) will develop sensorineural hearing loss (SNHL), and 30 to 35% will suffer some form of central nervous system (CNS) sequelae (70). Since it is not possible to time nonprimary maternal infection, it is not known whether the timing of maternal infection is associated with the risk for sequelae in this group.

It is estimated that more than two-thirds of infants with congenital CMV infection are born to mothers who are already CMV seropositive (14, 15, 72). Emerging observations demonstrate that the risk for symptomatic infection at birth and sequelae, especially

FIG 1 Estimates of the prevalence of congenital CMV infection and sequelae in infected children in high (90%)- and low (50%)-seroprevalence settings. The following assumptions are made: the risk of primary infection is 2% in both settings, and the risk of intrauterine transmission is 40% during primary infection and 1% in CMV-seropositive mothers. The rates of sequelae are based on estimates from a systematic review of study populations from high-income countries with a range of maternal seroprevalence and congenital infection identified through universal screening (44). Proportions with each category of sequelae do not correspond to 100% because a child may have more than one complication. The figure does not take into account the effect of HIV infection in maternal populations, which would be expected to increase the risk of CMV vertical transmission and sequelae in infected infants. It also does not account for differences in congenital transmission rates observed in mothers of different racial or ethnic backgrounds. *, most of the children in the asymptomatic group will have hearing loss, and there are insufficient data to accurately estimate the number of children with cognitive/motor deficits and vision impairment.

stantially higher, although this has not been systematically studied to date.
hearing loss, in these children may be similar to that in infants born to mothers experiencing a primary infection (8, 73–77). In addition, in resource-poor settings, specific risk subgroups may exist, such as mothers with concomitant immunosuppressive chronic diseases (see below). Unfortunately, maternal and birth CMV prevalence and long-term follow-up data for congenitally infected children for many parts of the world are lacking, likely underestimating the global impact of congenital CMV infection.

Impact of the HIV Epidemic on Congenital CMV

HIV-infected women are often CMV seropositive and experience more frequent CMV recurrences with progressive immune impairment (78–80). Studies in Europe and the Americas support an increased risk for congenital CMV infection in neonates born to HIV-CMV-coinfected mothers (79, 81, 82). A French perinatal cohort that included 4,797 HIV-infected mothers between 1993 and 2004 demonstrated an increased risk for congenital CMV in HIV-infected newborns compared with HIV-negative infants (10.3% versus 2.2%). HIV-infected newborns also had a 3-fold-higher risk for symptomatic congenital CMV infection than uninfected newborns (23% versus 6.7%). Furthermore, CMV may act as a cofactor for HIV disease progression. The risk for infant mortality is increased in HIV-CMV-coinfected infants, and there is accelerated progression of CNS disease in survivors, especially developmental delay and worsening motor deficits (83, 84).

The French perinatal cohort study also showed that in the era of highly active antiretroviral therapy (HAART), the incidence of vertical CMV infection in HIV-positive mothers was falling, which was associated with improvements in CD4 count (81). However, in a more recent study, Frederick et al. have not observed a significant decrease in the prevalence of congenital CMV infection in children of HIV-infected mothers receiving prenatal antiretroviral therapy (85). The overall prevalence of congenital CMV infection in that study was 3.6%.

In resource-limited settings, the high rate of coinfections in pregnant women with HIV-1 and bacterial and parasitic pathogens likely influences the transplacental transmissibility of CMV (51, 79, 86–88). In sub-Saharan Africa, the burden of HIV-1 in women of reproductive age is alarming, reaching 40% in some regions (89). Despite improvements in, and access to, antiretroviral therapy, maternal HIV acquisition and mother-to-child transmission (MTCT) of HIV in developing countries continue, leading to a sizeable proportion of infants born HIV exposed or infected. In studies of HIV-1-infected and HIV-1-exposed Kenyan women and children, a strong correlation between CMV and HIV loads was observed in both mothers and infants (88), with CMV DNAemia in the mother being associated with an increased risk of maternal mortality and mortality in the HIV-infected infants by 24 months (88).

To our knowledge, there are no published data on the risk of transmission of CMV in HIV-positive mothers in resource-lim-
ited settings. Therefore, in order to illustrate the potential impact of HIV infection on congenital CMV infection, we extrapolate from findings in high-resource settings and use South Africa and Thailand as examples (Table 1). In South Africa, maternal HIV seroprevalence is about 30%, with the most recently reported overall HIV MTCT at around 3.5% (90). Assuming a 1%, 3%, and 10% (79, 81, 85) risk of CMV transmission in HIV-unexposed (n/H11005700,000), HIV-exposed uninfected (n/H11005265,000), and HIV-infected (n/H1100535,000) newborns, respectively, we estimate that around 18,450 newborns (an excess of 8,450 infected newborns due to maternal HIV) are born congenitally infected with CMV each year. The number of cases in South Africa equates to just over 40% of the total annual number of congenital CMV cases in the United States. In other words, South Africa is likely to have roughly 2.5 times the number of congenital CMV infections per capita as in the United States. In Thailand, which has an annual birth rate of 830,000 and a maternal HIV seroprevalence of 0.7% (91), assuming the above congenital CMV transmission risks and an HIV MTCT of 2.8% (T. Naiwatanakul, N. Punsuwan, N. Kullerk, W. Faikratok, R. Lolekha, and O. Sangwanloy, presented at the 5th International AIDS Society Conference on HIV Pathogenesis and Treatment, Cape Town, South Africa, 19 to 22 July

TABLE 1 Estimates of the prevalence of congenital CMV infection in two resource-poor settings (South Africa and Thailand) according to maternal HIV-CMV coinfection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>South Africa</th>
<th>Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual birth rate</td>
<td>1,000,000</td>
<td>830,000</td>
</tr>
<tr>
<td>Antenatal HIV prevalence (%)</td>
<td>30</td>
<td>0.7</td>
</tr>
<tr>
<td>HIV perinatal transmission rate (%)</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>No. (no. of congenital CMV infections)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV unexposed (risk, 1%)</td>
<td>700,000 (7,000)</td>
<td>824,190 (8,242)</td>
</tr>
<tr>
<td>HIV exposed (risk, 3%)</td>
<td>265,000 (7,950)</td>
<td>5,647 (169)</td>
</tr>
<tr>
<td>HIV infected (risk, 10%)</td>
<td>35,000 (3,500)</td>
<td>163 (16)</td>
</tr>
<tr>
<td>Total no. of congenital CMV infections</td>
<td>18,450</td>
<td>8,427</td>
</tr>
</tbody>
</table>
2009), we estimate that 8,427 newborns are born congenitally infected with CMV each year.

**ADVANCES IN DIAGNOSIS AND MANAGEMENT OF THE NEWBORN**

The majority of congenital CMV infections from both resource-poor and upper-income settings are asymptomatic at birth, and the diagnosis of intrauterine infection relies on virus detection by culture-based methods or PCR. Saliva or urine (see below) specimens should be obtained within the first 2 weeks of life (92), as virological testing cannot discriminate intrauterine from postnatal CMV infection beyond 2 weeks. When an early specimen is not available for testing, clinical features highly indicative of congenital CMV infection, such as CNS, retinal, or auditory findings, can suggest the diagnosis in symptomatic infants.

The presence of CNS disease in the symptomatic neonate with laboratory-confirmed congenital infection warrants the consideration of specific antiviral therapy. While there is no evidence for the effectiveness of treatment in children without CNS disease, it is reasonable to consider antiviral treatment in those with disseminated disease which is life threatening (93–95). Ganciclovir (GCV) or its prodrug valganciclovir (VGCV), an acyclic nucleoside analogue, is the preferred antiviral agent for the treatment of CMV disease (96). The efficacy of ganciclovir for the prevention of progressive hearing loss in infants with proven congenital CMV CNS disease as evidenced by microcephaly, other neurological findings, neuroimaging abnormalities, or hearing loss was evaluated in a randomized trial nearly a decade ago. At 12 months of follow-up, a considerably higher rate of preserved normal hearing, as well as improved hearing and prevention of worsening of hearing in those with a baseline hearing deficit, was demonstrated following a 6-week course of intravenous GCV, compared with no therapy (95). However, the frequency of drug toxicity, the absence of a placebo group, and high attrition rates in this study limit the significance of the findings. More recently, a secondary analysis on the same study population showed that infants who received GCV therapy appeared to have fewer developmental delays at 6 and 12 months than untreated infants (97). Based on these findings, a 6-week course of intravenous ganciclovir or oral valganciclovir (VGCV) is considered for children with CNS involvement (93, 98). Pharmaceutical liquid preparations of VGCV provide stable systemic exposure, and plasma levels equivalent to those for intravenous therapy can be achieved; however, a head-to-head comparison of efficacy has not been performed (98, 99). Rates of neutropenia during a 6-week course are, however, substantial (63% for ganciclovir and 38% for valganciclovir) (99), and biochemical/hematological parameters should be carefully monitored when either drug formulation is used (93). Such toxicity also precludes the treatment of neonates with asymptomatic infection because their risk of longer-term sequelae is only about 13% (44).

It has been suggested that ongoing viral replication in end organs may contribute to adverse long-term outcomes (progressive hearing impairment was reported for 21% of treated patients) (95), and prolonged antiviral therapy has been considered. A recent retrospective study of 6 weeks of intravenous GCV followed by VGCV up to a year showed that prolonged antiviral therapy may prevent hearing loss in children with normal baseline hearing and result in lower rates of deterioration in those with baseline deficits (100). However, these findings were limited by the absence of a control group. It is anticipated that the randomized multi-center placebo-controlled trial (CASG112) (NCT00466817) commenced in 2008 to compare the clinical benefit of 6 weeks versus 6 months of valganciclovir in symptomatic infants will define the role of prolonged antiviral therapy. A role for antiviral therapy in the prevention of SHNL and adverse psychomotor outcomes in asymptomatic infants has also been suggested (101). However, formally evaluating a toxic drug in a large cohort of asymptomatic children, most of whom will not go on to develop sequelae, remains problematic.

The prognostic value of clinical signs, imaging findings, and laboratory parameters in the newborn with confirmed congenital CMV has been extensively evaluated. Among infants with symptomatic congenital CMV infection, microcephaly (102, 103), cho-rioretinitis (102), abnormal neurological examination findings (102, 104), abnormal auditory brain stem evoked response (105), and petechiae and thrombocytopenia (104, 105) are each associated with an unfavorable clinical outcome. Furthermore, newborn neuroimaging (ultrasound [US], computed tomography [CT], and magnetic resonance imaging [MRI]) abnormalities (105, 106) carry a high risk for CNS sequelae. In asymptomatic infants, on the other hand, clinical or laboratory predictors of adverse outcomes have not been identified. However, low CMV blood viral loads (<10^5 copies/10^5 polymorphonuclear leukocytes) appear to predict normal development with reasonable certainty (>95%) (107–110). In the absence of well-defined predictors of outcome, monitoring of all congenitally infected newborns is advised. This includes regular neurological, developmental, auditory, and visual assessments at least until school age in symptomatic newborns, whereas recommendations for follow-up of asymptomatic newborns are usually restricted to audiology. Regular monitoring for progressive and late-onset deficits permits early rehabilitation (93, 94). At 1 year of follow-up, the absence of neurodevelopmental delay appears to predict a normal intellectual outcome (111).

Owing to the late presentation of most congenital CMV sequelae, diagnosing vertical infection in children beyond the newborn period is a key challenge for both the clinician and the epidemiologist. Dried blood spots (DBS), or Guthrie cards, which are collected routinely at birth in certain countries for newborn genetic and metabolic diseases screening, can be stored for extended periods of time. Since CMV DNA is stable on such DBS cards for up to 18 years, they offer an attractive tool for the retrospective molecular diagnosis of congenital infection in individual children who present with delayed-onset sequelae (112–115). DBS also have appeal for use in newborn congenital CMV screening programs. However, the variable and disappointing rates of detection of CMV DNA (34 to 100%) have made DBS unsuitable for these purposes (112, 114, 116–122), possibly because not all newborns are viremic at birth or due to technical factors (118, 122–124). However, a positive DBS PCR finding is diagnostic of congenital CMV infection and accordingly can be useful to retrospectively diagnose congenital CMV infection beyond the neonatal period.

The recent demonstration that real-time PCR detection of CMV in saliva swabs, either air dried or in viral transport medium, is equally sensitive as virus culture techniques has made wide-scale newborn screening realizable (125). Universal newborn CMV screening would identify infants at risk for hearing loss, who can then be targeted for prompt interventions that prevent significant speech and language deficits (44, 126). However, the cost of testing, the modest efficacy of available antiviral therapy, the high
proportion of asymptomatic infections, and potentially adverse psychosocial effects are considered barriers to implementation, even in countries with newborn screening programs for the detection of genetic and metabolic disorders and hearing loss (126, 127). In spite of these issues, newborn virological screening can be justified on the grounds that congenital CMV infection is likely the most common nongenetic cause of sensorineural hearing loss and screening can now be undertaken noninvasively (125). In addition, the delayed onset of most cases of CMV-associated hearing loss makes newborn hearing screening an inadequate tool for the detection of CMV-associated hearing loss (67, 68). In resource-limited settings, reliable estimates of prevalence and disease burden from congenital CMV infection are needed before the cost-effectiveness and utility of newborn CMV screening can be determined.

ADVANCES IN PREVENTION OF ADVERSE OUTCOMES

Prenatal Screening and Diagnosis of Infection in the Mother and Fetus

Maternal (prenatal) screening may permit early identification of at-risk pregnancies or infected infants and thus the use of interventions to reduce morbidity has attracted increasing interest in recent years (128). The feasibility of prenatal screening has been argued on the basis that eight European countries have overcome commonly cited obstacles to this strategy (129, 130). However, universal antibody screening of pregnant women in most resource-rich countries has not been recommended because of the absence of proven specific interventions for maternal primary infection, and challenges in deciphering the prognosis of an individual mother and fetus have been discouraging. It is also becoming increasingly apparent that at a population level, the effectiveness of such prenatal screening programs will be limited, as around two-thirds of infants with congenital CMV infection in the United States and the vast majority in resource-limited settings are born to women who are seropositive preconceptionally (14, 15). In these settings, it has been assumed that reactivation of endogenous virus or reinfec tion with a different strain leads to intrauterine transmission (9, 13). However, since such events are clinically silent and simple virological or immunological markers for nonprimary infection do not exist, identifying women at risk of transmission is presently not possible.

Clinical suspicion of maternal primary infection, i.e., glandular fever or flu-like illness, and the detection during routine ultrasound screening of abnormalities suggestive of intrauterine CMV that lack an apparent cause are the common indications for specific diagnostic testing (131). Maternal primary infection can be confirmed reliably by the demonstration of serumoconversion (CMV IgG negative to CMV IgG positive) when a baseline serum sample from either the earliest antenatal visit or prior to conception is available (Fig. 4). When such a comparison serum is not available, the detection of both CMV IgG and IgM antibodies may indicate a recent primary infection (132). However, as a reactive CMV IgM may be found in both primary and nonprimary infections and may persist for many months following primary infection, it does not reliably predict the risk for congenital infection (133). Therefore, a reactive CMV IgM should be further evaluated by determining the maturity of the CMV IgG antibodies using the avidity assay. Low-affinity CMV IgG antibodies (those that bind less tightly with their target protein) are produced in the first 18 to 20 weeks after infection (134). A subsequent maturation process generates IgG antibodies with higher avidities (affinity maturation). A high CMV IgG avidity index therefore excludes a recent primary infection and when detected before 12 to 16 weeks of gestation indicates a significantly lower risk of congenital infection (134, 135). Conversely, low-avidity IgG antibodies together with a reactive CMV IgM strongly supports the diagnosis of maternal primary infection in the preceding 3 or 4 months (136).

The substantial risk of vertical transmission following primary maternal infection justifies invasive prenatal testing. Amniotic fluid (AF) CMV PCR is the test of choice for confirming fetal infection. As the interval between maternal and detectable fetal infection is at least 6 to 8 weeks, amniocentesis should be performed at 20 to 21 weeks of gestation and at least 7 weeks following maternal infection (69, 137–143). It is well established that the sensitivity of PCR (70 to 90%) for prenatal diagnosis is superior to that of virus culture techniques; when correctly timed, it approaches 100% (137, 143). However, as PCR may occasionally give false-positive results, it is generally recommended that screening be performed using a combination of PCR and virus culture or, where culture-based testing is not available, a second (confirmatory) molecular test (139, 144, 145) (Fig. 4). When both PCR and virus isolation tests are positive, congenital infection can be diagnosed with 100% certainty. On the other hand, when both tests are negative, fetal infection can be ruled out with a high degree of certainty (negative predictive value, >94%) (42). False-negative culture and PCR results have occasionally been reported and may be a result of delayed transmission of CMV to the fetus (69, 146, 147). Invasive prenatal testing may also be justified in nonprimary infections when sonographic findings suggest in utero CMV abnormalities (77). However, at present, firm guidelines in this area are lacking.

In the case of confirmed fetal infection, since a significant proportion of infected infants have a normal outcome, parents should be counseled on the established risks of symptomatic infection and long-term morbidity following intrauterine CMV infection, in order to guide decision-making regarding the options of termination of pregnancy (TOP) or expectant management (131), while intrauterine therapies (discussed below) remain experimental. In the absence of virological correlates or biomarkers that can definitively distinguish a symptomatic from an asymptomatic course of infection, defining the prognosis for an infected fetus may be aided by 2 to 4 weekly fetal ultrasound (US) examinations and appropriately timed (see above) amniotic fluid viral load testing (131). It has been shown that cerebral ultrasound abnormalities are strongly associated with a poor prognosis (148), and recent findings also show that combining ultrasound with magnetic resonance imaging improves the sensitivity of prenatal screening for cerebral lesions, in particular, after 30 to 34 weeks of gestation (149, 150). On the other hand, the predictive value of nonspecific findings, such as intrauterine growth restriction (IUGR), bowel hyperechogenicity, or isolated other noncerebral abnormalities, for symptomatic infection or adverse outcomes is relatively low (69, 148, 151). Amir et al. suggested that lenticulostriate vascu lopathy (LSV) is a possible marker of hearing loss in congenital CMV infection (152). However, LSV is nonspecific, and other studies have not confirmed the prognostic value of this finding (148, 153). When no ultrasound findings are detected, the risk for symptomatic congenital infection and sequelae is significantly reduced, but these cannot be excluded (69, 139, 149, 151, 154).
FIG 4 Proposed diagnostic and management algorithm for maternal and congenital CMV infection. The presence of high-avidity CMV IgG antibodies before 16 weeks of gestation excludes primary infection; however, nonprimary infection is still a possibility. Indications for prenatal testing in nonprimary infections are less clear, and decisions should be made on a case-by-case basis when sonographic findings are suggestive of congenital infection. Baseline investigations for newborns with symptomatic congenital CMV infection should include complete blood count, liver function tests, CMV real-time PCR (blood and urine), audiometry, ophthalmology screen, and cranial US/CT/MRI. A low CMV DNA blood viral load in the first month of life can predict a normal development in asymptomatic newborns. Since the cutoff values for amniotic fluid viral load measurements were derived from a few studies and have not been validated with international standards, they may not be generalizable.
Several studies suggest that low AF virus loads can provide reassurance for lower risks of both symptomatic infection and long-term sequelae (42, 140, 143, 155, 156). Although an association between high AF virus loads and symptomatic infection at birth has been documented in some studies (42, 140, 155), other studies have failed to show such an association (146, 157, 158). Virus load was also found to correlate with gestational age (146, 157). It is important to bear in mind that in the absence of international PCR quantification standard, the different assays deployed in these studies would have suffered from substantial inter- and intralaboratory variations, making the use of predictive cutoff values less generalizable. In addition, differing study designs make it difficult to compare the data among the various studies. The recently approved first WHO international standards for CMV PCR will reduce this variability and should be used to reevaluate the prognostic role of AF virus levels in future multicenter studies (159). Even if the predictive role for low AF virus load in symptomatic disease and sequelae is confirmed, these invasive diagnostics are beyond the reach of most public health systems in low-income countries, and therefore it is unlikely that the diagnosis and treatment of in utero CMV infection will become part of routine obstetric practice in these settings.

Antiviral Therapy and Passive Immunization

The results of ongoing controlled trials involving oral valaciclovir (NCT01037712), and CMV hyperimmune globulin (HIG) (NCT00881517) for prenatal intervention are awaited (160). Ganciclovir cannot be used for prenatal therapy due to its mutagenic potential in animals, but oral valaciclovir administered to mothers with evidence of fetal infection appears to be safe and decreases the circulating fetal viral load (161). However, evidence for improved outcomes with treatment has yet to be demonstrated.

The rationale for passive immunization of seronegative mothers comes from the observed lower risk of fetal infection in mothers with preexisting antibodies (162). This is further supported by evidence that CMV HIG can inhibit viral spread in vitro (163, 164), restore placental health in mothers with primary infection (165), and lead to regression of cerebral ultrasound abnormalities (166). A prospective study has demonstrated that monthly intravenous infusions of CMV HIG to mothers with confirmed primary infection (including those with virological evidence of fetal infection) are safe and can both prevent (adjusted odds ratio [OR], 0.32) and treat (adjusted OR, 0.02) fetal infection (167). Furthermore, recent retrospective studies have suggested that CMV HIG can protect against poor outcomes in infants (168, 169). In spite of these promising findings, though, a recent Cochrane Library Review underscored the lack of data from randomized controlled studies and accordingly the need for further research to assess the efficacy of antenatal interventions for the prevention of intrauterine transmission and adverse outcomes (170). Therefore, the results from two randomized controlled trials of CMV HIG that are under way (NCT00881517 and NCT01326778) should be awaited to confirm the effect on transmission or prevention of disease. Regardless of the outcome of these studies, since most seropositive individuals appear to have high levels of antiviral antibodies (as a result of boosting following frequent reactivation and/or reinfection), it can be inferred that CMV HIG will have little to no role in high-seroprevalence populations.

Maternal Antiviral Immune Responses and Intrauterine Transmission

CMV infection and risk of transmission to the fetus are intimately linked to immunity, although the temporal appearance and quality of the humoral and T-cell-mediated responses against CMV during primary and nonprimary maternal infection remain incompletely understood.

The importance of immune responses in protecting against intrauterine transmission of CMV is borne out by the significantly decreased risk of congenital infection in infants born to women who were seropositive prior to pregnancy (~1%) in contrast to those with primary infection during pregnancy (~30%) (14, 27) and the beneficial effects of administering hyperimmune globulin (HIG) in women with primary infection during pregnancy (167). The observation that differential levels of neutralizing anti-glycoprotein B titers exist at the time of delivery in transmitter and nontransmitter mothers undergoing a primary infection also supports the role of the humoral arm of the immune system in modulating intrauterine transmission of CMV (171). The gB protein is relatively well conserved among different virus strains and is considered the major target of the neutralizing antibody response to CMV (172). Recent data, however, suggest that the pentameric complex comprising gH, gL, UL128, UL130, and UL131 is the most important antigenic complex for neutralizing antibody responses (173). High titers of neutralizing antibody are thought to protect against transmission by blocking receptor-mediated transcytosis of CMV in the placenta (174) and by reducing viral replication (87). It will be interesting to investigate the temporal appearance of humoral responses against the pentameric glycoprotein complex in both primary and recurrent infections in pregnant women and to determine whether they are a potential marker for risk of transmission and/or congenital CMV disease.

There is increasing evidence in transplant recipients that high levels of virus replication and disease are associated with the suboptimal quality of the T-cell response against CMV (175, 176). In addition, in healthy adolescents, it has been shown that the plasma CMV DNAemia was still evident despite the detection of a strong neutralizing antibody response within 6 to 8 weeks following primary infection, although lymphoproliferative responses were weak (177). Therefore, cellular immunity is indispensable during the acute phase of infection, as well as for the control of chronic infection and the prevention of reinfection (10, 178–180). Although a range of CMV proteins are targeted by the CD4 and CD8 immune system (181), major targets include the pp65 tegument protein and the IE1 antigen (and to a lesser extent gB) (182). In pregnant women experiencing primary infection, the evolution of the lymphoproliferative response has been shown to be relatively slow until a memory T-cell response develops (183). The cytokine profile of these T cells is dominated by gamma interferon producers, with relatively little interleukin-2 (IL-2) production. In mothers who experienced primary infection and who transmitted the virus to their fetuses, CMV CD4+ T-cell responses appear to be delayed and of lower frequency, and there were lower levels of CMV CD45RA+ cells in mothers who transmitted CMV to their fetuses (183, 184). In seropositive pregnant women, it has been shown that naive CD8+ T cells were reduced by 50%, with the CD45RA effector population showing a more highly differentiated state (CD27 and CD28 low) while the CD45RA revertant
memory cell population was expanded and was composed mainly of CMV-specific cells (185).

Notwithstanding these data, the precise components of protective immune responses against intrauterine transmission of CMV in women experiencing primary infection and in seropositive women remain to be defined and undoubtedly will contribute to the development of a successful vaccine.

**Vaccines**

The economic impact of congenital CMV was assessed by the Institute of Medicine nearly a decade ago. They estimated that the costs of medical and educational care for the thousands of children with asymptomatic and symptomatic congenital infection in the United States amounted to $1.9 billion per year, whereas the investment needed to develop a CMV vaccine would be approximately $360 million. The Institute of Medicine accordingly ranked the development of a CMV vaccine as the highest priority (4). Knowledge that CMV exhibits a high level of molecular diversity and carries an extensive array of virus immune evasion genes is increasing (10, 23, 186, 187). Consistent with this, it has been demonstrated that infection within a host can occur with multiple virus strains concomitantly, including at the time of initial infection, or sequentially (10, 23, 186, 187). Broad and cross-neutralizing cellular and humoral responses have therefore become a major goal of vaccine design (188). Whereas the traditional focus of CMV vaccines has been the prevention of primary maternal infection, this view has been challenged by recent data demonstrating that nonprimary infection drives most congenital infections, and that the rates of symptomatic infection at birth and hearing loss are similar in infants infected following primary and nonprimary maternal infections (7, 8, 74).

A recent phase II trial evaluated the efficacy of a recombinant genetically modified gB protein in a novel adjuvant, MF59 (189), in seropositive women and found a modest (~50%) reduction in the rate of primary maternal infection in the vaccinated group compared to the placebo group (190). However, this protection was observed predominantly within the first year after immunization. Although boosting of both antibody and CD4 T-cell responses by the gB vaccine was also demonstrated in CMV-seropositive women, whether such boosting will provide protection against nonprimary infection in mothers with preexisting immunity is not known (191). The same vaccine deployed in patients awaiting solid organ transplantation (the cohort consisted of seropositive and seronegative patients) was immunogenic and reduced the duration of viremia in patients with CMV infection posttransplantation (192).

Several proof-of-concept studies of various candidate vaccines have also been conducted in recent years. A two-component alphavirus replicon vaccine containing gB and a pp65/IE1 fusion protein has shown to be immunogenic in phase I clinical trials. In seronegative subjects, the vaccine elicited neutralizing antibodies and multifunctional T-cell responses (193), and it also boosted T-cell responses in CMV-seropositive renal transplant patients (194). A DNA vaccine comprising both gB and pp65 has also undergone phase I studies and a placebo-controlled phase II trial in stem cell transplant recipients. Although there was no difference in the number of vaccine and placebo recipients who received CMV-specific antiviral therapy, a significant reduction in the incidence and recurrence of DNAemia was seen (195). More recently, combining gB with a Toll-like receptor 9 (TLR9) agonist has produced durable polyfunctional cellular and cross-neutralizing humoral responses in transgenic mice (196). While there is some evidence for protection against nonprimary infection in these studies, evaluation of these candidate vaccines for the prevention of maternal and congenital infection seems to be far in the future. Even in low-seroprevalence settings, where vaccination of seronegative mothers could be cost-effective, it is unclear, in light of emerging findings on the epidemiology of congenital CMV, whether a CMV vaccine would provide substantial reductions in morbidity.

**Behavioral Measures**

In the absence of effective immunization strategies, the restriction of maternal infection relies predominantly on behavioral measures such as frequent hand washing after exposure to young children’s body fluids and avoiding intimate contact with young children (197). Children, when infected vertically or in the first few years of life, can shed virus in urine and saliva for many years either continuously or intermittently (108, 198–200). CMV therefore spreads readily in settings where preschool children are concentrated, with fomites on wet absorbent surfaces most able to harbor viable viruses (33, 201). This places seronegative pregnant women who work in child care centers or who have a young child in the home or in day care at increased risk of seroconversion (31, 32, 34, 202). Accordingly, specific advice to seronegative women on measures that interrupt child-to-mother transmission has been shown to be effective (16, 18, 203). Besides contact with young children, sexual transmission from a seropositive male partner is an additional established route by which women may be infected with CMV (25, 160, 197, 204–207). It is quite likely that these modes of transmission are also responsible for reinfection of seropositive mothers with new or different virus strains. Indeed, sexual transmission probably frequently results in maternal reinfection in high-seroprevalence populations, where young women often report multiple sex partners and unsafe sex practices. However, the contribution of sexual and child-to-mother transmission to maternal reinfection in these settings remains to be virologically documented. Moreover, the role of reinfection compared with reactivation in delivering a child with CMV is also unknown. It is therefore difficult to speculate on the impact of behavioral changes in resource-limited settings. On the whole, promoting education and awareness of congenital CMV infection and ways to avoid exposure for all prospective mothers remains a key health educational objective (160, 208).

**CONCLUSIONS**

Congenital CMV is a major cause of disability in children, with little evidence for change in disease burden over time in high- and middle-income countries despite large scientific and clinical advances in the CMV field. This results from a general neglect of the problem, contributed to by the absence of clinical disease at birth in the majority of babies who develop complications and the lack of safe and effective antiviral therapy to prevent or reduce sequelae in most children with congenital CMV infection. Therefore, prevention of maternal infection and transmission is the main priority. Vaccines may offer protection against primary infection, and the efficacy of vaccines in mothers following nonprimary infection should be assessed.

The neglect of congenital CMV infection in the developing world reflects not only delayed onset of sequelae but also compet-
ing health priorities in such populations. Given that early detection of hearing loss can limit long-term disabilities, PCR-based newborn screening to identify those at risk of sequelae deserves consideration. However, it would be premature to consider newborn CMV screening in resource-poor settings because the disease burden from congenital CMV and the cost/benefit ratio of long-term follow-up have not been defined. In addition, the cost and the competing health priorities for these settings make it difficult to envision such a screening program. While studies to define the disease burden should be undertaken as a matter of urgency, for the present, raising awareness of congenital CMV should be prioritized.

ACKNOWLEDGMENTS

We gratefully acknowledge Patrick Lane and Rajesh Narotam for assistance with the figures. Thanks also go to Dave le Roux, Michael Harrison, and Raveen Parboosingh for reading an earlier version of this paper and to Noelle Nicholls for editorial assistance.

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Manicklal et al.

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Continued next page
Sheetal Manicklal is a Registrar in Medical Virology at the University of Cape Town, with a particular interest in vertically transmitted infections. She recently initiated a collaborative project to better understand the interrelationship between congenital CMV and HIV-1 and to define the disease burden in South Africa.

Vincent Emery is Pro-Vice-Chancellor (International Relations) and Professor of Translational Virology at the University of Surrey and holds an honorary Professorship of Virology at University College London (UCL). He started his scientific career as a biochemist but has been a virologist for the last 27 years. His current research aims to provide a holistic approach to understanding viral infections in immunocompromised hosts such as HIV-infected patients and transplant recipients. His particular interests have been focused on cytomegalovirus in solid organ and stem cell transplant recipients by combining viral replication measures with assessment of the immune response and mathematical biology to improve patient management. During his career, he has obtained in excess of £14.4 million of grant money from government agencies in the United Kingdom and the United States, charitable organizations, and the private sector. In addition, Professor Emery is also a named inventor on 5 patents in the area of biotechnology and molecular diagnostics, is a member of a UCL-Imperial College nanotechnology consortium funded by a £1.7-million grant from the EPSRC to develop novel nanodiagnostics for HIV, and is part of a team of researchers from UCL and OJ-Bio who have secured NIHR i4i funding of £1 million to develop novel point-of-care HIV diagnostics. Professor Emery has published in excess of 200 research articles, reviews, and books, including a “Pocket Guide to Cytomegalovirus” and “A Patient’s Guide to Cytomegalovirus” published in 2009 and “A Spotlight on Cytomegalovirus Infection and Disease” as part of the Lectures in Transplantation series, published in 2010.

Tiziana Lazzarotto graduated with a degree in Biological Science from the University of Bologna and received scientific training for her specialty degree in Microbiology and Virology at the University of Bologna (Italy). She is Associate Professor of Microbiology and Clinical Microbiology, School of Medicine, Alma Mater Studiorum-University of Bologna (Italy). She works at the Operative Unit of Clinical Microbiology at St. Orsola Malpighi University General Hospital, Bologna, and she is the head of the Laboratory of Virology. For over 15 years, she has an expertise in the field of virology with specific reference to diagnosis and management of congenital human cytomegalovirus (CMV) infection. In particular she has made significant contributions to knowledge of the immune response to CMV, study on the pre- and postnatal diagnosis of congenital CMV infection, and identification of prognostic markers for in utero transmission.

Suresh Boppana is a Professor of Pediatrics and Microbiology at the University of Alabama at Birmingham and has been studying the natural history and pathogenesis of maternal and congenital cytomegalovirus (CMV) infection for the past 20 years. Dr. Boppana’s work challenged the dogma that children with congenital CMV infection born to women with primary CMV infection during pregnancy experience most of the disease burden from this intrauterine infection. He has shown that CMV reinfections occur frequently in healthy seropositive women and that such reinfections could lead to intrauterine infection, symptomatic disease, and sequelae. His work with collaborators in Brazil and India is beginning to document the impact of congenital CMV infection in highly seropositive settings, including developing countries. He is currently the principal investigator of large multicenter study to define the contribution of congenital CMV infection to overall hearing loss and to develop diagnostic methodologies that can be used to screen large number of newborns. The findings from this study, demonstrating low sensitivity of the dried blood spot PCR assay and the development of a highly sensitive and specific saliva real-time PCR assay for congenital CMV infection, have been published in the Journal of the American Medical Association and the New England Journal of Medicine, respectively. His current research is focused on understanding the pathogenesis of CMV-associated hearing loss. He mentored several undergraduate, graduate, and postdoctoral trainees. He served as a consultant member of several NIH study sections.

Ravi Gupta is a consultant in infectious diseases at University College Hospital London and has a particular interest in viral infections. His research group studies host-virus interactions and HIV drug resistance. He is a member of the WHO HIV global surveillance resistance committee. His portfolio is broad, from teaching about HIV and viral hemorrhagic fever in the tropics to working on retroviral latency and HIV cure as part of the multicenter United Kingdom collaboration CHERUB.
Objective To evaluate the impact of race and ethnicity upon the prevalence and clinical spectrum of congenital cytomegalovirus infection (cCMV).

Study design From 2007 to 2012, 100 332 infants from 7 medical centers were screened for cCMV while in the hospital. Ethnicity and race were collected and cCMV prevalence rates were calculated.

Results The overall prevalence of cCMV in the cohort was 4.5 per 1000 live births (95% CI, 4.1-4.9). Black infants had the highest cCMV prevalence (9.5 per 1000 live births; 95% CI, 8.3-11.0), followed by multiracial infants (7.8 per 1000 live births; 95% CI, 4.7-12.0). Significantly lower prevalence rates were observed in non-Hispanic white infants (2.7 per 1000 live births; 95% CI, 2.2-3.3), Hispanic white infants (3.0 per 1000 live births; 95% CI, 2.4-3.6), and Asian infants (1.0 per 1000 live births; 95% CI, 0.3-2.5). After adjusting for socioeconomic status and maternal age, black infants were significantly more likely to have cCMV compared with non-Hispanic white infants (adjusted prevalence OR, 1.9; 95% CI, 1.4-2.5). Hispanic white infants had a slightly lower risk of having cCMV compared with non-Hispanic white infants (adjusted prevalence OR, 0.7; 95% CI, 0.5-1.0). However, no significant differences in symptomatic cCMV (9.6%) and sensorineural hearing loss (7.8%) were observed between the race/ethnic groups.

Conclusions Significant racial and ethnic differences exist in the prevalence of cCMV, even after adjusting for socioeconomic status and maternal age. Although once infected, the newborn disease and rates of hearing loss in infants are similar with respect to race and ethnicity. (J Pediatr 2018;200:196-201).

Congenital cytomegalovirus (CMV) infection (cCMV) occurs worldwide and contributes to permanent disabilities including hearing loss, vision loss, cerebral palsy, and/or cognitive impairment in thousands of children born each year. In the US, Canada, Western Europe, and Australia, cCMV is estimated to occur in about 5-7 per 1000 live births.1-3 Higher cCMV rates of 10-20 per 1000 live births have been reported in South America, Africa, and most countries in Asia.4-8 The vast majority of the infants born with cCMV (approximately 90%) are asymptomatic during the newborn period.9 However, asymptomatic infants along with symptomatic infants are at risk for CMV-related disabilities.

Few data are available on the prevalence and the clinical spectrum of cCMV according to race and ethnicity. Previous studies in Birmingham, Alabama, reported that cCMV rates were higher in black infants than white infants.1 Although higher cCMV rates have been reported in Hispanic white infants in the US, the number of Hispanic infants studied is small and the differences did not attain statistical significance.10,11 The lack of accurate prevalence estimates in the US could contribute to the underrecognition of cCMV as a common cause of disabilities in infants and young children. Therefore, regional and national estimates of the prevalence and clinical spectrum of cCMV in the US according to race and ethnicity are needed. As part of a multicenter study, more than 100 000 infants were tested for CMV while in the hospital nursery, allowing us to determine the impact of race and ethnicity on the prevalence and clinical spectrum of cCMV in newborns.
Methods

From March 2007 to March 2012, infants born at 7 US medical centers were enrolled in the CMV and Hearing Multicenter Screening (CHIMES) Study.\textsuperscript{12} Saliva specimens were collected from the newborn and additional dried blood spots were obtained at the time of newborn metabolic screening and tested for CMV, as previously described.\textsuperscript{13-15} Infants with positive saliva or dried blood spots screening specimens were enrolled in the follow-up component of the study within the first 3 to 6 weeks of life to confirm cCMV.\textsuperscript{14} CMV infection was confirmed by a follow-up saliva or urine sample which was positive using the rapid culture and/or polymerase chain reaction (PCR) methods.\textsuperscript{16} Race and ethnicity data were self-reported by the mothers for their infants at time of consent.\textsuperscript{1,3} National Institutes of Health definitions were used to categorize ethnicity and race. The 2 categories for ethnicity were Hispanic or non-Hispanic. The 5 individual categories for race were American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or other Pacific Islander, and white. In addition, infants with reported multiple races were categorized as multiracial. All infants who were either black, multiracial, Asian, or American Indian race were non-Hispanic. Newman medical records were reviewed for infants with cCMV to determine if the infants had symptomatic infection. The a priori definition of symptomatic cCMV included generalized petechial rash, purpuric rash, hepatomegaly, splenomegaly, jaundice with direct bilirubin of 3 mg/dL or greater, unexplained neurologic/central nervous system abnormalities (eg, microcephaly, seizures, focal or generalized neurologic deficits), or chorioretinitis diagnosed by eye examination.\textsuperscript{12} The physicians at each study site made clinical decisions about further evaluations and possible treatment of the infants with CMV as part of the infant’s standard medical care. Infants with cCMV enrolled in the follow-up component of the CHIMES study received an initial diagnostic audiologic assessment at 3-8 weeks of age. Local institutional review board approval was obtained at each site.

Statistical Analyses

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina). To determine statistical significance, routine methods for calculating $\chi^2$ or Fisher exact test, and the 2-tailed t test were used where appropriate. For prevalence, the unit of measure was the total number of cCMV infection per 1000 live births. CIs for prevalence rates were based on the Binomial distribution. Also, univariate prevalence ORs (PORs) and 95% CIs using the exact method were calculated to evaluate the association of race and ethnicity with cCMV. Because socioeconomic status and maternal age have been previously reported to be associated with cCMV and might confound the association of race and ethnicity with cCMV, multivariable logistic regression analysis was used to adjust for the effect of insurance status (as a proxy for socioeconomic status) and maternal age on the race/ethnicity-specific adjusted PORs for cCMV. Adjusted PORs and 95% CIs were calculated by exponentiating the regression coefficients and the standard errors of the respective coefficients.

Results

Of the 108,925 mothers approached for participation in the CHIMES Study, 100,607 mothers consented and 8318 (7.6%) mothers declined to participate in the study. Adequate enrollment specimens were available for 100,332 of the infants and 497 infants screened positive for CMV. In 391 infants, CMV was confirmed by a follow-up positive saliva or urine sample using the rapid culture or PCR methods.\textsuperscript{16} Thirty-five infants were considered uninfected because the follow-up saliva and urine samples were negative. Another 13 infants had indeterminate positive screening results by saliva PCR and did not enroll in follow-up to obtain confirmation samples.\textsuperscript{13,14,16} None of these infants had clinical findings consistent with cCMV on medical record review. These 13 infants were not included as cCMV cases. An additional 58 infants did not enroll in follow-up owing to death (n = 3), refusal (n = 17), loss to follow-up (n = 33), or migration (n = 5), but had positive screening saliva rapid culture and/or PCR.\textsuperscript{14,16} Five of these infants had symptomatic CMV. These 58 infants are included in the estimates of cCMV prevalence for a total to 449 cCMV cases.

Most of the 100,332 enrolled infants were from the well-baby nurseries with 6 of the 7 sites having more than 10,000 infants who underwent CMV screening (Table I). Non-Hispanic white infants, Hispanic white infants, and black infants were the largest racial/ethnic groups in the cohort with most infants having public or no insurance. Infants with cCMV sig-

### Table I. Study characteristics for the 100,332 newborns who underwent newborn CMV screening at the 7 sites

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital site</strong></td>
<td></td>
</tr>
<tr>
<td>Birmingham, Alabama</td>
<td>12,193 (12.1)</td>
</tr>
<tr>
<td>Jackson, Mississippi</td>
<td>6,360 (6.3)</td>
</tr>
<tr>
<td>New Brunswick, New Jersey</td>
<td>10,715 (10.7)</td>
</tr>
<tr>
<td>Charlotte, North Carolina</td>
<td>15,093 (15.0)</td>
</tr>
<tr>
<td>Cincinnati, Ohio</td>
<td>14,126 (14.1)</td>
</tr>
<tr>
<td>Pittsburgh, Pennsylvania</td>
<td>19,200 (19.1)</td>
</tr>
<tr>
<td>Dallas, Texas</td>
<td>22,645 (22.6)</td>
</tr>
<tr>
<td><strong>Infant sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49,320 (49.2)</td>
</tr>
<tr>
<td>Male</td>
<td>51,012 (50.8)</td>
</tr>
<tr>
<td><strong>Infant race/ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>101 (0.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>4,166 (4.1)</td>
</tr>
<tr>
<td>Black</td>
<td>24,100 (24.0)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>32,310 (32.2)</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>37,219 (37.1)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>2,436 (2.4)</td>
</tr>
<tr>
<td><strong>Insurance status for hospital stay</strong></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>35,270 (35.2)</td>
</tr>
<tr>
<td>Public or no insurance</td>
<td>65,062 (64.8)</td>
</tr>
<tr>
<td><strong>Hospital nursery</strong></td>
<td></td>
</tr>
<tr>
<td>Well-baby</td>
<td>96,873 (96.6)</td>
</tr>
<tr>
<td>Neonatal intensive care</td>
<td>3,459 (3.4)</td>
</tr>
</tbody>
</table>
significantly differed by race and ethnicity, insurance status, and hospital nursery from infants who were CMV negative (Table II). Also, infants who were CMV positive had significantly younger mothers than infants without cCMV.

The overall prevalence rate of cCMV was 4.5 per 1000 live births (95% CI, 4.1-4.9 per 1000 live births). The prevalence of cCMV differed by race and ethnicity (Figure 1). Black infants had the highest cCMV prevalence (9.5 per 1000 live births), followed by multiracial infants (7.8 per 1000 live births). Both black and multiracial infants had a significantly higher cCMV prevalence rate than the rate observed for non-Hispanic white infants (2.7 per 1000 live births), Hispanic white infants (3.0 per 1000 live births), and Asian infants (1.0 per 1000 live births). The unadjusted PORs for cCMV in black infants and multiracial infants were significantly higher compared with non-Hispanic white infants (Table III), whereas the unadjusted PORs for cCMV in Hispanic white infants and Asian infants did not differ from non-Hispanic white infants.

To adjust for potential confounding by socioeconomic status and maternal age on the association of race and ethnicity with cCMV, a multivariable logistic regression model that included race and ethnicity, insurance status (as a proxy for socioeconomic status), and maternal age was fit. After adjusting for socioeconomic status and maternal age, race and ethnicity were independently associated with cCMV (Table III). Black infants and multiracial infants were almost 2 times more likely to have cCMV compared with non-Hispanic white infants. However, Hispanic white infants had a lower risk of having cCMV compared with non-Hispanic white infants, although this was of borderline significance. Asian infants did not significantly differ in risk of having cCMV compared with non-Hispanic white infants.

Symptomatic cCMV was observed in 9.6% (95% CI, 7.0%-12.7%) of all the infants with cCMV. When symptomatic cCMV was stratified by race and ethnicity, no differences were observed between the groups (Figure 2, A). Sensorineural hearing

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**Table II. Characteristics of infants with CMV vs infants without CMV**

<table>
<thead>
<tr>
<th>Sites</th>
<th>CMV positive (n = 449, % (95% CI))</th>
<th>CMV negative (n = 99883, % (95% CI))</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant race and ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>0.2 (0.01-1.2)</td>
<td>0.1 (0.08-0.12)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Asian</td>
<td>0.9 (0.2-2.3)</td>
<td>4.2 (4.0-4.3)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>51.0 (46.3-55.7)</td>
<td>23.9 (23.6-24.2)</td>
<td></td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>21.4 (17.7-25.5)</td>
<td>32.2 (32.0-32.5)</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>22.3 (18.5-26.4)</td>
<td>37.2 (36.9-37.5)</td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>4.2 (2.6-6.5)</td>
<td>2.4 (2.3-2.5)</td>
<td></td>
</tr>
<tr>
<td>Infant sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48.3 (43.6-53.1)</td>
<td>49.2 (48.8-49.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>51.7 (46.9-56.4)</td>
<td>50.8 (50.5-51.2)</td>
<td></td>
</tr>
<tr>
<td>Insurance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>17.2 (13.8-21.0)</td>
<td>35.2 (34.9-35.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Public or no insurance</td>
<td>82.8 (79.0-86.2)</td>
<td>64.8 (64.5-65.1)</td>
<td></td>
</tr>
<tr>
<td>Hospital nursery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well baby</td>
<td>89.8 (86.6-92.4)</td>
<td>96.6 (96.5-96.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Neonatal intensive care unit</td>
<td>10.2 (7.6-13.4)</td>
<td>3.4 (3.3-3.5)</td>
<td></td>
</tr>
<tr>
<td>Maternal age, mean ± SD, y</td>
<td>23.1 ± 5.6</td>
<td>27.4 ± 6.1</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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**Figure 1.** Prevalence per 1000 live births of congenital CMV infection and 95% CIs by race and ethnicity.
loss in the neonatal period occurred in 7.8% of all the infants with cCMV (95% CI, 5.5%-10.7%). Sensorineural hearing loss at birth did not significantly differ for any of the racial and ethnic groups (Figure 2, B).

**Discussion**

Significant racial and ethnic differences exist in the prevalence of cCMV, although once infected, the clinical manifestations and rates of hearing loss in infants are similar with respect to race and ethnicity. The overall cCMV rate of 4.5 per 1000 live births found in our cohort of more than 100 000 infants is lower than previous reported prevalence rates of 6.4 per 1000 live births and 7 per 1000 live births from 2 meta-analysis studies. Most of the data on cCMV prevalence from these reviews are based on smaller cohorts from individual hospitals in different cities or countries. Thus, the difference in cCMV prevalence rates may be due to the selection of the underlying delivery populations in these studies. These studies likely have overrepresented some high-risk groups of infants and may not reflect a more general population of newborns. Only 2 studies have assessed cCMV prevalence rates for a city or a region. A study in Malmö, Sweden (1977-1986), where 16 474 infants were tested for cCMV, reported a prevalence rate of 4.6 per 1000 live births. The other study was in Hamilton, Ontario, Canada (1973-1976) where 15 212 live born infants in the city hospitals were screened for cCMV, finding a cCMV prevalence rate of 4.2 per 1000.

The significantly higher cCMV prevalence observed in black infants is similar to what has been previously reported in black infants in Birmingham, Alabama. An earlier study in London, UK, also found that black infants had high cCMV prevalence rates, even after adjusting for maternal age, socioeconomic status, and parity. In our study, higher cCMV prevalence was observed in black infants compared with non-Hispanic white infants in all 7 hospitals located in different southern and eastern regions of the US. Multiracial infants also had a significantly higher cCMV prevalence rate similar to the black infants in our cohort. Among the multiracial infants in our cohort, 77% included black race along with 1 or more other races. All multiracial infants who were CMV positive included black race. After adjusting for the confounding effects of maternal age and socioeconomic status, both black infants and multiracial infants were almost twice as likely to be congenitally infected with CMV compared with non-Hispanic white infants.

Non-Hispanic black women have reported higher CMV seroprevalence rates compared with non-Hispanic white women. It has been consistently shown that higher cCMV prevalence rates are found in populations with higher maternal seroprevalence; however, the exact reasons for this association are not known. It is possible that the higher prevalence of cCMV in black and multiracial infants in our study could be due to higher maternal CMV infection as well as cCMV. These findings suggest the need for a thorough evaluation of the role of genetic factors in cCMV. Our study did not have maternal CMV seroprevalence or genetic data to explore these possible hypotheses.

A surprising finding of our study was the low cCMV prevalence rate for Hispanic white infants. In fact, after adjusting for confounding by maternal age and socioeconomic status, Hispanic white women had a slightly lower risk of having an infant with cCMV compared with non-Hispanic white women. Previous National Health and Nutrition Examination Survey data in the US reported high CMV seroprevalence rates for

<table>
<thead>
<tr>
<th>Infant race and ethnicity</th>
<th>POR (95% CI)</th>
<th>aPOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black, non-Hispanic</td>
<td>3.5 (2.8-4.5)</td>
<td>1.9 (1.4-2.5)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>2.9 (1.8-4.8)</td>
<td>1.9 (1.1-3.0)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>1.1 (0.8-1.5)</td>
<td>0.7 (0.5-1.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.4 (0.1-1.0)</td>
<td>0.6 (0.2-1.2)</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

aPOR, Adjusted prevalence OR.

*Model included race and ethnicity, insurance status, and maternal age.

**Figure 2.** A, Symptomatic congenital CMV infection (%) and 95% CIs by race and ethnicity and B, sensorineural hearing loss at birth (%) and 95% CIs by race and ethnicity.
Mexican American women and, therefore, a higher cCMV prevalence rate similar to that in black infants was expected in Hispanic white infants. An earlier study of 132 Hispanic infants in Houston, Texas (1980), reported a cCMV prevalence of 15 per 1000 live births. In addition to the small number of infants, the higher observed rate in Hispanic infants in the Texas study might be explained by whether the mother was US born or was born outside of the US. A more recent study using dried blood spots from the California Newborn Screening Program reported a cCMV prevalence rate of 9 per 1000 live births for Hispanic infants. However, the sensitivity and specificity of their dried blood spots testing for detection of cCMV in that study could not be determined because the dried blood spots screening assay results were not compared with testing of urine or saliva. Also, the study did not follow-up to confirm cCMV in infants who were positive on screening. The 32 310 enrolled Hispanic white infants in our cohort comprise the largest study to date of Hispanic infants in the US for CMV screening, and 4 of 7 hospitals enrolled 500 or more Hispanic white infants in the study. It is possible that cCMV prevalence vary among the US Hispanic population based on the country of origin. We do not have study data on the country of origin for Hispanic white women nor whether they were US born. However, cCMV prevalence rates were similar across the 4 hospitals in the different regions of the US for all the Hispanic white infants in our cohort.

The lowest cCMV prevalence rate was observed in Asians in our study. These findings are similar to cCMV prevalence reports in Japan, but are significantly lower than the reported cCMV prevalences in China, Korea, and India. Other than the dried blood spots study by Kharrazi et al described herein that included Asian infants, no other data on the cCMV prevalence in Asian infants in the US exists previously. The definition used in the CHIMES study was based on the National Institutes of Health definition of “Asian” and, because this is a very heterogeneous group in the US, cCMV prevalence may differ when country origin is considered.

Although black and multiracial infants are at increased risk for cCMV compared with non-Hispanic white infants, once infected, symptomatic infection and sensorineural hearing loss rates at birth do not differ significantly by race and ethnicity. The finding that approximately 10% of infants with cCMV were symptomatic is similar to previous meta-analysis where 12.7% of the infants with cCMV were symptomatic. However, the use of differing definitions of symptomatic cCMV in different studies and in different countries has made it difficult to compare studies. Applying the same symptomatic definition to all infants in our study, we did not find significant differences in the rate of symptomatic infections between the race/ethnic groups.

A limitation of our study is that it does not include the total population of newborns in the regions where the hospitals were located; therefore, our estimate of the overall prevalence of cCMV may not be representative for the region or the US. However, because the cCMV prevalence differs by race and ethnicity, the use of an overall cCMV prevalence could be obscuring the burden of cCMV in certain populations, such as blacks. The consistency of the race- and ethnicity-specific cCMV prevalence rates across the 7 hospitals in this study, and the fact that more than 96% of the infants were in the well-baby nurseries and not a selected population, would argue that our race/ethnicity-specific cCMV prevalence rates could be used to estimate prevalence in specific race/ethnic groups.

CMV is the most frequent cause of congenital infection, and hospital or regional cCMV prevalence rates reflect the underlying racial and ethnic groups of the delivery populations. Although CMV affects infants from all race and ethnic groups, black infants and multiracial infants are at significantly increased risk for cCMV. Our findings highlight the need for developing strategies to increase awareness of cCMV and prevention messages for all women, including culturally relevant messages for black and multiracial women whose offspring bear a disproportionately higher burden of cCMV.

A list of additional members of the CHIMES study is available at www.jpeds.com (Appendix).

References


Appendix

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Commentary

Congenital cytomegalovirus (CMV) epidemiology and awareness

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ARTICLE INFO

Article history:
Received 11 June 2009
Accepted 4 September 2009

Keywords:
Cytomegalovirus
Congenital
Epidemiology
Awareness

ABSTRACT

This commentary highlights and discusses the implications of a number of recent studies that refine epidemiologic knowledge of CMV infection and assess awareness of congenital CMV among clinicians and the public. These studies highlight that: (1) congenital CMV results in a disease burden that is substantial and severe; (2) a high proportion of United States women of reproductive age are susceptible to CMV infection; (3) the majority of congenital CMV infections in the United States result from recurrent infections among pregnant women; (4) CMV seroprevalence and seroincidence are much higher among racial/ethnic minorities and persons of lower socioeconomic status (SES); (5) household transmission of CMV appears to be an important transmission route in the United States; (6) sexual transmission of CMV appears to be an important transmission route in some population sub-groups in the United States; (7) women have limited awareness and knowledge about congenital CMV; (8) most obstetrician/gynecologists do not counsel women about prevention of congenital CMV; (9) most women view CMV prevention messages positively.

Published by Elsevier B.V.

1. Findings

Over the past 50 years, numerous studies have illuminated the epidemiology of congenital CMV infection and disease. This commentary highlights and discusses the implications of a number of recent studies that refine epidemiologic knowledge of CMV infection and assess awareness of congenital CMV among clinicians and the public.

1.1. Congenital CMV infection results in a disease burden that is substantial and severe

A comparison of literature estimates shows that congenital CMV-related disabilities are as common among newborns and children as other better known diseases such as Down syndrome, fetal alcohol syndrome, or spina bifida (Fig. 1). Among the estimated 30,000 United States children born annually with congenital CMV infection (~0.7% of all newborns), nearly 20% are born with or develop permanent sequelae such as hearing loss, vision loss, cerebral palsy, or cognitive impairment (Fig. 2). Worldwide, many thousands more suffer permanent disability. The contribution of congenital CMV infection to childhood hearing loss is particularly substantial, with nearly 20% of bilateral moderate to profound sensorineural hearing loss being caused by congenital CMV infection. Nearly 90% of congenitally infected newborns are asymptomatic at birth; if symptoms are present they are frequently non-specific. When disabilities such as hearing loss become apparent, it is usually too late to make a retrospective diagnosis that identifies congenital CMV infection as the culprit.

1.2. A high proportion of United States women of reproductive age are susceptible to CMV infection

For an individual woman, the highest risk for having a congenitally infected baby comes from primary maternal infection during pregnancy. Thus, the babies of women who were CMV seronegative prior to conception are especially vulnerable to poor outcomes if the mother becomes infected during pregnancy. A nationally representative survey found that between 30% and 50% of United States women under age 45 are CMV seronegative (Fig. 3), and that as many as a half million United States women of reproductive age experience primary CMV infections each year.

1.3. The majority of congenital CMV infections in the United States result from recurrent infections among pregnant women

Although individual risk of congenital CMV infection is highest for the children of women who were CMV seronegative prior to pregnancy, an estimated 3/4 of congenital infections in the United States occur among women who were CMV seropositive prior to conception (Fig. 4). This proportion is likely to be even higher in

Disclaimer: The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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countries with higher CMV seroprevalences. These recurrent CMV infections can be due to reactivation of latent virus or by reinfections with a different viral strain.\textsuperscript{12}

1.4. CMV seroprevalence and seroincidence are higher among racial/ethnic minorities and persons of lower SES

CMV seroprevalence in the overall United States population is 59\%, ranging from 36\% among 6–11 year-olds to 91\% among those aged ≥80 years.\textsuperscript{9} CMV seroprevalence is 25–30\% higher among non-Hispanic blacks and Mexican Americans than among non-Hispanic whites, and is higher among foreign-born individuals than among United States-born individuals.\textsuperscript{9} In addition, CMV seroprevalence is 15–25\% higher among persons living in low- and middle-income households than among those living in high-income households.\textsuperscript{9} In multivariate analyses, race/ethnicity was more strongly associated with CMV seropositivity than was household income. Among seronegative populations, rates of new CMV infection are nearly five times higher among non-Hispanic blacks and Mexican Americans than among non-Hispanic whites (Fig. 5).\textsuperscript{10}
Birth prevalences of congenital CMV infection have mirrored seroprevalences of the maternal population. Women who are poorer or of African American race are significantly more likely to give birth to children with congenital CMV infection than are other women. A recent population-based study of infants born in California found elevated congenital CMV birth prevalences among African American and Hispanic children, although the differences were not statistically significant (Dollard et al., 2008 Congenital CMV Conference abstract). Although data are insufficient to assess frequency of CMV-related disabilities in different racial/ethnic populations, it is likely that higher rates of congenital infection are associated with higher rates of disabilities.

1.5. Household transmission of CMV appears to be an important transmission route in the United States

Several CMV transmission routes have been clearly demonstrated. During childhood, these routes include mother-to-child via breastfeeding, parents- or siblings-to-child via close contact, or child-to-child via close contact in out-of-home settings such as day care centers. However, the impact that each of these transmission routes has on the population seroprevalence of CMV among children has been unclear; in other words, the relative frequency of these transmission routes in the overall population was unknown. A recent nationally representative study of the United States population suggests that among children, having a CMV seropositive mother or sibling is a very important risk factor for infection, while a

![CMV Force of Infection by Race/Ethnicity, SES, and Region](image)

![CMV seroprevalence differences among 6–10-year-old children by sources of infection—adjusted by 1-year-age groups (from Staras et al.21). Point estimates for prevalence differences are represented by black symbols and the 95% confidence intervals for these differences are represented by lines. For each childhood source of CMV there are four prevalence difference estimates: one for each of the four racial/ethnic and householder status categories. The prevalence in the less exposed risk category (i.e., children with CMV-seronegative older siblings or mothers, children who were not breast-fed, children who did not attend child care) was subtracted from the more exposed category (i.e., children with CMV seropositive older siblings or mothers, children who were breast-fed, children who did attend child care); therefore, positive prevalence differences represent a higher CMV seroprevalence estimate in the more exposed group compared to the less exposed group. aWe were unable to compare Mexican American children with foreign-born householders by maternal serostatus because only nine mothers were seronegative. bBreast-feeding information only collected for 4–5 year olds.)

![Fig. 5. Estimated CMV force of infection by race/ethnicity, socioeconomic status (SES), and region (adapted from Colugnati et al.10). Data are from the Third National Health and Nutrition Examination Survey, 1988–1994.](image)

![Fig. 6. CMV seroprevalence differences among 6–10-year-old children by sources of infection—adjusted by 1-year-age groups (from Staras et al.21). Point estimates for prevalence differences are represented by black symbols and the 95% confidence intervals for these differences are represented by lines. For each childhood source of CMV there are four prevalence difference estimates: one for each of the four racial/ethnic and householder status categories. The prevalence in the less exposed risk category (i.e., children with CMV-seronegative older siblings or mothers, children who were not breast-fed, children who did not attend child care) was subtracted from the more exposed category (i.e., children with CMV seropositive older siblings or mothers, children who were breast-fed, children who did attend child care); therefore, positive prevalence differences represent a higher CMV seroprevalence estimate in the more exposed group compared to the less exposed group. aWe were unable to compare Mexican American children with foreign-born householders by maternal serostatus because only nine mothers were seronegative. bBreast-feeding information only collected for 4–5 year olds.]
1.6. Sexual transmission of CMV appears to be an important transmission route in some population sub-groups in the United States

It has been demonstrated that CMV can be found in semen and cervicovaginal secretions, and that persons with sexual risk factors (e.g., multiple partners, laboratory or clinical evidence of sexually transmitted infections) are more likely to be infected with CMV. The impact of sexual transmission on CMV general population seroprevalence, however, remained unclear. A recent national study showed that sexual risk factors, such as number of lifetime sex partners, age at first intercourse, and herpes simplex virus type 2 (HSV-2), were associated with elevated CMV seroprevalence among non-Hispanic black and white women. Among other demographic groups the associations between CMV seropositivity and sexual risk factors were weaker and not statistically significant, possibly due to stronger competing exposures throughout life.

1.7. Women have limited awareness and knowledge about congenital CMV

Despite its substantial disease burden, two recent surveys have shown that fewer than one in five women have heard of CMV and that among these women, most have no knowledge of disease outcomes, transmission modes, or preventive measures. In one survey, awareness of CMV was lower than for any other condition included in the survey (Fig. 7).

1.8. Most obstetrician/gynecologists (OB/GYNs) do not counsel women about congenital CMV

The American College of Obstetricians and Gynecologists (ACOG) recommends that its members counsel pregnant women about CMV prevention. Nevertheless, a recent survey suggests that fewer than half of OB/GYNs routinely counsel patients about CMV prevention. Survey responses about preventive behaviors also suggest that OB/GYNs may not fully appreciate the important role children play in CMV transmission.

1.9. Most women view CMV prevention messages positively

CMV prevention messages are intended to reduce the likelihood of a pregnant woman getting urine or saliva from young children into her eyes, nose, or mouth. To begin to understand how women view these prevention messages, a recent survey asked about the perceived difficulty of practicing certain preventive behaviors during pregnancy. Most women responded that they would consider it “very easy” or “somewhat easy” to wash their hands after changing a baby’s dirty diaper (97%), not share cups or utensils with a young child (86%), or not kiss a young child on the mouth (68%). Only 1%, 3%, and 14% responded that those respective activities would be “very hard”.

2. Implications

The burden of disease caused by congenital CMV highlights the urgent need for prevention and treatment options. Many United States women of reproductive age are CMV seronegative and thus are in need of interventions to prevent primary CMV infection. There is also a need to develop methods of preventing recurrent CMV infections, since recurrent maternal infections are responsible for the majority of congenital CMV infections in the United States and other countries. Additional studies are needed to determine the frequency with which recurrent maternal CMV infection results in permanent disability among congenitally infected children.

A number of prevention and treatment options can be pursued. Development of a CMV vaccine should remain a high priority. Recent results from a phase II vaccine trial are encouraging. Trials to test the effectiveness of prenatal treatments such as CMV hyperimmunoglobulin (HIG) and valacyclovir need to be accelerated. Newborn screening, along with postnatal antiviral treatments and early interventions to improve language and educational outcomes, need to be assessed. Prevention and treatment efforts should include a focus on minority populations in order to reduce health disparities.

In the meantime, behavioral interventions should be developed and evaluated to identify ways to effectively change behavior and reduce the incidence of CMV infection during pregnancy. A large intervention study in France recently showed that counseling on hygiene practices was effective in reducing rates of CMV infection among pregnant women. Prevention messages for pregnant women should include ways to reduce exposure to the urine and saliva of young children, with a special emphasis on reducing household transmission. Because CMV can also be transmitted through activities associated with sex, pregnant women should also receive messages about safe sex. Further research of CMV transmission is needed in order to develop effective behavioral interventions, including studies of CMV presence and persistence in the environment, the impact of various hand cleansing methods, and transmission in the home environment. Formative research is also needed to better understand how to develop prevention messages that pregnant women will understand, accept, and be capable and motivated to follow. Although most women will be unable to completely eliminate exposure to CMV during pregnancy, it is likely that reducing the number of exposures will reduce the risk of becoming infected.

The survey findings reviewed herein demonstrate that women need to be educated about congenital CMV and that they are generally receptive to CMV prevention messages. Because many women get health messages from their physicians, it is important that physicians become fully informed about congenital CMV prevention and that they have appropriate educational tools for instructing their patients. The immediate goal of CMV prevention messages is to reduce the risk of CMV infection among pregnant women, but such messages will also have a broader effect. As
CMV prevention messages become better understood and more prevalent, awareness will increase among healthcare providers, children’s advocacy groups, policy makers, and funding agencies, leading to an increased sense of urgency for the development of a CMV vaccine and other tools to prevent and treat congenital CMV.

Conflict of interest

The author has no conflicts of interest to report.

Acknowledgment

I thank Dr. Stephanie Bialek for helpful comments.

References

Hearing Loss and Congenital CMV Infection: A Systematic Review

abstract

BACKGROUND AND OBJECTIVE: Hearing loss caused by congenital cytomegalovirus (cCMV) infection was first observed in 1964. Today cCMV is the most common cause of nonhereditary sensorineural hearing loss in childhood. Our objective was to provide an overview of the prevalence of cCMV-related hearing loss, to better define the nature of cCMV-associated hearing loss, and to investigate the importance of cCMV infection in hearing-impaired children.

METHODS: Two reviewers independently used Medline and manual searches of references from eligible studies and review articles to select cohort studies on children with cCMV infection with audiological follow-up and extracted data on population characteristics and hearing outcomes.

RESULTS: Thirty-seven studies were included: 10 population-based natural history studies, 14 longitudinal cohort studies, and 13 retrospective studies. The prevalence of cCMV in developed countries is 0.58% (95% confidence interval, 0.41–0.79). Among these newborns 12.6% (95% confidence interval, 10.2–16.5) will experience hearing loss: 1 out of 3 symptomatic children and 1 out of 10 asymptomatic children. Among symptomatic children, the majority have bilateral loss; among asymptomatic children, unilateral loss predominates. In both groups the hearing loss is mainly severe to profound. Hearing loss can have a delayed onset, and it is unstable, with fluctuations and progression. Among hearing-impaired children, cCMV is the causative agent in 10% to 20%. Despite strict selection criteria, some heterogeneity was found between selected studies.

CONCLUSIONS: This systematic review underscores the importance of cCMV as a cause of sensorineural hearing loss in childhood. Pediatrics 2014;134:972–982

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KEY WORDS cytomegalovirus, congenital infection, hearing, auditory, prevalence, symptomatic infection, systematic review

ABBREVIATIONS
cCMV—congenital cytomegalovirus
CI—confidence interval
DBS—dried blood spots
PCR—polymerase chain reaction
SNHL—sensorineural hearing loss
UNHS—universal neonatal hearing screening

Dr Goderis designed this review, performed the literature search, drafted the initial manuscript, and improved revised versions; Drs De Leenheer, Smets, Van Hoecke, and Keymeulen revised the analysis and interpretation of data and critically reviewed the manuscript; Dr Dhooge conceptualized this review, coordinated and supervised the process, approved the literature search and selection, and critically reviewed and revised the manuscript, and all authors approved the final manuscript as submitted.

doi:10.1542/peds.2014-1173

Accepted for publication Aug 27, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
The first article on hearing loss by congenital cytomegalovirus (cCMV) infection was published in 1964 by Medearis et al. Over the past 50 years, numerous studies explored the relationship between cCMV infection and hearing loss. Today cCMV is acknowledged as the most common nongenetic cause of childhood sensorineural hearing loss (SNHL) and an important cause of neurodevelopmental delay.

Worldwide, cCMV infection affects 0.2% to 2.5% of all live-born neonates. In industrialized countries, the average prevalence of cCMV infection is 0.64% to 0.70%. The incidence of cCMV infection is highest in developing countries, 1% to 5% of all live births, and is probably driven by nonprimary maternal infections. The prevalence of cCMV infection increases with increasing maternal CMV seroprevalence. Most European countries have a maternal CMV seroprevalence ranging from 40% to 60%. In developing countries it is >90%. Maternal seroprevalence depends on age, socioeconomic status, and parity. But between industrialized countries there are clear differences in prevalence, probably because of race-bound predilection in addition to differences in sexual behavior, day care attendance, breastfeeding, and profession. Spreading of CMV occurs through close contact with infected body fluids. Children aged 1 to 2 years are the most important source of infection for women of reproductive age.

In seropositive mothers, reactivation of a latent virus or reinfection with a new CMV strain can cause cCMV disease as well, with or without permanent sequelae. The risk of vertical transmission seems to be higher in primary infections than in nonprimary infections. In a meta-analysis, Kenneson and Cannon found rates of vertical transmission of 32% and 1.4% for primary and nonprimary infections, respectively. The rate of vertical transmission increases with older gestational age at infection, but there is a significantly higher risk of fetal anomalies and symptomatic disease when maternal infection occurs during the preconceptional and periconceptional period and during the first trimester of pregnancy. Approximately 10% to 15% of children with cCMV are symptomatic at birth. Outcomes for these infants are poor, and most survivors suffer from severe neurologic sequelae. The overall mortality rate is <5%. The majority of children with cCMV are asymptomatic and therefore not diagnosed at birth. However, 7% to 15% of clinically asymptomatic patients may develop late sequelae, including SNHL, which is far more common a sequel than SNHL.

Because the majority of children are asymptomatic at birth and because there is no systematic newborn screening, the impact of cCMV is ill defined. Population-based natural history studies that accurately estimate the prevalence of disease and morbidity burden are scarce, but the economic burden is estimated to be similar to that for congenital rubella before the introduction of vaccination. Because SNHL is the most common sequela of cCMV infection, it is a major contributor to disease burden. Reliable estimates of the hearing loss caused by cCMV are needed to increase vigilance among health care workers and the public.

Retrospective studies performed on a population of deaf children report frequencies of cCMV-related hearing loss ranging from 2% to 18%. However, it is assumed that the importance of asymptomatic cCMV as a cause of hearing loss may be higher than currently believed. This systematic review provides an overview of the prevalence of cCMV-related hearing loss based on the literature of the past 50 years and aims at better defining the nature of cCMV-associated hearing loss and the importance of cCMV among patients with childhood hearing loss.

METHODS
A systematic literature search was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The Medline database was searched for relevant articles published from inception to December 2013. In order to find all articles about hearing loss and cCMV infection, we used the following subject headings: congenital cytomegalovirus AND (hearing OR deafness OR auditory), combined with the results for perinatal cytomegalovirus AND (hearing OR deafness OR auditory) in all fields. This resulted in 476 citations, of which titles and abstracts were read by 2 reviewers independently. A manual search of reference lists of the retrieved articles resulted in 8 additional articles. Duplicates and non-English articles were excluded, because omission of non-English articles has been shown to have minimal impact on the results. Also, nonrelevant papers, defined as not focusing on the topic as indicated by the abstract, were excluded. A total of 101 articles were read in detail and narrowed to 37 relevant studies (Fig 1). Variable definitions of symptomatic cCMV are found in the literature. The most common definition of symptomatic disease is the presence of ≥1 of the following symptoms at birth: petechiae, jaundice with conjugated hyperbilirubinemia, hepatosplenomegaly, thrombocytopenia, chorioretinitis, seizures, microcephaly, and intracranial calcifications. Only studies that mentioned ≥3 of these symptoms were included. If there was no description or definition, studies were nevertheless included if there was a reference to an article with a similar definition. Diagnosis of cCMV had to be confirmed by virus isolation or polymerase chain reaction (PCR) of CMV in urine or saliva, collected within 3 weeks of birth to distinguish it from postnatally acquired infections.
Only articles with data from primary sources were included. In case of multiple reports from 1 research group, the most recent or the most detailed report was chosen. Methods for hearing evaluations were not standardized across the studies, nor were follow-up protocols. Only studies where transient middle ear pathology was excluded by otoscopy, admittance measurements, and absence of air–bone gap were included. Hearing loss includes both unilateral and bilateral SNHL, with thresholds $>20$ dB. Individual study quality was assessed through evaluation of study design, number of evaluations, length of follow-up, outcome measurement method, and reporting of confounding factors for hearing loss. Selected articles were divided according to 3 different approaches.

**Quantitative Approach**

To determine the prevalence of cCMV-associated hearing loss on a population level, we selected studies where cCMV infection was diagnosed through universal newborn screening for cCMV. The following articles were included: original peer-reviewed articles where screening for cCMV was done in all newborns during a given period and studies where the diagnosis of cCMV was made by virus isolation or PCR of CMV in urine or saliva, collected within 3 weeks of birth. Studies with cases identified by immunoglobulin M detection in blood samples were not included because such assays lack sensitivity. The use of the aforementioned definition of symptomatic cCMV was required. We were especially interested in studies with a longitudinal prospective design. Data on the number of symptomatic and asymptomatic patients and the associated hearing loss had to be available. Studies with children treated with ganciclovir or valganciclovir were excluded to determine the exact number of affected children in the natural course of infection.

**Qualitative Approach**

To determine the nature of cCMV-associated hearing loss, we selected cohort studies with a longitudinal audiological follow-up. Those studies include children detected by systematic cCMV screening or diagnosed because of known seroconversion of the mother, or children with clinical signs suggestive of the disease. We selected all studies that
conducted longitudinal testing in a group of ≥20 children with cCMV infection. The use of the aforementioned definition of symptomatic cCMV was mandatory. Children had to have ≥2 audiological evaluations during follow-up. In such studies an overrepresentation of symptomatic children is expected, so to stratify the results according to symptomatic or asymptomatic cCMV infection, we needed data on the number of symptomatic and asymptomatic patients and the associated hearing loss. Concerning the different characteristics of cCMV-related hearing loss, we used the studies with the most complete information on that specific parameter. An additional goal was to determine the relationship between primary and nonprimary (reactivation or reinfection) infection and hearing loss.

Retrospective Approach

A method for retrospective diagnosis of cCMV was introduced in 1994 by Shibata et al.53 They detected CMV DNA by means of PCR on neonatal dried blood spots (DBS). Since then several studies tested and adapted this method, with sensitivity ranging from 71% to 100% and specificities of 99% to 100%.54 A recent study found much lower sensitivities, near 34%, when DBS were used as screening test.55 However, it is the only way to detect a cCMV infection retrospectively. Detection of CMV DNA can vary depending on the method of DNA extraction from the cards, the amplification method, and the part of the CMV genome being detected.56–58 It may also be influenced by the time and conditions in which the cards have been stored. Cross-contamination of adjacent stored cards has been reported.54,58–61

To understand the importance of cCMV as a cause of childhood hearing loss, we reviewed studies that conducted retrospective testing in a group of hearing-impaired children. Requirements were testing by real-time PCR for quantitative analysis of CMV DNA on DBS or on dried umbilical cords. A distinction was made between studies that excluded other risk factors for hearing loss and those that did not.

Statistical Analysis

We performed a meta-analysis by using a random effects model of DerSimonian and Laird to calculate estimated proportions. R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to make calculations. For each inquiry a confidence interval (CI) was calculated and a forest plot was developed. \( P^2 \) is a measure of heterogeneity; it indicates the percentage of variance attributable to study heterogeneity rather than chance. The \( P \) value reflects the significance of the heterogeneity. The study was conducted in accordance with the instructions of the PRISMA statement for reporting systematic reviews and of the Meta-analysis of Observational Studies in Epidemiology group for reporting meta-analyses of observational studies.48,62

RESULTS

Quantitative Approach

Ten studies were selected according to the aforementioned protocol. An overview of the studies is shown in the Supplemental Information. We found an overall prevalence of cCMV infection of 0.58%. The proportions for symptomatic and asymptomatic infected children were 9.8% and 90.2%, respectively. Hearing loss occurred in 32.8% of symptomatic cases, compared with 9.9% of asymptomatic children. The overall rate of hearing loss in cCMV infection was 12.6%. The overall rate of hearing loss by cCMV infection in the population was estimated to be 0.5 in 1000 children. Table 1 includes an overview of the estimated proportions.

Qualitative Approach

Fourteen longitudinal cohort studies of children with cCMV infection that focused on hearing were included (Supplemental Information). In those studies, symptomatic children were overrepresented, so we stratified the results according to symptomatic or asymptomatic cCMV infection. In symptomatic cCMV infection hearing loss was bilateral in 71.2% and unilateral in 28.8% of cases. The majority of hearing loss was severe to profound, with 65.1% of bilateral hearing loss severe to profound, necessitating hearing amplification and rehabilitation. Of all symptomatic children with hearing loss, 18.1% had a delayed onset. Approximately 1 in 6 symptomatic children with hearing loss exhibited progressive hearing loss, and 1 in 5 symptomatic children with hearing loss experienced fluctuations. In the asymptomatic group, hearing loss was unilateral in 57%. The majority of hearing loss was also severe to profound, but the percentage of children with bilateral severe to profound hearing loss was less than in the symptomatic group. However, in 42.6% of the hearing-impaired asymptomatic children, hearing loss necessitated hearing amplification and rehabilitation. Of all asymptomatic children with hearing loss, 9% had a delayed onset. Approximately 1 in 5 asymptomatic children with hearing loss exhibited progressive hearing loss, and 1 in 4 asymptomatic children with hearing loss experienced fluctuations.

To evaluate the impact of maternal seroimmunity on hearing status, we selected 3 additional studies that reported the amount of hearing loss in relation to type of infection (primary or nonprimary). Hearing loss occurred in 12.1% of the primary infections and in 11.8% of the nonprimary infections. A summary of the qualitative approach is found in Tables 2 and 3.

Retrospective Approach

Thirteen studies were selected for a retrospective approach (Supplemental
Information). In the first analysis, all selected retrospective studies were included. In the next 2 analyses the distinction was made between studies that excluded children with other risk factors for hearing loss (eg, known hereditary and environmental causes) and studies that did not. In the group of hearing-impaired children the prevalence of cCMV-related hearing loss was ~8% (Table 4). In the group of hearing-impaired children with hearing loss from unknown origin where known risk factors for hearing loss were excluded, the prevalence of hearing loss by cCMV was ~20%.

Quality of Studies

The majority of studies included in the quantitative and qualitative approach had a prospective study design. The number of hearing evaluations in studies used in the quantitative approach was low in comparison to studies in the qualitative approach. Also, the follow-up was longer in the studies included in the qualitative approach. Methods of outcome measurement seemed not to differ greatly between the studies. Only a few studies reported other risk factors for hearing loss.

**DISCUSSION**

This systematic review estimates the prevalence and nature of the hearing loss attributable to cCMV infection, based on a meta-analysis of a number of selected articles. We found an overall prevalence of cCMV infection of 0.58% in industrialized countries. This is consistent with the 0.64% found in a previous meta-analysis by Kennerson and Cannon. Globally significant differences in epidemiology exist between and within countries. In developing nations with highly seropositive populations, prevalence ranges between 1% and 6%. This correlation is explained by the fact that cCMV birth prevalence increases with maternal seroprevalence. A high seroprevalence means that there are more pregnant women at risk for reactivation or reinfection next to a higher prevalence of risk behavior and a higher rate of exposure to CMV. The increased rate of nonprimary infections leads to a higher birth prevalence on population level, despite the lower risk of vertical transmission. The risk of symptomatic infection and permanent sequelae is higher among infants whose mothers experienced a primary infection, but disabilities have also been observed as a result of nonprimary infection. Percentages of newborns with symptomatic disease or long-term sequelae after nonprimary infection vary between 1% and 10%. Data are currently insufficient to estimate the exact proportion of cCMV-disabled children attributable to nonprimary infection.

The overall incidence of hearing loss in cCMV is 12.6%. One in 3 symptomatic children will experience loss, in comparison with 1 in 10 asymptomatic children. Extrapolation of these results to the population level shows that of every 10,000 children born each year, 5 will have cCMV-related hearing loss. In combination with birth rate statistics in Europe, this means that each year 2600 live-born children will experience immediate or delayed hearing impairment caused by cCMV. In the United States, the number is 1975 children per year. The results in the quantitative approach all have a strikingly high heterogeneity, which in most of the cases was significant. So despite our strict selection criteria, the results should be interpreted with caution. The majority of symptomatic children had bilateral hearing loss. In the asymptomatic group unilateral losses predominated. Presumably, a large number of unilateral hearing losses, often diagnosed at school age, are attributable to a missed asymptomatic cCMV infection. The challenge is to confirm the diagnosis
TABLE 3 Hearing Loss According to Type of Infection

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Estimated Proportion, %</th>
<th>95% CI</th>
<th>I², %</th>
<th>P of Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss in case of primary infection</td>
<td>12.1</td>
<td>8.6–16</td>
<td>18.8</td>
<td>.2814</td>
</tr>
<tr>
<td>Hearing loss in case of nonprimary infection</td>
<td>11.8</td>
<td>7.5–18.8</td>
<td>21.7</td>
<td>.2568</td>
</tr>
</tbody>
</table>

TABLE 4 Results of the Retrospective Approach

<table>
<thead>
<tr>
<th></th>
<th>Estimated Proportion, %</th>
<th>95% CI</th>
<th>I², %</th>
<th>P of Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss by cCMV among hearing impaired</td>
<td>10.4</td>
<td>8–13</td>
<td>54.1</td>
<td>.0103</td>
</tr>
<tr>
<td>Exclusion of other risk factors for hearing loss</td>
<td>19.8</td>
<td>14.6–25.7</td>
<td>0</td>
<td>.5601</td>
</tr>
<tr>
<td>No exclusion of other risk factors for hearing loss</td>
<td>8.2</td>
<td>6.5–10</td>
<td>0</td>
<td>.7938</td>
</tr>
</tbody>
</table>

retrospectively by PCR on DBS. In both groups, 3 in 4 children with hearing loss had a severe to profound hearing loss in ≥1 ear. In the symptomatic group 65% had a disabling bilateral severe to profound hearing loss with the need for hearing amplification and rehabilitation. In the asymptomatic group, 42.6% of hearing-impaired children had bilateral severe to profound hearing loss.

The hearing loss caused by cCMV infection has an exclusively sensorineural character. Its pathogenesis is poorly understood. Most studies describe injuries to endolymphatic structures and the stria vascularis that may cause potassium imbalance and subsequent degeneration of the sensory structures. Some authors attribute hearing loss to the cytopathic effect of the virus itself and the host immune response on inner ear structures. Regarding a possible delayed onset of hearing loss, percentages in the literature range from 0% to 50%. We calculated ~18% in the symptomatic group and ~9% in the asymptomatic group, but in both groups there was significant heterogeneity between studies. This was also the case for progression and fluctuation of hearing loss. Part of the heterogeneity in delayed onset probably results from the fact that the first studies of cCMV and hearing loss date from the period before the implementation of universal neonatal hearing screening (UNHS), so that the onset of hearing loss could not be determined exactly. Furthermore, in this population middle ear problems and testing difficulties are important confounders, despite the fact that we tried to control for these confounding factors when selecting articles. The mechanisms behind delayed onset, progression, and fluctuation have not been elucidated. Like other herpesviruses, CMV establishes latency after primary infection. It is hypothesized that viral reactivation and localized host inflammatory responses to reactivation might play a role.

Because of the high heterogeneity and low P values, the exact percentages for delayed onset, progression, and fluctuation are hard to define. It is important to inform the parents that hearing loss in cCMV can be delayed in onset and might progress and fluctuate over varying time frames. It is also important to realize that UNHS is not an absolute safeguard. This along with the unstable nature of the hearing loss makes longitudinal audiologic follow-up of children with cCMV infection mandatory. Delayed-onset hearing loss usually occurs before 6 years of age, mainly in the first year after birth, but hearing loss at older ages is reported occasionally. Most authors suggest follow-up until the age of 6 years. The risk of hearing loss does not vary between primary and nonprimary infections. Nonprimary infections usually result in an asymptomatic infection. The incidence of hearing loss in the nonprimary group therefore is comparable to the incidence of hearing loss in the asymptomatic group.

In our meta-analysis, we found a high I² for each parameter of hearing loss we investigated, despite strict selection criteria for the inclusion of articles. The high rate for I² indicates that most of the variability across studies results from heterogeneity rather than chance. Using strict eligibility criteria for studies selected, we tried to obtain high study quality and low heterogeneity, but some limitations exist. Baseline measurements were not always provided, and time points for collecting outcomes and method of measuring outcomes differed between studies. Most striking was the variability in defining symptomatic cCMV, the main indicator of permanent disabilities. A clear definition is crucial if we want to analyze and compare the results of different studies. The global study quality of selected studies was deemed to be moderate to good. With this systematic selection, the most appropriate articles to represent hearing outcomes in cCMV infection were included.

Regarding the importance of cCMV-related hearing loss in the total population of children with SNHL, we calculated that 1 in 10 hearing-impaired children has cCMV-related hearing loss. When known risk factors or causes of hearing loss are excluded, cCMV is the cause of hearing loss in 1 out of 5 children. Quantitative PCR assays have not been standardized across laboratories, which makes comparison of data from different studies difficult. When relying on a DBS test, we also have to consider that viral DNA levels are lower in peripheral neonatal blood than in urine or saliva. It is possible that viremia had not yet occurred at the time of sampling. Moreover, as mentioned earlier, length of storage of the DBS might decrease the apparent viral load. These factors might lead to
underestimation of the role of cCMV. Therefore, this retrospective approach suggests an important etiological role for cCMV in hearing loss in childhood.

We did not focus on risk factors for hearing loss in our systematic review. Much research has already been done on that subject, but it remains controversial. Symptomatic infection; disseminated disease, especially with petechiae and intrauterine growth retardation; and a high viral load at birth seem to be associated with hearing loss.\textsuperscript{75,106–107} Identification of risk factors might be helpful for a more directed and rigorous follow-up of infants at risk for hearing loss. Furthermore, it might decrease the number of dropouts in longitudinal follow-up of asymptomatic infants. Accurate prospective longitudinal studies would also help reveal the full spectrum of cCMV disease and identify such risk factors.

The absence of specific medical interventions for seronegative mothers and uncertainty about fetal prognosis has discouraged routine maternal antibody screening. To date, universal systematic screening of newborns for cCMV has not been implemented. Recent screening techniques such as PCR on urine, saliva, or blood are potentially simple, low-cost methods that could be used in future newborn screening programs.\textsuperscript{30,35,108} In our center an ongoing prospective study is comparing sensitivity and specificity between PCR on DBS and urine culture. At present urine or saliva culture, with or without PCR, remains the gold standard.

A systematic screening together with UNHS could identify the most suitable candidates for antiviral therapy. Currently, antiviral treatment with ganciclovir or valganciclovir is recommended only for symptomatic newborns with severe symptomatic focal organ disease or central nervous system involvement.\textsuperscript{109–112} The remainder could be enrolled in a longitudinal follow-up program to detect delayed-onset or progressive hearing loss and other developmental delays. Early detection of hearing loss leads to early intervention and better patient outcomes.\textsuperscript{113,114} Prevention strategies, such as CMV vaccination or passive immunization with hyperimmune globulin, are currently subjected to clinical trials but are not yet in clinical use. Preliminary results are promising, but currently there are insufficient data to support the use of prenatal interventions.\textsuperscript{115–117} Preconceptional seroimmunity provides only partial protection against newborn disease and adverse outcomes. Infected infants born to seroimmune mothers are not completely protected from SNHL, but their hearing loss is often milder and less frequently bilateral.\textsuperscript{4,25,28,29} Increasing awareness of cCMV infection and implementing behavioral measures such as frequent hand-washing after exposure to young children’s body fluids and avoiding intimate contact with young children for all prospective mothers remain the most important preventive strategies.

CONCLUSIONS

This systematic review confirms the important role of cCMV in childhood SNHL. However, because of the lack of systematic screening for cCMV in newborns and the characteristics of the disease, underestimation of its role in hearing loss is likely. Despite the threefold lower prevalence of hearing loss in asymptomatic cCMV, the numerous asymptomatic cases mean that this group is an important component of the group of hearing-impaired children. There is no pathognomonic configuration of hearing loss caused by cCMV. Rather, it is characterized by its unstable nature, with progression and fluctuations. Delayed-onset hearing loss is not uncommon. Long-term audiological follow-up for \( \geq 6 \) years is strongly recommended. Systematic screening could identify the most suitable candidates for therapy, and the remainder could be enrolled in a longitudinal follow-up program to detect delayed-onset hearing loss.

Until a CMV vaccine becomes available, behavioral and educational interventions are the most effective strategy to prevent maternal CMV infection.\textsuperscript{118–120} The high incidence and the devastating morbidity associated with cCMV emphasize the importance of preventive measures and of clinical research on prenatal and postnatal interventions. There is still a lot of work to do, but with this systematic review we hope to increase awareness of the cCMV disease burden.

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preventing the transmission of cytomegalovirus (CMV) from the mother to fetus during pregnancy and adverse outcomes in the congenitally infected infant. Cochrane Database Syst Rev. 2011;(3):CD008371


**HIDE AND SEEK:** When the kids were little, we used to play hide and seek all the time. There were innumerable hiding places around the house and yard, and we always had a great time. In the oceans, hide and seek has a different and much more serious context. Fish are hiding from other fish; if found, they are often eaten. Fish in coastal waters try to avoid this by using camouflage, blending into sand, rocks, and plants, or hiding among coral and kelp. However, in the middle of the ocean, there are no places to hide. Fish in these areas (particularly small fish) have to hide in plain sight.

As reported in The New York Times (Science: August 19, 2014), some fish living in the middle of the ocean have evolved clever ways to go unseen. Their bodies have a density and refraction index that is so similar to their watery environment that light actually passes through them, making them almost invisible. One problem with this transparency is that there is no protection from the sun, which can not only burn the external structures but internal organs as well. Secretions—similar to suntan lotions—protect them from the sun, but then they are no longer invisible to predators that can detect ultraviolet light.

Terrestrial animals, of course, are unlikely to ever become transparent because they are so much denser than air and have a significantly different refraction index. As for me, I have no reason to become invisible. I want my family to be able to find me when I am home and I don’t believe there are predators in my neighborhood that are trying to dine on me.

Noted by WVR, MD
Hearing Loss and Congenital CMV Infection: A Systematic Review
Julie Goderis, Els De Leenheer, Koenraad Smets, Helen Van Hoecke, Annelies Keymeulen and Ingeborg Dhooge
Pediatrics 2014;134;972
DOI: 10.1542/peds.2014-1173 originally published online October 27, 2014;

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including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/134/5/972

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Data Supplement at:
http://pediatrics.aappublications.org/content/suppl/2014/10/21/peds.2014-1173.DCSupplemental
A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening

Karen B. Fowler, DrPH,a Faye P. McCollister, EdD,b Diane L. Sabo, PhD,c Angela G. Shoup, PhD,d Kris E. Owen, AuD,e Julie L. Woodruff, AuD,f Edith Cox, AuD,f Lisa S. Mohamed, AuD,f Daniel I. Choo, MD,g Suresh B. Boppana, MD,h on behalf of the CHIMES Study

abstract

BACKGROUND AND OBJECTIVE: Congenital cytomegalovirus (cCMV) infection remains a leading cause of childhood hearing loss. Currently universal CMV screening at birth does not exist in the United States. An alternative approach could be testing infants who do not pass their newborn hearing screening (NHS) for cCMV. This study was undertaken to evaluate whether a targeted approach will identify infants with CMV-related sensorineural hearing loss (SNHL).

METHODS: Infants born at 7 US medical centers received NHS and were also screened for cCMV while in the newborn nursery. Infants who tested positive for CMV received further diagnostic audiologic evaluations to identify or confirm hearing loss.

RESULTS: Between 2007 and 2012, 99,945 newborns were screened for both hearing impairment and cCMV. Overall, 7.0% of CMV-positive infants did not pass NHS compared with 0.9% of CMV-negative infants (P < .0001). Among the cCMV infants who failed NHS, diagnostic testing confirmed that 65% had SNHL. In addition, 3.6% of CMV-infected infants who passed their NHS had SNHL confirmed by further evaluation during early infancy. NHS in this cohort identified 57% of all CMV-related SNHL that occurred in the neonatal period.

CONCLUSIONS: A targeted CMV approach that tests newborns who fail their NHS identified the majority of infants with CMV-related SNHL at birth. However, 43% of the infants with CMV-related SNHL in the neonatal period and cCMV infants who are at risk for late onset SNHL were not identified by NHS.

WHAT’S KNOWN ON THIS SUBJECT: Congenital cytomegalovirus (CMV) infection is a leading cause of childhood hearing loss. Although CMV saliva screening of newborns for CMV identifies infected infants for monitoring and early intervention, routine CMV screening does not occur in the United States.

WHAT THIS STUDY ADDS: A targeted CMV testing approach identifies infants with CMV-related hearing loss at birth. However, 43% of the infants with CMV-related hearing loss and congenital CMV infants who are at risk for late onset hearing loss will not be identified.

Congenital cytomegalovirus (cCMV) infection is found worldwide and contributes to thousands of children each year being born with or developing permanent disability such as hearing loss, vision loss, cerebral palsy, cognitive impairment, and developmental delay. In the United States, Canada, Western Europe, and Australia, cCMV is estimated to occur in ~0.5% to 0.7% of all live births. In other parts of the world, such as Latin America, Africa, and most countries in Asia, cCMV rates are even higher at ~1% to 2% of all births. Approximately 10% of infants with cCMV will have clinical findings at birth (symptomatic infection). The vast majority of infected infants (~90%), however, will have no clinical manifestations present during the newborn period (asymptomatic infection). Approximately 40% to 60% of symptomatic infants will manifest permanent sequelae, with sensorineural hearing loss (SNHL) being the most common, followed by cognitive impairment, retinitis, and cerebral palsy. Asymptomatic infants are also at risk for CMV-related disabilities, and ~10% to 15% of asymptomatic infants will develop SNHL. Disabilities from symptomatic and asymptomatic cCMV infection are more common in children in the United States than other more recognized diseases such as Down syndrome, fetal alcohol syndrome, or spina bifida.

cCMV infection significantly contributes to permanent childhood hearing loss, with CMV-related SNHL being second only to genetic causes both at birth and during the early years of life. SNHL after cCMV may be present at birth or occur later in childhood (late onset). Children with SNHL after cCMV may also have further worsening or progression of their losses.

Although CMV is a leading cause of SNHL in children and is more common than any of the other screened newborn conditions in the United States, routine newborn CMV screening does not occur in the United States. Limited CMV awareness by both providers and parents, the difficulty in confirming the diagnosis of cCMV after the newborn period, the inability to predict which children with cCMV will have sequelae, the lack of effective treatments to prevent or ameliorate the effects of the virus, and the absence of an inexpensive and rapid screening test have been some of the obstacles preventing the implementation of widespread CMV screening in the past. Recent advances in the development of a rapid, high-throughput method for detecting CMV in saliva, success with antiviral treatment in symptomatic infants, and the recognition that early identification for targeted monitoring and intervention during critical stages of speech and language acquisition improves outcomes have led to renewed interest in both targeted and universal approaches to screening newborns for cCMV.

As part of the CMV and Hearing Multicenter Screening (CHIMES) study, ~100 000 infants were tested for CMV and received a newborn hearing screening (NHS) while in the hospital nursery, thus allowing us to examine the effectiveness of a targeted approach in identifying infants with CMV-related hearing loss where only newborns who did not pass NHS would be tested for cCMV.

**METHODS**

**Study Population**

Between March 2007 and March 2012, 100 607 infants were born at 7 US medical centers (University of Alabama at Birmingham Hospital, Birmingham, AL; The University of Mississippi Medical Center, Jackson, MS; Saint Peter’s University Hospital, New Brunswick, NJ; Carolinas Medical Center, Charlotte, NC; Good Samaritan Hospital, Cincinnati, OH; Magee Womens Hospital, Pittsburgh, PA; and Parkland Memorial Hospital, Dallas, TX) were consented and enrolled prospectively in the CHIMES Study. All live-born infants were eligible for participation. Mothers were approached postpartum to obtain written informed consent for their infant’s enrollment in the study. Upon enrollment, saliva specimens were collected from the newborn and additional dried blood spots were obtained at the time of routine newborn metabolic screening and tested for CMV as previously described. Infants with positive saliva or dried blood spots screening specimens were enrolled in the follow-up component of the study to confirm cCMV and to monitor their hearing outcome. Newborn medical records were reviewed for infants with cCMV to determine if the infants had clinically apparent disease. An a priori definition of symptomatic cCMV was established at the beginning of the CHIMES study by study investigators. Infants were considered to have symptomatic cCMV if they had any of the following symptoms in the newborn period: generalized petechial rash, purpuric rash, hepatomegaly, splenomegaly, jaundice with direct bilirubin of 3 mg/dL or greater, unexplained neurologic/CNS abnormalities (eg, microcephaly, seizures, focal or generalized neurologic deficits), or chorioretinitis. Clinical decisions about further evaluations and possible treatment of the CMV-infected infants were made by the physicians at each study site. The CHIMES study did not include treatment of cCMV infants. Local institutional review board approval was obtained at each site.

**NHS**

NHS results and any additional outpatient hearing screens or diagnostic follow-up audiologic testing results were collected from
the individual hospital’s audiology program for each infant enrolled in the study. Each study site followed the NHS protocol designed for their hospital. Most of the hospitals used a 2-stage protocol where infants who did not pass in the hospital were scheduled for an additional outpatient hearing screen, and infants not passing their outpatient hearing screen were scheduled for a follow-up diagnostic audiologic evaluation. Infants with cCMV, regardless of hearing screen status, received a diagnostic audiologic assessment at 3 to 8 weeks of age as part of the CHIMES study. The CHIMES study diagnostic audiology protocol included a tone burst Auditory Brainstem Response with thresholds at 0.5, 1.0, 2.0, and 4.0 kHz and Distortion Product Otoacoustic Emissions for each ear. Bone conduction, tympanometry, and ipsilateral acoustic reflexes were performed with a 1000-Hz probe tone if hearing loss was suspected. CMV-negative infants who referred (ie, did not pass) on NHS were audiologically managed per their hospital’s and state’s recommendations for a diagnostic audiologic assessment by 3 months of age for the identification of possible hearing loss in the infants.21 CMV-negative infants did not receive their audiological assessments as part of the CHIMES study.

**Statistical Analysis**

All statistical analyses were performed by using SAS software, version 9.3 (SAS Institute, Inc, Cary, NC).

The results of CMV screening were compared with the newborn hearing results. Binomial 95% confidence intervals (CIs) were calculated for point estimates. Statistical significance was determined by using a 2-tailed \( \chi^2 \) or Fisher’s exact test with a 5% level of significance, where appropriate.

**RESULTS**

Of the 100 332 enrolled infants with a CMV test result, 99 945 (99.6%) had an NHS result (Fig 1). Reasons for not having NHS results included the following: hearing screen not completed before discharge from the nursery; infant death; or parental refusal. Of the 6 CMV-positive infants who did not complete their hearing screen, 3 not passing their hearing screen.

Of the 31 (7%) CMV-positive infants who did not pass NHS, 20 (65%) were confirmed to have SNHL by diagnostic audiologic evaluations. The other 11 (35%) who failed NHS were confirmed to have normal hearing by diagnostic evaluation. An additional 15 (3.6%) CMV-positive infants who passed NHS had SNHL confirmed by a diagnostic hearing evaluation in the first 3 to 8 weeks of life.
the hearing loss in cCMV infants is seen in Table 3. Those infants who failed NHS were more likely diagnosed with bilateral loss (60%) and also were diagnosed with at least moderate hearing loss (65%). Of the 15 CMV-positive infants who passed their hearing screen but were diagnosed with SNHL during infancy, 9 (60%) had mild loss and 4 of these 9 infants had bilateral loss. The other 6 (40%) of 15 infants were diagnosed with at least a moderate to severe SNHL and 3 of these 6 infants had bilateral loss. None of the 31 CMV-positive infants who failed NHS nor the 15 additional infants who had SNHL were diagnosed as having syndromes or other malformations associated with hearing loss, or had a family history of hearing loss.

Overall, NHS identified 20/35 (57%, 95% CI, 39%–74%) infants who had CMV-related SNHL in the newborn period leaving 43% not identified with hearing loss. In asymptomatic infants, NHS identified only 9/19 (47%, 95% CI, 24%–71%) of the CMV-related SNHL in these infants, missing 53% with hearing loss. Among symptomatic infants, NHS identified CMV-related hearing loss in 11/16 (69%, 95% CI, 41%–89%) infants.

CMV-positive infants with SNHL identified by NHS and those who passed their hearing screen but had SNHL in the neonatal period comprised 7.9% (95% CI, 5.6%–10.8%) of all infants with cCMV. As expected when infants were categorized by the presence of clinical findings at birth, those with symptomatic infection had a significantly higher rate of hearing loss than those with asymptomatic cCMV at birth. SNHL occurred in 38.1% (95% CI, 23.6%–54.4%) of the symptomatic infants compared with 4.7% (95% CI, 2.9%–7.3%) of the asymptomatic infants (P < .0001).

### TABLE 1
Study Characteristics for the 98945 Newborns Who Underwent NHS and CMV Testing at the 7 Sites

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant sex</td>
<td></td>
</tr>
<tr>
<td>Girl</td>
<td>49.2 (49 160)</td>
</tr>
<tr>
<td>Boy</td>
<td>50.8 (50 784)</td>
</tr>
<tr>
<td>Infant race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4.1 (4160)</td>
</tr>
<tr>
<td>Black</td>
<td>24.0 (23 948)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>32.3 (32 269)</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>37.1 (37 048)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>2.5 (2527)</td>
</tr>
<tr>
<td>Insurance status for hospital stay</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>35.2 (35 156)</td>
</tr>
<tr>
<td>Public or no insurance</td>
<td>64.8 (64 783)</td>
</tr>
<tr>
<td>Maternal age, mean (SD), y</td>
<td>27.4 (6 1)</td>
</tr>
<tr>
<td>Hospital site</td>
<td></td>
</tr>
<tr>
<td>Birmingham, Alabama</td>
<td>12.0 (12 015)</td>
</tr>
<tr>
<td>Jackson, Mississippi</td>
<td>6.3 (6 346)</td>
</tr>
<tr>
<td>New Brunswick, New Jersey</td>
<td>10.7 (10 706)</td>
</tr>
<tr>
<td>Charlotte, North Carolina</td>
<td>15.1 (15 081)</td>
</tr>
<tr>
<td>Cincinnati, Ohio</td>
<td>14.1 (14 071)</td>
</tr>
<tr>
<td>Pittsburgh, Pennsylvania</td>
<td>19.1 (19 103)</td>
</tr>
<tr>
<td>Dallas, Texas</td>
<td>22.6 (22 923)</td>
</tr>
<tr>
<td>Hospital nursery</td>
<td></td>
</tr>
<tr>
<td>Well-infant</td>
<td>96.5 (96 735)</td>
</tr>
<tr>
<td>NICU</td>
<td>3.5 (3209)</td>
</tr>
</tbody>
</table>

### TABLE 2
Newborn Hearing Screen Referral Rates for Infants by CMV Status, Overall and by Nursery

<table>
<thead>
<tr>
<th>CMV Screen</th>
<th>No. Screened</th>
<th>No. Referred</th>
<th>Hearing Screen Referral Rates, % (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV positive</td>
<td>443</td>
<td>31</td>
<td>7.0% (4.8%–9.8%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CMV negative</td>
<td>99 502</td>
<td>930</td>
<td>0.9% (0.8%–1.0%)</td>
<td></td>
</tr>
<tr>
<td>Well-Infant Nursery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV positive</td>
<td>400</td>
<td>22</td>
<td>5.5% (3.5%–8.2%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CMV negative</td>
<td>96 336</td>
<td>768</td>
<td>0.8% (0.7%–0.9%)</td>
<td></td>
</tr>
<tr>
<td>NICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV positive</td>
<td>43</td>
<td>9</td>
<td>20.9% (10.0%–36.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CMV negative</td>
<td>31 68</td>
<td>162</td>
<td>5.1% (4.4%–5.9%)</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3
SNHL Severity by Newborn Hearing Screen Status for Infants With cCMV Infection

<table>
<thead>
<tr>
<th>Did Not Pass Hearing Screen, No. (%)</th>
<th>Passed Hearing Screen, No. (%)</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral loss</td>
<td>8 (40)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Bilateral loss</td>
<td>12 (60)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Mild loss (21–40 dB HL)</td>
<td>7 (35)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Moderate or greater loss (&gt;40 dB HL)</td>
<td>13 (65)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Total SNHL</td>
<td>20 (57)</td>
<td>15 (43)</td>
</tr>
</tbody>
</table>
DISCUSSION

Our large study of almost 100,000 infants revealed that a targeted CMV screening approach that only tests newborns who do not pass NHS identified the majority of infants with CMV-related SNHL at birth. However, this approach failed to identify a significant number of infants with CMV-related SNHL (43%) during infancy. Among infants with asymptomatic cCMV, 53% of those with CMV-related SNHL at birth will not be identified by a targeted approach. In addition, only testing infants who failed their hearing screen will miss the CMV-positive infants who are without symptoms at birth, pass NHS, and who go on to develop late onset hearing loss. A previous retrospective study in Texas revealed 6% of hearing impairment in newborns was attributable to CMV when they used a targeted CMV screening approach.23 Another study in Italy revealed that 10% of infants with SNHL detected <2 months of age had CMV infection.24 Although these studies indicated that testing infants who fail NHS for CMV could identify CMV-related SNHL, both studies were retrospective and did not include CMV screening of all infants. Our study included both CMV and hearing screening of all infants and provides reliable estimates of the effectiveness of a targeted CMV screening approach in identifying infants with CMV-related SNHL.

An important finding of our study is that newborns with cCMV have a significantly higher NHS referral rate (7%) than CMV-negative infants. These results indicate that newborns who do not pass their hearing screen and have no other known etiology for their possible hearing loss should be screened for CMV infection. In fact, existing clinical guidelines from the 2007 Statement by the Joint Committee on Infant Hearing recommend that infants with confirmed hearing loss and an uncertain etiology after an initial medical evaluation should have an expanded multidisciplinary evaluation protocol that includes testing for CMV.21 However, by the time permanent hearing loss is confirmed by the diagnostic audiologic evaluation and the initial medical evaluation is completed, it will be too late to confirm cCMV. Testing of infants who refer on NHS for CMV by saliva or urine polymerase chain reaction before hospital discharge or by 2 to 3 weeks of age by the pediatric medical home provider will provide confirmation of CMV as the cause of any suspected congenital hearing loss. After 3 weeks of age, cCMV cannot be reliably diagnosed as the etiology for infants with SNHL.

NHS programs have been successful in identifying congenital hearing loss but do have some limitations because of the sensitivity and specificity of hearing screen tools and testing protocols.23 In many programs, the majority of infants who fail NHS will not have permanent hearing loss.26, 27 Although it would be expected that more infants with cCMV who failed their hearing screen would have permanent loss, our finding that 64% of the infants had SNHL was a higher confirmation rate than expected on the basis of other studies.26,27

It is unclear why 43% of all CMV-positive infants and 53% of asymptomatic cCMV infants passed NHS but were confirmed to have CMV-related SNHL in the newborn period. A previous multicenter study estimated that ~23% of infants who passed a 2-stage hospital screening protocol had permanent hearing loss at 9 months of age; however, it is estimated that their protocol missed up to 70% of all cases of mild unilateral and bilateral hearing loss.28,29 At another center, one-third of the pediatric cochlear implant population had previously passed NHS.30 The percentage of CMV-positive infants with SNHL who passed their hearing screen was higher than these previously reported studies. It is possible that some of the infants who passed NHS but were confirmed to have SNHL were missed because of limitations of the NHS algorithms that were unable to reliably detect mild or isolated frequency region hearing losses. However, this does not explain the infants who had moderate to severe hearing loss identified on their diagnostic evaluation. It is also possible that the hearing loss occurred after the first week after birth or progressed to a measurable level by 6 to 8 weeks after birth. However, this is speculative and no previous data exist to suggest that CMV-related hearing loss is unstable in the neonatal period.

In addition to the fact that NHS failed to detect 43% of CMV-positive infants who had SNHL in the newborn period, the progressive nature of CMV-related hearing loss in ~50% of children with SNHL underscores the limitations of the targeted CMV screening approach.12,13 The rate of hearing loss progression in cCMV infection seems to be similar regardless of whether a child has an asymptomatic or a symptomatic infection, although the symptomatic infants have a greater degree of severity and also earlier progression of their hearing loss.12 With current pediatric newborn screening practices, CMV-positive infants who pass NHS but have CMV-related SNHL, whether stable or progressive loss, will be missed by any targeted screening program and otherwise will remain unidentified because routine CMV screening does not occur.

There are limitations in our study in that although all live-born infants were eligible to participate at the hospitals not all were enrolled in the study. Infants who were in the NICU were less likely to be approached by study staff because of the fragility of the infant and to not place any additional burdens on their families.
Infants who were discharged early or who were delivered on weekends or evenings may have been missed if study personnel were not available to obtain consent. It is possible that we missed cCMV infants, especially asymptomatic infants, and underestimated the rate of cCMV infection for our hospital sites. Our study revealed a 0.4% cCMV rate that is lower than some previously reported studies, although not lower for other large studies of cCMV. However, the lower cCMV rate should not impact the observed difference in the hearing referral rates between CMV-positive and CMV-negative infants, because there is no evidence to suggest the missed cCMV infants would have had a different hearing referral rate than those infants diagnosed. Also, the rates of CMV-related SNHL in the study were similar to previous reports, so it is not likely that the study missed a significant number of CMV-positive infants at the sites.

Targeted CMV screening will minimize the diagnostic etiology odyssey for some of the infants with suspected hearing loss because cCMV can only be reliably diagnosed within the first few weeks after birth. Also, infants identified with CMV-related hearing loss through targeted screening will have the opportunity for more focused audiologic monitoring, early intervention, and antiviral treatment. However, the limitations of a targeted CMV screening approach are the failure to identify all CMV-related SNHL in the newborn period and missing the cCMV infants who pass NHS but are at risk for late onset hearing loss.

CONCLUSIONS
A targeted CMV screening approach does identify the majority of infants with CMV-related SNHL in the newborn period. However, this method fails to identify a significant number of infants with CMV-related SNHL during infancy highlighting the need to develop approaches to improve detection of CMV-related hearing loss at birth. Strategies to identify all infants with cCMV who remain at risk for late onset and progressive hearing losses are needed.

ACKNOWLEDGMENTS
We are indebted to our medical, nursing, and audiology colleagues, and the infants and their parents who agreed to take part in this study.

ABBREVIATIONS
cCMV: congenital cytomegalovirus
CHIMES: CMV and Hearing Multicenter Screening
CI: confidence interval
CMV: cytomegalovirus
NHS: newborn hearing screening
SNHL: sensorineural hearing loss

REFERENCES


A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening
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Pediatrics; originally published online January 3, 2017; DOI: 10.1542/peds.2016-2128

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/content/early/2017/01/02/peds.2016-2128.full.html
Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?†

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SUMMARY

Congenital CMV infection is a leading cause of childhood disability. Many children born with congenital CMV infection are asymptomatic or have nonspecific symptoms and therefore are typically not diagnosed. A strategy of newborn CMV screening could allow for early detection and intervention to improve clinical outcomes. Interventions might include antiviral drugs or nonpharmaceutical therapies such as speech-language therapy or cochlear implants. Using published data from developed countries, we analyzed existing evidence of potential benefit that could result from newborn CMV screening. We first estimated the numbers of children with the most important CMV-related disabilities (i.e. hearing loss, cognitive deficit, and vision impairment), including the age at which the disabilities occur. Then, for each of the disabilities, we examined the existing evidence for the effectiveness of various interventions. We concluded that there is good evidence of potential benefit from nonpharmaceutical interventions for children with delayed hearing loss that occurs by 9 months of age. Similarly, we concluded that there is fair evidence of potential benefit from antiviral therapy for children with hearing loss at birth and from nonpharmaceutical interventions for children with delayed hearing loss occurring between 9 and 24 months of age and for children with CMV-related cognitive deficits. We found poor evidence of potential benefit for children with delayed hearing loss occurring after 24 months of age and for children with vision impairment. Overall, we estimated that in the United States, several thousand children with congenital CMV could benefit each year from newborn CMV screening, early detection, and interventions. Copyright © 2014 John Wiley & Sons, Ltd.

INTRODUCTION

Congenital CMV is an important public health problem in pediatric populations (Table 1) [1]. It is a leading cause of childhood hearing loss, cognitive deficit, and vision impairment [2,3]. The number of children with congenital CMV-related disabilities is similar to or greater than the number with better-known conditions such as Down syndrome or spina bifida [4].

The economic burden caused by congenital CMV is substantial, as many affected children require significant ongoing care and special therapeutic and educational services [5]. This has led to calls for improved strategies to reduce the burden of congenital CMV [6–8], including earlier identification through maternal or newborn screening [9–11], vaccines [12,13], behavioral interventions [1,14–16], treatment for infected pregnant women [17,18], and treatment of affected infants [19–21]. The objective of this article is to address the strategy of newborn CMV screening in developed countries, reviewing the existing evidence for potential benefit.

Diagnosis and classification of congenital CMV

Diagnosis of congenital CMV infection based on clinical signs or symptoms alone is not definitive.

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†The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations used
NAT, nucleic acid testing; DBS, dried blood spots; RCT, randomized controlled trial.
Rather, a definitive diagnosis requires the detection in urine, saliva, or blood of CMV via viral culture or of CMV DNA via nucleic acid testing (NAT) within the first 2–3 weeks after birth [22,23]. Detection of CMV after this age could be due to postnatal infection, which has not been associated with birth defects or developmental disabilities [24]. Therefore, if hearing loss or cognitive deficit becomes apparent at a later age, a post hoc diagnosis of congenital CMV infection generally cannot be made.

Children with congenital CMV infection may be symptomatic or asymptomatic at birth. The diagnostic criteria and definition of symptomatic congenital CMV infection vary in the literature despite attempts at standardization [25], partly because the clinical signs and symptoms (e.g. small for gestational age, petechiae, hemolytic anemia, splenomegaly, hepatomegaly, jaundice, pneumonia, microcephaly, and seizures) are not pathognomonic for congenital CMV infection and have significant variability ranging from minimal damage to fetal death [26]. For the purposes of this article, we classify children as symptomatic if they have acute symptoms present at birth. We also describe children who have CNS sequelae according to those clinical sequelae at their appearance, but we classify them as symptomatic or asymptomatic depending on the presence or absence of acute symptoms at birth. Literature definitions of symptomatic congenital CMV frequently include many children whose symptoms are sufficiently nonspecific that they generally do not prompt the physician to order a CMV test that could lead to a diagnosis of congenital CMV infection. Therefore, in the absence of universal newborn CMV screening, not only asymptomatic infections but also many symptomatic infections go undiagnosed [3].

Newborn CMV screening

Whether screening for a given condition should become an established health practice requires weighing the benefits versus the harms and is usually determined on the basis of a number of criteria, such as those described by Wilson and Jungner, and others [27–29]. Congenital CMV infection already meets many screening criteria. For example, it is an important public health problem [1] whose incidence is similar to the combined incidence of all metabolic or endocrine disorders in the current US core screening panel [9,30]; there is a presymptomatic or early symptomatic stage [31]; the test would generally be acceptable to the population [32], and much is known of the natural

Table 1. Estimates of children with congenital CMV-related disability: examples from Australia, England and Wales, and the United States

<table>
<thead>
<tr>
<th>Annual number of:</th>
<th>Australia (population ~22 million)</th>
<th>England and Wales (Population ~50 million)</th>
<th>United States (Population ~307 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>296,600^c</td>
<td>709,000^d</td>
<td>4,248,000^e</td>
</tr>
<tr>
<td>Congenital CMV infections (0.6%)^a</td>
<td>1,780</td>
<td>4,254</td>
<td>25,488</td>
</tr>
<tr>
<td>Symptomatic at birth (12.8%)^a</td>
<td>228</td>
<td>544</td>
<td>3,262</td>
</tr>
<tr>
<td>Symptomatic at birth who have or develop disability (50%)^b</td>
<td>114</td>
<td>272</td>
<td>1,631</td>
</tr>
<tr>
<td>Asymptomatic at birth (87.2%)^a</td>
<td>1,552</td>
<td>3,710</td>
<td>22,226</td>
</tr>
<tr>
<td>Asymptomatic at birth who have or develop disability (13.5%)^b</td>
<td>210</td>
<td>501</td>
<td>3,001</td>
</tr>
<tr>
<td>Total with congenital CMV-related disabilities</td>
<td>324</td>
<td>773</td>
<td>4,632</td>
</tr>
</tbody>
</table>

^a From Dollard et al. [46].
^b From Martin et al. [106].
^c From Australia census.
^d From Office for National Statistics [105].

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DOI: 10.1002/rmv
Newborn CMV screening evidence of benefits

history of the condition [22]. Furthermore, there is reason to believe that suitable screening technology, such as CMV DNA testing from dried blood spots (DBS), saliva, or urine, will be available soon [33–38]. On the other hand, potential harms may include increased parental stress or altered parent–child relationships from a false positive or true positive screening result (approximately three fourths of truly positive children never develop sequelae) [39], inappropriate antiviral treatment, or added costs from unnecessary medical visits or tests [40]. One criterion that merits greater examination, however, is whether screening can lead to beneficial interventions.

Potential benefits of newborn CMV screening

Congenital CMV would be atypical as a newborn screening condition, in that making a definitive diagnosis requires testing during the newborn period and cannot generally be accomplished at a later age. The exception is when stored biological specimens from the newborn period, such as DBS, are available for testing at a later time. However, such specimens are often stored for a limited period under less-than-ideal conditions, and accessing them has unresolved ethical difficulties in some populations [41]. Therefore, a key benefit of newborn CMV screening is that it could ensure a definitive diagnosis, which otherwise would be precluded for the majority of infected children.

Several immediate benefits may then follow. A diagnostic odyssey [42–44] could be avoided for children with congenital CMV infection who are born with nonspecific symptoms or who are asymptomatic at birth but who subsequently develop disabilities, preventing some of the difficulties introduced by multiple tests that may have limited diagnostic utility [45] (Box 1). Substantial cost savings could be created by avoiding unnecessary diagnostic tests, hospital admissions, and therapies that might otherwise occur in the quest to diagnose other diseases. Parents would have more confidence that symptoms were not the result of genetic causes, clarifying the child’s prognosis and the parents’ future reproductive decision-making. Furthermore, a definitive diagnosis of congenital CMV infection could reduce the considerable stress and anxiety caused by an uncertain diagnosis [44]. Conversely, it is possible that additional diagnostic tests, particularly of the CNS, will be undertaken in some CMV-infected infants who ultimately do not have neurological disease at birth. We have not included this in the analysis as the costs and benefits of such investigation cannot be easily quantified, while acknowledging that this will occur in some infants who have congenital CMV infection but no clinical disease.

Box 1. Case example of diagnostic odyssey

Ms. SI was born preterm (34 weeks gestation), with weight <10th centile, and breast-fed normally, with normal neonatal hearing screening. She attained her developmental milestones until 4 months of age when she presented in winter with severe, bilateral pneumonitis, and minor hepatosplenomegaly. She was admitted via emergency to intensive care (CICU), was ventilated, and treated with antibiotics for community acquired pneumonia and oseltamivir for possible influenza. The diagnosis was made from chlamydia IgM seropositivity and possible influenza from single high titer serology. Her respiratory status improved over the 8-day CICU and ward admission, and she was discharged 2 weeks following admission. At home, Ms. SI was feeding poorly, and failed to gain weight, with continuing minor hepatosplenomegaly and occasional lack of response to some auditory stimuli. She was readmitted at 5 months of age with deteriorating respiratory status, required continuous positive airway pressure support, and investigations showed chlamydia IgG+/IgM+, mycoplasma IgM+, and nucleic acid tests (NAT) negative for influenza A/B, RSV, parainfluenza 1/2/3, and adenovirus; she was restarted on antibiotics. Over the following week, she required intubation and ventilation by high frequency oscillation. She developed bilateral pneumothoraces requiring intercostal drainage and intravenous support via subclavian lines. Additional testing demonstrated CMV NAT positivity on bronchial washings and CMV IgG+/IgM+. She received intravenous ganciclovir for a total of 6 weeks and CMV immunoglobulin on two occasions. Ms. SI’s Guthrie (neonatal blood screening) card was CMV NAT positive, diagnostic of congenital CMV. The lack of initial diagnosis of CMV pneumonitis resulted in inappropriate antibiotic therapy; missed opportunities for early antiviral therapy;

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DOI: 10.1002/rmv
in this review, we assessed the benefits for which there are more existing data. Specifically, we focused our attention on benefits that directly impact the child’s health and typically are excluded from assessments of the value of newborn screening for other conditions. As a result, we assessed the benefits that might accrue from early detection and intervention for children who are asymptomatic at birth or whose nonspecific symptoms do not lead to a CMV test and definitive diagnosis. Possible interventions might include antiviral drugs or nonpharmaceutical therapies such as speech-language therapy, occupational therapy, physical therapy, cochlear implants, and/or special education services.

METHODS

We categorized measurable potential benefits according to the most common disabilities associated with congenital CMV infection: hearing loss, cognitive deficit (defined as in Dollard et al. [46] as intellectual disability or developmental delay), and vision impairment. For each disability, we evaluated the evidence of benefit for early detection and intervention with nonpharmaceutical interventions or pharmaceutical treatments. For the former, studies have not specifically measured outcomes in children known to have congenital CMV infection but have measured outcomes in children with disabilities that can be caused by congenital CMV infection.

Parameters and assumptions

The parameters we estimated are shown in Table 2. We used these parameters to compute the numbers of children with disabilities in Figures 1–3. Rather than reinvent the wheel, we based many of the parameter estimates on a recent comprehensive literature review by Dollard et al. [46], which used systematic search criteria and explicit inclusion/exclusion criteria. In particular, studies were only included if their populations had been identified through universal screening at birth (i.e. no patients referred to the study because of symptomatic congenital CMV), if they screened at least 800 children in order to identify congenitally infected children, if they were from high-income countries, and if they used viral culture or PCR detection methods. We also included relevant studies published since the Dollard review (2007–2012), which we identified using the same systematic search criteria and inclusion/exclusion criteria (e.g. screened populations only) [46]. To estimate specific parameters for hearing loss, cognitive deficit, and vision impairment, we manually reviewed studies that fit the original search criteria and included all those that reported follow-up outcome data for these sequelae (Table 2). As most of the available outcome data were from the United States, we computed estimates for each of the three types of disability based on live births in the United States, but where necessary, we derived parameters using studies from other developed countries where CMV epidemiology is similar to that of the United States.

Several parameter estimates (Table 2) require additional explanation. Children born with symptomatic congenital CMV who would be tested for CMV because of their presenting clinical signs or symptoms are referred to herein as “diagnosed clinically.” We presumed these children would derive no additional benefit from newborn CMV screening, except perhaps for the very limited benefit of a more immediate diagnosis. We estimated the proportion of symptomatic children diagnosed...
Table 2. Calculation of estimates related to the epidemiology of congenital CMV-related hearing loss, cognitive deficit, and vision impairment in the United States

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Calculation</th>
<th>Rationale</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Figures 1–3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births per year</td>
<td>4,248,000</td>
<td>US national vital statistics report [106]</td>
<td></td>
</tr>
<tr>
<td>Birth prevalence of congenital CMV infection</td>
<td>93/17662 + 810/117986 + 74/14021 + 66/21272 + 4/2841 = 1047/173782 → 0.6%</td>
<td>Summary result from studies of screened populations [33,35,46,107,108]</td>
<td></td>
</tr>
<tr>
<td>Percentage of children born without congenital CMV infection</td>
<td>100% − 0.6% = 99.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of infected children who were symptomatic at birth</td>
<td>103/810 + 4/74 + 15/66 + 0/4 = 122/954 → 12.8%</td>
<td>Summary result from studies of screened populations [33,46,107,108]</td>
<td></td>
</tr>
<tr>
<td>Percentage of infected children who were asymptomatic at birth</td>
<td>100% − 12.8% = 87.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Figure 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of symptomatic children likely to be diagnosed clinically with congenital CMV infection</td>
<td>25% (maximum of 3.8%, 12.5%, 15.7%, 25.0%)</td>
<td>Highest estimate from studies of symptomatic cases identified through surveillance divided by expected number of symptomatic cases [3,47–49]</td>
<td></td>
</tr>
<tr>
<td>Percentage of symptomatic children unlikely to be diagnosed clinically with congenital CMV infection</td>
<td>100% − 25% = 75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of symptomatic children with hearing loss at birth</td>
<td>5/9 + 12/53 = 17/62 → 27.4%</td>
<td>Hearing loss occurring in first 3 months. Determined or extrapolated from data in figures and/or text [31,109]</td>
<td></td>
</tr>
<tr>
<td>Percentage of symptomatic children with delayed hearing loss occurring by 9 months of age</td>
<td>0/9 + 2/53 = 2/62 → 3.2%</td>
<td>Hearing loss occurring between months 3 and 9. Determined or extrapolated from data in figures and/or text [31,109]</td>
<td></td>
</tr>
<tr>
<td>Percentage of symptomatic children with delayed hearing loss occurring between 9 and 24 months of age</td>
<td>0/9 + 2/53 = 2/62 → 3.2%</td>
<td>Hearing loss occurring between months 9 and 24. Determined or extrapolated from data in figures and/or text [31,109]</td>
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<thead>
<tr>
<th>Estimate</th>
<th>Calculation</th>
<th>Rationale</th>
<th>References</th>
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<tr>
<td>Percentage of symptomatic children with delayed hearing loss occurring between 24 and 72 months of age</td>
<td>$0/9 + 3/53 = 3/62 \rightarrow 4.8%$</td>
<td>Hearing loss occurring between months 24 and 72. Determined or extrapolated from data in figures and/or text</td>
<td>[31,109]</td>
</tr>
<tr>
<td>Percentage of symptomatic children with no hearing loss</td>
<td>$100% - 27.4% - 3.2% - 3.2% - 4.8% = 61.4%$</td>
<td>No hearing loss developed by 72 months</td>
<td>[31,109]</td>
</tr>
<tr>
<td>Percentage of asymptomatic children with hearing loss at birth</td>
<td>$9/59 + 13/335 = 22/394 \rightarrow 5.6%$</td>
<td>Hearing loss occurring in first 3 months. Determined or extrapolated from data in figures and/or text</td>
<td>[31,109]</td>
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<tr>
<td>Percentage of asymptomatic children with delayed hearing loss occurring by 9 months of age</td>
<td>$1/59 + 3/335 = 4/394 \rightarrow 1%$</td>
<td>Hearing loss occurring between months 3 and 9. Determined or extrapolated from data in figures and/or text</td>
<td>[31,109]</td>
</tr>
<tr>
<td>Percentage of asymptomatic children with delayed hearing loss occurring between 9 and 24 months of age</td>
<td>$0/59 + 3/335 = 3/394 \rightarrow 0.8%$</td>
<td>Hearing loss occurring between months 9 and 24. Determined or extrapolated from data in figures and/or text</td>
<td>[31,109]</td>
</tr>
<tr>
<td>Percentage of asymptomatic children with delayed hearing loss occurring between 24 and 72 months of age</td>
<td>$1/59 + 18/335 = 19/394 \rightarrow 4.8%$</td>
<td>Hearing loss occurring between months 24 and 72. Determined or extrapolated from data in figures and/or text</td>
<td>[31,109]</td>
</tr>
<tr>
<td>Percentage of asymptomatic children with no hearing loss</td>
<td>$100% - 5.6% - 1% - 0.8% - 4.8% = 87.8%$</td>
<td>No hearing loss developed by 72 months</td>
<td>[31,109]</td>
</tr>
<tr>
<td>Figure 2</td>
<td></td>
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</tr>
<tr>
<td>Percentage of children with cognitive deficits (intellectual disability or developmental delay)</td>
<td>$9/22 \rightarrow 41%$</td>
<td>Summary result from studies of CMV-screened populations that assessed cognitive deficit. Assumed</td>
<td>[46]</td>
</tr>
<tr>
<td>Percentage of symptomatic children with cognitive deficits who would</td>
<td>$4/7 \rightarrow 57.1%$</td>
<td>Summary result from studies of CMV-screened populations that assessed cognitive deficit. Assumed</td>
<td>[46]</td>
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</tbody>
</table>
likely be diagnosed clinically with congenital CMV infection

Percentage of symptomatic children with cognitive deficits who would not likely be diagnosed clinically with congenital CMV infection

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<tbody>
<tr>
<td>Percentage of asymptomatic children with cognitive deficits</td>
<td>$\frac{12}{261} + \frac{4}{49} + \frac{6}{159} = \frac{22}{469} = 4.7%$</td>
<td>Summary result from studies of CMV-screened populations that assessed cognitive deficit. Assumed that children with only one sequela would not be diagnosed clinically</td>
<td>[46]</td>
</tr>
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Summary results plus results from two later publications that assessed cognitive deficits among asymptomatic children

Percentage of asymptomatic children with no cognitive deficits

$100\% - 4.7\% = 95.3\%$

**Figure 3**

Percentage of symptomatic children with vision impairment

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<tbody>
<tr>
<td>Percentage of asymptomatic children with vision impairment</td>
<td>$\frac{4}{41} + 0/22 = \frac{4}{63} \rightarrow 6.3%$</td>
<td>Results from CMV-screened populations where vision impairment was assessed</td>
<td>[50,110]</td>
</tr>
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</table>

Percentage of symptomatic children with no vision impairment

$100\% - 6.3\% = 93.7\%$

Percentage of asymptomatic children with vision impairment

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<tbody>
<tr>
<td>Percentage of asymptomatic children with no vision impairment</td>
<td>$0/54 + 14/332 + 2/83 + \frac{0/44 = 16/513 = 3.1%}{0/44 = 16/513 = 3.1%}$</td>
<td>Results from studies that assessed vision impairment</td>
<td>[50,88,90,111]</td>
</tr>
<tr>
<td>Percentage of asymptomatic children with no vision impairment</td>
<td>$100% - 3.1% = 96.9%$</td>
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</table>
clinically by using studies that identified children through active surveillance in well-defined populations in the absence of newborn CMV screening. For each study, we divided the observed number of symptomatic congenital CMV cases by the expected number of symptomatic cases derived using the appropriate parameters in Table 2. The proportions were 3.8% [47], 12.5% [3], 15.7% [48], and 25.0% [49]. Active clinical surveillance misses some symptomatic cases correctly diagnosed by health care providers; hence, we assigned our parameter the highest percentage (i.e. 25%) in order to be conservative. We also made an alternative calculation of this parameter for comparison, in which we assumed that children who had only one CMV-associated symptom (e.g. Apgar score <7, small for gestational age, and petechiae) would not be diagnosed clinically with congenital CMV infection in the absence of screening, whereas those with more than one CMV-associated symptom would be diagnosed clinically [50]. This calculation from a screened population showed that 13% of newborns with symptomatic congenital CMV had more than one symptom. Using health insurance claims data as another source of comparison, we found that few newborns (0–10%) who have CMV-associated symptoms are tested for CMV [51], and therefore, few would be diagnosed.

For our estimate of the percentage of children born with symptomatic congenital CMV infection and who have cognitive deficits, we assumed that only those with additional CNS sequelae such as hearing loss or motor disability would be diagnosed clinically, whereas those with isolated cognitive deficits would not. We made this assumption because isolated cognitive deficit is not typically diagnosed until months or years after birth [52], at which time it is usually too late for a definitive diagnosis of congenital CMV infection.

Finally, for the various groups of children whose outcomes might be affected by newborn CMV screening, we categorized the quality of evidence...
for potential benefit as good, fair, or poor, where good included consistent evidence from well-designed studies; fair included evidence limited by the number, quality, or consistency of the individual studies; and poor included evidence limited by the number or power of studies, flaws in their design or conduct, or gaps in the chain of evidence [53].
RESULTS

Hearing loss

The epidemiology of CMV-related hearing loss is shown in Figure 1. On the basis of the parameter values calculated in Table 2, we estimated that each year in the United States, approximately 25,000 children are born with congenital CMV infection. We divided the children into groups based on whether they were symptomatic at birth and diagnosed clinically (i.e. because their signs and symptoms led to a CMV test), were symptomatic at birth and not diagnosed clinically, or were asymptomatic at birth. We further divided the latter two groups into their various hearing-related outcomes. Hearing loss can occur in any of these groups, sometimes being present at birth and other times developing over months or years.

Nonpharmaceutical interventions. Aside from the indirect potential benefits mentioned earlier (avoidance of diagnostic odyssey, parental peace of mind, physician awareness of diagnosis, etc.), we concluded that children with hearing loss at birth would derive no additional direct benefit from newborn CMV screening and nonpharmaceutical interventions, because these children would presumably be detected through universal newborn hearing screening. Because newborn hearing screening misses some children born with hearing loss, it is possible that having a congenital CMV diagnosis would lead to higher clinical suspicion and more careful monitoring for hearing loss, thus increasing opportunities for early intervention. However, we did not include this as a direct benefit because there are insufficient data to quantify it.

For children with delayed congenital CMV-associated hearing loss that occurs by 9 months of age, we concluded that there is good evidence of benefit from newborn CMV screening (Figure 1). In a landmark study assessing the benefit of universal newborn hearing screening, Kennedy et al. [54] demonstrated that children diagnosed with hearing loss by 9 months of age were significantly more likely to develop better receptive and expressive language than children diagnosed after 9 months of age.

We next considered children whose delayed hearing loss occurs between 9 and 24 months of age because they would, on average, still be diagnosed earlier with newborn CMV screening than they would in its absence. Prior to universal newborn hearing screening, the average age at diagnosis of hearing loss was approximately 24–30 months [55,56]. For these children, we concluded that newborn CMV screening has fair evidence of benefit from nonpharmaceutical intervention because a number of studies (summarized by Nelson et al. [57]) found evidence of better receptive and expressive language among children whose hearing loss was identified earlier rather than later, but these studies had more methodological limitations than Kennedy et al. [54]. The nonpharmaceutical interventions varied across the studies, but they all could be classified as early intervention services, which may include speech-language therapy, occupational therapy, assistive technology devices, and so on.

Finally, we considered the children with congenital CMV infection whose delayed hearing loss occurs between 24 and 72 months of age (Figure 1) [31]. If they were screened for congenital CMV at birth, they might receive closer clinical follow-up and an earlier diagnosis of hearing loss; although moderate to profound hearing loss is frequently recognized and treated before school age, mild or unilateral hearing loss can remain undiagnosed for years [58]. An earlier diagnosis of hearing loss may be beneficial even among children between 24 and 72 months of age, because the many benefits derived from cochlear implants are greater for children with a shorter time from hearing loss until implantation [59–63]. Therefore, we concluded that children whose onset of hearing loss happens between 24 and 72 months of age may receive limited benefit, but the quality of evidence remains poor.

Pharmaceutical interventions. Treatment with IV ganciclovir was shown in a randomized controlled trial (RCT) to reduce the progression of hearing loss in children with symptomatic congenital CMV who have CNS manifestations [20]. However, the subset of symptomatic children who are diagnosed clinically and who meet the trial eligibility requirements (e.g. CNS manifestations) may benefit from pharmaceutical treatment, but newborn screening would not provide an added benefit because they are already identified in the absence of screening. The subset of symptomatic newborns who are not diagnosed clinically but who have hearing loss may also benefit from pharmaceutical treatment because they fit the trial criteria (e.g. clinically apparent disease and hearing deficit). For them, newborn screening would provide a diagnosis that
would make them potential candidates for such treatment, and thus, we concluded that they have fair evidence of benefit from newborn CMV screening. Newborns who are asymptomatic at birth but who have hearing loss might benefit from pharmaceutical treatment, but the benefit is less certain because this category of children was excluded from the trial. Ongoing trials of valganciclovir are looking for benefit in this subgroup (clinicaltrials.gov, study identifiers NCT02005822 and NCT01649869), but for the time being, we concluded that they have poor evidence of benefit from newborn screening.

**Cognitive deficits**

Estimates of the frequency of cognitive deficit (i.e. intellectual disability or developmental delay) among children with congenital CMV infection are shown in Figure 2. Congenital CMV-related cognitive deficits most likely have a natural history that is similar to other neurodevelopmental disorders where the condition is present at birth, but recognition by providers and parents is often delayed until the first or second year of life. Frequently, a confirmatory diagnosis may not occur until the child is even older [52,64]. Among children with symptomatic congenital CMV who have cognitive deficits, some will have severe manifestations at birth that would likely lead to a CMV test and subsequent diagnosis. However, some are likely to be diagnosed only through newborn CMV screening.

The occurrence of cognitive deficits is clearly higher among children with symptomatic congenital CMV infection (Figure 2) than in the general population of children. It is less clear whether children born with asymptomatic congenital CMV infection have a higher prevalence of cognitive deficits than the general population of children. On the basis of a combined population of 469 asymptomatic children, we found a prevalence of cognitive deficit of 4.7% (Table 2). A recent summary estimate of cognitive deficit among the general population was only slightly lower, at 3.8% [65], but this would include some children with congenital CMV-induced deficits. Some studies have reported a moderately lower mean IQ among children with asymptomatic congenital CMV infection compared with controls but only among children younger than 6 years of age [66–70]. Studies of children older than 6 years have not found significant differences in mean IQ [67,68,71–73].

**Nonpharmaceutical interventions.** Children with CMV-associated cognitive deficits (albeit unknown at birth) who screen positive for congenital CMV infection could be considered to be at risk for poor developmental outcomes. Some studies indicate that children with an identified at-risk condition or a clinical diagnosis have an earlier age of first concern from parents or caregivers, an earlier development of an Individual Family Service Program, and an earlier receipt of early intervention services [74–77]. Other studies indicate that children with risk factors for cognitive deficits are more likely to be screened for developmental delays and that screened children are more likely to be referred for and receive early intervention services [76,78]. Importantly, children with cognitive deficits who receive early intervention services have better outcomes than similar children who do not receive such services [79–84]. On the basis of these studies, we concluded that there is fair evidence of benefit related to newborn CMV screening for children with CMV-associated cognitive benefits.

**Pharmacological interventions.** In the same RCT of children with symptomatic congenital CMV and CNS involvement [20], those who received 6 weeks of iv ganciclovir treatment had better developmental outcomes than children who received no treatment [85]. It is unlikely, however, that newborn CMV screening would lead to added benefit for these children because they most likely would be diagnosed because of their clinical presentation. For the children who would only be detected early if newborn screening were in place (i.e. children with cognitive deficit who are asymptomatic or who have nonspecific symptoms), no evidence is available to assess whether they would experience improved developmental outcomes because of antiviral drug treatment.

**Vision impairment**

Although less common than hearing loss or cognitive deficit, vision impairment is another significant disability that can be caused by congenital CMV infection. Vision impairment may be present at birth or it may occasionally be delayed [86,87]. Vision impairment typically occurs among children who are symptomatic at birth, but in some studies, it has been reported in children who were asymptomatic at birth [86,88–90]. Estimates of the epidemiology of congenital CMV-related vision impairment are shown in Figure 3.
Nonpharmaceutical interventions. Although CMV-related blindness is likely to be identified early, partial vision impairment may be less apparent. Such vision impairment may not be detected because approximately one third of children aged 3–5 years do not receive vision testing [91,92]. For children whose vision impairment is diagnosed, there is some evidence that developmental outcomes can be improved through training of visual functions [93,94]. Therefore, if newborn CMV screening leads to better follow-up and more vision screening, it could also lead to early intervention for vision impairment and thus contribute to improved outcomes among these children. Because of insufficient data, we concluded that the evidence for newborn CMV screening leading to better outcomes for children with CMV-related vision impairment remains poor (Figure 3).

Pharmaceutical interventions. Little evidence is available on the effect of antiviral treatment on vision impairment. The previously cited RCT did not measure vision impairment as an endpoint [20], and even if it had, the enrolled children would have been diagnosed with congenital CMV in the absence of screening. One case report found that intravitreal injections of ganciclovir led to regression of ocular disease in a child with congenital CMV infection [95].

DISCUSSION
On the basis of available evidence, we conclude that each year in the United States as many as several thousand children with congenital CMV could benefit from newborn CMV screening, early detection, and intervention. These analyses may apply to other developed countries as well, suggesting that many more thousands of infected children could benefit worldwide. None of the benefits of newborn CMV screening will occur without adequate follow-up for early detection and intervention. Therefore, newborn screening represents the potential for benefit that can accrue as a result of integration of screening for CMV into the newborn screening program.

To provide some perspective, each year in the United States, approximately 6400 children with potential adverse health conditions are detected through the newborn DBS screening program [30], and approximately 5100 children with hearing loss are detected through newborn hearing screening programs (Figure 4) [96]. The type and magnitude of the benefit that can result for these children is variable, ranging from the prevention of adverse outcomes for children with hearing loss to improved outcomes for children with congenital CMV-related vision impairment.
of death or cognitive deficit to the improvement of developmental or educational outcomes. The potential screening benefits for congenital CMV would not include the prevention of death or severe disability but would be similar to the types of benefits associated with the newborn hearing screening program, with improved outcomes through early detection and intervention.

The potential benefits of newborn CMV screening would be maximized by monitoring and screening children identified with congenital CMV infection in order to detect hearing loss, cognitive deficit, and vision impairment as early as possible. Some practical guidelines for a follow-up and monitoring schedule have been proposed and would include confirmation of screening results, tests to aid the prognosis (e.g., CMV viral load), regular audiological, neurodevelopmental, and ophthalmologic assessments, as well as provision of family support [97]. The US Joint Committee on Infant Hearing also provides specific guidance for follow-up of children with risk conditions such as congenital CMV infection [98].

The evidence of potential benefit for newborn CMV screening is limited by the scarcity of data to generate estimates for some parameters. As a result, we were unable to generate a precise estimate of potential benefit, and the numbers we provide should be considered approximate and provisional until more data become available. Furthermore, the numbers of children with each disability who might benefit from screening cannot be added together, because some children are affected by multiple disabilities [99]. In addition, not every child will benefit from the interventions, because neither the nonpharmaceutical nor the pharmaceutical interventions are 100% effective. For example, in the RCT, ganciclovir did not lead to improved hearing, although it did appear to limit hearing deterioration, and its efficacy remains controversial because nearly 60% of the trial participants did not have evaluable outcomes. Nevertheless, on the basis of our analyses, we conclude that newborn CMV screening has the potential to provide a meaningful benefit to at least as many children as are already helped by existing newborn screening programs for some other conditions.

Another limitation of our analyses was the subjective grading of the potential benefits. We based our grading on a scale used previously by the US Preventive Services Task Force that seemed to best fit this type of evidence review [53]. The grading was complicated by the different medical conditions we evaluated, the different types of evidence, the different ways of linking the evidence, and the absence of intervention studies in children known to have congenital CMV. Therefore, we presented our subjective judgment of the totality of the evidence, while providing readers with the supporting data on which we based these judgments.

We did not attempt to address targeted newborn CMV screening, although such an approach might be worth pursuing. For example, rather than screen all newborns for CMV, screening could be limited to those children having particular risk factors, such as being small for gestational age or having failed their initial hearing screen. Targeted CMV screening would benefit fewer children, but it may also have fewer negative effects and could possibly be more cost-effective than universal screening.

Our review clearly highlights some deficiencies in research on congenital CMV. Relatively few studies have been carried out on longitudinal outcomes of congenital CMV infection, undoubtedly because of the substantial resources required to screen tens of thousands of children and then follow hundreds of them for years. In addition, few treatment options exist for infected mothers or children, and no effective vaccine is imminent. The high disease burden that we chronicled suggests the importance of better epidemiology and better treatment and prevention options.

Finally, we examined only the evidence of benefit and did not attempt to provide a complete accounting of the value of newborn CMV screening. Such analyses can be found elsewhere [8,9,100]. As with all medical screening programs, potential benefits need to be weighed against potential harms [101]. The costs of newborn CMV screening need to be evaluated, and appropriate screening tests need to be available. Because newborn CMV screening might be considered a public health service rather than public health emergency [102], prenatal or postnatal counseling and consent may be more ethical than mandatory screening [103,104]. Nevertheless, the evidence for potential benefits to thousands of children each year in the United States alone should lead to careful consideration of newborn CMV screening.

**CONFLICTS OF INTEREST**
The authors have no competing interest.

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DOI: 10.1002/rmv
REFERENCES

Newborn CMV screening evidence of benefits


Newborn CMV screening evidence of benefits

Language Ability after Early Detection of Permanent Childhood Hearing Impairment

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BACKGROUND
Children with bilateral permanent hearing impairment often have impaired language and speech abilities. However, the effects of universal newborn screening for permanent bilateral childhood hearing impairment and the effects of confirmation of hearing impairment by nine months of age on subsequent verbal abilities are uncertain.

METHODS
We studied 120 children with bilateral permanent hearing impairment identified from a large birth cohort in southern England, at a mean of 7.9 years of age. Of the 120 children, 61 were born during periods with universal newborn screening and 57 had hearing impairment that was confirmed by nine months of age. The primary outcomes were language as compared with nonverbal ability and speech expressed as z scores (the number of standard deviations by which the score differed from the mean score among 63 age-matched children with normal hearing), adjusted for the severity of the hearing impairment and for maternal education.

RESULTS
Confirmation of hearing impairment by nine months of age was associated with higher adjusted mean z scores for language as compared with nonverbal ability (adjusted mean difference for receptive language, 0.82; 95 percent confidence interval, 0.31 to 1.33; and adjusted mean difference for expressive language, 0.70; 95 percent confidence interval, 0.13 to 1.26). Birth during periods with universal newborn screening was also associated with higher adjusted z scores for receptive language as compared with nonverbal ability (adjusted mean difference, 0.60; 95 percent confidence interval, 0.07 to 1.13), although the z scores for expressive language as compared with nonverbal ability were not significantly higher. Speech scores did not differ significantly between those who were exposed to newborn screening or early confirmation and those who were not.

CONCLUSIONS
Early detection of childhood hearing impairment was associated with higher scores for language but not for speech in midchildhood.
Bilateral Permanent Childhood Hearing Impairment

Bilateral permanent childhood hearing impairment that is moderate, severe, or profound affects 1 in 750 children and is present at birth in more than 80 percent of affected children. Such impairments are associated with impaired language acquisition, learning, and speech development.

Currently, screening for bilateral permanent childhood hearing impairment, with the use of transiently evoked otoacoustic emissions and automated measurement of auditory brain-stem responses, is recommended for all infants before the age of three months in the United States, the United Kingdom, and Europe. The value of these recommendations is supported by studies showing that enrollment in an intervention program by nine months of age, as compared with later intervention, is associated with improvements in the verbal ability quotient by as much as 19 points (equivalent to 0.5 to 0.6 SD) and that birth during periods in which universal hearing screening of newborns was in place is associated with a similar benefit.

The U.S. Preventive Services Task Force, however, has rated the quality of evidence linking early treatment or birth during periods with universal newborn hearing screening with improved language function as fair or poor.

In a previous controlled trial in the Wessex region of southern England, we showed that universal newborn screening increased the rate of early referral (i.e., before six months of age) for audiological assessment of babies with bilateral permanent childhood hearing impairment, defined as a hearing loss of at least 40 dB hearing level (HL), on two assessments at least 12 months apart. In the present study, we assessed speech and oral language abilities in a sample of children with bilateral permanent childhood hearing impairment, including children enrolled in the earlier trial, and the relationship of these measures to the timing of confirmation of hearing impairment (by nine months of age or later) and to the availability of universal screening of newborns.

Methods

The study sample included all children with bilateral permanent childhood hearing impairment of at least 40 dB HL identified from a cohort of 157,000 children born in eight districts of southern England. We did not include children with a known postnatal cause of bilateral permanent childhood hearing impairment (e.g., bacterial meningitis). The children in the sample were born between 1993 and 1996 in four districts in the Wessex region or between 1992 and 1997 in two pairs of adjacent districts in the Greater London region.

The four districts in the Wessex subgroup had provided the birth cohort for the Wessex trial, in which a program of universal newborn screening was or was not in place in each pair of districts for birth cohorts born in alternate four- or six-month periods. The Greater London subgroup consisted of children born in the only two districts in the United Kingdom that provided universal newborn screening for permanent childhood hearing impairment in the early 1990s (Whipps Cross and Hillingdon) and in two other districts, one adjacent to Whipps Cross and one adjacent to Hillingdon. Other than variation in providing the newborn screening, protocols for the identification and confirmation of bilateral permanent childhood hearing impairment, previously reported, were similar at all sites.

Follow-up of this birth cohort included audiological screening at school entry and information both from multiple sources within the participating regions and from primary care teams in other regions. We obtained details of the detection and management of all cases of bilateral permanent childhood hearing impairment from pediatric audiologists, family practitioners, and other involved professionals and by review of the case records of the audiology service in each district. The severity of hearing loss was categorized from recent audiological records as moderate (40 to 69 dB HL), severe (70 to 94 dB HL), or profound (≥95 dB HL) (Table 1) according to four-frequency averaging of the pure-tone thresholds from 500 to 2000 Hz (or, if pure-tone thresholds were unavailable, sound fields and electrophysiologic-test results).

We prespecified the definition of early confirmation of permanent childhood hearing impairment as confirmation by nine completed months of age. This was consistent with the definition in our previous trial of universal newborn screening and with the U.S. Preventive Services Task Force benchmark for diagnosing or treating infants before 10 months of age.

Two researchers unaware of the child’s early hearing or audiological history evaluated the child during a home visit. One researcher interviewed the principal caregiver (usually the mother), which included completion of the speech scale of the
Simultaneously, the child was assessed by the other researcher in a separate space on the following: the Test for Reception of Grammar, the British Picture Vocabulary Scale (receptive language); the Renfrew Bus Story Test (expressive language); and the Children’s Communication Checklist. Simultaneously, the child was assessed by the other researcher in a separate space on the following: the Test for Reception of Grammar, the British Picture Vocabulary Scale (receptive language); the Renfrew Bus Story Test (expressive language); and the Children’s Communication Checklist. Simultaneously, the child was assessed by the other researcher in a separate space on the following: the Test for Reception of Grammar, the British Picture Vocabulary Scale (receptive language); the Renfrew Bus Story Test (expressive language); and the Children’s Communication Checklist. Simultaneously, the child was assessed by the other researcher in a separate space on the following: the Test for Reception of Grammar, the British Picture Vocabulary Scale (receptive language); the Renfrew Bus Story Test (expressive language); and the Children’s Communication Checklist.

Table 1. Characteristics of Children with Hearing Impairment, Children with Normal Hearing, and Their Families.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hearing Impairment (N = 120)</th>
<th>Normal Hearing* (N = 63)</th>
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<tbody>
<tr>
<td></td>
<td>Age at Confirmation ≤9 Months (N = 57)</td>
<td>Age at Confirmation &gt;9 Months (N = 63)</td>
</tr>
<tr>
<td>Female sex</td>
<td>23 (40)</td>
<td>30 (48)</td>
</tr>
<tr>
<td>English first language at home</td>
<td>50 (88)</td>
<td>49 (78)</td>
</tr>
<tr>
<td>Nonverbal ability — z score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>−0.80</td>
<td>−0.44</td>
</tr>
<tr>
<td>Interquartile range†</td>
<td>−1.38 to −0.03</td>
<td>−1.12 to 0.30</td>
</tr>
<tr>
<td>Age at assessment — yr</td>
<td>7.54</td>
<td>8.18</td>
</tr>
<tr>
<td>Range</td>
<td>5.42 to 10.00</td>
<td>5.92 to 11.67</td>
</tr>
<tr>
<td>Degree of hearing loss — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>32 (56)</td>
<td>33 (52)</td>
</tr>
<tr>
<td>Severe</td>
<td>12 (21)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Profound</td>
<td>13 (23)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Other disabilities — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Visual disability</td>
<td>2 (4)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Learning disability</td>
<td>4 (7)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Of chromosomal or syndromic origin</td>
<td>11 (19)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>None</td>
<td>42 (74)</td>
<td>55 (87)</td>
</tr>
<tr>
<td>Mother’s education — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No qualifications or &lt;5 O-level examinations</td>
<td>22 (39)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>≥5 O-level examinations or some A-level examinations</td>
<td>30 (53)</td>
<td>32 (51)</td>
</tr>
<tr>
<td>≥University degree</td>
<td>5 (9)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Occupation of head of household — no. (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never worked or unemployed</td>
<td>5 (9)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Lower occupations</td>
<td>8 (14)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Intermediate occupations</td>
<td>20 (35)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Higher occupations</td>
<td>24 (42)</td>
<td>23 (37)</td>
</tr>
</tbody>
</table>

* NA denotes not applicable.
† Age-adjusted z scores are listed for Raven’s Progressive Matrices total score. The z scores are the number of standard deviations by which the age-adjusted score differed from the mean score in children with normal hearing. Values are missing for eight children who had early confirmation (by nine months of age) of permanent hearing impairment and for four children who had late confirmation.
‡ O-level examinations (now replaced by general certificates of education) are usually taken at 16 years of age; A-level examinations (now replaced by A2s) are taken two years later as qualifications for entry to higher education.
§ Data are from the Office for National Statistics, London. Lower occupations include semiroutine and routine occupations; intermediate include small employers, own-account workers, and lower supervisory and technical occupations; and higher include higher managerial and professional occupations.

Children’s Communication Checklist. Simultaneously, the child was assessed by the other researcher in a separate space on the following: the Test for Reception of Grammar, the British Picture Vocabulary Scale (receptive language); the Renfrew Bus Story Test (expressive language); and the Children’s Communication Checklist.
and Raven’s Progressive Matrices Test (nonverbal abilities). For all these measures, a higher score indicates better function. Normal receptive language is the ability to understand communication through gestures, facial expressions, and words, whereas expressive language is the ability to express needs with the use of gestures, vocalization, facial expressions, and words.

Other characteristics of the child and family, including maternal education according to the 2001 census in the United Kingdom, were also documented (Table 1). The mean age at assessment of language and speech was 7.9 years (range, 5.4 to 11.7).

Our study was approved by the South and West Multicenter Research Ethics Committee, United Kingdom. Principal caregivers provided written informed consent.

For the purpose of comparisons within the group of children with hearing impairment in this report, we used norms obtained from a group of 63 English-speaking children with normal hearing, matched for place of birth and age at assessment with our group of 120 children with hearing impairment. The group mean score and standard-deviation scores in children with normal hearing were used to derive z scores for the children with hearing impairment, equal to the number of standard deviations of the distribution of scores in children with normal hearing by which their age-adjusted score differed from the mean score in children with normal hearing. We also calculated aggregate scores as follows: the z score for receptive language was equal to half the sum of the z score for the Test for Reception of Grammar and the z score for the British Picture Vocabulary Scale; and the z score for expressive language equal to half the sum of the z score for sentence information and the z score for five longest sentences. We calculated difference scores as follows: the z score for a deficit of receptive (or expressive) language as compared with nonverbal skills was equal to the difference between the z score for receptive (or expressive) language and the z score for nonverbal ability.

We assessed the associations between exposure to universal newborn screening (i.e., birth during periods when universal newborn screening was in place), or to confirmation by nine months of age, and age-adjusted individual and aggregate language and speech scores with the use of a two-sample t-test. The preplanned primary outcomes of our study were language and speech scores and differences between language and nonverbal scores at primary-school age after adjustment in a multiple linear regression (Stata software, version 8) for severity of hearing impairment, maternal education, and (except in the case of difference scores) nonverbal ability, which were recognized as potential confounders of the primary outcomes. Normality and homogeneity of the residual variance were examined for all measures to ensure that the regression model was appropriate. All reported P values are two-sided. Adjustment was not made for multiple testing.

On the basis of an expected overall sample size of 154 children with bilateral permanent childhood hearing impairment (determined according to the expected rates in the general population), we anticipated a statistical power of 80 percent to detect a difference of 0.5 SD in verbal ability between the two groups, with a two-sided P value of 0.05. We also performed a subgroup analysis of children who were enrolled in the Wessex controlled trial of universal newborn screening. The subgroup was expected to be balanced with respect to both known and unknown confounding factors, although that trial was not powered for the end points of speech and language.

Results

Seventy-seven infants with bilateral permanent childhood hearing impairment (i.e., ≥40 dB HL) were identified among the 68,714 infants born during periods in which universal newborn screening was in place, and 91 infants were identified among the 88,019 infants born during periods without universal screening. These numbers are equivalent to an overall prevalence in our sample of 107 per 100,000, which is close to the expected population prevalence of 112 per 100,000. Estimates of the completeness of ascertainment in our study sample exceeded 95 percent for both the London and Wessex subgroups. Of the 168 cases identified, the principal caregivers of 120 children gave consent for participation in the study (Fig. 1). Of these 120 children, 61 were born during periods with universal newborn screening and 59 during periods without the screening. Participants were similar to nonparticipants with respect to age, sex, and severity of hearing loss. Hearing impairment was confirmed in 72 infants (60 percent) by one year of age, 90 children (75 percent)
by two years of age, 106 children (88 percent) by four years of age, and in all 120 children (100 percent) by six years of age.

Remedial therapy for hearing impairment was provided to all participants, since it is a public service available to all deaf preschool children in the United Kingdom. All the children with hearing impairment in this study had received advice in their homes from a teacher of the deaf and hard of hearing (87 percent within three months after confirmation of impairment), and all had been offered audiology services, including high-quality commercial hearing aids fitted according to published national quality standards. Hearing aids were always in place during the assessments reported here. Five participants born during periods with universal newborn screening had cochlear implants, as did 11 children born during periods without the screening. Confirmation of hearing loss occurred at a median of 10 months of age.
Baseline characteristics, including the severity of hearing impairment, were similar between the 61 children who were exposed to universal newborn screening and the 59 who were not (data not shown), and between 57 children whose impairment was confirmed by nine months of age and 63 whose impairment was confirmed later (Table 1). Confirmation of impairment by nine months of age was significantly more common among children exposed to universal newborn screening (41 of 61 [67 percent]) than among children not exposed to such screening (16 of 59 [27 percent]) (absolute difference, 40 percent; 95 percent confidence interval, 24 to 56 percent; P<0.001).

Children whose impairment was confirmed by nine months of age had significantly higher adjusted mean aggregate scores for receptive language than did children whose hearing impairment was confirmed later (difference in mean z scores, 0.76; 95 percent confidence interval, 0.26 to 1.27) and for expressive language ability (difference in mean z scores, 0.50; 95 percent confidence interval, <0.01 to 1.01). Furthermore, their difference scores (i.e., the z score for language minus the z score for nonverbal ability) showed smaller deficits in receptive and expressive language relative to nonverbal ability (Fig. 2A and Table 2). Children who were exposed to universal newborn screening also had higher adjusted mean aggregate scores for receptive language than those who were not exposed (difference in mean z scores, 0.56; 95 percent confidence interval, 0.03 to 1.08), and their difference scores showed a smaller deficit in receptive language relative to nonverbal ability (difference in mean z scores, 0.60; 95 percent confidence interval, 0.07 to 1.13) but no significant difference in expressive language ability (Fig. 2B and Table 3).

Because expressive language scores were not available for all children, we performed a post hoc analysis in the 88 children for whom both receptive and expressive oral language scores were available. We found that the effect size for the relationship between early confirmation of hearing impairment and receptive scores (0.73; 95 percent confidence interval, 0.19 to 1.27) was very similar to that between early confirmation and expressive scores among the same children (Table 2). There were no significant differences in measures of speech between those whose hearing impairment was confirmed by nine months of age and those whose impairment was confirmed after nine months of age or between those exposed to universal newborn screening and those not exposed to such screening (Tables 2 and 3).

Associations between early confirmation of hearing impairment or exposure to universal newborn screening and later language abilities were similar in the Wessex and Greater London subgroups (data not shown). In the Wessex subgroup, for whom the chance of confounding factors should have been reduced because the exposure to newborn screening occurred in a controlled trial, the unadjusted difference between receptive language and nonverbal scores in children born during periods with universal newborn screening as compared with those born during periods without newborn screening was 1.00 (95 percent confidence interval, 0.001 to 2.00; P=0.05) (see Table 2 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). In addition, associations between early confirmation of impairment or newborn screening and higher language scores in this cohort were similar to, or higher than, those observed in the whole sample (Tables 2 and 3, and the Supplementary Appendix).

**DISCUSSION**

We observed significantly higher scores for language, but not for speech, in midchildhood among a population-based sample of children with bilateral permanent hearing impairment who were exposed to universal newborn screening or who had confirmation of hearing impairment by nine months of age than among those who were not exposed to newborn screening or whose impairment was confirmed after nine months of age. In the case of children whose hearing impairment was confirmed by nine months of age, this difference was equivalent to an increase of 10 to 12 points in the verbal as compared with the nonverbal intelligence quotient.

The estimated size of the benefit of newborn screening and of early confirmation of impairment in this sample may be conservative. This birth cohort was the first in the United Kingdom in which
newborn screening was applied, and systems to ensure short intervals between positive results on newborn screening and confirmation of hearing impairment, now standard in the United Kingdom and the United States, were still evolving. Intervals between confirmation and the fitting of hearing aids were also longer than is the current standard of care in the United Kingdom.13,24 Delays in confirmation and intervention might have decreased the benefit to language that was associated with early detection.

We excluded children whose hearing impairment was of known postnatal cause, but a minority of cases may have been postnatal in onset. Children who lost hearing after infancy would be expected to benefit less from early confirmation than children with an unchanging congenital hearing impairment. On the basis of the Wessex cohort, the maximum proportion of children with progressive hearing loss during childhood (derived by adding the proportion with negative results on newborn screening to the proportion with a positive result and in which a subsequent increase in the severity of hearing impairment was documented) was 23 percent; a lower percentage was derived for the Greater London subgroup. A sensitivity analysis (not shown) based on the estimate that impairment worsens after birth in 23 percent of children suggests that the true benefit to language acquisition for those with congenital and unchanging hearing impairment would have been larger by a factor of 1.05 to 1.30 than the benefit that we reported for the whole sample.

In contrast to the higher language scores observed among children whose hearing impairment was confirmed early, measures of speech did not differ significantly between groups. Speech was assessed on the basis of parental or professional report, rather than by direct measurement, and may reflect a lack of sensitivity to relevant aspects of speech. Objective analysis of audiotaped samples of speech, recorded for the assessments of language, is currently being performed to further evaluate speech in these children.

Data collected in the Greater London subgroup were observational and cannot prove causality. However, conclusions from these data are strengthened by the similarity of results between the Greater London and Wessex subgroups, since exposure or lack of exposure to newborn screening and the resulting variation in early confirmation was quasi-experimental in design in the latter subgroup. The trial among the Wessex subgroup was not statistically powered to detect differences in language and speech in midchildhood.

The severity of hearing impairment measured at the time of speech and language evaluation, rather than at the time of confirmation of impairment, was used in the regression models. This approach
Table 2. Timing of Confirmation of Permanent Childhood Hearing Impairment and Language and Speech Scores.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean z Score (SD) for Age at Confirmation†</th>
<th>Unadjusted Mean Difference (95% CI)‡</th>
<th>P Value</th>
<th>Adjusted Mean Difference (95% CI)§</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at Confirmation of Hearing Impairment</td>
<td>≤9 months &gt;9 months</td>
<td>≤9 months &gt;9 months</td>
<td>P Value</td>
<td>≥9 months &gt;9 months</td>
</tr>
<tr>
<td>Receptive language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for Reception of Grammar</td>
<td></td>
<td>44 54</td>
<td>−1.46 (1.50) −2.25 (1.91)</td>
<td>0.78 (0.08 to 1.48)</td>
<td>0.03</td>
</tr>
<tr>
<td>British Picture Vocabulary Scale</td>
<td></td>
<td>45 56</td>
<td>−1.86 (1.40) −2.36 (1.65)</td>
<td>0.50 (−0.11 to 1.11)</td>
<td>0.11</td>
</tr>
<tr>
<td>Aggregate score</td>
<td></td>
<td>45 56</td>
<td>−1.76 (1.47) −2.38 (1.72)</td>
<td>0.61 (−0.02 to 1.24)</td>
<td>0.06</td>
</tr>
<tr>
<td>Aggregate minus nonverbal</td>
<td></td>
<td>45 56</td>
<td>−0.82 (1.23) −1.68 (1.44)</td>
<td>0.86 (0.32 to 1.40)</td>
<td>0.002</td>
</tr>
<tr>
<td>Expressive language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renfrew Bus Story Test: sentence information</td>
<td></td>
<td>39 48</td>
<td>−0.73 (1.32) −1.23 (1.15)</td>
<td>0.50 (−0.02 to 1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Renfrew Bus Story Test: 5 longest sentences</td>
<td></td>
<td>39 48</td>
<td>−0.46 (1.48) −0.87 (1.48)</td>
<td>0.42 (−0.22 to 1.05)</td>
<td>0.20</td>
</tr>
<tr>
<td>Aggregate score</td>
<td></td>
<td>39 48</td>
<td>−0.59 (1.31) −1.07 (1.21)</td>
<td>0.46 (−0.08 to 1.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>Aggregate minus nonverbal</td>
<td></td>
<td>39 48</td>
<td>0.14 (1.29) −0.50 (1.34)</td>
<td>0.64 (−0.08 to 1.21)</td>
<td>0.03</td>
</tr>
<tr>
<td>Speech</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children’s Communication Checklist, speech scale</td>
<td></td>
<td>44 51</td>
<td>−1.15 (1.42) −1.33 (1.54)</td>
<td>0.18 (−0.43 to 0.79)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
† Mean scores are adjusted for age at assessment. The group mean score and SD scores in children with normal hearing were used to derive z scores for the children with permanent childhood hearing impairment, equal to the number of SDs by which their age-adjusted score differed from the mean score in children with normal hearing. Negative group mean z scores indicate that scores were lower than those seen in the comparison group of children with normal hearing.
‡ The unadjusted mean difference was calculated by subtracting the mean z score for children whose hearing impairment was confirmed after nine months of age from the mean z score for those whose impairment was confirmed by nine months of age. The differences were affected by rounding.
§ This category shows the difference between mean scores adjusted (in a linear regression model) for severity of permanent childhood hearing impairment, maternal education, and except in the case of mean difference scores, age-adjusted total Raven’s Progressive Matrices scores.
<table>
<thead>
<tr>
<th>Measure</th>
<th>No Universal Newborn Screening</th>
<th>Universal Newborn Screening</th>
<th>Mean z Score (SD)†</th>
<th>Unadjusted Mean Difference (95% CI)‡</th>
<th>P Value</th>
<th>Adjusted Mean Difference (95% CI)§</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No Universal Newborn Screening</td>
<td>Universal Newborn Screening</td>
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<tr>
<td>Receptive language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for Reception of Grammar</td>
<td>46</td>
<td>52</td>
<td>-2.10 (1.75)</td>
<td>-1.71 (1.78)</td>
<td>0.39 (-0.32 to 1.11)</td>
<td>0.27</td>
<td>0.59 (-0.01 to 1.19)</td>
</tr>
<tr>
<td>British Picture Vocabulary Scale</td>
<td>49</td>
<td>52</td>
<td>-2.34 (1.58)</td>
<td>-1.94 (1.52)</td>
<td>0.41 (-0.20 to 1.02)</td>
<td>0.19</td>
<td>0.47 (-0.05 to 1.00)</td>
</tr>
<tr>
<td>Aggregate score</td>
<td>49</td>
<td>52</td>
<td>-2.32 (1.61)</td>
<td>-1.89 (1.65)</td>
<td>0.45 (-0.18 to 1.08)</td>
<td>0.16</td>
<td>0.56 (0.03 to 1.08)</td>
</tr>
<tr>
<td>Aggregate minus nonverbal</td>
<td>49</td>
<td>52</td>
<td>-1.67 (1.29)</td>
<td>-0.94 (1.45)</td>
<td>0.73 (0.19 to 1.28)</td>
<td>0.01</td>
<td>0.60 (0.07 to 1.13)</td>
</tr>
<tr>
<td>Expressive language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renfrew Bus Story Test: sentence information</td>
<td>41</td>
<td>46</td>
<td>-1.13 (1.18)</td>
<td>-0.90 (1.31)</td>
<td>0.24 (-0.30 to 0.77)</td>
<td>0.38</td>
<td>0.27 (-0.23 to 0.78)</td>
</tr>
<tr>
<td>Renfrew Bus Story Test: 5 longest sentences</td>
<td>41</td>
<td>46</td>
<td>-0.81 (1.61)</td>
<td>-0.58 (1.38)</td>
<td>0.22 (-0.41 to 0.86)</td>
<td>0.49</td>
<td>0.32 (-0.30 to 0.94)</td>
</tr>
<tr>
<td>Aggregate score</td>
<td>41</td>
<td>46</td>
<td>-0.99 (1.33)</td>
<td>-0.74 (1.23)</td>
<td>0.23 (-0.32 to 0.78)</td>
<td>0.40</td>
<td>0.30 (-0.22 to 0.81)</td>
</tr>
<tr>
<td>Aggregate minus nonverbal</td>
<td>41</td>
<td>46</td>
<td>-0.44 (1.35)</td>
<td>-0.02 (1.34)</td>
<td>0.43 (-0.15 to 1.00)</td>
<td>0.14</td>
<td>0.39 (-0.19 to 0.98)</td>
</tr>
<tr>
<td>Speech</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children’s Communication Checklist, speech scale</td>
<td>47</td>
<td>50</td>
<td>-1.30 (1.47)</td>
<td>-1.20 (1.50)</td>
<td>0.10 (-0.51 to 0.71)</td>
<td>0.75</td>
<td>0.12 (-0.46 to 0.71)</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
† Mean scores are adjusted for age at assessment. The group mean score and SD scores in children with normal hearing were used to derive z scores for the children with permanent childhood hearing impairment, equal to the number of SDs by which their age-adjusted score differed from the mean score in children with normal hearing. Negative group mean z scores indicate that scores were lower than those seen in the comparison group of children with normal hearing.
‡ The unadjusted mean difference was calculated by subtracting the mean z score for children born in periods without universal newborn screening from the mean z score for those born in periods with universal newborn screening. The differences were affected by rounding.
§ This category shows the difference between mean scores adjusted (in a linear regression model) for the severity of permanent childhood hearing impairment, maternal education, and except in the case of mean difference scores, age-adjusted total Raven’s Progressive Matrices scores.
minimizes the chance of bias due to possible differences in the estimates of the severity of impairment between groups with early confirmation of impairment and those with late confirmation among children in whom severity increased with age. This adjustment did not in any case materially alter our estimate of the size of the benefits of early confirmation, since the groups with early confirmation and those with late confirmation were similar in their distribution of severity of hearing impairment.

Our data extend findings from previous studies of the relationship between early identification of hearing impairment and later outcomes. Adjusted mean vocabulary scores of children with hearing impairment, assessed at the age of 5 years, were higher in children enrolled before 11 months of age in an early intervention program in Nebraska than in those enrolled at 11 to 23 months of age (by 0.69 SD) or at 24 to 35 months of age (by 0.99 SD).27 Similar findings were reported from a study in Washington State comparing children enrolled before 24 months of age with those enrolled after 24 months of age with those enrolled later.28 Both these studies lacked clear criteria for inclusion, selected as participants only those who adhered to the early intervention programs, and used unblinded assessment of children whose language ability may have been greater than that of children whose hearing impairment was identified early but who were not available for follow-up.3 In contrast to these studies, a population-based Australian study reported no benefit of early diagnosis before 6 or 12 months of age on speech, language, and other outcomes at 7 to 8 years of age among children with congenital hearing impairment.29 All three studies excluded children with developmental disabilities, and none included sufficient children enrolled before 12 months of age to estimate reliably the benefit of early intervention in that age group.

In the largest previous study,8 the language abilities of 150 children enrolled in the Colorado Home Intervention Program, assessed at 13 to 36 months by parental report, were 0.5 to 0.6 SD higher (scaled according to subsequently published norms30) in those in whom hearing impairment was identified by 6 months of age and who enrolled after a mean of 3 months more than in those whose impairment was identified later. In a smaller case–control study, these investigators used similar assessment methods and reported a benefit of 0.5 to 0.8 SD to language and speech associated with birth in hospitals providing universal newborn screening, as compared with those not providing it.10 However, these Colorado studies did not adjust for differences between the baseline characteristics of the groups, were subject to possible selection bias, and relied on unblinded assessments of parental reports of language abilities.3 The greater benefits reported, as compared with those reported in the present study, may have arisen from these potential sources of bias or from the differing ages at assessment.

Universal newborn screening and early confirmation of permanent childhood hearing impairment had clinically important benefits to the language abilities of children at primary-school age in this population-based study. Other data from this cohort suggest that such screening may be cost-effective.31 Longer follow-up is needed to establish whether these children have higher academic achievement and continue to show superior language skills at high-school age.

Supported by the Wellcome Trust (061839).

No potential conflict of interest relevant to this article was reported.

We are indebted to the children, families, school staff, specialist teachers of the hearing impaired, speech and language pathologists, and audiology professionals in the local area teams for their help and assistance; to Margaret Baldwin, Joy Bhattacharya, Alyson Bumby, Irene Curtis, Carol Hunter, David Reed, Scott Richards, Peter Savundra, Huw Thomas, Tim Williamson, Jan Nanor, Helen Davis, Shirley Golden, Eleanor Lutman, Kristen Paul, and Helen Ryder; to Julie Brinton for her advice on assessments of speech and language; and to Sue Robinson for her advice on audiology.

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Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs

Joint Committee on Infant Hearing

THE POSITION STATEMENT
The Joint Committee on Infant Hearing (JCIH) endorses early detection of and intervention for infants with hearing loss. The goal of early hearing detection and intervention (EHDI) is to maximize linguistic competence and literacy development for children who are deaf or hard of hearing. Without appropriate opportunities to learn language, these children will fall behind their hearing peers in communication, cognition, reading, and social-emotional development. Such delays may result in lower educational and employment levels in adulthood.1 To maximize the outcome for infants who are deaf or hard of hearing, the hearing of all infants should be screened at no later than 1 month of age. Those who do not pass screening should have a comprehensive audiological evaluation at no later than 3 months of age. Infants with confirmed hearing loss should receive appropriate intervention at no later than 6 months of age from health care and education professionals with expertise in hearing loss and deafness in infants and young children. Regardless of previous hearing-screening outcomes, all infants with or without risk factors should receive ongoing surveillance of communicative development beginning at 2 months of age during well-child visits in the medical home.2 EHDI systems should guarantee seamless transitions for infants and their families through this process.

2007 JCIH POSITION STATEMENT UPDATES
The following are highlights of updates made since the 2000 JCIH statement3:

1. Definition of targeted hearing loss
   • The definition has been expanded from congenital permanent bilateral, unilateral sensory, or permanent conductive hearing loss to include neural hearing loss (eg, “auditory neuropathy/dyssynchrony”) in infants admitted to the NICU.

2. Hearing-screening and -rescreening protocols
   • Separate protocols are recommended for NICU and well-infant nurseries. NICU infants admitted for more than 5 days are to have auditory brainstem response (ABR) included as part of their screening so that neural hearing loss will not be missed.
   • For infants who do not pass automated ABR testing in the NICU, referral should be made directly to an audiologist for rescreening and, when indicated, comprehensive evaluation including ABR.
   • For rescreening, a complete screening on both ears is recommended, even if only 1 ear failed the initial screening.
   • For readmissions in the first month of life for all infants (NICU or well infant), when there are conditions associated with potential hearing loss (eg, hyper-
bilirubinemia that requires exchange transfusion or culture-positive sepsis), a repeat hearing screening is recommended before discharge.

3. Diagnostic audiology evaluation

- Audiologists with skills and expertise in evaluating newborn and young infants with hearing loss should provide audiology diagnostic and auditory habilitation services (selection and fitting of amplification device).
- At least 1 ABR test is recommended as part of a complete audiology diagnostic evaluation for children younger than 3 years for confirmation of permanent hearing loss.
- The timing and number of hearing reevaluations for children with risk factors should be customized and individualized depending on the relative likelihood of a subsequent delayed-onset hearing loss. Infants who pass the neonatal screening but have a risk factor should have at least 1 diagnostic audiology assessment by 24 to 30 months of age. Early and more frequent assessment may be indicated for children with cytomegalovirus (CMV) infection, syndromes associated with progressive hearing loss, neurodegenerative disorders, trauma, or culture-positive postnatal infections associated with sensorineural hearing loss; for children who have received extracorporeal membrane oxygenation (ECMO) or chemotherapy; and when there is caregiver concern or a family history of hearing loss.
- For families who elect amplification, infants in whom permanent hearing loss is diagnosed should be fitted with an amplification device within 1 month of diagnosis.

4. Medical evaluation

- For infants with confirmed hearing loss, a genetics consultation should be offered to their families.
- Every infant with confirmed hearing loss should be evaluated by an otolaryngologist who has knowledge of pediatric hearing loss and have at least 1 examination to assess visual acuity by an ophthalmologist who is experienced in evaluating infants.
- The risk factors for congenital and acquired hearing loss have been combined in a single list rather than grouped by time of onset.

5. Early intervention

- All families of infants with any degree of bilateral or unilateral permanent hearing loss should be considered eligible for early intervention services.
- There should be recognized central referral points of entry that ensure specialty services for infants with confirmed hearing loss.
- Early intervention services for infants with confirmed hearing loss should be provided by professionals who have expertise in hearing loss, including educators of the deaf, speech-language pathologists, and audiologists.
- In response to a previous emphasis on “natural environments,” the JCIH recommends that both home-based and center-based intervention options be offered.

6. Surveillance and screening in the medical home

- For all infants, regular surveillance of developmental milestones, auditory skills, parental concerns, and middle-ear status should be performed in the medical home, consistent with the American Academy of Pediatrics (AAP) pediatric periodicity schedule. All infants should have an objective standardized screening of global development with a validated assessment tool at 9, 18, and 24 to 30 months of age or at any time if the health care professional or family has concern.
- Infants who do not pass the speech-language portion of a medical home global screening or for whom there is a concern regarding hearing or language should be referred for speech-language evaluation and audiology assessment.

7. Communication

- The birth hospital, in collaboration with the state EHDI coordinator, should ensure that the hearing-screening results are conveyed to the parents and the medical home.
- Parents should be provided with appropriate follow-up and resource information, and hospitals should ensure that each infant is linked to a medical home.
- Information at all stages of the EHDI process is to be communicated to the family in a culturally sensitive and understandable format.
- Individual hearing-screening information and audiology diagnostic and habilitation information should be promptly transmitted to the medical home and the state EHDI coordinator.
- Families should be made aware of all communication options and available hearing technologies (presented in an unbiased manner). Informed family choice and desired outcome guide the decision-making process.

8. Information infrastructure

- States should implement data-management and tracking systems as part of an integrated child health information system to monitor the quality of EHDI services and provide recommendations for improving systems of care.
• An effective link between health and education professionals is needed to ensure successful transition and to determine outcomes of children with hearing loss for planning and establishing public health policy.

BACKGROUND

It has long been recognized that unidentified hearing loss at birth can adversely affect speech and language development as well as academic achievement and social-emotional development. Historically, moderate-to-severe hearing loss in young children was not detected until well beyond the newborn period, and it was not unusual for diagnosis of milder hearing loss and unilateral hearing loss to be delayed until children reached school age.

In the late 1980s, Dr C. Everett Koop, then US Surgeon General, on learning of new technology, encouraged detection of hearing loss to be included in the Healthy People 2000 goals for the nation. In 1988, the Maternal and Child Health Bureau (MCHB), a division of the US Health Resources and Services Administration (HRSA), funded pilot projects in Rhode Island, Utah, and Hawaii to test the feasibility of a universal statewide screening program to screen newborn infants for hearing loss before hospital discharge. The National Institutes of Health, through the National Institute on Deafness and Other Communication Disorders (NIDCD), issued in 1993 a consensus statement on early identification of hearing impairment in infants and young children. In the statement the authors concluded that all infants admitted to the NICU should be screened for hearing loss before hospital discharge and that universal screening should be implemented for all infants within the first 3 months of life. In its 1994 position statement, the JCIH endorsed the goal of universal detection of infants with hearing loss and encouraged continuing research and development to improve methods for identification of and intervention for hearing loss. The AAP released a statement that recommended newborn hearing screening and intervention in 1999. In 2000, citing advances in screening technology, the JCIH endorsed the universal screening of all infants through an integrated, interdisciplinary system of EHDI. The Healthy People 2010 goals included an objective to “increase the proportion of newborns who are screened for hearing loss by one month, have audiological evaluation by 3 months, and are enrolled in appropriate intervention services by 6 months.”

The ensuing years have seen remarkable expansion in newborn hearing screening. At the time of the National Institutes of Health consensus statement, only 11 hospitals in the United States were screening more than 90% of their newborn infants. In 2000, through the support of Representative Jim Walsh (R-NY), Congress authorized the HRSA to develop newborn hearing screening and follow-up services, the Centers for Disease Control and Prevention (CDC) to develop data and tracking systems, and the NIDCD to support research in EHDI. By 2005, every state had implemented a newborn hearing-screening program, and approximately 95% of newborn infants in the United States were screened for hearing loss before hospital discharge. Congress recommended cooperation and collaboration among several federal agencies and advocacy organizations to facilitate and support the development of state EHDI systems.

EHDI programs throughout the United States have demonstrated not only the feasibility of universal newborn hearing screening (UNHS) but also the benefits of early identification and intervention. There is a growing body of literature indicating that when identification and intervention occur at no later than 6 months of age for newborn infants who are deaf or hard of hearing, the infants perform as much as 20 to 40 percentile points higher on school-related measures (vocabulary, articulation, intelligibility, social adjustment, and behavior). Still, many important challenges remain. Despite the fact that approximately 95% of newborn infants have their hearing screened in the United States, almost half of newborn infants who do not pass the initial screening do not have appropriate follow-up to either confirm the presence of a hearing loss and/or initiate appropriate early intervention services (see www.infanthearing.org, www.cdc.gov/ncbddd/ehdi, and www.nidcd.nih.gov/health).

State EHDI coordinators report system-wide problems including failure to communicate information to families in a culturally sensitive and understandable format at all stages of the EHDI process, lack of integrated state data-management and -tracking systems, and a shortage of facilities and personnel with the experience and expertise needed to provide follow-up for infants who are referred from newborn screening programs. Available data indicate that a significant number of children who need further assessment do not receive appropriate follow-up evaluations. However, the outlook is improving as EHDI programs focus on the importance of strengthening follow-up and intervention.

PRINCIPLES

All children with hearing loss should have access to resources necessary to reach their maximum potential. The following principles provide the foundation for effective EHDI systems and have been updated and expanded since the 2000 JCIH position statement.

1. All infants should have access to hearing screening using a physiologic measure at no later than 1 month of age.

2. All infants who do not pass the initial hearing screening and the subsequent rescreening should have appropriate audiological and medical evaluations to
confirm the presence of hearing loss at no later than 3 months of age.

3. All infants with confirmed permanent hearing loss should receive early intervention services as soon as possible after diagnosis but at no later than 6 months of age. A simplified, single point of entry into an intervention system that is appropriate for children with hearing loss is optimal.

4. The EHDI system should be family centered with infant and family rights and privacy guaranteed through informed choice, shared decision-making, and parental consent in accordance with state and federal guidelines. Families should have access to information about all intervention and treatment options and counseling regarding hearing loss.

5. The child and family should have immediate access to high-quality technology including hearing aids, cochlear implants, and other assistive devices when appropriate.

6. All infants and children should be monitored for hearing loss in the medical home. Continued assessment of communication development should be provided by appropriate professionals to all children with or without risk indicators for hearing loss.

7. Appropriate interdisciplinary intervention programs for infants with hearing loss and their families should be provided by professionals who are knowledgeable about childhood hearing loss. Intervention programs should recognize and build on strengths, informed choices, traditions, and cultural beliefs of the families.

8. Information systems should be designed and implemented to interface with electronic health charts and should be used to measure outcomes and report the effectiveness of EHDI services at the patient, practice, community, state, and federal levels.

GUIDELINES FOR EHDI PROGRAMS

The 2007 guidelines were developed to update the 2000 JCIH position statement principles and to support the goals of universal access to hearing screening, evaluation, and intervention for newborn and young infants embodied in Healthy People 2010. The guidelines provide current information on the development and implementation of successful EHDI systems.

Hearing screening should identify infants with specifically defined hearing loss on the basis of investigations of long-term, developmental consequences of hearing loss in infants, currently available physiologic screening techniques, and availability of effective intervention in concert with established principles of health screening. Studies have demonstrated that current screening technologies are effective in identifying hearing loss of moderate and greater degree. In addition, studies of children with permanent hearing loss indicate that moderate or greater degrees of hearing loss can have significant effects on language, speech, academic, and social-emotional development. High-risk target populations also include infants in the NICU, because research data have indicated that this population is at highest risk of having neural hearing loss.

The JCIH, however, is committed to the goal of identifying all degrees and types of hearing loss in childhood and recognizes the developmental consequences of even mild degrees of permanent hearing loss. Recent evidence, however, has suggested that current hearing-screening technologies fail to identify some infants with mild forms of hearing loss. In addition, depending on the screening technology selected, infants with hearing loss related to neural conduction disorders or “auditory neuropathy/auditory dyssynchrony” may not be detected through a UNHS program. Although the JCIH recognizes that these disorders may result in delayed communication, currently recommended screening algorithms (ie, use of otoacoustic emission [OAE] testing alone) preclude universal screening for these disorders. Because these disorders typically occur in children who require NICU care, the JCIH recommends screening this group with the technology capable of detecting auditory neuropathy/dyssynchrony: automated ABR measurement.

All infants, regardless of newborn hearing-screening outcome, should receive ongoing monitoring for development of age-appropriate auditory behaviors and communication skills. Any infant who demonstrates delayed auditory and/or communication skills development, even if he or she passed newborn hearing screening, should receive an audiological evaluation to rule out hearing loss.

Roles and Responsibilities

The success of EHDI programs depends on families working in partnership with professionals as a well-coordinated team. The roles and responsibilities of each team member should be well defined and clearly understood. Essential team members are the birth hospital, families, pediatricians or primary health care professionals (ie, the medical home), audiologists, otolaryngologists, speech-language pathologists, educators of children who are deaf or hard of hearing, and other early intervention professionals involved in delivering EHDI services. Additional services including genetics, ophthalmology, developmental pediatrics, service coordination, supportive family education, and counseling should be available.

The birth hospital is a key member of the team. The birth hospital, in collaboration with the state EHDI coordinator, should ensure that parents and primary health care professionals receive and understand the hearing-screening results, that parents are provided with appropriate follow-up and resource information, and
that each infant is linked to a medical home. The hospital ensures that hearing-screening information is transmitted promptly to the medical home and appropriate data are submitted to the state EHDI coordinator.

The most important role for the family of an infant who is deaf or hard of hearing is to love, nurture, and communicate with the infant. From this foundation, families usually develop an urgent desire to understand and meet the special needs of their infant. Families gain knowledge, insight, and experience by accessing resources and through participation in scheduled early intervention appointments including audiological, medical, habilitative, and educational sessions. This experience can be enhanced when families choose to become involved with parental support groups, people who are deaf or hard of hearing, and/or their children’s deaf or hard-of-hearing peers. Informed family choices and desired outcomes guide all decisions for these children. A vital function of the family’s role is ensuring direct access to communication in the home and the daily provision of language-learning opportunities. Over time, the child benefits from the family’s modeling of partnerships with professionals and advocating for their rights in all settings. The transfer of responsibilities from families to the child develops gradually and increases as the child matures, growing in independence and self-advocacy.

Pediatricians, family physicians, and other allied health care professionals, working in partnership with parents and other professionals such as audiologists, therapists, and educators, constitute the infant’s medical home. A medical home is defined as an approach to providing health care services with which care is accessible, family centered, continuous, comprehensive, coordinated, compassionate, and culturally competent. The primary health care professional acts in partnership with parents in a medical home to identify and access appropriate audiology, intervention, and consultative services that are needed to develop a global plan of appropriate and necessary health and habilitative care for infants identified with hearing loss and infants with risk factors for hearing loss. All children undergo surveillance for auditory skills and language milestones. The infant’s pediatrician, family physician, or other primary health care professional is in a position to advocate for the child and family.

An audiologist is a person who, by virtue of academic degree, clinical training, and license to practice, is qualified to provide services related to the prevention of hearing loss and the audiological diagnosis, identification, assessment, and nonmedical and nonsurgical treatment of persons with impairment of auditory and vestibular function, and to the prevention of impairments associated with them. Audiologists serve in a number of roles. They provide newborn hearing-screening program development, management, quality assessment, service coordination and referral for audiological diagnosis, and audiological treatment and management. For the follow-up component, audiologists provide comprehensive audiological diagnostic assessment to confirm the existence of the hearing loss, ensure that parents understand the significance of the hearing loss, evaluate the infant for candidacy for amplification and other sensory devices and assistive technology, and ensure prompt referral to early intervention programs. For the treatment and management component, audiologists provide timely fitting and monitoring of amplification devices. Other audiologists may provide diagnostic and auditory treatment and management services in the educational setting and provide a bridge between the child/family and the audiologist in the clinic setting as well as other service providers. Audiologists also provide services as teachers, consultants, researchers, and administrators.

Otolaryngologists are physicians whose specialty includes determining the etiology of hearing loss; identifying related risk indicators for hearing loss, including syndromes that involve the head and neck; and evaluating and treating ear diseases. An otolaryngologist with knowledge of childhood hearing loss can determine if medical and/or surgical intervention may be appropriate. When medical and/or surgical intervention is provided, the otolaryngologist is involved in the long-term monitoring and follow-up with the infant’s medical home. The otolaryngologist provides information and participates in the assessment of candidacy for amplification, assistive devices, and surgical intervention, including reconstruction, bone-anchored hearing aids, and cochlear implantation.

Early intervention professionals are trained in a variety of academic disciplines such as speech-language pathology, audiology, education of children who are deaf or hard of hearing, service coordination, or early childhood special education. All individuals who provide services to infants with hearing loss should have specialized training and expertise in the development of audition, speech, and language. Speech-language pathologists provide both evaluation and intervention services for language, speech, and cognitive-communication development. Educators of children who are deaf or hard of hearing integrate the development of communicative competence within a variety of social, linguistic, and cognitive/academic contexts. Audiologists may provide diagnostic and habilitative services within the individualized family service plan (IFSP) or school-based individualized education plan. To provide the highest quality of intervention, more than 1 provider may be required.

The care coordinator is an integral member of the EHDI team and facilitates the family’s transition from screening to evaluation to early intervention. This person must be a professional (eg, social worker, teacher, nurse) who is knowledgeable about hearing loss. The care coordinator incorporates the family’s preferences for outcomes into an IFSP as required by federal legisla-
tion. The care coordinator supports the family members in their choice of the infant’s communicative development. Through the IFSP review, the infant’s progress in language, motor, cognitive, and social-emotional development is monitored. The care coordinator assists the family in advocating for the infant’s unique developmental needs.

The deaf and hard-of-hearing community includes members with direct experience with signed language, spoken language, hearing-aid and cochlear implant use, and other communication strategies and technologies. Optimally, adults who are deaf or hard-of-hearing should play an integral part in the EHDI program. Both adults and children in the deaf and hard-of-hearing community can enrich the family’s experience by serving as mentors and role models. Such mentors have experience in negotiating their way in a hearing world, raising infants or children who are deaf or hard of hearing, and providing families with a full range of information about communication options, assistive technology, and resources that are available in the community.

A successful EHDI program requires collaboration between a variety of public and private institutions and agencies that assume responsibility for specific components (eg, screening, evaluation, intervention). Roles and responsibilities may differ from state to state. Each state has defined a lead coordinating agency with oversight responsibility. The lead coordinating agency in each state should be responsible for identifying the public and private funding sources available to develop, implement, and coordinate EHDI systems.

Hearing Screening
Multidisciplinary teams of professionals, including audiologists, physicians, and nursing personnel, are needed to establish the UNHS component of EHDI programs. All team members work together to ensure that screening programs are of high quality and are successful. An audiologist should be involved in each component of the hearing-screening program, particularly at the level of statewide implementation and, whenever possible, at the individual hospital level. Hospitals and agencies should also designate a physician to oversee the medical aspects of the EHDI program.

Each team of professionals responsible for the hospital-based UNHS program should review the hospital infrastructure in relationship to the screening program. Hospital-based programs should consider screening technology (ie, OAE or automated ABR testing); validity of the specific screening device; screening protocols, including the timing of screening relative to nursery discharge; availability of qualified screening personnel; suitability of the acoustical and electrical environments; follow-up referral criteria; referral pathways for follow-up; information management; and quality control and improvement. Reporting and communication protocols must be well defined and include the content of reports to physicians and parents, documentation of results in medical charts, and methods for reporting to state registries and national data sets.

Physiologic measures must be used to screen newborns and infants for hearing loss. Such measures include OAE and automated ABR testing. Both OAE and automated ABR technologies provide noninvasive recordings of physiologic activity underlying normal auditory function, both are easily performed in neonates and infants, and both have been successfully used for UNHS. However, there are important differences between the 2 measures. OAE measurements are obtained from the ear canal by using a sensitive microphone within a probe assembly that records cochlear responses to acoustic stimuli. Thus, OAEs reflect the status of the peripheral auditory system extending to the cochlear outer hair cells. In contrast, ABR measurements are obtained from surface electrodes that record neural activity generated in the cochlea, auditory nerve, and brainstem in response to acoustic stimuli delivered via an earphone. Automated ABR measurements reflect the status of the peripheral auditory system, the eighth nerve, and the brainstem auditory pathway.

Both OAE and ABR screening technologies can be used to detect sensory (cochlear) hearing loss; however, both technologies may be affected by outer or middle-ear dysfunction. Consequently, transient conditions of the outer and middle ear may result in a “failed” screening-test result in the presence of normal cochlear and/or neural function. Moreover, because OAEs are generated within the cochlea, OAE technology cannot be used to detect neural (eighth nerve or auditory brainstem pathway) dysfunction. Thus, neural conduction disorders or auditory neuropathy/dyssynchrony without concomitant sensory dysfunction will not be detected by OAE testing.

Some infants who pass newborn hearing screening will later demonstrate permanent hearing loss. Although this loss may reflect delayed-onset hearing loss, both ABR and OAE screening technologies will miss some hearing loss (eg, mild or isolated frequency region losses).

Interpretive criteria for pass/fail outcomes should reflect clear scientific rationale and should be evidence based. Screening technologies that incorporate automated-response detection are necessary to eliminate the need for individual test interpretation, to reduce the effects of screener bias or operator error on test outcome, and to ensure test consistency across infants, test conditions, and screening personnel. When statistical probability is used to make pass/fail decisions, as is the case for OAE and automated ABR screening devices, the likelihood of obtaining a pass outcome by chance alone is increased when screening is performed repeatedly.
This principle must be incorporated into the policies of rescreening. There are no national standards for the calibration of OAE or ABR instrumentation. Compounding this problem, there is a lack of uniform performance standards. Manufacturers of hearing-screening devices do not always provide sufficient supporting evidence to validate the specific pass/fail criteria and/or automated algorithms used in their instruments. In the absence of national standards, audiologists must obtain normative data for the instruments and protocols they use.

The JCIH recognizes that there are important issues differentiating screening performed in the well-infant nursery from that performed in the NICU. Although the goals in each nursery are the same, numerous methodologic and technological issues must be considered in program design and pass/fail criteria.

Screening Protocols in the Well-Infant Nursery
Many inpatient well-infant screening protocols provide 1 hearing screening and, when necessary, a repeat screening no later than at the time of discharge from the hospital, using the same technology both times. Use of either technology in the well-infant nursery will detect peripheral (conductive and sensory) hearing loss of 40 dB or greater. When automated ABR is used as the single screening technology, neural auditory disorders can also be detected. Some programs use a combination of screening technologies (OAE testing for the initial screening followed by automated ABR for rescreening [i.e., 2-step protocol]) to decrease the fail rate at discharge and the subsequent need for outpatient follow-up. With this approach, infants who do not pass an OAE screening but subsequently pass an automated ABR test are considered a screening “pass.” Infants in the well-infant nursery who fail automated ABR testing should not be rescreened by OAE testing and “passed,” because such infants are presumed to be at risk of having a subsequent diagnosis of auditory neuropathy/dyssynchrony.

Screening Protocols in the NICU
An NICU is defined as a facility in which a neonatologist provides primary care for the infant. Newborn units are divided into 3 categories:

- Level I: basic care, well-infant nurseries
- Level II: specialty care by a neonatologist for infants at moderate risk of serious complications
- Level III: a unit that provides both specialty and subspecialty care including the provision of life support (mechanical ventilation)

A total of 120 level-II NICUs and 760 level-III NICUs have been identified in the United States by survey, and infants who have spent time in the NICU represent 10% to 15% of the newborn population. The 2007 JCIH position statement includes neonates at risk of having neural hearing loss (auditory neuropathy/auditory dyssynchrony) in the target population to be identified in the NICU, because there is evidence that neural hearing loss results in adverse communication outcomes. Consequently, the JCIH recommends ABR technology as the only appropriate screening technique for use in the NICU. For infants who do not pass automated ABR testing in the NICU, referral should be made directly to an audiologist for rescreening and, when indicated, comprehensive evaluation, including diagnostic ABR testing, rather than for general outpatient rescreening.

Conveying Test Results
Screening results should be conveyed immediately to families so that they understand the outcome and the importance of follow-up when indicated. To facilitate this process for families, primary health care professionals should work with EHDI team members to ensure that:

- communications with parents are confidential and presented in a caring and sensitive manner, preferably face-to-face;
- educational materials are developed and disseminated to families that provide accurate information at an appropriate reading level and in a language they are able to comprehend; and
- parents are informed in a culturally sensitive and understandable manner that their infant did not pass screening and informed about the importance of prompt follow-up; before discharge, an appointment should be made for follow-up testing.

To facilitate this process for primary care physicians, EHDI systems should ensure that medical professionals receive:

- the results of the screening test (pass, did not pass, or missed) as documented in the hospital medical chart; and
- communication directly from a representative of the hospital screening program regarding each infant in its care who did not pass or was missed and recommendations for follow-up.

Outpatient Rescreening for Infants Who Do Not Pass the Birth Admission Screening
Many well-infant screening protocols will incorporate an outpatient rescreening within 1 month of hospital discharge to minimize the number of infants referred for follow-up audiological and medical evaluation.
Confirmation of Hearing Loss in Infants Referred From UNHS
Infants who meet the defined criteria for referral should receive follow-up audiological and medical evaluations with fitting of amplification devices, as appropriate, at no later than 3 months of age. Once hearing loss is confirmed, coordination of services should be expedited by the infant’s medical home and Part C coordinating agencies for early intervention services, as authorized by the Individuals With Disabilities Education Act, following the EHDI algorithm developed by the AAP (Appendix 1).

Audiological Evaluation
Comprehensive audiological evaluation of newborn and young infants who fail newborn hearing screening should be performed by audiologists experienced in pediatric hearing assessment. The initial audiological test battery to confirm a hearing loss in infants must include physiologic measures and, when developmentally appropriate, behavioral methods. Confirmation of an infant’s hearing status requires a test battery of audiological test procedures to assess the integrity of the auditory system in each ear, to estimate hearing sensitivity across the speech frequency range, to determine the type of hearing loss, to establish a baseline for further monitoring, and to provide information needed to initiate amplification-device fitting. A comprehensive assessment should be performed on both ears even if only 1 ear failed the screening test.

Evaluation: Birth to 6 Months of Age
For infants from birth to a developmental age of approximately 6 months, the test battery should include a child and family history, an evaluation of risk factors for congenital hearing loss, and a parental report of the infant’s responses to sound. The audiological assessment should include:

- Child and family history.
- A frequency-specific assessment of the ABR using air-conducted tone bursts and bone-conducted tone bursts when indicated. When permanent hearing loss is detected, frequency-specific ABR testing is needed to determine the degree and configuration of hearing loss in each ear for fitting of amplification devices.
- Click-evoked ABR testing using both condensation and rarefaction single-polarity stimulus, if there are risk indicators for neural hearing loss (auditory neuropathy/auditory dysynchrony) such as hyperbilirubinemia or anoxia, to determine if a cochlear microphonic is present. Furthermore, because some infants with neural hearing loss have no risk indicators, any infant who demonstrates “no response” on ABR elicited by tone-burst stimuli must be evaluated by a click-evoked ABR.
- Distortion product or transient evoked OAEs.
- Tympanometry using a 1000-Hz probe tone.
- Clinician observation of the infant’s auditory behavior as a cross-check in conjunction with electrophysiologic measures. Behavioral observation alone is not adequate for determining whether hearing loss is present in this age group, and it is not adequate for the fitting of amplification devices.
Evaluation: 6 to 36 Months of Age
For subsequent testing of infants and toddlers at developmental ages of 6 to 36 months, the confirmatory audiological test battery includes:

- Child and family history.
- Parental report of auditory and visual behaviors and communication milestones.
- Behavioral audiometry (either visual reinforcement or conditioned-play audiometry, depending on the child’s developmental level), including pure-tone audiometry across the frequency range for each ear and speech-detection and -recognition measures.
- OAE testing.
- Acoustic immittance measures (tympanometry and acoustic reflexes).
- ABR testing if responses to behavioral audiometry are not reliable or if ABR testing has not been performed in the past.

Other Audiological Test Procedures
At this time, there is insufficient evidence for use of the auditory steady-state response as the sole measure of auditory status in newborn and infant populations. Auditory steady-state response is a new evoked-potential test that can accurately measure auditory sensitivity beyond the limits of other test methods. It can determine frequency-specific thresholds from 250 Hz to 8 kHz. Clinical research is being performed to investigate its potential use in the standard pediatric diagnostic test battery. Similarly, there are insufficient data for routine use of acoustic middle-ear muscle reflexes in the initial diagnostic assessment of infants younger than 4 months. Both tests could be used to supplement the battery or could be included at older ages. Emerging technologies, such as broad-band reflectance, may be used to supplement conventional measures of middle-ear status (tympanometry and acoustic reflexes) as the technology becomes more widely available.

Medical Evaluation
Every infant with confirmed hearing loss and/or middle-ear dysfunction should be referred for otologic and other medical evaluation. The purpose of these evaluations is to determine the etiology of hearing loss, to identify related physical conditions, and to provide recommendations for medical/surgical treatment as well as referral for other services. Essential components of the medical evaluation include clinical history, family history of childhood-onset permanent hearing loss, identification of syndromes associated with early- or late-onset permanent hearing loss, a physical examination, and indicated radiologic and laboratory studies (including genetic testing). Portions of the medical evaluation, such as urine culture for CMV, a leading cause of hearing loss, might even begin in the birth hospital, particularly for infants who spend time in the NICU.

Pediatrician/Primary Care Physician
The infant’s pediatrician or other primary health care professional is responsible for monitoring the general health, development, and well-being of the infant. In addition, the primary care physician must assume responsibility to ensure that the audiological assessment is conducted on infants who do not pass screening and must initiate referrals for medical specialty evaluations necessary to determine the etiology of the hearing loss. Middle-ear status should be monitored, because the presence of middle-ear effusion can further compromise hearing. The primary care physician must partner with other specialists, including the otolaryngologist, to facilitate coordinated care for the infant and family. Because 30% to 40% of children with confirmed hearing loss will demonstrate developmental delays or other disabilities, the primary care physician should closely monitor developmental milestones and initiate referrals related to suspected disabilities. The medical home algorithm for management of infants with either suspected or proven permanent hearing loss is provided in Appendix 1.

The pediatrician or primary care physician should review every infant’s medical and family history for the presence of risk indicators that require monitoring for delayed-onset or progressive hearing loss and should ensure that an audiological evaluation is completed for children at risk of hearing loss at least once by 24 to 30 months of age, regardless of their newborn screening results. Infants with specific risk factors, such as those who received ECMO therapy and those with CMV infection, are at increased risk of delayed-onset or progressive hearing loss and should be monitored closely. In addition, the primary care physician is responsible for ongoing surveillance of parent concerns about language and hearing, auditory skills, and developmental milestones of all infants and children regardless of risk status, as outlined in the pediatric periodicity schedule published by the AAP.

Children with cochlear implants may be at increased risk of acquiring bacterial meningitis compared with children in the general US population. The CDC recommends that all children with, and all potential recipients of, cochlear implants follow specific recommendations for pneumococcal immunization that apply to cochlear implant users and that they receive age-appropriate Haemophilus influenzae type b vaccines. Recommendations for the timing and type of pneumococcal vaccine vary with age and immunization history and should be discussed with a health care professional.
Otolaryngologist

Otolaryngologists are physicians and surgeons who diagnose, treat, and manage a wide range of diseases of the head and neck and specialize in treating hearing and vestibular disorders. They perform a full medical diagnostic evaluation of the head and neck, ears, and related structures, including a comprehensive history and physical examination, leading to a medical diagnosis and appropriate medical and surgical management. Often, a hearing or balance disorder is an indicator of, or related to, a medically treatable condition or an underlying systemic disease. Otolaryngologists work closely with other dedicated professionals, including physicians, audiologists, speech-language pathologists, educators, and others, in caring for patients with hearing, balance, voice, speech, developmental, and related disorders.

The otolaryngologist’s evaluation includes a comprehensive history to identify the presence of risk factors for early-onset childhood permanent hearing loss, such as family history of hearing loss, having been admitted to the NICU for more than 5 days, and having received ECMO (see Appendix 2).70,71

A complete head and neck examination for craniofacial anomalies should document defects of the auricles, patency of the external ear canals, and status of the eardrum and middle-ear structures. Atypical findings on eye examination, including irises of 2 different colors or abnormal positioning of the eyes, may signal a syndrome that includes hearing loss. Congenital permanent conductive hearing loss may be associated with craniofacial anomalies that are seen in disorders such as Crouzon disease, Klippel-Feil syndrome, and Goldenhar syndrome.72 The assessment of infants with these congenital anomalies should be coordinated with a clinical geneticist.

In large population studies, at least 50% of congenital hearing loss has been designated as hereditary, and nearly 600 syndromes and 125 genes associated with hearing loss have already been identified.72,77 The evaluation, therefore, should include a review of family history of specific genetic disorders or syndromes, including genetic testing for gene mutations such as GJB2 (connexin-26), and syndromes commonly associated with early-onset childhood sensorineural hearing loss72,74–76 (Appendix 2). As the widespread use of newly developed conjugate vaccines decreases the prevalence of infectious etiologies such as measles, mumps, rubella, H influenzae type b, and childhood meningitis, the percentage of each successive cohort of early-onset hearing loss attributable to genetic etiologies can be expected to increase, prompting recommendations for early genetic evaluations. Approximately 30% to 40% of children with hearing loss have associated disabilities, which can be of importance in patient management. The decision to obtain genetic testing depends on informed family choice in conjunction with standard confidentiality guidelines.77

In the absence of a genetic or established medical cause, a computed tomography scan of the temporal bones may be performed to identify cochlear abnormalities, such as Mondini deformity with an enlarged vestibular aqueduct, which have been associated with progressive hearing loss. Temporal bone imaging studies may also be used to assess potential candidacy for surgical intervention, including reconstruction, bone-anchored hearing aid, and cochlear implantation. Recent data have shown that some children with electrophysiological evidence suggesting auditory neuropathy/dysynchrony may have an absent or abnormal cochlear nerve that may be detected with MRI.78

Historically, an extensive battery of laboratory and radiographic studies was routinely recommended for newborn infants and children with newly diagnosed sensorineural hearing loss. However, emerging technologies for the diagnosis of genetic and infectious disorders have simplified the search for a definitive diagnosis, which obviates the need for costly diagnostic evaluations in some instances.70,71,79

If, after an initial evaluation, the etiology remains uncertain, an expanded multidisciplinary evaluation protocol including electrocardiography, urinalysis, testing for CMV, and further radiographic studies is indicated. The etiology of neonatal hearing loss, however, may remain uncertain in as many as 30% to 40% of children. Once hearing loss is confirmed, medical clearance for hearing aids and initiation of early intervention should not be delayed while this diagnostic evaluation is in process. Careful longitudinal monitoring to detect and promptly treat coexisting middle-ear effusions is an essential component of ongoing otologic management of these children.

Other Medical Specialists

The medical geneticist is responsible for the interpretation of family history data, the clinical evaluation and diagnosis of inherited disorders, the performance and assessment of genetic tests, and the provision of genetic counseling. Geneticists or genetic counselors are qualified to interpret the significance and limitations of new tests and to convey the current status of knowledge during genetic counseling. All families of children with confirmed hearing loss should be offered, and may benefit from, a genetics evaluation and counseling. This evaluation can provide families with information on etiology of hearing loss, prognosis for progression, associated disorders (eg, renal, vision, cardiac), and likelihood of recurrence in future offspring. This information may influence parents’ decision-making regarding intervention options for their child.

Every infant with a confirmed hearing loss should have an evaluation by an ophthalmologist to document...
visual acuity and rule out concomitant or late-onset vision disorders such as Usher syndrome. Indicated referrals to other medical subspecialists, including developmental pediatricians, neurologists, cardiologists, and nephrologists, should be facilitated and coordinated by the primary health care professional.

**Early Intervention**

Before newborn hearing screening was instituted universally, children with severe-to-profound hearing loss, on average, completed the 12th grade with a 3rd- to 4th-grade reading level and language levels of a 9- to 10-year-old hearing child. In contrast, infants and children with mild-to-profound hearing loss who are identified in the first 6 months of life and provided with immediate and appropriate intervention have significantly better outcomes than later-identified infants and children in vocabulary development, receptive and expressive language, syntax, speech production, and social-emotional development. Children enrolled in early intervention within the first year of life have also been shown to have language development within the normal range of development at 5 years of age.

Therefore, according to federal guidelines, once any degree of hearing loss is diagnosed in a child, a referral should be initiated to an early intervention program within 2 days of confirmation of hearing loss (CFR 303.321d). The initiation of early intervention services should begin as soon as possible after diagnosis of hearing loss but at no later than 6 months of age. Even when the hearing status is not determined to be the primary disability, the family and child should have access to intervention with a provider who is knowledgeable about hearing loss.

UNHS programs have been instituted throughout the United States for the purpose of preventing the significant and negative effects of hearing loss on the cognitive, language, speech, auditory, social-emotional, and academic development of infants and children. To achieve this goal, hearing loss must be identified as quickly as possible after birth, and appropriate early intervention must be available to all families and infants with permanent hearing loss. Some programs have demonstrated that most children with hearing loss and no additional disabilities can achieve and maintain language development within the typical range of children who have normal hearing. Because these studies were descriptive and not causal studies, the efficacy of specific components of intervention cannot be separated from the total provision of comprehensive services. Thus, the family-centered philosophy, the intensity of services, the experience and training of the provider, the method of communication, the curricula, the counseling procedures, the parent support and advocacy, and the deaf and hard-of-hearing support and advocacy are all variables with unknown effects on the overall outcomes of any individual child. The key component of providing quality services is the expertise of the provider specific to hearing loss. These services may be provided in the home, a center, or a combination of the 2 locations.

The term “intervention services” is used to describe any type of habilitative, rehabilitative, or educational program provided to children with hearing loss. In some cases of mild hearing losses, amplification technology may be the only service provided. Some parents choose only developmental assessment or occasional consultation, such as parents with infants who have unilateral hearing losses. Children with high-frequency losses and normal hearing in the low frequencies may only be seen by a speech-language pathologist, and those with significant bilateral sensorineural hearing losses might be seen by an educator of the deaf and receive additional services.

**Principles of Early Intervention**

To ensure informed decision-making, parents of infants with newly diagnosed hearing loss should be offered opportunities to interact with other families who have infants or children with hearing loss as well as adults and children who are deaf or hard of hearing. In addition, parents should also be offered access to professional, educational, and consumer organizations and provided with general information on child development, language development, and hearing loss. A number of principles and guidelines have been developed that offer a framework for quality early intervention service delivery systems for children who are deaf or hard of hearing and their families. Foundational characteristics of developing and implementing early intervention programs include a family-centered approach, culturally responsive practices, collaborative professional-family relationships and strong family involvement, developmentally appropriate practice, interdisciplinary assessment, and community-based provision of services.

**Designated Point of Entry**

States should develop a single point of entry into intervention specific for hearing impairment to ensure that, regardless of geographic location, all families who have infants or children with hearing loss receive information about a full range of options regarding amplification and technology, communication and intervention, and accessing appropriate counseling services. This state system, if separate from the state’s Part C system, should integrate and partner with the state’s Part C program. Parental consent must be obtained according to state and federal requirements to share the IFSP information with providers and transmit data to the state EHDI coordinator.
Regular Developmental Assessment
To ensure accountability, individual, community, and state health and educational programs should assume the responsibility for coordinated, ongoing measurement and improvement of EHDI process outcomes. Early intervention programs must assess the language, cognitive skills, auditory skills, speech, vocabulary, and social-emotional development of all children with hearing loss at 6-month intervals during the first 3 years of life by using assessment tools that have been standardized on children with normal hearing and norm-referenced assessment tools that are appropriate to measure progress in verbal and visual language.

The primary purpose of regular developmental monitoring is to provide valuable information to parents about the rate of their child’s development as well as programmatic feedback concerning curriculum decisions. Families also become knowledgeable about expectations and milestones of typical development of hearing children. Studies have shown that valid and reliable documentation of developmental progress is possible through parent questionnaires, analysis of videotaped conversational interactions, and clinically administered assessments.* Documentation of developmental progress should be provided on a regular basis to parents and, with parental release of information, to the medical home and audiologist. Although criterion-referenced checklists may provide valuable information for establishing intervention strategies and goals, these assessment tools alone are not sufficient for parents and intervention professionals to determine if a child’s developmental progress is comparable with his or her hearing peers.

Opportunities for Interaction With Other Parents of Children With Hearing Loss
Intervention professionals should seek to involve parents at every level of the EHDI process and develop true and meaningful partnerships with parents. To reflect the value of the contributions that selected parents make to development and program components, these parents should be paid as contributing staff members. Parent representatives should be included in all advisory board activities. In many states, parents have been integral and often have taken leadership roles in the development of policy, resource material, communication mechanisms, mentoring and advocacy opportunities, dissemination of information, and interaction with the deaf community and other individuals who are deaf or hard of hearing. Parents, often in partnership with people who are deaf and hard of hearing, have also participated in the training of professionals. They should be participants in the regular assessment of program services to ensure ongoing improvement and quality assurance.

Opportunities for Interaction With Individuals Who Are Deaf or Hard of Hearing
Intervention programs should include opportunities for involvement of individuals who are deaf or hard of hearing in all aspects of EHDI programs. Because intervention programs serve children with mild-to-profound, unilateral or bilateral, permanent conductive, and sensory or neural hearing disorders, role models who are deaf or hard of hearing can be significant assets to an intervention program. These individuals can serve on state EHDI advisory boards and be trained as mentors for families and children with hearing loss who choose to seek their support. Almost all families choose at some time during their early childhood programs to seek out both adults and child peers with hearing loss. Programs should ensure that these opportunities are available and can be delivered to families through a variety of communications means, such as Web sites, e-mail, newsletters, videos, retreats, picnics and other social events, and educational forums for parents.

Provision of Communication Options
Research studies thus far of early-identified infants with hearing loss have not found significant differences in the developmental outcomes by method of communication when measured at 3 years of age.† Therefore, a range of options should be offered to families in a nonbiased manner. In addition, there have been reports of children with successful outcomes for each of the different methods of communication. The choice is a dynamic process on a continuum, differs according to the individual needs of each family, and can be adjusted as necessary on the basis of a child’s rate of progress in developing communication skills. Programs need to provide families with access to skilled and experienced early intervention professionals to facilitate communication and language development in the communication option chosen by the family.

Skills of the Early Intervention Professional
All studies with successful outcomes reported for early-identified children who are deaf or hard of hearing have intervention provided by specialists who are trained in parent-infant intervention services.12,90,97 Early intervention programs should develop mechanisms to ensure that early intervention professionals have special skills necessary for providing families with the highest quality of service specific to children with hearing loss. Professionals with a background in deaf education, audiology, and speech-language pathology will typically have the skills needed for providing intervention services. Professionals should be highly qualified in their respective fields and should be skilled communicators who are knowledgeable and sensitive to the importance of en-

*Refs 10–13, 51, 85, 87–90, and 93–96.
†Refs 10–13, 85, 87, 88, 90, 93, and 96.
hancing families’ strengths and supporting their priorities. When early intervention professionals have knowledge of the principles of adult learning, it increases their success with parents and other professionals.

Quality of Intervention Services

Children with confirmed hearing loss and their families have the right to prompt access to quality intervention services. For newborn infants with confirmed hearing loss, enrollment into intervention services should begin as soon after hearing-loss confirmation as possible and no later than 6 months of age. Successful early intervention programs (1) are family centered, (2) provide families with unbiased information on all options regarding approaches to communication, (3) monitor development at 6-month intervals with norm-referenced instruments, (4) include individuals who are deaf or hard of hearing, (5) provide services in a natural environment in the home or in the center, (6) offer high-quality service regardless of where the family lives, (7) obtain informed consent, (8) are sensitive to cultural and language differences and provide accommodations as needed, and (9) conduct annual surveys of parent satisfaction.

Intervention for Special Populations of Infants and Young Children

Developmental monitoring should also occur at regular 6-month intervals for special populations of children with hearing loss, including those with minimal and mild bilateral hearing loss,36 unilateral hearing loss,99,100 and neural hearing loss,22 because these children are at risk of having speech and language delay. Research findings indicate that approximately one third of children with permanent unilateral loss experience significant language and academic delays.99–101

Audiological Habilitation

Most infants and children with bilateral hearing loss and many with unilateral hearing loss benefit from some form of personal amplification device.32 If the family chooses personal amplification for its infant, hearing-aid selection and fitting should occur within 1 month of initial confirmation of hearing loss even when additional audiological assessment is ongoing. Audiological habilitation services should be provided by an audiologist who is experienced with these procedures. Delay between confirmation of the hearing loss and fitting of an amplification device should be minimized.31,102

Hearing-aid fitting proceeds optimally when the results of physiologic audiological assessment including diagnostic ABR, OAE, and tympanometry and medical examination are in accord. For infants who are below a developmental age of 6 months, hearing-aid selection will be based on physiologic measures alone. Behavioral threshold assessment with visual reinforcement audiometry should be obtained as soon as possible to cross-check and augment physiologic findings (see www.audiology.org).

The goal of amplification-device fitting is to provide the infant with maximum access to all of the acoustic features of speech within an intensity range that is safe and comfortable. That is, amplified speech should be comfortably above the infant’s sensory threshold but below the level of discomfort across the speech frequency range for both ears. To accomplish this in infants, amplification-device selection, fitting, and verification should be based on a prescriptive procedure that incorporates individual real-ear measures that account for each infant’s ear canal acoustics and hearing loss.32 Validation of the benefits of amplification, particularly for speech perception, should be examined in the clinical setting as well as in the child’s typical listening environments. Complementary or alternative technology, such as frequency modulation (FM) systems or cochlear implants, may be recommended as the primary and/or secondary listening device depending on the degree of the infant’s hearing loss, the goals of auditory habilitation, the infant’s acoustic environments, and the family’s informed choices.3 Monitoring of amplification, as well as the long-term validation of the appropriateness of the individual habilitation program, requires ongoing audiological assessment along with electroacoustic, real-ear, and functional checks of the hearing instruments. As the hearing loss becomes more specifically defined through audiological assessments and as the child’s ear canal acoustics change with growth, refinement of the individual prescriptive hearing-aid gain and output targets is necessary. Monitoring also includes periodic validation of communication, social-emotional, and cognitive development and, later, academic performance to ensure that progress is commensurate with the child’s abilities. It is possible that infants and young children with measurable residual “hearing” (auditory responses) and well-fit amplification devices may fail to develop auditory skills necessary for successful spoken communication. Ongoing validation of the amplification device is accomplished through interdisciplinary evaluation and collaboration with the early intervention team and family.

Cochlear implantation should be given careful consideration for any child who seems to receive limited benefit from a trial with appropriately fitted hearing aids. According to US Food and Drug Administration guidelines, infants with profound bilateral hearing loss are candidates for cochlear implantation at 12 months of age and children with bilateral severe hearing loss are eligible at 24 months of age. The presence of developmental conditions (eg, developmental delay, autism) in addition to hearing loss should not, as a rule, preclude the consideration of cochlear implantation for an infant or child who is deaf. Benefits from hearing aids and cochlear implants in children with neural hearing loss
have also been documented. The benefit of acoustic amplification for children with neural hearing loss is variable.\textsuperscript{28,103} Thus, a trial fitting is indicated for infants with neural hearing loss until the usefulness of the fitting can be determined. Neural hearing loss is a heterogeneous condition; the decision to continue or discontinue use of hearing aids should be made on the basis of the benefit derived from amplification. Use of cochlear implants in neural hearing loss is growing, and positive outcomes have been reported for many children.\textsuperscript{28}

Infants and young children with unilateral hearing loss should also be assessed for appropriateness of hearing-aid fitting. Depending on the degree of residual hearing in unilateral loss, a hearing aid may or may not be indicated. Use of “contralateral routing of signals” amplification for unilateral hearing loss in children is not recommended.\textsuperscript{104} Research is currently underway to determine how to best manage unilateral hearing loss in infants and young children.

The effect of otitis media with effusion (OME) is greater for infants with sensorineural hearing loss than for those with normal cochlear function.\textsuperscript{73} Sensory or permanent conductive hearing loss is compounded by additional transient conductive hearing loss associated with OME. OME further reduces access to auditory cues necessary for the development of spoken English. OME also negatively affects the prescriptive targets of the hearing-aid fitting, decreasing auditory awareness and requiring adjustment of the amplification characteristics. Prompt referral to either the primary care physician or an otolaryngologist for treatment of persistent OME is indicated in infants with sensorineural hearing loss.\textsuperscript{105} Definitive resolution of OME should never delay the fitting of an amplification device.\textsuperscript{73,106}

\textbf{Medical and Surgical Intervention}

Medical intervention is the process by which a physician provides medical diagnosis and direction for medical and/or surgical treatment options for hearing loss and/or related medical disorder(s) associated with hearing loss. Treatment varies from the removal of cerumen and the treatment of OME to long-term plans for reconstructive surgery and assessment of candidacy for cochlear implants. If necessary, surgical treatment of malformation of the outer and middle ears, including bone-anchored hearing aids, should be considered in the intervention plan for infants with permanent conductive or mixed hearing loss when they reach an appropriate age.

\textbf{Communication Assessment and Intervention}

Language is acquired with greater ease during certain sensitive periods of infant and toddler development.\textsuperscript{107–109} The process of language acquisition includes learning the precursors of language, such as the rules that pertain to selective attention and turn taking.\textsuperscript{20,110,111} Cognitive, social, and emotional development are influenced by the acquisition of language. Development in these areas is synergistic. A complete language evaluation should be performed at regular intervals for infants and toddlers with hearing loss. The evaluation should include an assessment of oral, manual, and/or visual mechanisms as well as cognitive abilities.

A primary locus of language intervention is to support families in fostering the communication abilities of their infants and toddlers who are deaf or hard of hearing.\textsuperscript{20} Spoken- and/or sign-language development should be commensurate with the child’s age and cognitive abilities and should include acquisition of phonologic (for spoken language), visual/spatial/motor (for signed language), morphologic, semantic, syntactic, and pragmatic skills, depending on the family’s preferred mode of communication.

Early intervention professionals should follow family-centered principles to assist in developing communicative competence of infants and toddlers who are deaf or hard of hearing.\textsuperscript{112–114} Families should be provided with information specific to language development and access to peer and language models as well as family-involved activities that facilitate language development of children with normal hearing and children who are hard of hearing or deaf.\textsuperscript{115,116} Depending on family choices, families should be offered access to children and adults with hearing loss who are appropriate and competent language models. Information on spoken language and signed language, such as American Sign Language\textsuperscript{117} and cued speech, should be provided.

\textbf{Continued Surveillance, Screening, and Referral of Infants and Toddlers}

Appendix 2 presents 11 risk indicators that are associated with either congenital or delayed-onset hearing loss. A single list of risk indicators is presented in the current JCIH statement, because there is significant overlap among those indicators associated with congenital/neonatal hearing loss and those associated with delayed-onset/acquired or progressive hearing loss. Heightened surveillance of all infants with risk indicators, therefore, is recommended. There is a significant change in the definition of risk-indicator 3, which has been modified from NICU stay more than 48 hours to NICU stay more than 5 days. Consistent with 2000 JCIH position statement,\textsuperscript{3} the 2007 position statement recommends use of risk indicators for hearing loss for 3 purposes. Historically, the first use of risk indicators is for the identification of infants who should receive audiological evaluation but who live in geographic locations (eg, developing nations, remote areas) where universal hearing screening is not yet available.\textsuperscript{†} This use has become less common as a result of the expansion of\

\textsuperscript{†}Refs 3, 19, 21, 24, 25, 64, and 118–124.

\textsuperscript{‡}Refs 3, 15, 21, 24, 25, 64, and 118–124.
UNHS. The second purpose of risk-indicator identification is to help identify infants who pass the neonatal screening but are at risk of developing delayed-onset hearing loss and, therefore, should receive ongoing medical, speech and language, and audiological surveillance. Third, the risk indicators are used to identify infants who may have passed neonatal screening but have mild forms of permanent hearing loss.25

Because some important indicators, such as family history of hearing loss, may not be determined during the course of UNHS,14,72 the presence of all risk indicators for acquired hearing loss should be determined in the medical home during early well-infant visits. Risk indicators that are marked with a section symbol in Appendix 2 are of greater concern for delayed-onset hearing loss. Early and more frequent assessment may be indicated for children with CMV infection,118,125,126 syndromes associated with progressive hearing loss,72 neurodegenerative disorders,72 trauma,127–129 or culture-positive postnatal infections associated with sensorineural hearing loss130,131; for children who have received ECMO64 or chemotherapy132; and when there is caregiver concern or a family history of hearing loss.16

For all infants with and without risk indicators for hearing loss, developmental milestones, hearing skills, and parent concerns about hearing, speech, and language skills should be monitored during routine medical care consistent with the AAP periodicity schedule. The JCIH has determined that the previously recommended approach to follow-up of infants with risk indicators for hearing loss only addressed children with identifiable risk indicators and failed to consider the possibility of delayed-onset hearing loss in children without identifiable risk indicators. In addition, concerns were raised about feasibility and cost associated with the 2000 JCIH recommendation for audiological monitoring of all infants with risk indicators at 6-month intervals. Because approximately 400 000 infants are cared for annually in NICUs in the United States, and the 2000 JCIH recommendation included audiology assessments at 6-month intervals from 6 months to 36 months of age for all infants admitted to a NICU for more than 48 hours, an unreasonable burden was placed on both providers of audiology services and families. In addition, there was no provision for identification of delayed-onset hearing loss in infants without an identifiable risk indicator. Data from 2005 for 12 388 infants discharged from NICUs in the National Perinatal Information Network indicated that 52% of infants were discharged within the first 5 days of life, and these infants were significantly less likely to have an identified risk indicator for hearing loss other than NICU stay. Therefore, the 2007 JCIH recommends an alternative, more inclusive strategy of surveillance of all children within the medical home based on the pediatric periodicity schedule. This protocol will permit the detection of children with either missed neonatal or delayed-onset hearing loss irrespective of the presence or absence of a high-risk indicator.

The JCIH recognizes that an optimal surveillance and screening program within the medical home would include the following:

- At each visit, consistent with the AAP periodicity schedule, infants should be monitored for auditory skills, middle-ear status, and developmental milestones (surveillance). Concerns elicited during surveillance should be followed by administration of a validated global screening tool.133 A validated global screening tool is administered to all infants at 9, 18, and 24 to 30 months or, if there is physician or parental concern about hearing or language, sooner.133

- If an infant does not pass the speech-language portion of the global screening in the medical home or if there is physician or caregiver concern about hearing or spoken-language development, the child should be referred immediately for further evaluation by an audiologist and a speech-language pathologist for a speech and language evaluation with validated tools.133

- Once hearing loss is diagnosed in an infant, siblings who are at increased risk of having hearing loss should be referred for audiological evaluation.14,75,134,135

- All infants with a risk indicator for hearing loss (Appendix 2), regardless of surveillance findings, should be referred for an audiological assessment at least once by 24 to 30 months of age. Children with risk indicators that are highly associated with delayed-onset hearing loss, such as having received ECMO or having CMV infection, should have more frequent audiological assessments.

- All infants for whom the family has significant concerns regarding hearing or communication should be promptly referred for an audiological and speech-language assessment.

- A careful assessment of middle-ear status (using pneumatic otoscopy and/or tympanometry) should be completed at all well-child visits, and children with persistent middle-ear effusion that last for 3 months or longer should be referred for otologic evaluation.136

Protecting the Rights of Infants and Families

Each agency or institution involved in the EHDI process shares responsibility for protecting infant and family rights in all aspects of UNHS, including access to information including potential benefits and risks in the family’s native language, input into decision-making, and confidentiality.77 Families should receive information about childhood hearing loss in easily understood language. Families have the right to accept or decline hearing screening or any follow-up care for their newborn...
infant within the statutory regulations, just as they have for any other screening or evaluation procedures or intervention.

EHDI data merit the same level of confidentiality and security afforded all other health care and education information in practice and law. The infant’s family has the right to confidentiality of the screening and follow-up assessments and the acceptance or rejection of suggested intervention(s). In compliance with federal and state laws, mechanisms should be established that ensure parental release and approval of all communications regarding the infant’s test results, including those to the infant’s medical home and early intervention-coordinating agency and programs. The Health Insurance Portability and Accountability Act (Pub L No. 104-191 [1996]) regulations permit the sharing of health information among health care professionals.

**Information Infrastructure**

In its 2000 position statement, the JCIH recommended development of uniform state registries and national information databases that incorporate standardized methodology, reporting, and system evaluation. EHDI information systems are to provide for the ongoing and systematic collection, analysis, and interpretation of data in the process of measuring and reporting associated program services (eg, screening, evaluation, diagnosis, and/or intervention). These systems are used to guide activities, planning, implementation, and evaluation of programs and to formulate research hypotheses.

EHDI information systems are generally authorized by legislators and implemented by public health officials. These systems vary from a simple system that collects data from a single source to electronic systems that receive data from many sources in multiple formats. The number and variety of systems will likely increase with advances in electronic data interchange and integration of data, which will also heighten the importance of patient privacy, data confidentiality, and system security. The appropriate agencies and/or officials should be consulted for any projects regarding public health surveillance.

Federal and state agencies are collaborating in the standardization of data definitions to ensure the value of data sets and to prevent misleading or unreliable information. Information management is used to improve services to infants and their families; to assess the quantity and timeliness of screening, evaluation, and enrollment into intervention; and to facilitate collection of demographic data on neonatal and infant hearing loss.

The JCIH endorses the concept of a limited national database to permit documentation of the demographics of neonatal hearing loss, including prevalence and etiology across the United States. The information obtained from the information-management system should assist both the primary health care professional and the state health agency in measuring quality indicators associated with program services (eg, screening, diagnosis, and intervention). The information system should provide measurement tools to determine the degree to which each process is stable and sustainable and conforms to program benchmarks. Timely and accurate monitoring of relevant quality measures is essential.

Since 1999, the CDC and the Directors of Speech and Hearing Programs in State Health and Welfare Agencies (DSHPSHWA) have collected annual aggregate EHDI program data needed to address the national EHDI goals. In 1999, a total of 22 states provided data for the DSHPSHWA survey. Participation had increased to 48 states, 1 territory, and the District of Columbia in 2003. However, many programs have been unable to respond to all the questions on the survey because of lack of a statewide comprehensive data-management and reporting system.

The Government Performance and Results Act (GPRA) of 1993 (Pub L No. 103-62) requires that federal programs establish measurable goals approved by the US Office of Management and Budget (OMB) that can be reported as part of the budgetary process, thus linking future funding decisions with performance. The HRSA has modified its reporting requirements for all grant programs. The GPRA measures that must be reported to the OMB by the MCHB annually for the EHDI program are:

- the number of infants screened for hearing loss before discharge from the hospital;
- the number of infants with confirmed hearing loss at no later than 3 months of age;
- the number of infants enrolled in a program of early intervention at no later than 6 months of age;
- the number of infants with confirmed or suspected hearing loss referred to an ongoing source of comprehensive health care (ie, medical home); and
- the number of children with nonsyndromic hearing loss who have developmentally appropriate language and communication skills at school entry.

One GPRA measure that must be reported to the OMB by the CDC annually for the EHDI program is the percentage of newborn infants with a positive screening result for hearing loss who are subsequently lost to follow-up.

EHDI programs have made tremendous gains in their ability to collect, analyze, and interpret data in the process of measuring and reporting associated program services. However, only a limited number of EHDI programs are currently able to accurately report the number of infants screened, evaluated, and enrolled in intervention, the age of time-related objectives (eg, screening by 1 month of age), and the severity or laterality of hearing loss. This is complicated by the lack of data standards and
by privacy issues within the regulations of the Family Educational Rights and Privacy Act of 1974 (Pub L No. 93-380).

Given the current lack of standardized and readily accessible sources of data, the CDC EHDI program, in collaboration with the DSHPSHWA, developed a revised survey to obtain annual EHDI data from states and territories in a consistent manner to assess progress toward meeting the national EHDI goals and the Healthy People 2010 objectives. In October 2006, the OMB, which is responsible for reviewing all government surveys, approved the new EHDI hearing screening and follow-up survey. To facilitate this effort, the CDC EHDI Data Committee is establishing the minimum data elements and definitions needed for information systems to be used to assess progress toward the national EHDI goals.

The JCIH encourages the CDC and HRSA to continue their efforts to identify barriers and explore possible solutions with EHDI programs to ensure that children in each state who seek hearing-related services in states other than where they reside receive all recommended screening and follow-up services. EHDI systems should also be designed to promote the sharing of data regarding early hearing loss through integration and/or linkage with other child health information systems. The CDC currently provides funds to integrate the EHDI system with other state/territorial screening, tracking, and surveillance programs that identify children with special health care needs. Grantees of the MCHB are encouraged to link hearing-screening data with such child health data sets as electronic birth certificates, vital statistics, birth defects registries, metabolic or newborn dried “blood-spot” screenings, immunization registries, and others.

To promote the best use of public health resources, EHDI information systems should be evaluated periodically, and such evaluations should include recommendations for improving quality, efficiency, and usefulness. The appropriate evaluation of public health surveillance systems becomes paramount as these systems adapt to revise case definitions, address new health-related events, adopt new information technology, ensure data confidentiality, and assess system security.

Currently, federal sources of support include Title V block grants to states for maternal and child health care services, Title XIX (Medicaid) federal and state funds for eligible children, and competitive US Department of Education personnel preparation and research grants. The NICHD provides grants for research related to early identification and intervention for children who are deaf or hard of hearing.

Universities should assume responsibility for special-track, interdisciplinary, professional education programs for early intervention for infants and children with hearing loss. Universities should also provide training in family systems, the grieving process, cultural diversity, auditory skill development, and deaf culture. There is a critical need for in-service and preservice training of professionals related to EHDI programs, which is particularly acute for audiologists and early interventionists with expertise in hearing loss. This training will require increased and sustained funding for personnel preparation.

Benchmarks and Quality Indicators

The JCIH supports the concept of regular measurements of performance and recommends routine monitoring of these measures for interprogram comparison and continuous quality improvement. Performance benchmarks represent a consensus of expert opinion in the field of newborn hearing screening and intervention. The benchmarks are the minimal requirements that should be attained by high-quality EHDI programs. Frequent measures of quality permit prompt recognition and correction of any unstable component of the EHDI process.

Quality Indicators for Screening

- Percentage of all newborn infants who complete screening by 1 month of age; the recommended benchmark is more than 95% (age correction for preterm infants is acceptable).
- Percentage of all newborn infants who fail initial screening and fail any subsequent rescreening before comprehensive audiological evaluation; the recommended benchmark is less than 4%.

Quality Indicators for Confirmation of Hearing Loss

- Of infants who fail initial screening and any subsequent rescreening, the percentage who complete a comprehensive audiological evaluation by 3 months of age; the recommended benchmark is 90%.
- For families who elect amplification, the percentage of infants with confirmed bilateral hearing loss who receive amplification devices within 1 month of confirmation of hearing loss; the recommended benchmark is 95%.

Quality Indicators for Early Intervention

- For infants with confirmed hearing loss who qualify for Part C services, the percentage for whom parents have signed an IFSP by no later than 6 months of age; the recommended benchmark is 90%.
- For children with acquired or late-identified hearing loss, the percentage for whom parents have signed an IFSP within 45 days of the diagnosis; the recommended benchmark is 95%.
- The percentage of infants with confirmed hearing loss who receive the first developmental assessment with
standardized assessment protocols (not criterion reference checklists) for language, speech, and nonverbal cognitive development by no later than 12 months of age; the recommended benchmark is 90%.

CURRENT CHALLENGES, OPPORTUNITIES, AND FUTURE DIRECTIONS

Despite the tremendous progress made since 2000, there are challenges to the success of the EHDI system.

Challenges

All of the following listed challenges are considered important for the future development of successful EHDI systems:

- Too many children are lost between the failed screening and the rescreening and between the failed rescreening and the diagnostic evaluation.
- There is a shortage of professionals with skills and expertise in both pediatrics and hearing loss, including audiologists, deaf educators, speech-language pathologists, early intervention professionals, and physicians.
- There is often a lack of timely referral for diagnosis of, and intervention for, suspected hearing loss in children.
- Consistent and stable state and federal funding is needed for program sustainability.
- When compared with services provided for adults, pediatric services in all specialties are poorly reimbursed.
- Access to uniform Part C services is inadequate among states and within states.
- There is a lack of integrated state data-management and tracking systems.
- Demographics and cultural diversity are changing rapidly.
- Funding for hearing aids, loaner programs, cochlear implants, and FM systems is needed.
- There is a lack of specialized services for children with multiple disabilities and hearing loss.
- Children may not qualify for services (state Part C guidelines) before demonstrating language delays (prevention model versus deficit model).
- Children may not qualify for assistive technology (prevention model versus deficit model).
- There is a lack of in-service education for key professionals.
- There are regulatory barriers to sharing information among providers and among states.
- No national standards exist for the calibration of OAE or ABR instrumentation, and there is a lack of uniform performance standards.

Opportunities for System Development and Research

- Establish programs to ensure the development of communication for infants and children with all degrees and types of hearing loss, allowing them access to all educational, social, and vocational opportunities throughout their life span.
- Develop improved, rapid, reliable screening technology designed to differentiate specific types of hearing loss.
- Develop and validate screening technologies for identifying minimal hearing loss.
- Develop state data-management systems with the capacity for the accurate determination of the prevalence for delayed-onset or progressive hearing loss.
- Develop state data-tracking systems to follow infants with suspected and confirmed hearing loss through individual state EHDI programs.
- Track the certification credentials of the service providers for children with confirmed hearing loss who are receiving Part C early intervention services and early childhood special education.
- Track genetic, environmental, and pharmacologic factors that contribute to hearing loss, thus allowing for tailored prevention and intervention strategies.
- Continue to refine electrophysiologic diagnostic techniques, algorithms, and equipment to enable frequency-specific threshold assessment for use with very young infants.
- Continue to refine techniques to improve the selection and fitting of appropriate amplification devices in infants and young children.
- Conduct translational research pertaining to young children with hearing loss, in particular, genetic, diagnostic, and outcomes studies.
- Initiate prospective population-based studies to determine the prevalence and natural history of auditory neural conduction disorders.
- Conduct efficacy studies to determine appropriate early intervention strategies for infants and children with all degrees and types of hearing loss.
- Conclude additional studies on the efficacy of intervention for infants and children who receive cochlear implants at younger than 2 years.
- Conduct additional studies on the efficacy of hearing-aid use in infants and children younger than 2 years.
• Conduct additional studies of the auditory development of children who have appropriate amplification devices in early life.
• Expand programs within health, social service, and education agencies associated with early intervention and Head Start programs to accommodate the needs of the increasing numbers of early-identified children.
• Adapt education systems to capitalize on the abilities of children with hearing loss who have benefited from early identification and intervention.
• Develop genetic and medical procedures that will determine more rapidly the etiology of hearing loss.
• Ensure transition from Part C (early intervention) to Part B (education) services in ways that encourage family participation and ensure minimal disruption of child and family services.
• Study the effects of parents’ participation in all aspects of early intervention.
• Test the utility of a limited national data set and develop nationally accepted indicators of EHDI system performance.
• Encourage the identification and development of centers of expertise in which specialized care is provided in collaboration with local service providers.
• Obtain the perspectives of individuals who are deaf or hard of hearing in developing policies regarding medical and genetic testing and counseling for families who carry genes associated with hearing loss.139

CONCLUSIONS
Since the 2000 JCIH statement, tremendous and rapid progress has been made in the development of EHDI systems as a major public health initiative. The percentage of infants screened annually in the United States has increased from 38% to 95%. The collaboration at all levels of professional organizations, federal and state government, hospitals, medical homes, and families has contributed to this remarkable success. New research initiatives to develop more sophisticated screening and diagnostic technology, improved digital hearing-aid and FM technologies, speech-processing strategies in cochlear implants, and early intervention strategies continue. Major technological breakthroughs have been made in facilitating the definitive diagnosis of both genetic and nongenetic etiologies of hearing loss. In addition, outcomes studies to assess the long-term outcomes of special populations, including infants and children with mild and unilateral hearing loss, neural hearing loss, and severe or profound hearing loss managed with cochlear implants, have been providing information on the individual and societal impact and the factors that contribute to an optimized outcome. It is apparent, however, that there are still serious challenges to be overcome and system barriers to be conquered to achieve optimal EHDI systems in all states in the next 5 years. Follow-up rates remain poor in many states, and funding for amplification in children is inadequate. Funding to support outcome studies is necessary to guide intervention and to determine factors other than hearing loss that affect child development. The ultimate goal, to optimize communication, social, academic, and vocational outcomes for each child with permanent hearing loss, must remain paramount.

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ACKNOWLEDGMENTS
We acknowledge the contribution of John Eichwald, MA, and Irene Forsman, MS, RN.

Joint committee member organizations that have adopted this statement include (in alphabetical order): the Alexander Graham Bell Association for the Deaf and Hard of Hearing, the American Academy of Audiology, the American Academy of Otolaryngology-Head and Neck Surgery, the AAP, the American Speech-Language-Hearing Association, the Council on Education of the Deaf (see individual organizations listed above), and the Directors of Speech and Hearing Programs in State Health and Welfare Agencies.

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139. Brick K. Genetics of deafness, deaf people and the past, present and future. Presented at: Workshop on the Genetics of Congenital Hearing Impairment; June 7, 1999; Atlanta, GA


APPENDIX 2: RISK INDICATORS ASSOCIATED WITH PERMANENT CONGENITAL, DELAYED-ONSET, OR PROGRESSIVE HEARING LOSS IN CHILDHOOD

Risk indicators that are marked with a “§” are of greater concern for delayed-onset hearing loss.

1. Caregiver concern§ regarding hearing, speech, language, or developmental delay.

2. Family history§ of permanent childhood hearing loss.

3. Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: ECMO,§ assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia that requires exchange transfusion.

4. In utero infections, such as CMV,§ herpes, rubella, syphilis, and toxoplasmosis.

5. Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies.

6. Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss.

7. Syndromes associated with hearing loss or progressive or late-onset hearing loss,§ such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen.

8. Neurodegenerative disorders,§ such as Hunter syndrome, or sensorimotor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth disease.

9. Culture-positive postnatal infections associated with sensorineural hearing loss,§ including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis.

10. Head trauma, especially basal skull/temporal bone fractures§ that requires hospitalization.

11. Chemotherapy.§
Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs
Joint Committee on Infant Hearing

Pediatrics 2007;120;898
DOI: 10.1542/peds.2007-2333

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Joint Committee on Infant Hearing
Pediatrics 2007;120;898
DOI: 10.1542/peds.2007-2333

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EFFECT OF GANCICLOVIR THERAPY ON HEARING IN SYMPTOMATIC CONGENITAL CYTOMEGALOVIRUS DISEASE INVOLVING THE CENTRAL NERVOUS SYSTEM: A RANDOMIZED, CONTROLLED TRIAL

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Objective  To evaluate the efficacy and safety of ganciclovir therapy in neonates with congenital cytomegalovirus (CMV) disease.

Study design  Neonates with symptomatic CMV disease involving the central nervous system were randomly assigned to receive 6 weeks of intravenous ganciclovir versus no treatment. The primary end point was improved brainstem-evoked response (BSER) between baseline and 6-month follow-up (or, for patients with normal baseline hearing, normal BSER at both time points).

Results  From 1991 to 1999, 100 patients were enrolled. Of these, 42 patients had both a baseline and 6-month follow-up BSER audiometric examination and thus were evaluable for the primary end point. Twenty-one (84%) of 25 ganciclovir recipients had improved hearing or maintained normal hearing between baseline and 6 months versus 10 (59%) of 17 control patients ($P = .06$). None (0%) of 25 ganciclovir recipients had worsening in hearing between baseline and 6 months versus 7 (41%) of 17 control patients ($P < .01$). A total of 43 patients had a BSER at both baseline and at 1 year or beyond. Five (21%) of 24 ganciclovir recipients had worsening of hearing between baseline and $\geq 1$ year versus 13 (68%) of 19 control patients ($P < .01$). A total of 89 patients had absolute neutrophil counts determined during the course of the study; 29 (63%) of 46 ganciclovir-treated patients had grade 3 or 4 neutropenia during treatment versus 9 (21%) of 43 control patients ($P < .01$).

Conclusions  Ganciclovir therapy begun in the neonatal period in symptomatically infected infants with CMV infection involving the central nervous system prevents hearing deterioration at 6 months and may prevent hearing deterioration at $\geq 1$ year. Almost two thirds of treated infants have significant neutropenia during therapy. (J Pediatr 2003;143:16-25)

Congenital cytomegalovirus (CMV) infection is the most frequently identified viral cause of mental retardation and is the leading nongenetic cause of neurosensory hearing loss in developed countries, including the United States. It also is the most common congenital infection in human beings, with approximately 1% of all infants born alive in the United States being infected with CMV (approximately 40,000 infants per year). Of infected fetuses, approximately 10% are symptomatic at birth, and 90% of symptomatic survivors have significant neurologic sequelae, including hearing deficits in 30% to 65%. The overall societal costs of providing specialized services for
surviving infants and children with congenital CMV infections approaches $1.9 billion per year.\textsuperscript{14}

No effective antiviral therapy exists for the treatment of congenital CMV disease. Despite its associated toxicities, ganciclovir is the most promising antiviral agent currently available for evaluation in this population. After completing a phase II pharmacokinetic/pharmacodynamic study,\textsuperscript{15-17} the Collaborative Antiviral Study Group (CASG) of the National Institute of Allergy and Infectious Diseases conducted a randomized, controlled, phase III study of the effects of intravenous ganciclovir on hearing in the treatment of symptomatic congenital CMV disease involving the central nervous system (CNS).

METHODS

Study Population

Neonates with symptomatic (clinically apparent disease in the newborn period) congenital CMV disease involving the CNS were eligible for enrollment into this trial. All study subjects had confirmed isolation of CMV from a urine specimen obtained before study enrollment and within the first month of life,\textsuperscript{15} and all had evidence of CNS disease, such as (1) microcephaly; (2) intracranial calcifications; (3) abnormal cerebrospinal fluid (CSF) for age; (4) chorioretinitis; and/or (5) hearing deficits. Infants \( \leq 1 \) month of age, \( \geq 32 \) weeks' gestation, and weighing \( \geq 1200 \) g at birth were eligible for study participation. Patients were ineligible for the study if death was imminent, if they received other antiviral agents or immune globulin, had creatinine \( >1.5 \) mg/dL, were HIV-infected, or had hydranencephaly.

Study Design and Objectives

After informed consent from the parent(s) or legal guardian(s), patients were randomly assigned to receive ganciclovir treatment (6 mg/kg per dose administered intravenously every 12 hours for 6 weeks) or no treatment. A placebo arm was not used because of ethical concerns over maintaining intravenous access for 6 weeks. Institutional review boards at each participating study center approved the protocol. Ganciclovir was provided by F. Hoffmann-La Roche, Inc (Nutley, NJ).

The primary study end point was brainstem-evoked response (BSER) audiometry improvement by one gradation (eg, moderate impairment at baseline and mild impairment at follow-up) between baseline and the 6-month follow-up (or, for those patients with normal hearing at baseline, normal BSER at both time points). Nonprimary end points included evidence of laboratory (thrombocytopenia, hepatitis) and clinical (organomegaly, chorioretinitis) improvement, rate of growth, and death.

Audiologic Observations

Audiologic assessments were made by BSER at study entry, 6 weeks, 6 months, 1 year, and 2 years. For audiologic assessments beyond 2 years, only BSER hearing assessments were used in the efficacy analyses comparing baseline results and follow-up outcomes. The BSER thresholds were defined as normal hearing 0- to 20-dB thresholds, mild hearing loss 21- to 45-dB thresholds, moderate hearing loss 46 to 70 dB thresholds, and severe hearing loss \( \geq 71 \) dB thresholds.\textsuperscript{5,13} BSER threshold was defined as the lowest intensity level at which wave V could be detected and replicated. To eliminate variability between study sites, a single CASG Central Unit audiologist who was masked to randomization reviewed all BSER reports from all study patients and classified all evaluable ears as normal hearing, mild hearing loss, moderate hearing loss, and severe hearing loss.

Audiologic analyses were performed on best evaluable ear (“functional” assessment) and on total evaluable ears (“biological” assessment). The best-ear assessment correlates with functional hearing impairment in daily living (eg, a person with mild hearing impairment in one ear and severe hearing impairment in the other ear will function essentially as a mildly hearing impaired person).\textsuperscript{18,19} Total ear assessment further assesses the biological effects of ganciclovir therapy. Odd numbers of total ears by treatment category are reported because at a given follow-up visit, a patient may have had only one ear that was evaluable (eg, otitis media on one side [nonevaluable], normal ear on the other [evaluable]).

Laboratory Observations

Patients randomly assigned to receive ganciclovir therapy had laboratory assessments for drug toxicity (complete blood counts, alanine aminotransferase [ALT], bilirubin, uric acid, creatinine) performed at study entry and on days 3, 5, 7, 10, 14, 17, 21, 28, 35, and 42. Patients randomly assigned to no therapy had laboratory assessments obtained weekly. Toxicity assessments were quantified with the use of the NIAID Division of AIDS Toxicity Tables, 1994.\textsuperscript{20}

Modification of Dose

If a patient’s absolute neutrophil count (ANC) fell below 500 cells/mm\(^3\), ganciclovir was held until the ANC recovered to \( >750 \) cells/mm\(^3\), at which time it was resumed at the full dose. If bone marrow suppression recurred, the ganciclovir dosage was decreased by 50% until the ANC rose above 500 cells/mm\(^3\). If bone marrow suppression persisted at the 50% dosage, ganciclovir was discontinued.

Statistical Analysis

The Wilcoxon rank sum test and the Fisher exact test were used to compare the differences in baseline characteristics between the ganciclovir and the no-treatment groups or between evaluable (ie, patients who had both a baseline and a follow-up BSER assessment) and nonevaluable patients, by treatment category.

Treatment effect on change in BSER in the best ear was evaluated by means of the Fisher exact test. Logistic regression with generalized estimating equations\textsuperscript{21} was used to assess change in BSER between the two treatment groups for total evaluable ears.
In addition, hearing assessments for best ear and total evaluable ears were performed with adjustment for potential influential factors. The factors explored in these logistic regression analyses included CT scan abnormalities, baseline intracranial calcifications, hepatomegaly, splenomegaly, microcephaly, chorioretinitis, growth retardation at birth, petechial rash, CSF protein concentration, seizures, ANC, bilirubin, creatinine, platelet, ALT, prematurity, and baseline BSER. Significant factors that were incorporated in the final multivariate model included baseline BSER, prematurity, CT scan abnormality, CSF protein concentration, chorioretinitis, and seizures. Since none of the ganciclovir recipients had worsening of hearing between baseline and the 6-month follow-up, the Bayesian approach with Jeffrey’s prior shrinking toward zero was used for evaluation of hearing deterioration at 6 months.

To investigate potential effects of patients who did not complete the study, comparisons of baseline demographic and clinical characteristics between evaluable and nonevaluable patients within each treatment group were performed. In addition, logistic regression analyses with adjustment for the potential influential factors on hearing were also performed, as above, to evaluate the treatment effect on hearing change to take into account the potential differences between the two treatment groups resulting from the high dropout rate.

The Fisher exact test was used to compare other clinical efficacy end points and safety evaluations between treatment groups. The Wilcoxon rank-sum test was used to assess the effect of ganciclovir on growth. The log-rank test was applied to analyze time to resolution of clinical and laboratory abnormalities and mortality rate between treatment groups. SAS software was used for all analyses.

At the initiation of the study, sample size calculations projected 130 enrolled patients to provide 100 evaluable patients. Power calculations were based only on the primary end point. Interim analyses by the data and safety monitoring board were incorporated into the study protocol at the time of initial protocol development. Following the third of these interim analyses in December, 1999, the DSMB recommended early termination of the trial based on favorable preliminary study results and in recognition of the challenges in patient accrual and follow-up.

RESULTS

Population Characteristics

From 1991 through 1999, 100 patients from 18 CASG sites enrolled patients in this clinical trial. These sites and their corresponding enrollment numbers were University of Alabama at Birmingham, 15 subjects; University of Texas Southwestern Medical Center and University of Florida at Gainesville, 13 subjects each; Baylor College of Medicine, 11 subjects; University of Arkansas, 9 subjects; University of California at San Diego, 7 subjects; University of Alberta and Cook Fort Worth Children’s Medical Center, 6 subjects each; Vanderbilt University, 5 subjects; Medical College of Virginia and University of Southern California, 3 subjects each; Tulane University and Children’s Mercy Hospital in Kansas City, 2 subjects each; Carolinas Medical Center, University of Iowa, Maimonides Medical Center New York, Park Nicollet Medical Center Minnesota, and State University of New York, 1 subject each. Accrual by year was as follows: 1991, 4 subjects; 1992, 14 subjects; 1993, 12 subjects; 1994, 16 subjects; 1995, 9 subjects; 1996, 16 subjects; 1997, 13 subjects; 1998, 10 subjects; and 1999, 6 subjects.

Of these 100 subjects, 42 patients met all study entry criteria, had both a baseline and a 6-month follow-up BSER audiometric examination, and thus were evaluable for the primary end point. Two additional patients who had both baseline and 6-month follow-up BSERs did not meet all inclusion criteria (1 enrolled at 29 weeks’ gestational age and randomly assigned to no treatment, 1 enrolled at 33 days of life and randomly assigned to ganciclovir), and 3 additional patients who had not had their 6-month follow-up at the time of data analysis. Of the remaining 53 patients, 18 had hearing assessments that were not BSERs; 15 had parental hardships necessitating their withdrawal from the study; 7 patients died before the 6-month follow-up; 5 patients had transportation difficulties; 5 patients relocated; and 3 patients refused follow-up visits.

Comparisons of the baseline demographic and clinical characteristics by treatment category of patients who were evaluable for the primary end point and of those who were nonevaluable are presented in Table I. No significant differences existed at baseline between the evaluable and nonevaluable patients with regard to clinical and laboratory measures of severity of congenital CMV disease (baseline BSER assessments, head circumference, intracranial calcifications, serum transaminase elevation, neutropenia, thrombocytopenia, hyperbilirubinemia, and organomegaly). Among the ganciclovir recipients, a higher percentage of nonevaluable patients were black, and a majority were born prematurely.

Baseline demographic and clinical characteristics for patients whose BSER assessments were available at both baseline and 6 months and at both baseline and ≥ 1 year are shown in Table II. All characteristics at baseline were comparable between the ganciclovir and the no-treatment groups.

More than three quarters of enrolled patients were evaluable for each of the nonprimary end points. The analyses that follow include all evaluable patients for each of the respective end points.

Hearing Efficacy Analyses

Follow-up at 6 Months. A total of 42 patients meeting all entry criteria were available for assessment of hearing change in the best ear at 6 months. Of these, 25 received ganciclovir and 17 received no treatment. For the biological total ear hearing evaluation, there were 85 ears with both baseline and 6-month BSER assessments, with 49 ears from ganciclovir recipients and 36 ears from control patients.
Twenty-one (84%) of 25 ganciclovir recipients had hearing improvement or maintained normal hearing in their best ear at 6 months, compared with 10 (59%) of 17 patients in the no-treatment group (adjusted \( P = .06 \)) (Tables III and IV). Inclusion in the best-ear analyses of the 2 additional patients who did not meet all entry criteria (above) yielded an adjusted \( P \) value of .03. For total evaluable ears, the effect of ganciclovir on hearing improvement or maintenance of normal hearing at 6 months was statistically significant in both the unadjusted and adjusted analyses (Tables III and IV).

No ganciclovir recipient had hearing deterioration at 6 months compared with 41% of control patients (adjusted \( P < .01 \)) (Tables III and IV). Similar statistically significant effects on protection against hearing deterioration were seen in the total ear analyses as well (Tables III and IV).

For patients with best-ear hearing improvement between baseline and 6 months, the mean decibel change was >20 dB for ganciclovir recipients and was 25 dB for patients in the control group (Appendix 1). For patients with best-ear hearing deterioration between baseline and 6 months, the mean decibel change was >36.7 dB for patients in the control group (Appendix 1).

As noted above, 18 of the 53 patients who were nonevaluable for the primary end point had a follow-up
hearing assessment that was not a BSER. The alternative hearing tests performed were behavioral observation audiometry, visual reinforcement audiometry, and otoacoustics emissions. Of these 18 patients, 7 received ganciclovir (3 had hearing improvement, 3 maintained normal hearing, and 1 was unevaluable between baseline and 6 months) and 11 received no treatment (1 had hearing improvement, 1 maintained normal hearing, 1 maintained the same degree of hearing loss, 2 had worsened hearing [both of whom were deaf at follow-up] and 6 were unevaluable between baseline and 6 months).

**FOLLOW-UP AT OR BEYOND 1 YEAR.** A total of 43 patients were available for evaluation of BSER hearing change in the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ganciclovir (n = 24)</th>
<th>No treatment (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (d)</td>
<td>9.5</td>
<td>12</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (46%)</td>
<td>14 (74%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male</td>
<td>13 (54%)</td>
<td>5 (26%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (63%)</td>
<td>13 (68%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Black</td>
<td>5 (21%)</td>
<td>3 (16%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (17%)</td>
<td>3 (16%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Prematurity (≤ 37 wk)</td>
<td>11 (46%)</td>
<td>5 (26%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Median gestational age (wk)</td>
<td>38</td>
<td>38</td>
<td>0.50</td>
</tr>
<tr>
<td>Median weight (kg)</td>
<td>2.53</td>
<td>2.6</td>
<td>0.88</td>
</tr>
<tr>
<td>Median head circumference (cm)</td>
<td>31</td>
<td>31.5</td>
<td>0.81</td>
</tr>
<tr>
<td>Abnormal CT (calcifications)</td>
<td>21/24 (88%)</td>
<td>14/16 (88%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abnormal CSF indices</td>
<td>9/21 (43%)</td>
<td>9/15 (60%)</td>
<td>0.50</td>
</tr>
<tr>
<td>ALT ≥ 100 IU/L</td>
<td>5/23 (22%)</td>
<td>3/17 (18%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Platelet count ≤ 100,000/mm³</td>
<td>10/24 (42%)</td>
<td>7/17 (41%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abnormal bilirubin</td>
<td>3/24 (13%)</td>
<td>4/16 (25%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15 (60%)</td>
<td>13 (76%)</td>
<td>.33</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>16 (64%)</td>
<td>13 (76%)</td>
<td>.50</td>
</tr>
<tr>
<td>ANC grade 3-4</td>
<td>4/24 (17%)</td>
<td>1/16 (6%)</td>
<td>.63</td>
</tr>
<tr>
<td>Normal</td>
<td>15 (60%)</td>
<td>10 (59%)</td>
<td>.39</td>
</tr>
<tr>
<td>Mild</td>
<td>5 (20%)</td>
<td>5 (29%)</td>
<td>.41</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>.41</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (20%)</td>
<td>7 (29%)</td>
<td>.7</td>
</tr>
<tr>
<td>Baseline BSER (best ear)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23/49 (47%)</td>
<td>18/36 (50%)</td>
<td>.37</td>
</tr>
<tr>
<td>Mild</td>
<td>8/49 (16%)</td>
<td>11/36 (31%)</td>
<td>.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>3/49 (6%)</td>
<td>3/36 (8%)</td>
<td>.5</td>
</tr>
<tr>
<td>Severe</td>
<td>15/49 (31%)</td>
<td>4/36 (11%)</td>
<td>.9</td>
</tr>
</tbody>
</table>

*The denominator represents the number of total evaluable ears. P value was obtained from a logistic regression analysis using generalized estimating equations.

Table II. Comparison of baseline demographic and clinical characteristics in infants with evaluable hearing outcomes at 6 months and at ≥ 1 year.
**Table III. Unadjusted analyses of change in BSER**

<table>
<thead>
<tr>
<th></th>
<th>Change between baseline and 6 months</th>
<th>Change between baseline and ≥ 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best ear assessment</td>
<td>Total ear assessment</td>
</tr>
<tr>
<td>Ganciclovir (n = 25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ganciclovir (n = 49)</td>
<td>No treatment (n = 36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved hearing between baseline and follow-up</td>
<td>6 (24%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>No change—normal hearing at baseline and follow-up</td>
<td>15 (60%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>No change—same degree of hearing loss at both baseline and follow-up</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Worsening hearing between baseline and follow-up</td>
<td>0 (0%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Improved + no change (normal to normal)</td>
<td>Improved + no change (normal to normal)</td>
<td>Improved + no change (normal to normal)</td>
</tr>
<tr>
<td>vs other: P = .086</td>
<td>vs other: P = .011</td>
<td>vs other: P = .133</td>
</tr>
<tr>
<td>Worsening vs other: P &lt; .001</td>
<td>Worsening vs other: P &lt; .001</td>
<td>Worsening vs other: P = .002</td>
</tr>
</tbody>
</table>

*Improved or worsening hearing indicates changes in decibel, which result in movement to a different category of hearing (eg, normal to mild hearing, moderate to severe, moderate to mild, etc).
Table IV. Logistic regression analyses of change in BSER with adjustment for potential influential factors

| Follow-up interval | Best ear analysis | | Total ears analysis | | |
|--------------------|-------------------|---|-------------------|---|
|                    | Hearing improvement (or normal to normal) | Hearing deterioration | Hearing improvement (or normal to normal) | Hearing deterioration |
|                    | OR (95% CI)* | $P^i$ | OR (95% CI)* | $P^i$ | OR (95% CI)$^i$ | $P^i$ | OR (95% CI)$^i$ | $P^i$ |
| 6 mo               | 5.03 (0.84,45.94) | .06 | 21.11 (2.84, $\infty$) | $<.01$ | 9.96 (2.05,48.45) | $<.01$ | 42.40 (41.29,206.78) |
| $\geq 1$ y         | 4.77 (0.76,41.44) | .07 | 10.26 (1.79,81.92) | $<.01$ | 4.25 (1.25,14.44) | .02 | 4.38 (1.19,16.10) | .03 |

*Exact maximum conditional likelihood estimate and 95% CI.
†From exact conditional scores test.
‡From logistic regression analysis using generalized estimating equations.

best ear at 1 year or beyond. For patients with multiple hearing assessments beyond 1 year (eg, at 1 year, at 2 years, and at 3 years), the final assessment (in this example, the one at 3 years) was used for the comparative analyses below. Of the 43 patients, 24 received ganciclovir, with a mean (± SD) follow-up time of 728 (± 465) days (median, 666 days). The remaining 19 patients were randomly assigned to the no-treatment group and had a mean (± SD) follow-up time of 702 (± 336) days (median, 672 days). For the biological total ear hearing evaluation, there were 84 ears with both baseline and ≥ 1 year BSER assessments, with 48 in ganciclovir recipients and 36 in control patients.

Significantly fewer ganciclovir-treated patients had hearing deterioration at 1 year or beyond compared with patients in the control group in both the unadjusted analysis (Table III) and logistic regression analysis (Table IV). This protection against hearing deterioration was noted in both the best-ear analysis (adjusted $P < .01$) and the total ear analysis (adjusted $P = .03$).

For patients with best-ear hearing improvement between baseline and ≥ 1 year, the mean decibel change was 25 dB for ganciclovir recipients (Appendix 2). For patients with best-ear hearing deterioration between baseline and ≥ 1 year, the mean dB change was 25 dB for ganciclovir recipients and >30.6 dB for patients in the no-treatment group (Appendix 2).

Of the 43 patients with BSER assessments both at baseline and ≥ 1 year, 32 also had a BSER assessment at 6 months. Hearing evaluation at 1 year or beyond from these 32 patients yielded similar results compared with those of the larger group of 43.

Other Clinical Efficacy Analyses

Patients treated with ganciclovir did not have a more rapid resolution of splenomegaly or hepatomegaly compared with patients in the control group. There was no statistically significant difference in time to resolution of CMV retinitis between the two treatment groups ($P = .23$), although only 8 patients had retinitis at baseline. Median weight gain between baseline and 6 weeks for ganciclovir recipients was 1.2 kg (n = 40), compared with 1.0 kg for control patients (n = 40) ($P = .02$). Similarly, median increase in head circumference between baseline and 6 weeks for ganciclovir-treated patients was 3.6 cm (n = 41), compared with 2.5 cm for control patients (n = 40) ($P < .01$). Similar results were also seen in growth at 6 weeks after adjustment for prematurity. These differences were not sustained at the 6-month follow-up or beyond.

Laboratory Efficacy Analyses

Among infants with abnormal ALT at baseline, ganciclovir-treated patients had more rapid resolution of ALT abnormalities compared with control patients (median time to ALT normalization, 19 days versus 66 days, respectively) ($P = .03$). Times to resolution of thrombocytopenia (median time, 9.5 days) and hyperbilirubinemia (median time, 16 days) were not significantly different between the two treatment groups.

Safety Evaluations

The primary toxicity in ganciclovir recipients was neutropenia (Table V), with 63% of ganciclovir recipients developing grade 3 or 4 neutropenia, compared with 21% of patients in the control group ($P < .01$). Of the 29 ganciclovir-treated patients developing neutropenia, 14 required dosage adjustments, but only 4 had the drug permanently discontinued. Two patients received granulocyte colony stimulating factor for their neutropenia. The mean time (± SD) of onset of grade 3 or 4 neutropenia for ganciclovir recipients was 14.2 (± 12.3) days and for control patients was 14.3 (± 13.1) days. Neutropenia in ganciclovir recipients resolved in 12.8 (± 13.6) days and in control patients, 14.2 (± 13.5) days.

Three ganciclovir recipients had catheter infections related to an indwelling intravenous catheter. One patient who had grade 3 neutropenia had Gram-negative septicemia but recovered fully. Neither of the other two patients had grade 3 or 4 neutropenia. No other infectious complications occurred that were judged by the participating investigator to be related to the study medication.
Death

Nine patients died during the course of this study: 3 were in the ganciclovir group and 6 were in the control group ($P = .31$). No death was related to complications of study drug. Causes of death for the 3 ganciclovir recipients included complications of CMV, necrotizing enterocolitis, and cardiopulmonary arrest. Causes of death for 6 patients in the control group included sudden infant death syndrome, pneumonia, necrotizing enterocolitis, *Candida* septicemia, dehydration, and *Escherichia coli* septicemia.

**DISCUSSION**

Six weeks of intravenous ganciclovir therapy prevents best-ear hearing deterioration at 6 months for patients with symptomatic congenital CMV disease involving the CNS. Ganciclovir therapy also may prevent best-ear hearing deterioration at or beyond 1 year. Although an understanding of the full clinical relevance of this audiologic effect awaits further long-term follow-up of these patients, the ability to prevent a patient from worsening from one level of hearing impairment (eg, mild) to another (eg, moderate) is of direct relevance to an individual’s functional abilities, and preventing hearing deterioration can significantly affect a person’s quality of life.$^{18,24-26}$

The large number of patients who were nonevaluable for the primary end point raises the possibility of follow-up bias that could influence the conclusions of this trial. The potential for such bias cannot be eliminated. Among ganciclovir recipients, nonevaluable patients were more likely to be black and to be premature. Race has not been shown to correlate with severity of outcome in congenital CMV disease.$^{27}$ However, premature infants represent a population that may be at higher risk of adverse outcome, and while our adjusted logistic regression analyses controlled for prematurity, the possibility remains that this or other unrecognized imbalances could invalidate our findings. Reassuringly, other markers of severity of CMV disease were similar at baseline between the evaluable and nonevaluable patients. Furthermore,

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Laboratory values constituting “Significant toxicity”</th>
<th>Ganciclovir (N = 47)</th>
<th>No treatment (N = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>&lt; 7 days old: $\geq 2.5$ mg/dL</td>
<td>$1/44$ (2%)</td>
<td>$0/42$ (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>7–60 days old: $\geq 1.5$ mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61–90 days old: $\geq 1.2$ mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>$\geq 540$ IU/L ($\geq 10X$ Upper limit normal)</td>
<td>$0/40$ (0%)</td>
<td>$0/40$ (0%)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Preterm infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Term infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>3–6 days old: $\geq 25$ mg/dL</td>
<td>$11/43$ (26%)</td>
<td>$7/39$ (18%)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>7–30 days old: $\geq 36$ mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31–90 days old: $\geq 6$ mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>$&lt; 50,000$/mm$^3$</td>
<td>$3/45$ (7%)</td>
<td>$2/41$ (5%)</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td></td>
<td>Grade 3–4 ANC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–7 days old: $750–1,249$/mm$^3$</td>
<td>$18/46$ (39%)</td>
<td>$8/43$ (19%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8–56 days old: $500–899$/mm$^3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57–90 days old: $250–399$/mm$^3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>Grade 4 ANC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–7 days old: $&lt; 750$/mm$^3$</td>
<td>$11/46$ (24%)</td>
<td>$1/43$ (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8–56 days old: $&lt; 500$/mm$^3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57–90 days old: $&lt; 250$/mm$^3$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Grade 3 or Grade 4 Toxicity. The data reflect treatment-emergent toxicities; that is, subjects whose baseline values were $\leq$ Grade 2 abnormalities and whose values rose to $\geq$ Grade 3 abnormalities during study.

$^\dagger$The mean ($\pm$ SD) number of lab samples collected from subjects randomized to ganciclovir was 8.4 ($\pm$ 2.1), with range of 2 to 15.

$^\ddagger$The mean ($\pm$ SD) number of lab samples collected from subjects randomized to no treatment was 4.4 ($\pm$ 1.7), with range of 1 to 9.
analyses of the evaluable populations consistently demonstrated therapeutic benefit, including the subset of infants who had BSER assessments at baseline, 6 months, and ≥ 1 year. Developmental outcomes were not formally assessed in this study.

The difficulties in this trial with regard to loss to follow-up to a large degree mirror conditions in the “real world” that may limit the ability to use ganciclovir intravenously in patients with symptomatic congenital CMV disease involving the CNS. This was a rigorous trial that required major sacrifices on the part of study participants’ families. Babies with symptomatic congenital CMV disease frequently are born to adolescent mothers and/or mothers with other young children, as both factors are known risks for maternal acquisition of CMV infection during pregnancy. To have families with these circumstances continue the infants’ stay in the hospital for 6 weeks or to have frequent follow-up visits was difficult. Given the toxicities of ganciclovir documented in this study, however, such close monitoring throughout the course of intravenous ganciclovir therapy is essential. A thorough assessment of a family’s ability to complete a potentially difficult course of antiviral therapy must be considered before deciding to provide treatment.

Ganciclovir therapy was associated with significant hematologic toxicity in the majority of treated patients. The frequency of neutropenia in this study is similar to that seen in an earlier phase II trial, although it is in contrast to the lower frequencies seen in another small, uncontrolled evaluation of ganciclovir therapy in congenital CMV disease. Ganciclovir has both gonadal toxicity and carcinogenicity in animal models, and its long-term safety after administration to young children is not established.

At this time, ganciclovir therapy administered intravenously for 6 weeks may be considered in patients with symptomatic congenital CMV disease involving the CNS. Patients receiving therapy should be monitored closely for neutropenia throughout the course of therapy. By study design, this trial included only symptomatic patients, who began therapy within the first month of life; demonstration of efficacy cannot be extrapolated to other settings. In determining whether to administer ganciclovir to a patient, the treating physician and family must weigh the potential benefit of therapy as interpreted by review of the data from this study against the significant risk of neutropenia and complications thereof, the potential for long-term gonadal toxicity or carcinogenicity, and family circumstances that might impede completion of a full course of therapy.

This study is dedicated to Charles A. Alford, Jr, MD, whose vision and leadership were instrumental to this endeavor.

REFERENCES

Appendix 1. Sample of decibel readings of the best ear at baseline and 6 months

<table>
<thead>
<tr>
<th>Treatment assignment</th>
<th>Patient No</th>
<th>dB of best ear at Baseline</th>
<th>6 Months</th>
<th>Decibel change</th>
<th>Mean dB change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved hearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and 6 months</td>
<td></td>
<td>1 of 6</td>
<td>&gt;90</td>
<td>80</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td></td>
<td>2 of 6</td>
<td>50</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 of 6</td>
<td>40</td>
<td>20</td>
<td>&gt;20 dB</td>
</tr>
<tr>
<td>No Treatment</td>
<td></td>
<td>1 of 5</td>
<td>40</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 of 5</td>
<td>55</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 of 5</td>
<td>40</td>
<td>20</td>
<td>25 dB</td>
</tr>
<tr>
<td>Worsening hearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and 6 months</td>
<td></td>
<td>1 of 7</td>
<td>30</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td></td>
<td>(None of the 25 evaluable patients had hearing deterioration at 6 months)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 of 7</td>
<td>75</td>
<td>&gt;95</td>
<td>&gt;20 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 of 7</td>
<td>35</td>
<td>&gt;95</td>
<td>&gt;60 dB</td>
</tr>
<tr>
<td>No Treatment</td>
<td></td>
<td>1 of 7</td>
<td>30</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 of 7</td>
<td>75</td>
<td>&gt;95</td>
<td>&gt;20 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 of 7</td>
<td>35</td>
<td>&gt;95</td>
<td>&gt;60 dB</td>
</tr>
</tbody>
</table>

Several study centers completed the Case Record Forms for audiologic assessment in such a fashion that our independent audiologist could determine that the assessment of "normal," "mild," etc., was valid. The source documents (audiology reports) were not sent in, however, and thus dB cannot be reported for some patients.

Appendix 2. Sample of decibel readings of the best ear at baseline and ≥1 year

<table>
<thead>
<tr>
<th>Treatment assignment</th>
<th>Patient No</th>
<th>dB of best ear at Baseline</th>
<th>≥1 Year</th>
<th>Decibel change</th>
<th>Mean dB change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved hearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and ≥1 year</td>
<td></td>
<td>1 of 4</td>
<td>50</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td></td>
<td>2 of 4</td>
<td>40</td>
<td>20</td>
<td>25 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(None of the 19 evaluable patients had hearing improvement at ≥1 Year)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 of 5</td>
<td>20</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 of 5</td>
<td>20</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 of 5</td>
<td>40</td>
<td>75</td>
<td>35</td>
</tr>
<tr>
<td>Worsening hearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and ≥1 year</td>
<td></td>
<td>1 of 13</td>
<td>10</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td></td>
<td>2 of 13</td>
<td>75</td>
<td>&gt;95</td>
<td>&gt;20 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 of 13</td>
<td>55</td>
<td>&gt;95</td>
<td>&gt;40 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 of 13</td>
<td>40</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 of 13</td>
<td>40</td>
<td>70</td>
<td>&gt;30.6 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 of 13</td>
<td>60</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 of 13</td>
<td>90</td>
<td>&gt;100</td>
<td>&gt;10 dB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 of 13</td>
<td>35</td>
<td>40</td>
<td>5</td>
</tr>
</tbody>
</table>

Several study centers completed the Case Record Forms for audiologic assessment in such a fashion that our independent audiologist could determine that the assessment of "normal," "mild," etc., was valid. The source documents (audiology reports) were not sent in, however, and thus dB cannot be reported for some patients.
Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease


ABSTRACT

BACKGROUND
The treatment of symptomatic congenital cytomegalovirus (CMV) disease with intravenous ganciclovir for 6 weeks has been shown to improve audiologic outcomes at 6 months, but the benefits wane over time.

METHODS
We conducted a randomized, placebo-controlled trial of valganciclovir therapy in neonates with symptomatic congenital CMV disease, comparing 6 months of therapy with 6 weeks of therapy. The primary end point was the change in hearing in the better ear (“best-ear” hearing) from baseline to 6 months. Secondary end points included the change in hearing from baseline to follow-up at 12 and 24 months and neurodevelopmental outcomes, with each end point adjusted for central nervous system involvement at baseline.

RESULTS
A total of 96 neonates underwent randomization, of whom 86 had follow-up data at 6 months that could be evaluated. Best-ear hearing at 6 months was similar in the 6-month group and the 6-week group (2 and 3 participants, respectively, had improvement; 36 and 37 had no change; and 5 and 3 had worsening; P=0.41). Total-ear hearing (hearing in one or both ears that could be evaluated) was more likely to be improved or to remain normal at 12 months in the 6-month group than in the 6-week group (73% vs. 57%, P=0.01). The benefit in total-ear hearing was maintained at 24 months (77% vs. 64%, P=0.04). At 24 months, the 6-month group, as compared with the 6-week group, had better neurodevelopmental scores on the Bayley Scales of Infant and Toddler Development, third edition, on the language-composite component (P=0.004) and on the receptive-communication scale (P=0.003). Grade 3 or 4 neutropenia occurred in 19% of the participants during the first 6 weeks. During the next 4.5 months of the study, grade 3 or 4 neutropenia occurred in 21% of the participants in the 6-month group and in 27% of those in the 6-week group (P=0.64).

CONCLUSIONS
Treating symptomatic congenital CMV disease with valganciclovir for 6 months, as compared with 6 weeks, did not improve hearing in the short term but appeared to improve hearing and developmental outcomes modestly in the longer term. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00466817.)
Congenital cytomegalovirus (CMV) infection is the leading nongenetic cause of sensorineural hearing loss and is the most frequent known viral cause of mental retardation; the infection affects 0.6 to 0.7% of live births in industrialized countries. A total of 10% of congenitally infected neonates have symptomatic disease at birth, of whom 35% have sensorineural hearing loss, up to two thirds have neurologic deficits, and 4% die during the newborn period. Although congenital CMV infection is rare overall, it accounts for 21% of children with hearing loss at birth and 24% of those with hearing loss at 4 years of age.

The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CAGS) found that among neonates with symptomatic congenital CMV disease involving the central nervous system (CNS), ganciclovir administered intravenously over a period of 6 weeks was associated with improved audiologic outcomes at 6 months of life, but there was no evidence that this benefit could wane over the first 2 years of life. Treated infants had fewer developmental delays, according to Denver Developmental evaluations, than untreated infants.

In a follow-up study, the CAGS determined the dose of oral valganciclovir (the prodrug of ganciclovir) that results in systemic exposure to ganciclovir that is similar to that with intravenous ganciclovir. Therapy with intravenous ganciclovir or oral valganciclovir for 6 weeks is now an accepted treatment option for patients with symptomatic congenital CMV disease involving the CNS.

**Methods**

**Study Design and Population**

Neonates with symptomatic congenital CMV disease, with or without CNS involvement, were eligible for enrollment. Given the rarity of this disease, 40 study sites participated, and each was anticipated to contribute only a few study participants. All the study participants had CMV detected in urine or throat-swab specimens by means of culture, shell-vial culture, or polymerase-chain-reaction assay. Symptomatic disease was defined as one or more of the following: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis, or CNS involvement such as microcephaly, intracranial calcifications, abnormal cerebrospinal fluid indexes, chorioretinitis, sensorineural hearing loss, or the detection of CMV DNA in cerebrospinal fluid. Eligible participants had a gestational age of 32 weeks or more, were 30 days of age or less, and weighed at least 1800 g at the initiation of therapy.

The institutional review board at each study center approved the study protocol. After written informed consent was obtained from the parent or legal guardian, all participants received valganciclovir (at a dose of 16 mg per kilogram of body weight, orally twice daily) for 6 weeks. Participants then underwent randomization in a 1:1 ratio to receive either continued valganciclovir or placebo for 4.5 months. The dose of the study medication was adjusted monthly for growth. Study drugs (oral valganciclovir and placebo) were provided by Hoffmann-La Roche, which had no role in the study design or data analyses or in the writing of the manuscript or the decision to submit it for publication. Study personnel and the participants’ families were unaware of the randomization assignments.

The primary end point prespecified in the protocol was the change in hearing in the better ear (“best-ear” hearing), from baseline to the 6-month follow-up. Secondary end points prespecified in the protocol included the change in total-ear hearing (i.e., hearing in one or both ears that could be evaluated) from baseline to follow-up at 6, 12, and 24 months; change in best-ear hearing from baseline to follow-up at 12 and 24 months; neurologic impairment at 12 and 24 months; and adverse events leading to the permanent discontinuation of therapy. Tertiary end points included the correlation of viral load in whole blood with audiologic and neurodevelopmental outcomes, adverse events related to the study medication, and characterization of blood concentrations of ganciclovir.

**Audiologic Assessments**

Brain-stem auditory evoked response was assessed at entry, and assessment of brain-stem auditory evoked response or visual-reinforcement audiometry was performed at 6, 12, and 24 months. Hearing thresholds were defined as follows: 0 to 20 dB for normal hearing, 21 to 45 dB for mild hearing loss, 46 to 70 dB for moderate hearing loss, and 71 dB or higher for severe hearing loss.
An independent audiologist, who was unaware of the randomization assignments, reviewed all the audiometry reports and classified, according to hearing thresholds, all ears that could be evaluated, giving “total ear” classifications. The study audiologist then assigned the “best ear” classification for the participant at that study visit. For example, if a participant had mild hearing loss in the left ear and severe hearing loss in the right ear, the best-ear classification was mild hearing loss. Odd numbers of total ears according to treatment category are reported because a patient may have had only one ear that could be evaluated (e.g., if the patient had otitis media in one ear, such that the ear could not be evaluated, and a normal, second ear that could be evaluated).

OTHER ASSESSMENTS
The Bayley Scales of Infant and Toddler Development, third edition (Bayley-III), was administered at 12 and 24 months by a neuropsychologist at each study site who was unaware of the randomization assignments. Whole blood for the evaluation of CMV viral load was obtained at baseline, weekly for 4 weeks, every 2 weeks for 8 weeks, and monthly for 4 months. White-cell count, white-cell differential count, measurement of hemoglobin level, platelet count, and aspartate aminotransferase, alanine aminotransferase, total bilirubin, and creatinine measurements were performed serially. Assessments regarding toxic effects were quantified with the use of the NIAID Division of AIDS Toxicity Tables.

STATISTICAL ANALYSIS
The primary objective was to assess the difference between the 6-week group and 6-month group in the change in best-ear hearing from baseline to 6 months of age. The Wilcoxon–Mann–Whitney test was used for analysis of the primary end point; linear models were used for analysis of secondary end points with adjustment for covariates. We calculated that a sample of 37 participants per group would provide the study with 85% power to detect an effect size of 0.169 from the null value of 0.5. We assumed that 15% of participants would not be eligible for randomization at 6 weeks and that another 10% would not complete the hearing evaluation at 6 months; therefore, we determined that the original sample should be 94 participants. During the course of the study, the data and safety monitoring board suggested that, owing to inadequate baseline or 6-month data, the sample size should be increased to achieve the targeted 37 participants per group. The sample was increased to 104 participants to accommodate 10% of the participants with outcomes that could not be evaluated owing to inadequate hearing data at baseline or 6 months. A 5% overenrollment was allowed for operational purposes.

The modified intention-to-treat population included participants who underwent randomization and received at least one dose of blinded treatment. The prespecified statistical analysis plan dictated that efficacy outcomes be adjusted for CNS involvement. For the secondary audiologic end points, hearing results were analyzed on the basis of two sets of binary outcomes: first, improved hearing or maintenance of normal hearing from baseline to follow-up, as compared with worsened hearing or maintenance of the same degree of hearing loss from baseline to follow-up; and second, worsened hearing from baseline to follow-up, as compared with improved hearing, maintenance of normal hearing, or maintenance of the same degree of hearing loss from baseline to follow-up (see the Supplementary Appendix, available with the full text of this article at NEJM.org, for additional details).

Any hearing assessments completed after cochlear implantation were excluded, as were missing hearing assessments and those that were not able to be evaluated. P values of less than 0.05 for hearing outcomes and less than 0.0071 for neurodevelopmental outcomes were considered to indicate statistical significance. For full details of the study conduct and analyses, see the protocol (including the statistical analysis plan), available at NEJM.org.
(the 6-week group) (Fig. 1 and Table 1). Of the 96 participants, 9 (6 participants in the 6-month group, and 3 in the 6-week group) stopped taking the blinded drug before completing 6 months of the study. No participant discontinued the study drug owing to adverse events.

**AUDILOGIC OUTCOMES**

**Primary End Point**

Among 43 participants in the 6-month group who had assessments that could be evaluated at 6 months, the change in best-ear hearing from baseline to 6 months indicated improvement in 2 participants, no change in 36, and worsened hearing in 5. Similarly, among 43 participants in the 6-week group, 3 had improved hearing, 37 had unchanged hearing, and 3 had worsened hearing (P=0.41 by the Wilcoxon–Mann–Whitney test).

**Secondary End Points**

In the binary assessment, the change in best-ear hearing from baseline to 6 months was similar in the two treatment groups (P=0.24, after adjustment for baseline CNS involvement) (Table 2). The between-group difference in the change in best-ear hearing from baseline to 12 months and from baseline to 24 months approached significance after adjustment for baseline CNS involvement (P=0.05 and P=0.07, respectively) (Table 2).

In the assessment of total-ear hearing, participants who received 6 months of valganciclovir were more likely than those who received 6 weeks of therapy to have improved hearing or to have maintained normal hearing between baseline and 12 months, after adjustment for CNS involvement at baseline (73% vs. 57%; odds ratio, 3.04; 95% confidence interval [CI], 1.26 to 7.35; P=0.01) (Table 2). Similar results were evident when prematurity and age at the initiation of treatment were added to the model (P=0.01).
Among the 53 participants with baseline CNS involvement, the rate ratio for improved or protected (i.e., maintenance of normal) total-ear hearing at 12 months in the 6-month group, as compared with the 6-week group, was 1.66 (95% CI, 0.92 to 2.40), and the rate-ratio difference was 0.27 (95% CI, 0.09 to 0.45); for the 28 participants without baseline CNS involvement, the rate ratio was 1.22 (95% CI, 0.99 to 1.45), and rate-ratio difference was 0.16 (95% CI, 0.03 to 0.29).

The benefit of longer-term therapy in the total-ears analysis was maintained at 24 months, with improved outcomes after adjustment for CNS involvement at baseline (77% in the 6-month group vs. 64% in the 6-week group; odds ratio, 2.61; 95% CI, 1.05 to 6.43; P=0.04) (Table 2). Similar results were evident when prematurity and age at the initiation of treatment were added to the model (P=0.004). The rate ratio for improved or protected total-ear hearing at 24 months among the 42 participants with baseline CNS involvement in the 6-month group, as compared with the 6-week group, was 1.46 (95% CI, 0.87 to 2.05), and the rate-ratio difference was 0.23 (95% CI, 0.05 to 0.41); among the 26 participants without baseline CNS involvement, the rate ratio was 1.19 (95% CI, 0.98 to 1.40), and the rate-ratio difference was 0.14 (95% CI, 0.01 to 0.27). The timing of initiation of valganciclovir within the first month of life (e.g., <3 weeks of age vs. 3 to 4 weeks of age) did not correlate with audiologic outcomes at 12 months or at 24 months (P>0.23 for both comparisons).

NEURODEVELOPMENTAL OUTCOMES

In the analysis adjusted for CNS involvement at baseline, participants randomly assigned to receive 6 months of valganciclovir, as compared with those randomly assigned to 6 weeks of treatment, had higher Bayley-III language-composite scores at 24 months (P=0.005) and higher receptive-communication scale scores at 24 months (P=0.003). No significant interaction effects were found when outcome and CNS involvement at baseline were incorporated in a single model, indicating that the treatment benefits were similar in the group with CNS involvement and the group without CNS involvement. The differences between the 6-month group and the 6-week group with respect to Bayley-III scores were maintained when age at the initiation of treatment and prematurity were added to the model (P=0.004 and P=0.003, respectively) (Table 3). All the other components of the Bayley-III assessments trended toward improved outcomes among participants in the 6-month group, as compared with those in the 6-week group.

### Table 1. Characteristics of the Participants at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>6 Mo of Therapy (N = 47)</th>
<th>6 Wk of Therapy (N = 49)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age — no. (%)</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>32 to ≤37 wk</td>
<td>24 (51)</td>
<td>22 (45)</td>
<td></td>
</tr>
<tr>
<td>&gt;37 wk</td>
<td>23 (49)</td>
<td>27 (55)</td>
<td></td>
</tr>
<tr>
<td>Age at enrollment — no. (%)</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>&lt;7 days</td>
<td>6 (13)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>7–14 days</td>
<td>19 (40)</td>
<td>12 (24)</td>
<td></td>
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<tr>
<td>15–21 days</td>
<td>10 (21)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>22–29 days</td>
<td>12 (26)</td>
<td>24 (49)</td>
<td></td>
</tr>
<tr>
<td>Extent of CMV disease — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>38 (81)</td>
<td>34 (69)</td>
<td>0.24</td>
</tr>
<tr>
<td>Petechiae</td>
<td>22 (47)</td>
<td>20 (41)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>26 (55)</td>
<td>21 (43)</td>
<td>0.31</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>23 (49)</td>
<td>22 (45)</td>
<td>0.84</td>
</tr>
<tr>
<td>Intraterine growth restriction</td>
<td>17 (36)</td>
<td>22 (45)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>21 (45)</td>
<td>25 (51)</td>
<td>0.55</td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>34 (72)</td>
<td>29 (59)</td>
<td>0.20</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>14 (30)</td>
<td>17 (35)</td>
<td>0.19</td>
</tr>
<tr>
<td>Chorioretinitis — no. (%)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Neuroimaging results — no./total no. (%)‡</td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Normal</td>
<td>9/45 (20)</td>
<td>12/47 (26)</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>36/45 (80)</td>
<td>35/47 (74)</td>
<td></td>
</tr>
<tr>
<td>Baseline BSER of the best ear in participants with 6-mo follow-up data — no./total no. (%)§</td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Normal</td>
<td>32/43 (74)</td>
<td>25/43 (58)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5/43 (12)</td>
<td>8/43 (19)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3/43 (7)</td>
<td>2/43 (5)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3/43 (7)</td>
<td>8/43 (19)</td>
<td></td>
</tr>
</tbody>
</table>

* Table S1 in the Supplementary Appendix provides a full tabulation of the demographic and clinical characteristics at baseline.
† Participants could have multiple manifestations of cytomegalovirus (CMV) disease. Hepatitis was defined by an elevated aminotransferase or bilirubin level.
‡ Neuroimaging was performed with the use of magnetic resonance imaging, computed tomography, or ultrasonography of the head.
§ Hearing thresholds were assessed with the use of brain-stem auditory evoked response (BSER) and were defined as follows: a threshold of 0 to 20 dB for normal hearing, 21 to 45 dB for mild hearing loss, 46 to 70 dB for moderate hearing loss, and 71 dB or higher for severe hearing loss.
Table 2. Improvement and Protection in Best-Ear and Total-Ear Hearing between Baseline and Follow-up.*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of Participants or Ears</th>
<th>Comparison of Hearing at Baseline and Follow-up</th>
<th>Unadjusted Analysis†</th>
<th>Adjusted Analysis‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Improved Hearing at Follow-up</td>
<td>Odds Ratio (95% CI)</td>
<td>Rate Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal Hearing at Baseline and Follow-up</td>
<td>0.91 (0.60 to 1.39)</td>
<td>1.25 (0.93 to 1.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Same Degree of Hearing Loss at Baseline and Follow-up</td>
<td>2.12 (0.78 to 5.59)</td>
<td>1.32 (0.97 to 1.79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worsened Hearing at Follow-up</td>
<td>2.36 (0.77 to 7.75)</td>
<td>1.22 (0.94 to 1.58)</td>
</tr>
<tr>
<td>6-Mo analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary analysis:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>best ear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mo group</td>
<td>43</td>
<td>2 (5)</td>
<td>0.71 (0.34 to 1.51)</td>
<td>0.97 (0.67 to 1.42)</td>
</tr>
<tr>
<td>6-Wk group</td>
<td>43</td>
<td>3 (7)</td>
<td>1.13 (0.48 to 2.66)</td>
<td>1.26 (0.87 to 1.80)</td>
</tr>
<tr>
<td>Secondary analysis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total ears</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mo group</td>
<td>82</td>
<td>6 (7)</td>
<td>1.26 (0.69 to 2.29)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
<tr>
<td>6-Wk group</td>
<td>84</td>
<td>7 (8)</td>
<td>1.26 (0.69 to 2.29)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
<tr>
<td>12-Mo analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best ear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mo group</td>
<td>41</td>
<td>2 (5)</td>
<td>0.71 (0.34 to 1.51)</td>
<td>0.97 (0.67 to 1.42)</td>
</tr>
<tr>
<td>6-Wk group</td>
<td>40</td>
<td>2 (5)</td>
<td>0.71 (0.34 to 1.51)</td>
<td>0.97 (0.67 to 1.42)</td>
</tr>
<tr>
<td>Total ears</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mo group</td>
<td>79</td>
<td>6 (8)</td>
<td>1.26 (0.69 to 2.29)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
<tr>
<td>6-Wk group</td>
<td>77</td>
<td>4 (5)</td>
<td>1.26 (0.69 to 2.29)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
<tr>
<td>24-Mo analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best ear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mo group</td>
<td>37</td>
<td>2 (5)</td>
<td>0.71 (0.34 to 1.51)</td>
<td>0.97 (0.67 to 1.42)</td>
</tr>
<tr>
<td>6-Wk group</td>
<td>31</td>
<td>2 (6)</td>
<td>0.71 (0.34 to 1.51)</td>
<td>0.97 (0.67 to 1.42)</td>
</tr>
<tr>
<td>Total ears</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mo group</td>
<td>70</td>
<td>6 (9)</td>
<td>1.26 (0.69 to 2.29)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
<tr>
<td>6-Wk group</td>
<td>58</td>
<td>2 (3)</td>
<td>1.26 (0.69 to 2.29)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
</tbody>
</table>

*All the analyses for the primary and secondary end points were prespecified in the protocol. All the analyses at 12 months and 24 months were analyses of secondary end points. An independent audiologist, who was unaware of the randomization assignments, reviewed all the audiology reports and classified ears (those that could be evaluated) according to hearing thresholds, giving “total ear” classifications. The study audiologist then assigned the “best ear” classification for the participant at that study visit. For example, if a participant had mild hearing loss in the left ear and severe hearing loss in the right ear, the best-ear classification was mild hearing loss. Odd numbers of total ears according to treatment category are reported because a patient may have had only one ear that could be evaluated (e.g., if a patient had otitis media in one ear, such that it could not be evaluated, and a normal second ear that could be evaluated).†The unadjusted analysis compared participants who had improved hearing or normal hearing at baseline and follow-up with those who had worsened hearing or the same degree of hearing loss at baseline and follow-up. Univariate best-ear analyses of secondary audiologic end points were performed with the use of Fisher’s exact test, and univariate total-ear analyses with the use of logistic regression with generalized estimating equations in which assessments of hearing in the right and left ears were analyzed in one model. See the Supplementary Appendix for additional details.‡The adjusted analysis compared participants who had improved hearing or normal hearing at baseline and follow-up with those who had worsened hearing or the same degree of hearing loss at baseline and follow-up. The analysis that was adjusted for central nervous system involvement at baseline was a prespecified analysis.
VIROLOGIC RESULTS

Viral loads in whole blood decreased in parallel in the two study groups during the first 6 weeks of open-label valganciclovir therapy and then diverged after randomization (Fig. 2). In the analysis that was adjusted for an interaction effect between treatment and the area under the curve (AUC) of the viral load, lower viral loads, as compared with higher viral loads, correlated with better hearing outcomes at 6, 12, and 24 months among participants in the 6-month group (P<0.01 for all comparisons) but not among those in the

<table>
<thead>
<tr>
<th>Bayley-III Component†</th>
<th>12-Mo Follow-up</th>
<th>24-Mo Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-Mo Group</td>
<td>6-Wk Group</td>
</tr>
<tr>
<td>Cognitive composite</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>No. of participants</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>89.6±3.0</td>
<td>79.5±2.8</td>
</tr>
<tr>
<td>Range</td>
<td>55–115</td>
<td>9.5–120</td>
</tr>
<tr>
<td>Language composite</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>No. of participants</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Mean</td>
<td>87.6±3.0</td>
<td>76.8±2.9</td>
</tr>
<tr>
<td>Range</td>
<td>47–118</td>
<td>11–112</td>
</tr>
<tr>
<td>Receptive-communication scale</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>No. of participants</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Mean</td>
<td>7.5±0.5</td>
<td>6.1±0.5</td>
</tr>
<tr>
<td>Range</td>
<td>1–14</td>
<td>1–12</td>
</tr>
<tr>
<td>Expressive-communication scale</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>No. of participants</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Mean</td>
<td>8.0±0.5</td>
<td>6.5±0.5</td>
</tr>
<tr>
<td>Range</td>
<td>1–13</td>
<td>1–13</td>
</tr>
<tr>
<td>Motor composite</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>No. of participants</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Mean</td>
<td>82.6±3.2</td>
<td>73.2±3.0</td>
</tr>
<tr>
<td>Range</td>
<td>46–112</td>
<td>11–112</td>
</tr>
<tr>
<td>Fine-motor scale</td>
<td>41</td>
<td>44</td>
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<tr>
<td>No. of participants</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Mean</td>
<td>7.3±0.6</td>
<td>6.0±0.6</td>
</tr>
<tr>
<td>Range</td>
<td>1–11</td>
<td>0.1–13</td>
</tr>
<tr>
<td>Gross-motor scale</td>
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<td>44</td>
</tr>
<tr>
<td>No. of participants</td>
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<td>44</td>
</tr>
<tr>
<td>Mean</td>
<td>6.7±0.5</td>
<td>5.4±0.5</td>
</tr>
<tr>
<td>Range</td>
<td>1–14</td>
<td>0.1–15</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SE. Data were adjusted for central nervous system involvement at baseline, prematurity, and age at the initiation of treatment. A P value of less than 0.0071 (i.e., 0.05 divided by 7) was considered to indicate statistical significance, with the use of Bonferroni adjustment for multiple testing. Ranges represent the minimum and maximum values of the raw data.

† All the composite scores on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III), range from 40 to 160, with higher scores indicating better developmental outcomes. All the scale scores on the Bayley-III range from 1 to 19, with higher scores indicating better developmental outcomes. Decimal points in the ranges reflect the specific raw data in the scales for at least one study participant, as captured on the case-report form and verified during the on-site monitoring visits.
6-week group (P>0.68 for all comparisons). There was no correlation between the AUC of the viral load and neurodevelopmental outcomes beyond that provided by treatment.

SAFETY ASSESSMENTS

Of the 109 participants, 21 (19%) had grade 3 or 4 neutropenia during the first 6 weeks of open-label valganciclovir therapy. From week 6 through month 6, a total of 10 of the 47 participants (21%) who received the active drug had grade 3 or 4 neutropenia, as compared with 13 of 49 (27%) who received placebo (P=0.64). A total of 3 participants had the drug temporarily suspended because of an absolute neutrophil count of less than 500 per cubic millimeter. All treatment interruptions occurred within the first 6 weeks of the study, and treatment was resumed after resolution of the neutropenia.

The alanine aminotransferase and aspartate aminotransferase levels increased slightly at months 4 and 5 in the group of participants who received the active drug, although the differences between this group and the group that received placebo were not statistically significant (P>0.59 for both aminotransferase comparisons) or clinically significant (all mean values, <90 U per liter). No deaths occurred. There were no significant differences in the rate of adverse events between the two study groups.

DISCUSSION

We believe that only one randomized, controlled trial of antiviral treatment for symptomatic congenital CMV disease has been conducted previously, also by the NIAID CASG.13 Other reports in the literature involve individual cases20-24 or small, uncontrolled case series.25-27 The earlier randomized, controlled trial showed a benefit of 6 weeks of parenteral ganciclovir therapy with respect to best-ear hearing from baseline to 6 months, but there was a suggestion that this benefit wanes over the first 2 years of life.13 On the basis of these data, the change in best-ear hearing from baseline to 6 months was selected as the primary end point of this trial. This selection positioned the current study to extend our knowledge of the effect of antiviral therapy on hearing and allowed for sample-size assessments in the development of the study protocol.

We also selected numerous clinically relevant secondary end points before the initiation of the study to explore the effect of longer-term anti-
viral treatment on longer-term hearing improvement. These included the change in best-ear hearing and the change in total-ear hearing from baseline to 12 months and from baseline to 24 months in order to more completely ascertain the effect of antiviral treatment on short-term (to 6 months of age) and longer-term (to 2 years of age) time frames. Formal neurodevelopmental outcomes were incorporated as secondary end points in the study to assess the effect of antiviral treatment on neurodevelopmental outcome.

We did not find significant between-group differences in the primary study end point of change in best-ear hearing between baseline and 6 months. The change in total-ear hearing between baseline and 6 months also was similar in the two groups. However, the secondary study end points of change in total-ear hearing between baseline and 12 months and between baseline and 24 months differed significantly between the two groups, with participants receiving 6 months of therapy, as compared with those receiving 6 weeks of treatment, having improved hearing outcomes. Data from our prespecified secondary end points suggest that the 6-month regimen of antiviral treatment modestly improves hearing outcomes in the long term but does not provide an additional benefit with respect to short-term outcomes over that provided by 6 weeks of treatment.

The magnitude of the long-term benefit can be viewed in several ways. The calculation of odds ratios showed that, as compared with patients who received shorter therapy, patients who received longer therapy had 3.0 times the odds of having improved hearing or protection of normal hearing at 12 months and 2.6 times the odds at 24 months. The calculation of the rate ratio showed that among participants with CNS involvement at baseline, those in the 6-month group had a 65% greater likelihood of having better outcomes from baseline to 12 months than those in the 6-week group and a 46% greater likelihood of having better outcomes from baseline to 24 months than those in the 6-week group. Among participants without CNS involvement, the corresponding values were 22% and 19%. Rate-ratio differences between the groups range from 0.14 to 0.27, depending on the presence of CNS involvement at baseline and on the follow-up interval. We caution that spurious findings may have arisen from the multiple statistical tests conducted for the secondary hearing end points considered in this report.

With respect to neurodevelopmental outcomes, we found that the communicative end points of scores on the language-composite component and the receptive-communication scale of the Bayley-III assessment, with Bonferroni adjustment for multiple testing, were improved with the longer treatment, with low average results among participants treated for 6 months but borderline results among participants treated for 6 weeks (see the Supplementary Appendix for scoring definitions), after adjustment for factors that could affect development. All the scores on the other components of the Bayley-III were also higher in the 6-month treatment group than in the 6-week group (Table 3), although the differences were not significant. No significant interaction effects were found, indicating similar neurologic treatment benefits regardless of CNS involvement.

The rates of grade 3 or 4 neutropenia during the first 6 weeks of treatment were lower among the participants in the current study who received oral valganciclovir (19% of participants) than among participants in previous CASG studies who received intravenous ganciclovir for 6 weeks (63%) or intravenous ganciclovir for 2 weeks and oral valganciclovir for 4 weeks (38%), perhaps owing to the higher maximum concentration of the drug associated with intravenous versus oral drug delivery. From week 6 to month 7 in the current trial, the incidence of grade 3 or 4 neutropenia was similar among participants randomly assigned to continue valganciclovir and those randomly assigned to receive placebo (21% and 27%, respectively; P=0.64). Thus, drug-induced neutropenia is of primary concern during the first 6 weeks of treatment, and the risk appears to be reduced when treatment is solely with oral valganciclovir. Ganciclovir has toxic effects on the gonads and is carcinogenic in animal models, and although these toxic effects have not been seen in humans, the information should be conveyed to families of neonates for whom valganciclovir therapy is being considered.

The data from this controlled study suggest that among infants with symptomatic congenital CMV disease, 6 months of oral valganciclovir therapy has a moderately favorable effect on long-
term audiologic and neurodevelopmental outcomes, after adjustment for baseline CNS involvement; in addition, this regimen was not associated with an excess risk of neutropenia and avoided the need to maintain intravenous access for prolonged periods of time. These data do not apply to infants with asymptomatic congenital CMV infection, since there are no controlled studies showing a benefit in this population and the possibility of harm exists. Since CMV-associated sensorineural hearing loss fluctuates over time in more than one third of patients as part of the natural history of this disease, prospective, controlled trial designs are critical to assess treatment benefit in patients with congenital CMV infections.

Presented in part at the 2013 IDWeek Annual Meeting of the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society, San Francisco, October 2–6, 2013.

Supported by contract N01-AI-30025 from the Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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Valganciclovir for Symptomatic Congenital CMV Disease

943


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Neurodevelopmental Outcomes Following Ganciclovir Therapy in Symptomatic Congenital Cytomegalovirus Infections Involving the Central Nervous System

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Abstract

Background—Ganciclovir protects against hearing deterioration in infants with symptomatic congenital cytomegalovirus (CMV) disease involving the central nervous system (CNS).

Objectives—To assess the neurodevelopmental impact of ganciclovir therapy in this population.

Study Design—100 neonates were enrolled into a controlled Phase III study of symptomatic congenital CMV involving the CNS, and were randomized to either 6 weeks of intravenous ganciclovir or no treatment. Denver developmental tests were performed at 6 weeks, 6 months, and 12 months. For each age, developmental milestones that ≥90% of normal children would be expected to have achieved were identified. The numbers of milestones not met (“delays”) were determined for each subject. The average number of delays per subject was compared for each treatment group.
Results—At 6 months, the average number of delays was 4.46 and 7.51, respectively, for ganciclovir recipients and “no treatment” subjects (p=0.02). At 12 months, the average number of delays was 10.06 and 17.14, respectively (p=0.007). In a multivariate regression model, the effect of ganciclovir therapy remained statistically significant at 12 months (p=0.007).

Conclusions—Infants with symptomatic congenital CMV involving the CNS receiving intravenous ganciclovir therapy have fewer developmental delays at 6 and 12 months compared with untreated infants. Based on these data as well as the previously published data regarding ganciclovir treatment and hearing outcomes, six weeks of intravenous ganciclovir therapy can be considered in the management of babies with symptomatic congenital CMV disease involving the CNS. If treatment is initiated, it should be started within the first month of life and patients should be monitored closely for toxicity, especially neutropenia. Since existing data only address the treatment of symptomatic congenital CMV disease involving the CNS, these data cannot be extrapolated to neonates with other manifestations of CMV disease, including asymptomatic babies and symptomatic babies who do not have CNS involvement.

Keywords
Ganciclovir; antiviral treatment; congenital CMV; cytomegalovirus; neurologic outcomes; developmental outcomes

INTRODUCTION

Congenital cytomegalovirus (CMV) infection is the most frequent known viral cause of mental retardation,1·2 and is the leading non-genetic cause of sensorineural hearing loss in many countries including the United States.3·6 Approximately 1% of all live births in the United States are infected with CMV (~ 40,000 babies per year).7 Of those fetuses infected, approximately 10% are symptomatic at birth, and a majority of these patients subsequently experience significant neurological sequelae, including sensorineural hearing loss, mental retardation, microcephaly, seizures, or paresis/paralysis.8·14 The overall societal costs of providing specialized services for surviving infants and children with congenital CMV infections are in the billions of dollars annually.15

The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASHG) completed a Phase III randomized controlled investigation of intravenous ganciclovir for the treatment of symptomatic congenital CMV disease involving the central nervous system (CNS).16 Results from this study indicate that six weeks of intravenous (IV) ganciclovir therapy decreases the likelihood that hearing loss will worsen over at least the first two years of life. The impact of antiviral therapy on neurodevelopmental outcomes is unknown. To evaluate this important question, we analyzed in a blinded fashion the Denver II developmental assessments of babies previously enrolled in the Phase III randomized, controlled trial.

METHODS

Study Population

From 1991 to 1999, 100 neonates were enrolled in a Phase III controlled trial and randomized to 6 weeks of intravenous ganciclovir at 12 mg/kg/day delivered in two divided doses (n=48) or to no antiviral treatment (n=52).16 Block randomization by center was utilized. A placebo was not used in the study due to ethical concerns over maintaining intravenous access for six weeks in order to administer a placebo. All study subjects had confirmed isolation of CMV from a urine specimen obtained prior to study enrollment and within the first month of life, and all had evidence of CNS disease such as: 1) microcephaly; 2) intracranial calcifications;
3) abnormal cerebrospinal fluid (CSF) for age; 4) chorioretinitis; or 5) hearing loss. Infants ≤1 month of age, ≥32 weeks gestation, and ≥1200 grams at birth were eligible for study participation. The analysis of Denver developmental data presented herein were secondary analyses and followed the publication of the impact of antiviral therapy on hearing loss.16 Prior to participation in the treatment study, informed consent was obtained from the parent(s) or guardian(s). The analysis of the Denver developmental data stored in the Phase III dataset was approved by the University of Alabama at Birmingham’s Institutional Review Board.

**Denver II Developmental Assessment**

During the course of the clinical trial, Denver II developmental tests were performed on subjects at 6 weeks, 6 months, and 12 months of age by study personnel at each site, who were not able to be blinded due to the lack of a placebo. The Denver II is used routinely in pediatric care to assess developmental milestones, and has high inter-rater reliability. It consists of four objectively-assessed and -defined categories which evaluate different aspects of a child’s neurological development: Personal/Social, Fine Motor, Language, and Gross Motor. Each category in turn consists of many elements that a child achieves as they attain neurodevelopmental milestones. The Denver II categorizes a child’s performance as “Caution” (a child failing an element which between 75% and 90% of children who are his/her age would pass) or as “Delay” (a child failing an element which ≥90% of children who are his/her age would pass).17

Utilizing the Denver II, ≥90% of 6 week old babies would be expected to have achieved 6 total elements in the four categories. By 6 months of age, 21 total elements should be achieved by ≥90% of children. By 12 months of age, 38 total elements from the four Denver II categories should be achieved by ≥90% of children. The increasing number of elements expected to be achieved with increasing age is a reflection of developmental milestones that are met as a child grows. In this study, the total number of delays was determined for each subject at each testing age by an investigator at the CASG Central Unit who was blinded to their treatment randomization. These were then split into treatment versus no treatment categories, and the average for each group was determined. Since one of the most important outcomes of congenital CMV infection is hearing loss, and because the language category of the Denver II involves the subject’s ability to hear and respond to certain stimuli, total delays also were calculated for the Personal/Social, Fine Motor, and Gross Motor categories but excluding the Language category.

**Statistical Analyses**

Univariate descriptive statistics summarized each of the four Denver II categories, as well as the total number of delays. The Student’s t-test was utilized to compare each separate Denver II component and total delays with regard to therapy assignment and other prognostic indicators. Multivariate regression models were utilized to test independent factors known to be related to poor developmental outcome in congenital CMV infection.18, 19 Treatment interactions with developmental outcomes were also explored using regression models. A mixed model was utilized to analyze the Denver II test deficits longitudinally by using each subject as a random effect. Each subject’s individual scores were assessed across their follow-up visits, and a slope for that subject’s score changes was included in the final model.

**RESULTS**

Of the 100 subjects enrolled in the Phase III randomized controlled study, 74 had a Denver II developmental test performed at 6 weeks of age (34 ganciclovir, 40 no treatment), 74 had a 6 month evaluation (35 ganciclovir, 39 no treatment), and 71 had a 12 month evaluation (35 ganciclovir, 36 no treatment). Demographic data are presented in Table 1 by treatment category.
for those subjects with a 12 month Denver II assessment. Demographic and baseline characteristics for all three measurement times were similar between the two treatment regimens. Eighty-four of the 100 subjects had at least one Denver II assessment by 12 months of age, and 60 had Denver II tests during all three follow-up intervals (29 in the ganciclovir-treated group and 31 in the no treatment group). There were no significant differences in demographic and baseline characteristics between the 71 subjects with Denver II assessments at 12 months and the 29 subjects who did not have a Denver II developmental test and thus were unevaluable for this study (Table 2). The average subject age at the 6 week assessment was 8.05 weeks (range: 5 weeks to 11 weeks); at the 6 month (26 week) assessment was 27.42 weeks (range: 22 weeks to 34 weeks); and at the 12 month (52 week) assessment was 54.21 weeks (range: 41 weeks to 68 weeks).

With increasing age, subjects who received ganciclovir therapy experienced fewer developmental delays compared with subjects receiving no treatment (Table 3 and Figure 1A). At 6 months and 12 months, the numbers of delays in ganciclovir treated subjects were significantly lower compared with the number of delays among untreated controls (p=0.02 and p=0.007, respectively). Fewer delays were seen in each of the four components of the Denver developmental test for ganciclovir recipients compared with subjects receiving no treatment. Eliminating the language component from the analyses in order to minimize an association between developmental outcome and hearing status, ganciclovir-treated subjects continued to have fewer developmental delays at 6 months and 12 months (p=0.03 and p=0.005, respectively) (Table 3 and Figure 1B).

Of the factors explored in univariate analysis (abnormal CNS imaging, abnormal CSF protein concentration, premature birth, microcephaly, calcifications, and abnormal hearing at the given time period), intracranial calcification, abnormal computed tomography (CT) imaging of the head, and microcephaly at birth were significantly associated with developmental outcome and so were then controlled for in a cross-sectional regression model. The effect of ganciclovir therapy in this model remained statistically significant at 12 months for the 71 subjects with 12 month evaluations (P = 0.007). While we were not able to control for length of disease, timing of infection in utero, or primary vs. recurrent maternal infection, we were able to control for extent of disease, which has been shown to correlate with timing of the infection in utero as well as type of maternal infection.

All 84 subjects with at least one Denver II assessment were included in a longitudinal regression model to evaluate developmental delays across the year of evaluation. After adjusting for abnormal CT imaging of the head, microcephaly at birth, and intracranial calcifications, the beneficial effect of ganciclovir therapy on neurodevelopmental outcomes across the 12 months of testing trended toward significance (p = 0.07).

**DISCUSSION**

These data suggest that 6 weeks of intravenous ganciclovir treatment for infants with symptomatic congenital CMV disease involving the CNS may improve neurodevelopmental outcomes at 6 months and 12 months of age compared with babies who receive no antiviral therapy. Treated subjects had fewer neurodevelopmental delays compared with subjects who did not receive antiviral therapy, even when the language component of the Denver II developmental assessment was eliminated from the analysis. The 12 month assessment individually showed the largest impact on developmental outcomes, and therefore the trend toward significance in the longitudinal regression model, in which not all subjects had 12 month data, further supports a beneficial impact of antiviral therapy on neurodevelopment. These results, however, do not suggest that treatment with ganciclovir can prevent all neurodevelopmental delays from occurring. While the ganciclovir recipients had fewer delays
and appear to have more normal neurologic outcomes, most were still behind what would be considered “normal development” for 6 weeks, 6 months, or 12 months of age.

Prior to this study, no controlled data existed regarding the effect of antiviral treatment on neurological development in babies with congenital CMV disease. This study provides preliminary data suggesting that treatment with ganciclovir may improve the likelihood of affected children reaching age-appropriate milestones. Importantly, these results were demonstrable in the most severely affected group of infants with congenital CMV disease.

A weakness of this trial relates to the “screening” aspect of the Denver II developmental test. However, a recent comparison of the Denver II with the Wechsler Intelligence Scale for Children third edition (WISC-III), a more sophisticated assessment tool for cognitive function, in children with CNS injury due to viral disease found strong concordance between the two tests. Additionally, performance of the Denver II developmental test at six months of age has proven to be a good predictor of severe neurologic outcomes at two years of age in babies with neurologic injury due to hypoxic-ischemic encephalopathy, with a sensitivity of 100% and a specificity of 95%. In order to be as conservative as possible with our analyses, we considered a subject to have a “delay” for a given element only if they have failed to achieve a milestone that ≥90% of children at that age are able to do.

Based on these data as well as the previously published data regarding ganciclovir treatment and hearing outcomes, ganciclovir therapy can be considered in the management of babies with symptomatic congenital CMV disease involving the CNS. Approximately two-thirds of neonates and infants receiving intravenous ganciclovir will develop significant neutropenia, and the requirement of long-term intravenous access can allow for intravascular bacterial superinfections. Both family and physician should carefully consider the potential benefits of ganciclovir therapy versus the risks associated with treatment. If treatment is initiated, it should be started within the first month of life and patients should be monitored closely for toxicity, especially neutropenia. Since existing data only address the treatment of symptomatic congenital CMV disease involving the CNS, these data cannot be extrapolated to neonates with other manifestations of CMV disease, including asymptomatic babies and symptomatic babies who do not have CNS involvement. At this time, ganciclovir should not be used in infants with asymptomatic congenital CMV infection.

While not utilized during this study, the Bayley Scales of Infant Development – Revised are being utilized in a newly initiated study of oral valganciclovir being conducted by the NIAID Collaborative Antiviral Study Group (www.casg.uab.edu). It is anticipated that this will allow for more precise assessment of the impact of antiviral treatment on neurodevelopmental outcomes of babies with symptomatic congenital CMV disease.

**Acknowledgments**

This work was supported under contract with the Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases (NIAID) (N01-AI-30025, N01-AI -65306, N01-AI -15113, N01-AI-62554), and by grants from the General Clinical Research Center Program (M01-RR00032) and the State of Alabama.

**List of Abbreviations**

- ALT: Alanine Aminotransferase
- ANC: Absolute Neutrophil Count
- BSER: Brainstem Evoked Response
- CASG: Collaborative Antiviral Study Group

*J Clin Virol*. Author manuscript; available in PMC 2010 December 1.
References


Figure 1.
Figure 1A. Total Delays, including Personal/Social, Fine Motor, Language, and Gross Motor Components of the Denver II Developmental Test (mean ± SE)
Figure 1B. Total Delays, including Personal/Social, Fine Motor, and Gross Motor Components of the Denver II Developmental Test but Excluding the Language Component (mean ± SE)
## Table 1
Demographic and Baseline Characteristics for Subjects with a Denver II Developmental Assessment at 12 Months

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment (n=35)</th>
<th>No Treatment (n=36)</th>
<th>P-Value</th>
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<tr>
<td>Age at enrollment (days)</td>
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<tr>
<td>Median</td>
<td>12</td>
<td>12</td>
<td>0.77</td>
</tr>
<tr>
<td>Range</td>
<td>3–33</td>
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</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Female</td>
<td>16 (46%)</td>
<td>21 (58%)</td>
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</tr>
<tr>
<td>Male</td>
<td>19 (54%)</td>
<td>15 (42%)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>23 (66%)</td>
<td>22 (61%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Black</td>
<td>8 (23%)</td>
<td>8 (22%)</td>
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<tr>
<td>Hispanic</td>
<td>4 (11%)</td>
<td>5 (14%)</td>
<td></td>
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<tr>
<td>Other</td>
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<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Prematurity (≤37 weeks)</td>
<td>14 (40%)</td>
<td>11 (31%)</td>
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<tr>
<td>Gestational Age (weeks)</td>
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<td>Birth weight (grams)</td>
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<td>1012–3425</td>
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<td>Head Circumference (cm)</td>
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<td>Abnormal computed tomography (CT)</td>
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<td>(calcifications)</td>
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<tr>
<td>Median</td>
<td>9 (26%)</td>
<td>11 (31%)</td>
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<tr>
<td>Range</td>
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<td>Abnormal cerebrospinal fluid indices</td>
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<td>10 (28%)</td>
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<tr>
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<td>Median</td>
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<tr>
<td>Range</td>
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<tr>
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<td>Median</td>
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<td>6 (17%)</td>
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<td>25 (69%)</td>
<td>0.79</td>
</tr>
<tr>
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<tr>
<td>Median</td>
<td>24 (69%)</td>
<td>25 (69%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (ANC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7 (20%)</td>
<td>4 (11%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Brainstem Evoked Response (BSER) (Best Ear)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>17 (49%)</td>
<td>16 (44%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mild</td>
<td>5 (14%)</td>
<td>7 (19%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (3%)</td>
<td>5 (14%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7 (20%)</td>
<td>2 (6%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2
Demographic and Baseline Characteristics for Subjects with a Denver II Developmental Assessment at 12 Months versus No Assessment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Evaluable (Denver II Assessment) n=71</th>
<th>Un evaluable (No Denver II Assessment) n=29</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (days)</td>
<td>12 (2–33)</td>
<td>12.5 (3–33)</td>
<td>0.50</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (52%)</td>
<td>10 (34%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Male</td>
<td>34 (48%)</td>
<td>18 (62%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>45 (63%)</td>
<td>12 (41%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Black</td>
<td>16 (23%)</td>
<td>11 (38%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (13%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Prematurity (≤37 weeks)</td>
<td>25 (35%)</td>
<td>13 (45%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>38.0 (29–41)</td>
<td>37.0 (32–40)</td>
<td>0.82</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>2383 (1012–3730)</td>
<td>2314 (1256–3795)</td>
<td>0.92</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>30 (24.3–37.0)</td>
<td>30.5 (25.5–34.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Abnormal computed tomography (CT) (calcifications)</td>
<td>20 (28%)</td>
<td>8 (28%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Abnormal cerebrospinal fluid indices</td>
<td>15 (21%)</td>
<td>8 (28%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Alanine aminotransferase(ALT) ≥100 IU/ L</td>
<td>12 (17%)</td>
<td>5 (17%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Platelet count ≤100,000/mm³</td>
<td>26 (37%)</td>
<td>8 (28%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>11 (15%)</td>
<td>4 (14%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>40 (56%)</td>
<td>12 (41%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>41 (58%)</td>
<td>15 (52%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Absolute Neutrophil Count(ANC) Grade 3–4</td>
<td>11 (15%)</td>
<td>2 (7%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Randomized Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>35 (49%)</td>
<td>13 (45%)</td>
<td>0.68</td>
</tr>
<tr>
<td>No treatment</td>
<td>36 (51%)</td>
<td>16 (55%)</td>
<td></td>
</tr>
<tr>
<td>Baseline Brainstem Evoked Response (BSER) (Best Ear)</td>
<td>33 (46%)</td>
<td>11 (38%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Normal</td>
<td>12 (17%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>6 (8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (13%)</td>
<td>5 (17%)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3
Average Delays Per Subject by Denver II Category (mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal/Social (2 total*)</td>
<td>0.5 ± .12</td>
<td>0.78 ± .12</td>
<td>0.11</td>
</tr>
<tr>
<td>Fine Motor (1)</td>
<td>0.21 ± .07</td>
<td>0.28 ± .07</td>
<td>0.50</td>
</tr>
<tr>
<td>Gross Motor (1)</td>
<td>0.09 ± .05</td>
<td>0.18 ± .06</td>
<td>0.29</td>
</tr>
<tr>
<td>Language (2)</td>
<td>0.71 ± .14</td>
<td>0.83 ± .13</td>
<td>0.54</td>
</tr>
<tr>
<td>Total Delays (6)</td>
<td>1.5 ± .27</td>
<td>2.05 ± .27</td>
<td>0.15</td>
</tr>
<tr>
<td>Total Delays without Language (4)</td>
<td>0.79 ± .18</td>
<td>1.23 ± .19</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal/Social (4 total)</td>
<td>0.77 ± .16</td>
<td>1.21 ± .20</td>
<td>0.10</td>
</tr>
<tr>
<td>Fine Motor (6)</td>
<td>1.31 ± .29</td>
<td>2.46 ± .37</td>
<td>0.02</td>
</tr>
<tr>
<td>Gross Motor (7)</td>
<td>2.11 ± .32</td>
<td>2.90 ± .42</td>
<td>0.15</td>
</tr>
<tr>
<td>Language (4)</td>
<td>0.26 ± .13</td>
<td>0.95 ± .22</td>
<td>0.009</td>
</tr>
<tr>
<td>Total Delays (21)</td>
<td>4.46 ± .74</td>
<td>7.51 ± 1.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Delays without Language (17)</td>
<td>4.20 ± .65</td>
<td>6.56 ± .85</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal/Social (6 total)</td>
<td>1.28 ± .23</td>
<td>2.22 ± .28</td>
<td>0.01</td>
</tr>
<tr>
<td>Fine Motor (12)</td>
<td>3.31 ± .66</td>
<td>6.19 ± .72</td>
<td>0.004</td>
</tr>
<tr>
<td>Gross Motor (13)</td>
<td>4.00 ± .69</td>
<td>6.61 ± .75</td>
<td>0.01</td>
</tr>
<tr>
<td>Language (7)</td>
<td>1.23 ± .26</td>
<td>2.11 ± .31</td>
<td>0.03</td>
</tr>
<tr>
<td>Total Delays (38)</td>
<td>10.06 ± 1.67</td>
<td>17.14 ± 1.93</td>
<td>0.007</td>
</tr>
<tr>
<td>Total Delays without Language (31)</td>
<td>8.58 ± 1.49</td>
<td>15.03 ± 1.68</td>
<td>0.005</td>
</tr>
</tbody>
</table>

* Total potential number of delays for each category listed in parenthesis

* J Clin Virol, Author manuscript; available in PMC 2010 December 1.


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Treatment of children with congenital cytomegalovirus infection with ganciclovir

MARIAN G. MICHAELS, MD, MPH, DAVID P. GREENBERG, MD, DIANE L. SABO, PHD AND ELLEN R. WALD, MD

Background. Congenital cytomegalovirus (CMV) infection affects ~1% of live births in the US. Ten percent of these infants have symptoms at birth and another 10 to 15% acquire hearing loss or developmental problems. Congenital CMV is the most common cause of nonhereditary sensorineural hearing loss in children, and progressive hearing loss is common. To arrest the natural progression of congenital CMV, children referred to our center were treated with a prolonged course of ganciclovir.

Methods. Medical records of children with congenital CMV who were treated with ganciclovir were reviewed to tabulate their presenting symptoms, duration of treatment, audiologic and developmental assessments and complications.

Results. We treated nine children with symptomatic CMV with iv ganciclovir at a median age of 10 days (range, 3 days to 11 months). Findings at diagnosis included microcephaly (five of nine); petechiae (five of nine); thrombocytopenia (seven of nine); and intracranial calcifications (six of eight). Hearing loss was noted before therapy in five of nine. The median duration of iv and subsequent oral ganciclovir was 1 year and 0.83 year, respectively. Median follow-up was 2 years (range, 1 to 7 years). No child had progression of hearing loss; improvement occurred in two. Seven children had at least one complication of ganciclovir therapy: central venous catheter/site infection (six); catheter malfunction (three); and neutropenia (one).

Conclusion. Of nine children none treated with ganciclovir for congenital CMV had detectable progressive hearing loss. Complications associated with iv therapy occurred frequently. Currently available oral analogues of ganciclovir may facilitate earlier and more prolonged therapy for children with symptomatic congenital CMV and should be subjected to randomized controlled trials.

INTRODUCTION

Congenital cytomegalovirus (CMV) affects ~1% of all live births in the United States resulting in 30 000 to 40 000 congenitally infected children each year. Ten percent of infants with congenital CMV are symptomatic at birth and another 10 to 15% subsequently develop sensorineural hearing loss or developmental
Progression occurs during the first 6 years of life. Once a child is infected with CMV, the virus remains latent for the lifetime of the host with periodic reactivation. It is unclear whether progressive hearing loss is caused by reactivation of virus, the immunologic response of the host or the delayed clinical appearance of damage already present. Although neurologic damage that occurred in utero might not be expected to reverse, it is possible that antiviral treatment might prevent disease progression. In utero infection with Toxoplasma, similar to CMV, may not cause clinical symptoms until after birth, and children with congenital toxoplasmosis appear to benefit from prolonged therapy with drugs directed against Toxoplasma gondii.7

Although a specific therapeutic regimen for children with congenital CMV has not been established, ganciclovir is an antiviral agent with activity against herpesviruses and has been used successfully to treat CMV disease in immunosuppressed hosts.8 Ganciclovir interrupts active replication of CMV by competitively interfering with elongation of the viral DNA chain. Accordingly ganciclovir was offered as treatment for children with symptomatic congenital CMV who presented with evidence of neurologic disease or hearing impairment.

METHODS

Beginning in 1994 all children <1 year of age who were identified as having symptomatic congenital CMV infection with central nervous system involvement, hearing impairment or both were offered treatment with intravenous ganciclovir followed by oral ganciclovir. Risks and potential benefits of ganciclovir treatment were discussed with parents. Review of medical records included birth history, clinical presentation consisting of significant head lag and/or abnormal tone or movement were noted in all children between birth and 7 months of age (Table 2).

### RESULTS

**Clinical description.** Between 1994 and 2001 all (n = 9) children diagnosed with symptomatic congenital CMV infection were treated with ganciclovir. Viral culture of the urine was positive for CMV in all patients. Presenting features are shown in Table 1. Five children were microcephalic. Intracranial calcifications were identified by computerized tomography (CT) scan in five of the six children evaluated. In addition two children had ultrasound studies without CT scans; one had a ventricular abnormality but no calcifications, and the other had findings consistent with calcifications. No evaluation for calcification was performed on one child. Developmental/neurologic abnormalities, consisting of significant head lag and/or abnormal tone or movement were noted in all children between birth and 7 months of age (Table 2).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Race</th>
<th>Gestational Age (wks)*</th>
<th>Microcephaly</th>
<th>Intracranial Calcification</th>
<th>Neurologic Abnormality†</th>
<th>HSM</th>
<th>Thrombocytopenia</th>
<th>Petchiae/ Purpura</th>
<th>Hearing Loss at Birth Screen</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>F</td>
<td>W</td>
<td>32</td>
<td>No</td>
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<td>No</td>
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<td>Yes</td>
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</tr>
<tr>
<td>2</td>
<td>M</td>
<td>W</td>
<td>37</td>
<td>No</td>
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<td>No</td>
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<td>No†</td>
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<tr>
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<td>W</td>
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<td>Yes</td>
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</tr>
<tr>
<td>4</td>
<td>M</td>
<td>W</td>
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<td>Yes</td>
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<td>Yes*</td>
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<td>8</td>
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<td>W</td>
<td>33</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>B</td>
<td>33</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No*</td>
</tr>
</tbody>
</table>

* Newborn hearing screen reported from an outside center.
† Abnormal head lag, tone or motor abilities.
HSM, hepatosplenomegaly; FT, full term (≥38 weeks gestation to <42 weeks); NA, not available.
Ganciclovir therapy. Intravenous ganciclovir (10 mg/kg/day) was started between 7 days and 11 months of age; five children had medication begun within the first 10 days of life. These children were born after 1996 and had symptoms identified at birth. The first four children had ganciclovir started only after hearing loss was noted to be moderate to severe in at least one ear (Patients 1, 2 and 4). Patient 3 had moderate hearing loss identified at birth but was followed up after 10 days of life because of neutropenia. Intravenous ganciclovir was decreased to 5 mg/kg/day after 2 to 4 weeks and was administered for a median of 12 months (range, 5.5 to 18 months). Subsequent to intravenous therapy, ganciclovir was administered orally (550 mg/m2/dose three times a day) for a median of 10 months (range, 6 months to 3 years). Children were followed for a median of 2 years (range, 1 to 7 years). The ganciclovir dosage was decreased and then discontinued intermittently in one patient because of neutropenia.

Neurologic follow-up. At follow-up developmental abnormalities included spasticity, hemiparesis, developmental delay and/or seizures in all six children in whom intracranial calcifications were demonstrated. Three children with poor head control and abnormal tone between 3 and 4 months of age had normal examinations with appropriate acquisition of developmental skills when last examined between 1 and 4 years of age. Two of these children did not have intracranial calcifications, and the third did not have a CT scan or ultrasound performed.

Assessment of hearing. All children had serial audiologic examinations. Table 2 documents the hearing assessment performed before initiation of ganciclovir treatment and at the most recent follow-up evaluation. Three children had normal hearing at the time ganciclovir treatment was initiated and maintained normal hearing through the last follow-up (range, 1 to 4 years) (Patients 5, 6 and 9). Patient 8 also passed her newborn hearing screen. However, this test can fail to identify hearing losses of 35 dB or less. More extensive testing was performed, but middle ear fluid confounded the findings until 9 months of age when left sided 35-dB hearing loss was documented and the patient was free of middle ear effusion. Her hearing subsequently improved to the normal range and remained normal when last tested at 21 months of age. Five children had hearing loss before starting treatment; the loss was unilateral in four. In three children the loss was severe in at least one ear (Patients 1, 2 and 3). Patient 1 was the first patient to be offered ganciclovir therapy. It was not initiated until she had documented worsening of the hearing in her right ear at 10 months of age.
age. Her already severe left sided hearing loss prompted the consideration and use of this novel therapy to prevent progressive loss. Despite this delay in therapy the right ear improved to the normal hearing range whereas the left remained severely impaired. Patient 4 was suspected to have a sensorineural component to his hearing loss in the left ear. However, middle ear fluid was present at all test times until 2 months after initiating ganciclovir, when moderate sensorineural hearing loss could be confirmed in the left ear. By 17 months of age the left sided hearing loss had decreased to mild and the right side remained normal. Patient 7 passed his birth hearing screen on the right side but failed on the left and subsequently was found to have an unusual pattern of hearing loss. When fully evaluated at Children’s Hospital of Pittsburgh, the left ear had a moderate loss at low and high frequencies and mild loss in the middle frequency area. The right ear had mild hearing loss in the low and high frequency areas with normal hearing at the middle range. This pattern remained stable through 2 years of age and was consistent with the patient’s birth screen findings. Hearing did not worsen in any child after starting treatment.

**Complications.** Nine bacterial infections of the central intravenous catheter used to deliver ganciclovir occurred in six of the children. Infection necessitated the removal of the indwelling catheter in two children: one in whom two infections occurred; and another in whom there were three infections. All other episodes responded to intravenous antibiotic therapy without removal of the catheter. Four children experienced catheter malfunction or breakage during the course of intravenous ganciclovir. In one child neutropenia developed with an absolute neutrophil count of <500 × 10⁶ cells/l. Ganciclovir was discontinued for 1 month and then restarted at one-half the desired dose (2.5 mg/kg/day) for the next 2 months. Increasing the dose of medication to 5 mg/kg/day again led to a decrease in the neutrophil count, necessitating intermittent reductions of ganciclovir dosing until the patient reached 1 year of age and treatment was changed to oral ganciclovir. Granulocyte-stimulating factor was not used.

**DISCUSSION**

As many as 60% of children with symptomatic congenital CMV infection can be expected to have sensorineural hearing loss.¹,⁴,⁶,¹⁰–¹⁴ In addition 30 to 80% of children with hearing impairment have progressive loss of hearing.¹,³–⁵ Although hearing loss may develop in late childhood, the majority of reported children with symptoms of congenital CMV at birth had hearing loss diagnosed before 1 year of age.³,¹⁴

Nine children with symptomatic congenital CMV disease at our center were treated with prolonged sequential intravenous and oral ganciclovir. Five of the children began ganciclovir within the first month of life; duration of intravenous therapy varied between 5.5 and 15 months whereas oral therapy was given between 6 and 24 months. Although orally administered ganciclovir does not achieve concentrations in the central nervous system that are sufficient to prevent CMV replication, the rationale for its use is to prevent reactivation of CMV peripherally.¹⁵ A similar rationale has prompted the use of prophylactic acyclovir to prevent the reactivation of herpes simplex virus in children who have recovered from herpes neonatorum.¹⁶

The four children with normal hearing at the start of treatment had normal hearing at follow-up 1 to 4 years later. No progression of hearing loss was detected in the other five children with hearing abnormality at the start of treatment and followed through 1 to 7 years of age. Of the nine children in this report, two had improvement of at least 10 dB in one ear from the baseline test to the most recent testing. One of these children (Patient 1) in whom ganciclovir was started at 11 months of age had improvement of hearing in the right ear from mild loss to normal. Another child (Patient 4) had a documented improvement in the left ear from moderate to mild hearing loss at follow-up. Finally Patient 8 passed the birth hearing screen but had a mild hearing loss of 35 dB documented during a full audiologic examination at 9 months of age. Repeat evaluations at 19 and 21 months of age were normal. This may represent a true improvement in hearing given that the birth screening can fail to detect mild abnormalities. However, this cannot be confirmed in a retrospective review.

Several case reports have documented that treatment of symptomatic infants for 3 to 4 weeks with intravenous ganciclovir decreases the shedding of CMV during the time of administration.¹⁴,¹⁷–²¹ Nigro et al.²² reported a trial of 2 regimens of ganciclovir therapy for 12 infants with congenital CMV infection: infants in Group 1 received a 2-week course of 10 mg/kg/day; whereas those in Group 2 received a 2-week course of ganciclovir at 15 mg/kg/day followed by a 3-month course at 10 mg/kg/day 3 times a week. Cessation of virus shedding occurred during treatment for both groups. Four of 6 children receiving the more prolonged treatment course showed clinical improvement compared with only 2 of 6 in the short course group.²²

In a Phase II multicenter collaborative study, infants younger than 1 month of age with symptomatic congenital CMV were treated with intravenous ganciclovir at 8 or 12 mg/kg/day for 6 weeks. Hearing remained unchanged or improved in 5 of 30 children evaluated after at least 6 months; 14 children with abnormal hearing at baseline remained abnormal. However, 11 of the 13 children with normal hearing at baseline developed abnormal hearing over time.²³ Kimberlin et al.²⁴ recently presented data from a Phase III collaborative multicenter randomized study using a similar short course (6 weeks) of intravenous ganciclovir com-
pared with placebo for infants with symptomatic congenital CMV infection. Although hearing was protected and even improved in treated children, 50% of patients were lost to follow-up, limiting the conclusions of this investigation.

The natural history of progression of hearing loss in congenital CMV during the first 6 years of life suggests that long course therapy may be required to prevent reactivation of the virus when the child (or end-organ) is still vulnerable. Unlike other reports prolonged therapy was used in the current study, and all children have been followed for a minimum of 1 year.

The generalizability of the experience reported here is limited by the retrospective nature of the review, the lack of a randomized control group and variations in total duration of intravenous and oral therapy. In addition obtaining accurate audiologic assessments in young and/or behaviorally challenged children may be difficult. However, previous reports of untreated infants with symptomatic CMV infection at birth suggest that at least 30% of children will show progressive hearing loss over time. The absence of progression in this cohort of children treated with ganciclovir is encouraging but requires confirmation. In addition it is possible that children started belatedly on therapy may not have experienced further progression of disease even without therapy. This review of nine patients suggests possible therapeutic benefit of long term treatment with ganciclovir to preserve auditory function. Malfunction, breakage and infection of the intravenous catheter and neutropenia were important adverse events that occurred in these children. Prolonged intravenous administration of ganciclovir is a demanding therapeutic strategy, and longer follow-up is required. Valganciclovir, a prodrug of ganciclovir, is rapidly converted to ganciclovir after oral administration and has recently been approved for treatment of CMV retinitis in adults with acquired immunodeficiency syndrome. Although pharmacokinetic and safety data are still needed in infants, valganciclovir will likely offer an alternative oral treatment that can be prospectively studied in infants with congenital CMV to more thoroughly evaluate efficacy and potential toxicity of long term treatment strategies.

REFERENCES

Effect on hearing of ganciclovir therapy for asymptomatic congenital cytomegalovirus infection: four to 10 year follow up

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Abstract

Background: Congenital cytomegalovirus infection is the leading identified nongenetic cause of congenital sensorineural hearing loss. Most of the infections are asymptomatic but may be detected from umbilical cord vein and/or newborn serum positivity for human cytomegalovirus immunoglobulin M, and from urine positivity (on polymerase chain reaction) for human cytomegalovirus deoxyribonucleic acid in the newborn period. Children infected by cytomegalovirus may later develop sensorineural hearing loss. In symptomatically infected infants, ganciclovir therapy administered in the neonatal period prevents hearing deterioration. However, preventative therapy of asymptomatic congenital cytomegalovirus disease with ganciclovir is controversial, as side effects such as severe neutropenia may occur during treatment.

Methods: The study population consisted of 23 asymptomatic children with congenital cytomegalovirus infection. Twelve children were treated just after diagnosis of cytomegalovirus infection in the newborn period, with ganciclovir 10 mg/kg bodyweight for 21 days. The other 11 children were observed without therapy. Over a four to 10 year follow-up period, we evaluated all the children’s hearing status using pure tone audiometry.

Results: All 23 children had normal sensorineural hearing at one year follow up. Five of the 23 children (21.7 per cent) were lost to follow up over the four to 11 year follow-up period. Of the remaining 18 children, sensorineural hearing loss occurred in two (11.1 per cent). Neither child had been treated with ganciclovir in the newborn period. An eight-year-old boy showed bilateral high frequency loss and a 10-year-old girl showed severe unilateral sensorineural hearing loss. In the ganciclovir-treated group (nine children), none showed sensorineural hearing loss. During ganciclovir therapy, moderate neutropenia occurred as a side effect in two out of 12 (16.6 per cent) treated children. Speech and general development were normal in all children.

Conclusion: Asymptomatic congenital cytomegalovirus infection is likely to be a leading cause of sensorineural hearing loss in young children. Intravenous ganciclovir therapy seems to offer a medical option to prevent subsequent sensorineural hearing loss. Further studies including a greater number of children are needed. Cytomegalovirus screening models are mandatory if medical therapy is to be implemented in time.

Key words: Sensorineural deafness; Child; Cytomegalovirus; Ganciclovir

Introduction

Cytomegalovirus (CMV) is the leading nongenetic cause of congenital sensorineural hearing loss (SNHL) in developed countries. The prevalence of congenital CMV infection in our region of Austria is about 0.22 per cent. Other reports from Europe and the US show prevalence rates of between 0.2–2 per cent. Therefore, approximately one per cent of all neonates are congenitally infected with CMV.

Ten per cent of infants with congenital CMV are symptomatic, and SNHL accompanies these symptoms in 30 to 65 per cent whereas 90 per cent of congenital CMV infections are asymptomatic. However, SNHL occurs from 7 to 15 per cent in this primary asymptomatic group during the first six years of life; thus, the prevalence of SNHL caused by CMV infection in childhood ranges from 20 to 30 per cent.
The virus remains latent in the organism for the lifetime of the host, and it can be reactivated periodically. A large virus burden during the first month of life is associated with SNHL. However, until now, it has been unclear whether the development of SNHL in childhood is caused by the reactivation of the virus, the immunological response of the host or the delayed clinical appearance of symptoms. Several studies of medical treatment with ganciclovir (an antiviral agent administered to affected, symptomatic infants in the neonatal period) document the possibilities for prevention of hearing deterioration and the improvement of other neurological symptoms. As neutropenia and thrombocytopenia occur due to high dose and/or long term ganciclovir therapy, these possible side effects are dose-related and can be easily managed by dose reduction.

Deafness, severe SNHL or deterioration of existing, moderate, congenital SNHL directly affects the child’s intellectual skills. Therefore, use of ganciclovir to treat neonatal congenital CMV infection should enhance the child’s learning possibilities and promote a higher quality of life. Secondary prevention strategies (such as active human CMV immunisation or secondary passive immunisation of infected pregnant women) are currently undergoing clinical trials but are not currently in clinical use, to our knowledge.

Therefore, low dose ganciclovir therapy for asymptomatic congenital CMV-infected newborns, as secondary prevention of early childhood SNHL or neurological deficits, should be helpful in order to minimise the prevalence and development of SNHL in asymptomatic congenitally CMV-infected children.

In order to estimate the impact on SNHL development of early ganciclovir therapy in asymptomatic congenitally CMV-infected children, we evaluated the hearing status of already randomly treated children from a former study group over a four to 10 year follow-up period (from 1993 to 2000), by performing pure tone audiometry.

Materials and methods
Study subjects
This study examined 23 children with documented, asymptomatic congenital CMV infection, born between January 1993 and December 2000 at the authors’ hospital. Fourteen of the children had taken part in a previous prospective CMV screening and diagnosis study; in addition, nine others were included, up to December 2000. These 23 asymptomatic children were randomly allocated to receive either ganciclovir therapy or no therapy, as soon as CMV was detected. Congenital CMV infection was screened by detection of CMV immunoglobulin M (IgM) in maternal serum or newborn umbilical cord vein blood, and identified by isolation of the virus in urine during the first postnatal week.

Twelve of the children were treated with ganciclovir. In their first year, none of the 23 children developed severe, CMV-induced handicaps such as microcephaly, hydrocephaly, ventriculomegaly, choriorretinitis or other ophthalmological symptoms, hepatosplenomegaly, thrombocytopenia, neutropenia, anaemia, jaundice, or hearing disorders.

At the age of one year, normal bilateral hearing was documented in all 23 children by measurement of bilateral transient evoked oto-acoustic emissions and by behaviour observation audiometry. Follow-up data for five children were unavailable because they moved to unknown addresses. Parental consent for examination of the remaining 18 children was obtained beforehand.

Follow up
Assessment of the medical history of each study subject included a review of their birth history and previous study protocols and medical reports (including radiographic investigations if available). The results of hearing screening tests performed at one year of age were retrieved from each child’s medical record. Data on developmental status, health status and hearing level were obtained by the entries in each Mother-Child-Booklet.

Assessment of each child’s hearing threshold was performed using ear microscopy, middle-ear impedance tests and behavioural observation audiometry until the age of four years; pure tone audiometry was used for older children.

Sensorineural hearing loss was defined as a median sensorineural decrease in hearing of ≥10 dBHL at low (125 to 1000 Hz), middle (1000 to 4000 Hz) or high (4000 to 16000 Hz) frequencies and was graded as mild (25 to ≤40 dBHL), moderate (41 to ≤65 dBHL), severe (66 to ≤96 dBHL) or profound (>96 dBHL).

Therapy
Intravenous application of ganciclovir was commenced within the first 10 days of life. The dosage was 10 mg ganciclovir per kg body weight for 21 days. If any signs of toxicity occurred (such as leucopenia or diarrhoea), the dosage was lowered to 5 mg per kg body weight; therapy was stopped if side effects did not resolve.

Results
At our hospital between January 1993 and December 2000, a total of 23 children were identified as having asymptomatic congenital CMV infection. Normal hearing was documented for all 23 children before the age of one year.

Five of the 23 (21.7 per cent) children were lost to follow up during the four to 10 year follow-up period. The remaining study population (18 children) had an average age of 8.1 years, an age range of 4.2 to 11.2 years and a male:female ratio of 11:7.

Ten (55.5 per cent) of these 18 children received intravenous ganciclovir therapy within the first 10 days of life (Table I). None of the other eight children received any kind of medical treatment.

Speech and general development were normal in all the study children throughout follow up.
The children were followed up for a mean of 7.1 years (standard deviation (SD) 2.2; range 3.2–10.3). In the treatment group, the mean duration of follow up was 6.4 years (SD 2.5; range 3.2–10.3) and the median duration was 5.9 years. However, in the control group, the mean duration of follow up was 8.0 years (SD 1.6; range 4.6–9.8) and the median duration was 8.2 years. This difference in the observation times was not statistically significant according to the Wilcoxon exact test, performed because of tied data, \(p = 0.18\).

Statistical evaluation of the urine CMV titre in both groups was not performed, because follow-up data for only four control group patients were available.

Sensorineural hearing loss occurred in two of the 18 (11.1 per cent) children (Table II). Neither had been treated with ganciclovir as neonates. One eight-year-old boy showed bilateral, mild, high frequency hearing loss with a maximum of 30 dBHL at 8000 Hz (Figure 1). One 10-year-old girl showed unilateral, moderate to profound SNHL (Figure 2). These two children’s follow-up periods were greater than five years. The difference between the SNHL incidence in the treated and untreated groups did not achieve statistical significance \( (p = 0.18, \text{Fisher’s exact test})\).

None of the 10 children in the ganciclovir treatment group showed signs of SNHL.

During ganciclovir therapy, moderate neutropenia (i.e. neutrophil cell count 1.0–1.5 \(\times\) 10\(^9\)/l; normal range 1.5–10.0 \(\times\) 10\(^9\)/l)\(^18\) occurred in two of the 12 (16.6 per cent) treated children. After lowering the dosage to 5 mg ganciclovir per kg body weight, the leukocyte rate normalised within a few days. All 10 study patients receiving intravenous ganciclovir had finished their therapy after three weeks.

### Discussion

In symptomatic cytomegalovirus (CMV)-infected infants with symptoms involving the central nervous system, systemic ganciclovir therapy administered in the neonatal period prevents hearing deterioration or maintains normal hearing in early childhood.\(^{13,19}\) On the other hand, symptomatic CMV-infected infants receiving no such treatment develop sensorineural hearing loss (SNHL) in early childhood significantly more often, compared with ganciclovir-treated children.\(^{13}\) The results of our study suggest that

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic congenital CMV (n)</td>
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<td>11</td>
</tr>
<tr>
<td>Normal hearing ≤ 1 yr (n)</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Lost to follow up (n)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Age (mean ± SD (yrs))(^*)</td>
<td>7.4 ± 2.5</td>
<td>9.0 ± 1.6</td>
</tr>
<tr>
<td>Gender (male/female)(^*)</td>
<td>5/7</td>
<td>6/5</td>
</tr>
<tr>
<td>Urine CMV titre(^{13})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copies – median (n) (= 3.83E + 05 (11))</td>
<td></td>
<td>(= 6.59E + 03 (5))</td>
</tr>
<tr>
<td>Copies – range (= 1.06E + 05–1.17E + 07)</td>
<td></td>
<td>(= 2.00E + 03–8.28E + 05)</td>
</tr>
</tbody>
</table>

\(n\) refers to patient numbers throughout. \(^*n = 18\) complete observations. \(^{1}\)Includes patients lost to follow up. \(^{2}\)In first postnatal week. CMV = cytomegalovirus; yr = year; SD = standard deviation
ganciclovir given intravenously within the first 10 days of life for a total of three weeks helps maintain normal hearing during childhood in asymptomatic congenital CMV-infected children.

The total detection rate for SNHL in our study group was 11.1 per cent; this is similar to previous studies, which have found rates of up to 7.4 per cent, and rates of 18.2 per cent for delayed SNHL onset up to the age of 62 months. Although a statistical bias may be evident in this study, due to the small group of investigated children, the detection of SNHL in two children without treatment is significant.

The development of SNHL in congenitally CMV-infected neonates depends on a large virus burden during the first month of life. Higher amounts of infectious CMV in urine and the presence of CMV deoxyribonucleic acid (DNA) in the peripheral blood of children with asymptomatic congenital CMV infection during early infancy have
been found to be associated with an increased risk of subsequent SNHL development.\textsuperscript{12,20} Ganciclovir applied in the first week of life lowers the virus burden in the peripheral blood;\textsuperscript{12} a reduced urine virus load reflects the positive effect of ganciclovir therapy on the prevention of organic symptoms.\textsuperscript{14}

In our study group, SNHL was observed in two children: bilateral, mild hearing loss in the high frequencies in one case; and unilateral (left ear), moderate to severe hearing loss in all frequencies in the second case. The latter case, a 10-year-old girl, was handicapped in bidirectional hearing but did not complain of it in everyday life. Neither child showed delayed speech or general development, nor were such delays found in any other study patient. The late diagnosis of SNHL in both affected cases, at eight and 10 years of age, was perhaps due to these children being previously investigated only by their general practitioner. As no other symptoms of reactivation of CMV infection were evident and the hearing loss in both cases was unremarkable, both sets of parents unfortunately withheld consent for peripheral blood venepuncture in order to analyse CMV DNA virus load, and for further magnetic resonance imaging head scans. However, these children’s clinical histories indicated no other relevant aetiological factors for SNHL, so we believe that their hearing loss was due to their congenital CMV infection. Because of lack of evidence of a new CMV reactivation, subsequent ganciclovir therapy was not performed.

### Conclusion

Asymptomatic congenital CMV infection is likely to be a leading cause of SNHL in young children. Assuming a routine screening programme with appropriate testing for congenital CMV infection at birth, our results suggest that, in asymptomatic congenital CMV-infected neonates, hearing deterioration in early childhood could be prevented by early (within the first week of life), intravenous ganciclovir administration to pregnant women carrying a fetus with confirmed CMV infection. In this study, the CMV viral load in fetal blood decreased significantly after one to 12 weeks of treatment, and outcomes were better in the treated group than in the untreated group.

Other clinical trials have investigated intravenous\textsuperscript{23} or intruterine\textsuperscript{24} application of CMV immunoglobulin. However, there is currently no established modality for treating a pregnant woman with CMV infection.

### References

Dried Blood Spot Real-time Polymerase Chain Reaction Assays to Screen Newborns for Congenital Cytomegalovirus Infection

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CMV and Hearing Multicenter Screening (CHIMES) Study

Context Reliable methods to screen newborns for congenital cytomegalovirus (CMV) infection are needed for identification of infants at increased risk of hearing loss. Since dried blood spots (DBS) are routinely collected for metabolic screening from all newborns in the United States, there has been interest in using DBS polymerase chain reaction (PCR)–based methods for newborn CMV screening.

Objective To determine the diagnostic accuracy of DBS real-time PCR assays for newborn CMV screening.

Design, Setting, and Participants Between March 2007 and May 2008, infants born at 7 US medical centers had saliva specimens tested by rapid culture for early antigen fluorescent foci. Results of saliva rapid culture were compared with a single-primer (March 2007-December 2007) and a 2-primer DBS real-time PCR (January 2008-May 2008). Infants whose specimens screened positive on rapid culture or PCR had congenital infection confirmed by the reference standard method with rapid culture testing on saliva or urine.

Main Outcome Measures Sensitivity, specificity, and positive and negative likelihood ratios (LRs) of single-primer and 2-primer DBS real-time PCR assays for identifying infants with confirmed congenital CMV infection.

Results Congenital CMV infection was confirmed in 92 of 20,448 (0.45%; 95% confidence interval [CI], 0.36%-0.55%) infants. Ninety-one of 92 infants had positive results on saliva rapid culture. Of the 11,422 infants screened using the single-primer DBS PCR, 17 of 60 (28%) infants had positive results with this assay, whereas, among the 9,026 infants screened using the 2-primer DBS PCR, 11 of 32 (34%) screened positive. The single-primer DBS PCR identified congenital CMV infection with a sensitivity of 28.3% (95% CI, 17.4%-41.4%), specificity of 99.9% (95% CI, 99.9%-100.0%), positive LR of 803.7 (95% CI, 278.7-2,317.9), and negative LR of 0.7 (95% CI, 0.6-0.8). The positive and negative predictive values of the single-primer DBS PCR were 80.9% (95% CI, 58.1%-94.5%) and 99.6% (95% CI, 99.5%-99.7%), respectively. The 2-primer DBS PCR assay identified infants with congenital CMV infection with a sensitivity of 34.4% (95% CI, 18.6%-53.2%), specificity of 99.9% (95% CI, 99.9%-100.0%), positive LR of 3,088.9 (95% CI, 410.8-23,267), and negative LR of 0.7 (95% CI, 0.5-0.8). The positive and negative predictive values of the 2-primer DBS PCR were 91.7% (95% CI, 61.5%-99.8%) and 99.8% (95% CI, 99.6%-99.9%), respectively.

Conclusion Among newborns, CMV testing with DBS real-time PCR compared with saliva rapid culture had low sensitivity, limiting its value as a screening test.

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DRIED BLOOD SPOT PCR FOR NEWBORN CMV SCREENING

April 14, 2010—Vol 303, No. 14

examination and newborn hearing screening will miss potential diagnosis in many children who develop SNHL secondary to congenital CMV infection. To identify these at-risk infants early in life, rapid, reliable, and relatively inexpensive methods to screen newborns for congenital CMV infection are needed. Identification of children at increased risk of CMV-associated SNHL early in life will allow targeted monitoring of these children in order to intervene at critical stages of acquiring speech and language skills.

Although traditional virus isolation from saliva or urine specimens in tissue culture is considered the standard method for identification of infants with congenital CMV infection, it is not amenable to mass screening (even when modified to produce rapid results) because it is labor- and resource-intensive and requires tissue culture facilities. Real-time polymerase chain reaction (PCR) technology, in contrast, is well-suited for mass screening because it does not require tissue culture facilities and is amenable to automation with the screening of large numbers of specimens at low cost. A variety of newborn specimens including saliva, urine, and dried blood spots (DBS) can be tested with PCR-based methods for the diagnosis of congenital CMV infection.

Since DBS are collected routinely for newborn metabolic screenings from all infants born in the United States, there has been considerable interest in using PCR assays for detecting CMV in newborn DBS specimens. Despite the benefits of DBS PCR-based methods, the sensitivity and specificity of these assays for universal newborn CMV screening have not been determined. Most reports have studied selected infant populations and none have prospectively compared the results of a DBS PCR assay with a standard (ie, tissue culture) method for identifying CMV infection in an unselected newborn population. This study examined the diagnostic accuracy of real-time PCR analysis of DBS as an approach for mass screening of newborns for congenital CMV infection.

METHODS

Study Population

Between March 2007 and May 2008, infants born at 7 US medical centers (University of Alabama at Birmingham Hospital; The University of Mississippi Medical Center; Jackson; Carolinas Medical Center, Charlotte, North Carolina; Saint Peter’s University Hospital, New Brunswick, New Jersey; Good Samaritan Hospital, Cincinnati, Ohio; Magee Women’s Hospital, Pittsburgh, Pennsylvania; and Parkland Memorial Hospital, Dallas, Texas) were enrolled prospectively in the National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) study. Institutional review board approval was obtained at each site. Mothers were approached postpartum to obtain written informed consent for their newborn’s enrollment in the study. Upon enrollment, saliva specimens were collected from participating infants along with an additional blood spot obtained at the time of newborn metabolic screening. The DBS specimen for the study was collected only after the completion of metabolic screening and infants were not subjected to additional heel sticks for the CHIMES study. Infants with positive saliva or DBS screening specimens were enrolled in the follow-up component of the study to confirm congenital CMV infection, as well as evaluate hearing outcomes during the first 4 years of life (ongoing). Race and ethnicity data were collected as self-reported by parents because the prevalence of congenital CMV infection has been shown to vary according to racial and ethnic composition of the delivery population.

Specimen Collection

Saliva specimens were collected from the enrolled newborns at a mean (SD) age of 0.9 (0.6) days and before nursery discharge. Collection was made by swabbing inside the infant’s mouth using a sterile polyester fiber-tipped applicator (PurFybr Inc, Munster, Indiana) and placed in 1.0 mL of transport medium containing sucrose phosphate. The specimens were stored at 4°C until they were transported, on ice, within 1 week of collection. A temperature-monitoring device was included in shipments to monitor for temperature variation during transport (TL20, 3M, St Paul, Minnesota).

DBS specimens were collected at the time of newborn metabolic screening and the mean (SD) age at collection was 1.9 (1.8) days. The additional blood spots were collected on a separate filter paper (Whatman 903, Florham Park, New Jersey), placed in individual envelopes, and stored in plastic resealable bags containing desiccant. DBS specimens were maintained at room temperature and shipped once weekly. Saliva and DBS specimens were transported to the University of Alabama at Birmingham central laboratory.

Detection of CMV in Saliva Specimens

The mean (SD) interval between the collection of initial saliva specimens and testing at the University of Alabama at Birmingham central laboratory was 7.4 (4.0) days. The presence of CMV in saliva specimens was detected by a rapid culture method for detecting early antigen fluorescent foci using a monoclonal antibody against the CMV major immediate early antigen in duplicate wells of a 96-well microtiter plate. Each run included 2 positive control wells inoculated with the AD169 strain of CMV at a titer producing approximately 100 infectious foci per well. A specimen was considered positive if at least 1 focus of distinct nuclear fluorescence was detected in at least 1 well. Individuals ascertaining the results of the saliva rapid culture assay or the DBS PCR were blinded to the results of the other test.

DNA Extraction From DBS Specimens

From each DBS, two 3-mm disks were punched into 1.5-mL sample tubes...
using the BSD600 automated filter paper puncher (BSD Robotics, Acacia Ridge, Queensland, Australia). The punched filter paper disks were processed to extract DNA using the Qiagen M48 robotic system with MagAttract technology according to the manufacturer’s instructions (Qiagen Inc, Valencia, California). The extracted DNA specimens were stored at −20°C. A blank filter card was punched and included in each extraction run to serve as a negative control for DNA extraction and to monitor for cross contamination. In addition, a filter paper spotted with 10,000 copies of AD169 strain of CMV was punched and included in the extraction run to serve as a positive control and to monitor for consistency and reliability of the extraction protocol.

Real-time PCR

The mean (SD) interval between DBS specimen collection and PCR analysis was 14.6 (9.6) days. The detection of CMV DNA was performed using the ABI 7500 Real-time PCR System (Applied Biosystems Inc, Foster City, California) and ABSolute QPCR Low ROX Mix (ABgene USA, Rockford, Illinois). The reaction mixture contained primers at a concentration of 900 nM and the probe at 250 nM. Each specimen was run in duplicate using 25 µL of reaction mixture containing 20 µL of master mix and 5 µL of test specimen. To generate standard curves, each plate contained plasmid standards incorporating the target sequences in 10-fold dilutions ranging between 100,000 and 10 genomic equivalents per reaction. The real-time PCR amplification conditions have been previously described.27,28 During the first 10 months of the study, the real-time PCR assay included primers to detect the highly conserved AD-1 region of the major envelope glycoprotein B,27,29 During the final 5 months of the study, the PCR method was modified to include a second primer set from the highly conserved immediate 2 exon 5 region (forward primer, GAG CCC GAC TTT ACC ATC CA; reverse primer, CAG CCG GCA GTA TCG A; and probe, VIC-ACC GCA ACA AGA TT-MGBNFQ) in an effort to improve the sensitivity of the assay (GeneBank accession numbers GU179001, AY446871, AY446870, FJ616285, AY446868). The real-time PCR was repeated on all specimens with a positive signal in either well and a specimen was considered positive if 1 or more genomic equivalents per reaction were detected on both PCR runs. In addition, real-time PCR was repeated on DBS specimens from infants with saliva specimens positive by rapid culture assay that were negative on the first PCR run. The detection limit of our real-time PCR assay, as determined by the sensitivity titration analysis, was 250 genomic equivalents per milliliter for the single-primer assay and 50 genomic equivalents per milliliter for the 2-primer assay (eAppendix available at http://www.jama.com).

Efficiency of DNA Extraction and DBS PCR Performance Characteristics

To determine whether the sensitivity of DBS real-time PCR for CMV DNA detection was influenced by the extraction method, detection of CMV DNA by the 2-primer real-time PCR protocol was compared between a commercial column-extraction method (Qiagen Inc, Valencia, California) and the robot-extraction protocol used in this study (eAppendix). In addition, the amount of genomic DNA as determined by real-time PCR amplification of RNase P (TaqMan RNase P control reagents kit, Applied Biosystems Inc, Foster City, California) in 185 randomly selected DBS specimens from CMV-negative infants was compared within the robots- and column-extraction methods (eAppendix). A comparison of the 2-primer real-time PCR assay and a previously described nested PCR protocol was undertaken to assess whether our real-time PCR method would be as sensitive or more sensitive for detecting CMV DNA than a standard nested-PCR method (eAppendix).13

Confirmation of Screening Results

To account for the possibility that saliva rapid culture assay may be less than 100% sensitive in identifying CMV-infected newborns, infants with positive saliva specimens or DBS screening specimens were enrolled in the follow-up component of the CHIMES study to confirm congenital CMV infection.25 Urine and repeat saliva specimens were obtained from these infants at the enrollment visit for the follow-up study and were tested for CMV with the rapid culture assay (previously described). The rapid culture assay on the follow-up saliva or urine specimen was considered the reference standard for this study and therefore, a confirmed congenital CMV infection was defined as identification of CMV in either saliva or urine obtained at enrollment into the follow-up study. Infants were considered to be uninfected if both the saliva and the urine specimens tested negative by rapid culture assay. Newborns who were negative for CMV by both screening assays (saliva rapid culture and DBS PCR) were not enrolled in follow-up and not retested with the reference standard assay.

Data Analysis

Only infants enrolled in the follow-up component of the study for confirmation of congenital CMV infection status were included in determining the diagnostic ability of the DBS real-time PCR assays. Sensitivity, specificity, and predictive values for both the single-primer and the 2-primer DBS real-time PCR assays were calculated using standard methods for proportions and exact 95% confidence limits. The positive predictive value was the ratio of true positives to all positive DBS PCR results and the negative predictive value was the ratio of true negatives to all negative DBS test results. Likelihood ratios (LRs) were calculated to summarize the diagnostic accuracy of the DBS PCR assays. Positive LR was sensitivity/(1−specificity) and

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(Reprinted) JAMA, April 14, 2010—Vol 303, No. 14 1377
the negative LR was (1−sensitivity)/specificity. Confidence intervals (CIs) for LRs were determined using the method described by Simel et al.30 Statistical differences between nested and real-time PCR methods were calculated using the χ² test. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS
Study Population and Specimens
Of the 36 130 eligible infants, 22 758 (63%) infants were enrolled in the study. Although all live-born infants were eligible for participation, some of the infants born over holidays or weekends and those discharged prior to obtaining consent for participation in the study (n=10 876) were not enrolled. Additional reasons for nonenrollment included refusal to participate (n=1359); unable to obtain consent due to maternal factors such as illness, mental capacity, age, or language (n=677); and infant death or illness (n=460).

Both saliva and DBS specimens were collected from 20 613 (91%) infants, only saliva specimens were collected from 1837 infants, only DBS specimens were collected from 262 infants, and 46 infants had neither specimen collected (FIGURE).

Figure. Evaluation of DBS Real-time PCR Assays for Identifying Infants With Congenital CMV Infection

- 98 130 Eligible newborns identified
- 13 372 Excluded
  - 10 876 Not approached
  - 1359 Refused consent
  - 677 Unable to consent
  - 460 Infant death or illness
- 22 758 Newborns enrolled in study
- 2310 Excluded
  - 1837 Only saliva specimen collected
  - 262 Only DBS specimen collected
  - 165 Specimens damaged in shipping
  - 46 Neither specimen collected
- 20 448 Newborns included
- 11 422 Screening saliva for rapid culture and single-primer DBS PCR in the March 2007-December 2007 study period
- 9026 Screening saliva for rapid culture and 2-primer DBS PCR in the January 2008-May 2008 study period
- 11 341 Screened negative by both assays, no further testing
- 8983 Screened negative by both assays, no further testing
- 8 No reference standard testing
  - 8 Saliva rapid culture
  - 2 DBS PCR
- 60 CMV positive
  - 59 Saliva rapid culture
  - 17 DBS PCR
- 32 CMV positive
  - 32 Saliva rapid culture
  - 11 DBS PCR
- 6 CMV negative
  - 6 Saliva rapid culture
  - 4 DBS PCR
- 3 CMV negative
  - 3 Saliva rapid culture
  - 1 DBS PCR

DBS indicates dried blood spots; PCR, polymerase chain reaction; and CMV, cytomegalovirus.

- Infants born over holidays or weekends or discharged before consent could be obtained.
- Unable to obtain consent due to illness, mental capacity, maternal age, or language.
- Will not sum because some participants were counted multicategorically.
- Rapid culture on saliva and urine samples collected at enrollment into follow-up to confirm congenital CMV infection was considered the reference standard for the study.
The reasons that both specimens were not available from these newborns included (1) the infants were unavailable or discharged from the nursery prior to collection (n=1214); (2) the newborn metabolic screening was completed before infants were enrolled in the study or there was insufficient blood left for the study DBS specimen (n=731); or (3) the specimens were mislabeled or misplaced (n=200). The infants (n=2145) who did not have both specimens collected were more likely to be in the neonatal intensive care unit than infants who had both specimens collected (14.7% vs 2.9%; χ² test = 707.2; P < .001). Of the 20,613 infants who had both specimens collected, saliva specimens from 165 infants could not be tested due to leakage or temperature variations during shipment (Figure). Thus, the study population comprises the 20,448 infants who had both saliva and DBS specimens collected and tested.

Most of the study infants (19,858 [97.1%]) were from the well-baby nurseries (Table 1). The infants were evenly distributed by sex (male, 51.0% vs female, 49.0%). Mean (SD) maternal age was 27.3 (6.1) years. The mean (SD) age at enrollment into the follow-up study for confirmation of congenital CMV infection in infants positive by screening saliva rapid culture or DBS PCR was 6.4 (6.1) weeks of age. Overall, 92 of the 20,448 (0.45%; 95% CI, 0.36%-0.55%) infants had confirmed congenital CMV infection.

Newborn CMV Screening With Saliva Rapid Culture and the Single-Primer DBS PCR Assay

Between March 2007 and December 2007, 11,422 newborns were screened for congenital CMV infection using saliva rapid culture and the single-primer DBS PCR assay (Figure). Eighty-one newborns tested positive for CMV infection by either saliva rapid culture assay (n=71), the DBS PCR assay (n=26), or both methods (n=16). Sixty-six of the 81 infants (81%) who tested positive by either screening method were enrolled in the follow-up study and of those, 60 children were confirmed to have congenital CMV infection based on the positive reference standard assay. Congenital CMV infection status could not be determined in 15 infants because they were not enrolled in the follow-up study. Reasons for not enrolling in the follow-up study included refusing participation (n=8), loss to follow-up (n=6), and relocation (n=1).

Screening saliva rapid culture correctly identified 59 of the 60 infants (98%) with confirmed congenital CMV infection, whereas the single-primer DBS PCR only identified 17 of the 60 infants (28%) confirmed to have congenital CMV infection (TABLE 2). Congenital CMV infection was not confirmed in 2 of 61 infants (3%) with saliva specimens positive by rapid culture assay and in 4 of 21 infants (19%) who were DBS PCR-positive because of the negative reference standard assay. The sensitivity and specificity of the single-primer DBS PCR assay in identifying infants with confirmed congenital CMV infection were 28.3% (95% CI, 17.4%-41.4%) and 99.9% (95% CI, 99.9%-100%), respectively. The positive LR for the single-primer DBS PCR assay was 803.7 (95% CI, 278.7-2317.9) and the negative LR was 0.7 (95% CI, 0.6-0.8). The positive predictive value of the single-primer PCR assay was 80.9% (95% CI, 58.1%-94.5%) and the negative predictive value was 99.6% (95% CI, 99.5%-99.7%).

Newborn Screening With Saliva Rapid Culture and the 2-Primer DBS PCR Assay

During the study period between January 2008 and May 2008, there were 9026 newborns screened for congenital CMV infection using saliva rapid culture and the 2-primer DBS PCR assay (Figure). Forty-three newborns tested positive for CMV infection by either saliva rapid culture assay (n=43) or the DBS PCR assay (n=14). Thirty-five of the 43 infants (81%) who screened positive were enrolled in the follow-up study and of those, 32 children were confirmed to have congenital CMV infection based on a positive reference standard assay (Figure). Congenital infection status could not be determined in 8 infants since they did not enroll in the follow-up study. Reasons for not enrolling in the follow-up study included refusing participation (n=4), loss to follow-up (n=2), death (n=1), and relocation (n=1).

Screening saliva rapid culture correctly identified all 32 infants (100%) who were confirmed to have congenital CMV infection, whereas the 2-primer DBS PCR identified only 11 of the 32 infants (34%) confirmed to have congenital CMV infection (Table 2). Congenital CMV infection was not confirmed in 3 of 35 infants with saliva rapid culture (8%) and 1 of 12 screening DBS PCR-positive infants (8%) because the reference standard assay was negative. The sensitivity and specificity of the 2-primer DBS PCR assay for detecting infants with confirmed congenital CMV infection were 34.4% (95% CI, 18.6%-53.2%) and 99.9% (95% CI, 99.9%-100%), respectively. The positive LR for the 2-primer DBS PCR assay was 3088.9 (95% CI, 410.8-23,226.7) and the negative LR was 0.7 (95% CI, 0.5-0.8). The positive predictive value of the 2-primer as-

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say was calculated to be 91.7% (95% CI, 61.5%-99.8%) and the negative predic-
tive value was 99.8% (95% CI, 99.6%-99.9%).

**Extraction Methods**

Of the 71 DBS specimens from infants with positive saliva specimens, 29 robot-
eextracted specimens (41%) were positive for CMV DNA, whereas only 19 col-
umn-extracted specimens (29%) were positive ($\chi^2$ test, 3.14; $P=0.08$) (eTable 1
available at http://www.jama.com). In addition, in 185 randomly selected DBS
specimens from infants testing nega-
tive for CMV, the mean (SD) amount of
genomic DNA obtained using robotic ex-
traction (0.86 [0.46] µg/mL) and using
a commercial column kit (0.78 [0.44]
µg/mL) was similar ($r$ [368] =−1.58;
$P=0.1$) as measured by amplifying the
RNase P gene (TaqMan Gene Expres-
sion Assays Protocol, PN 4333458)
(eAppendix).

In 86 infants with confirmed con-
genital CMV infection, 40 (47%) were
positive on the 2-primer PCR and 30
(35%) were positive by the nested PCR
assay ($\chi^2$ test=2.41; $P=0.12$). Both meth-
ods failed to identify 48% (41/86) who
were confirmed CMV-positive (eTable 2
available at http://www.jama.com).

**COMMENT**

This study demonstrates that real-
time PCR analysis of DBS has low sen-
sitivity for correctly identifying in-
fants with congenital CMV infection. These results have major public health
implications because they indicate that
such methods, as currently per-
formed, will not be suitable for the mass
screening of newborns for congenital
CMV infection—the most common
nongenetic cause of deafness in the
United States. Our data indicate that as
many as 80% of infants with congeni-
tal CMV infections could be missed,
even when using 2-primer DBS real-
time PCR assays. The high positive LRs
for the single-primer and the 2-primer
PCR assays provide strong evidence that
a positive DBS PCR result using these
assays will identify infants with con-
genital CMV infection. However, the
negative LRs for both PCR assays are
not sufficiently small enough to rule out
congenital CMV infection in newborns
with a negative DBS PCR result.

PCR testing of peripheral blood has
been widely used as a standard diag-
nostic method to detect invasive CMV
infections in immunocompromised in-
dividuals including allograft recipi-
ents and patients with AIDS.31,32 These
results, together with those of several
studies that reported successful iden-
tification of infants with congenital
CMV infection by DBS PCR, has led to
anticipation that DBS PCR methods
would become valuable tools in new-
born CMV screening.13-16,20-22 How-
ever, the pathogenesis of congenital
CMV infection is likely to be different
from that in immunocompromised
hosts. Immunocompromised patients
usually experience acute CMV infec-
tion or symptomatic reactivation shortly
before blood CMV PCR testing, whereas
congenitally infected infants may have
acquired CMV infection months be-
fore birth and thus are no longer vire-
mic when tested as newborns.

This study, in which the 2 DBS real-
time PCR assays were directly and pro-
spectively compared with a reference
standard for identification of infants
with congenital CMV infection, pro-
vides important test measures of the use
of DBS PCR. Several previous reports
have demonstrated that newborns with
congenital CMV infection can be iden-
tified with varying degrees of success
by testing DBS using different PCR
methods.13,16,33,34 However, the prospec-
tive studies that confirmed CMV infec-
tion after identifying CMV DNA in DBS
did not determine the number of false
negatives (infants with congenital CMV
infection who tested negative on DBS
PCR). Having the complete denomina-
tor, as provided by this study, is essen-
tial to determine the use of DBS PCR
for newborn CMV screening.

The low sensitivity of the DBS PCR
method could possibly be explained by
several factors: (1) the method used for
DNA extraction; (2) the real-time PCR
techniques; or (3) the possibility that
not all infants with congenital CMV
infection have detectable CMV DNA in
their blood at birth. To evaluate extract-
ion methods, we compared the ability
of the 2-primer DBS real-time PCR
to detect CMV DNA in DBS speci-
mens processed with the robot-

**Table 2. Use of the 2 DBS Real-time PCR Assays to Identify Infants With Confirmed Congenital CMV Infection**

<table>
<thead>
<tr>
<th>Congenital CMV Infection</th>
<th>Single-Primer DBS PCR</th>
<th>2-Primer DBS PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>11343</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>11386</td>
</tr>
</tbody>
</table>

Other analyses, % (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Primer</td>
<td>28.3 (17.4-41.4)</td>
<td>99.9 (99.9-100)</td>
<td>803.7 (278.7-2317.9)</td>
<td>0.7 (0.6-0.8)</td>
<td>80.9 (58.1-94.5)</td>
<td>99.6 (99.5-99.7)</td>
</tr>
<tr>
<td>2-Primer</td>
<td>34.4 (18.6-53.2)</td>
<td>99.9 (99.9-100)</td>
<td>3088.9 (410.8-23226.7)</td>
<td>0.7 (0.5-0.8)</td>
<td>91.7 (61.5-99.8)</td>
<td>99.8 (99.6-99.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; DBS, dried blood spots; PCR, polymerase chain reaction.
tion had no detectable CMV DNA in infants with congenital CMV infection. but neither method identified most of the higher sensitivity than the nested PCR onstrated that the 2-primer PCR had a from laboratory to laboratory. A com- PCR method has been shown to vary sample panels, the sensitivity of the CMV DBS PCR assay was demonstrated to be at least 98% sensitive in identifying infants with congenital CMV infection. Finally, the results of our study showed that 99% (91 of 92) of infants with confirmed congenital CMV infection were identified on screening saliva rapid culture assay.

Another possible limitation is the relative overrepresentation of African Americans in our study population, which could make the findings of this study less generalizable to other populations. Although African American infants have a greater risk of infection, there is no scientific evidence that the clinical course or the sensitivity of diagnosto assays differs by race or ethnicity. However, the overrepresentation of African Americans may have influenced the prevalence of congenital CMV infection in our study. For populations with differing prevalences of congenital CMV infection than we found in this study, the predictive values calculated for the DBS PCR assays would not be appropriate since pre-dictive values are dependent on the underlying prevalence of disease in the population.

In summary, the results of this large, prospective newborn CMV screening study that included a direct comparison of the DBS real-time PCR assays with the culture-based method on saliva specimens demonstrated that real-time DBS PCR assays are not suitable for screening newborns for congenital CMV infection since they miss approxi-mately two-thirds of the infections. As the disease burden from congenital CMV infection remains a significant public health problem, there continues to be a need to identify the large number of infants with clinically inapparent congenital CMV infection early in life. The results of our study underscore the need for further evaluation of high-throughput methods performed on saliva or other specimens that can be adapted to large-scale newborn CMV screening.
We would like to thank the following members of the CHIMES study team for their contributions:

University of Alabama at Birmingham Health System: Nitin Arora, MBBS, MPH; Amita Bey, MPH; Belinda Blackstone, MS, CCC-A; Jennifer Blumen- thal, BS; Valisa Brown, MPH; Alice Brumbach, MS; Nazma Chawdhury, MSSed, PhD; Steven Fevers-Cordero; Monique Jackson, BS; Mirjam Kempf, PhD; David Kimberlin, MD; Noelle Le Lievre; Faye McCollister, EdD; Emily Mixon, MPH; Misty Purser, RN; and Julie Woodruff, AuD. Carolinas Medical Center: Edie Cox, AuD; Julie Courtney; Nubia Flores; Molly Ricart; Lisa Schneider, AuD; and Jennifer West, RN, BSN. Children’s Hospital of Pittsburgh of UPMC: Jena Colaberardino, BA; Noreen Jeffrey, RN; Anne Mace- rk, MS; Gretchen E. Probst, MAT, CCC-A; Cheryl Rosenberg; and Diane Sabo, PhD. Saint Peter’s Uni- versity Hospital: Melissa Calderon, RNC, BSN; Maria Class, RN; Kristina Feja, MD; and Marcia Schub, MD. University of Cincinnati and Cincinnati Children’s Hospital Medical Center: Daniel Choo, MD; Kate Cat- alanito, RN; BSN; and Linda Jackson, MSN; Patty Kern, RN; Kurt Schibler, MD; Maureen Sullivan-Mahoney, AuD; and Stacie Wethington, RN, CCRC. University of Mississippi Medical Center: Kathy Irving, AuD; Delia Owens, RN; Suzanne Roark, AuD; and Mindy Ware, AuD. University of Texas Southwest- ern Medical Center at Dallas, Parkland Health & Hos- pital System and Children’s Medical Center Dallas: Cathie Barri, MA; Jessica Esquivel; Gregory L. Jackson, MD, MBA; Kathy Katz-Gaynor; April Lierh Townsley, MA, CCC-A; Asuncion Mejias, MD; Kris- tine E. Owen, AuD; ACC-C, A; Peter S. Roland, MD; Os- car Rosado, MD; Angela G. Shoup, PhD; David Sosa; Jessica Santoyo; Elizabeth K. Stelh, MD; Lizette Torres, RN; and Fiker Zeray, RN, MS, CPNP. All the listed in- dividuals are part of the CHIMES study and have not received any other compensation.

Online-Only Material: eAppendix and eTables 1 and 2 are available at http://www.jama.com.

REFERENCES


Evaluation of DNA extraction methods for the detection of *Cytomegalovirus* in dried blood spots

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Abstract

**Background**—Dried blood spots (DBS) are collected universally from newborns and may be valuable for the diagnosis of congenital *Cytomegalovirus* (CMV) infection. The reported analytical sensitivity for DBS testing compared to urine or saliva varies greatly across CMV studies. The purpose of this study was to directly compare the performance of various DNA extraction methods for identification of CMV in DBS including those used most often in CMV studies.

**Study design**—Whatman® Grade 903 filter paper cards were spotted with blood samples from 25 organ transplant recipients who had confirmed CMV viremia. Six DNA extraction methods were compared for relative yield of viral and cellular DNA: 2 manual solution-based methods (Gentra Puregene, thermal shock), 2 manual silica column-based methods (QIAamp DNA Mini, QIAamp DNA Investigator), and 2 automated methods (M48 MagAttract Mini, QIAcube Investigator). DBS extractions were performed in triplicate followed by real-time quantitative PCR (qPCR).

**Results**—For extraction of both viral and cellular DNA, two methods (QIAamp DNA Investigator and thermal shock) consistently gave the highest yields, and two methods (M48 MagAttract Mini and QIAamp DNA Mini) consistently gave the lowest yields. There was an average 3-fold difference in DNA yield between the highest and lowest yield methods.

**Conclusion**—The choice of DNA extraction method is a major factor in the ability to detect low levels of CMV in DBS and can largely account for the wide range of DBS sensitivities reported in studies to date.
Keywords
qPCR; Dried blood spots; Newborn screening

1. Background

Human *Cytomegalovirus* (CMV) is a leading cause of congenital infections worldwide. The frequency of congenital CMV infection varies in different populations but on average is approximately 0.7% of live births, with 15–20% of infected children developing permanent disability including hearing loss, vision loss, and cognitive impairment [1–3]. The most common of these disabilities is hearing loss for which congenital CMV infection is a major cause in young children second only to genetic mutations [4].

US newborns are currently screened within the first week of life for a wide range of birth defects through the collection of blood on filter paper in the form of dried blood spots (DBS). DBS have been shown to provide >95% sensitivity compared to urine or saliva for the retrospective diagnosis of congenital *Cytomegalovirus* infection in children born with CMV-associated symptoms or born to mothers who had primary CMV infection during pregnancy [5,6]. In contrast, in studies where CMV screening was performed on unselected newborn populations the reported sensitivity of DBS relative to urine or saliva has varied widely from 28 to 80% [7–9]. Because of numerous differences between studies, it was difficult to ascertain the reason for the wide range in results. To establish that lab methods are an important variable in DBS testing sensitivity, de Vries and others compared available DNA extraction methods for DBS and showed large differences in performance among the methods [10].

2. Objectives

The aim of our study was to extend previous method comparisons and include the two DNA extraction methods most frequently used in CMV studies (QIAamp DNA Mini and thermal shock) [6,8,11–14] and the automated method used by the largest CMV newborn screening study to date (M48 MagAttract Mini) [9]. The goal was to contribute additional important information relevant to the ongoing debate over the potential utility of DBS for CMV testing in newborns.

3. Study design

3.1. Blood samples and dried blood spots

De-identified CMV DNA positive EDTA whole blood from 25 organ transplant recipients was kindly provided by The Cleveland Clinic Foundation, Dept. of Clinical Pathology, Cleveland, OH. Blood specimens had CMV viral loads ranging from a low of $7 \times 10^2$ copies/ml to a very high $1 \times 10^6$ copies/ml. Replica blood spots were prepared by dispensing 75 μl of blood onto the circles of Whatman® 903 Specimen Collection Paper. After drying the spots overnight, punches were prepared manually for DNA extraction methods with negative control punches between each sample. Remaining DBS material was stored at −20
°C with desiccant. CMV DNA-negative EDTA whole blood from healthy volunteers was spotted and used as negative controls.

### 3.2. Extraction of DNA from DBS

DNA was extracted from DBS using the following six extraction methods: (1) QIAamp DNA Investigator kit, (2) QIAamp DNA Investigator kit with QIAcube automation, (3) QIAamp DNA Mini kit, (4) MagAttract DNA Mini kit with BioRobot M48 automation, (5) thermal shock, and (6) Gentra Puregene. Sample input for all methods was 3 punches of 3.2 mm in size with the exception of the thermal shock method which used one 6 mm punch. Input volume of whole blood was calculated based on the area of the blood spots extracted. Samples were extracted in triplicate for each method. With the exception of thermal shock, all extraction methods were kit-based (Qiagen, Valencia, CA) and DNA extracted following the manufacturer’s protocols for isolation of total DNA from DBS. Carrier RNA was added to Buffer AL as recommended for small amounts of DNA. DNA extracted using thermal shock followed the method developed by Shibata and modified by Barbi [14,15]. Briefly, one 6-mm punch was soaked in 60 μl minimum essential medium (MEM) at room temperature for 2 h with shaking (300 rpm) followed by incubation at 56 °C for 1 h, and incubation at 100 °C for 7 min. Samples were placed on ice for at least 2 min, spun in a centrifuge at 14,000 rpm for 5 min, and stored at −80 °C overnight. Prior to PCR testing, samples were thawed and transferred to a DNA IQ Spin Basket (Promega) inserted into an elution tube, centrifuged at 14,000 rpm for 3 min and the liquid flow through used directly for qPCR.

### 3.3. Real-time PCR

Viral DNA was amplified using primers and probes that target the conserved envelope glycoprotein B as described [9] with addition of TaqMan Universal PCR master mix and an exogenous internal positive control (Applied Biosystems, Foster City, CA). PCR testing was performed in triplicate for all samples. AD169 (Advanced Biotechnologies) was used as quantitation standard. PCR cycling on the ABI 7900HT (Applied Biosystems) was as follows: 95 °C, 10 min.; 95 °C, 15 s., 60 °C, 1 min for 45 cycles; 4 °C hold. Genomic DNA was quantified using the same reaction conditions. The following primers and probe that target the cellular RNaseP gene were used: forward primer: 5′-AGATTGGACCTGCGAGCG-3′; reverse primer: 5′-GAGCGGCTGCTCCACAAGT; probe: FAM-5′-TTCTGACCTGAAGGCTCTGCGCG-3′.

### 3.4. Data analysis

For quantitative results, negative samples were included as zero when calculating mean viral loads. CMV quantitation results were used to classify specimens into three viral load categories: low (<10 copies/μl spotted blood), intermediate (~10–100 copies/μl spotted blood), and high (>100 copies/μl spotted blood). For qualitative results, DBS samples were counted positive when two or more of the triplicate PCR reactions tested positive.
4. Results

4.1. Quantitative results

Fig. 1 shows the DNA yields for six extraction methods used on DBS made with low CMV viral load blood (left panel, \( n = 8 \)) and intermediate CMV viral load blood (right panel, \( n = 11 \)). For low viral load specimens, manual extraction with Investigator and thermal shock produced the highest DNA yields; Qiagen Mini and M48 MagAttract gave the lowest yields. There was a 3-fold difference in mean DNA yield between the two highest and two lowest yield extraction methods (\( p < 0.0001 \), student’s \( t \)-test). For intermediate viral load specimens, manual Investigator and QIAcube Investigator produced the highest CMV DNA yields; Qiagen Mini and M48 MagAttract gave the lowest CMV DNA yields representing a 3-fold difference between the mean DNA yields for the two highest and two lowest yield extraction methods (\( p < 0.0006 \), student’s \( t \)-test). For high viral load specimens, differences between methods were not significant.

Mean CMV DNA yields expressed as \( \log_{10} \) for the low or intermediate viral load categories are displayed together in Fig. 2. For the low viral load category samples, the manual Investigator and thermal shock methods gave yields of CMV DNA significantly greater than those obtained from the Qiagen Mini (\( p \leq 0.05 \), student’s \( t \)-test) or the M48 MagAttract (\( p \leq 0.05 \), Student’s \( t \)-test). For the intermediate viral load category samples, all methods gave yields of CMV DNA significantly greater than those obtained from the M48 MagAttract (\( p \leq 0.05 \), student’s \( t \)-test). Moreover, the manual Investigator and QIAcube Investigator methods gave yields of CMV DNA significantly greater than those obtained from the Qiagen Mini kit (\( p \leq 0.05 \), student’s \( t \)-test).

For extraction of genomic DNA, relative performance of the various extraction methods was similar to that seen for viral DNA. Fig. 3 shows the results of qPCR for RNAseP performed on the same DNA extracts as that used for CMV qPCR. Investigator and thermal shock produced the highest DNA yields; Qiagen Mini and M48 MagAttract gave the lowest yields. There was a 3-fold difference in DNA yield between the two highest and the two lowest yield extraction methods.

4.2. Qualitative results

In addition to measuring DNA yields among extraction methods, we compared CMV positive and negative results for each method. Table 1 lists the percent of samples in each viral load category that was identified as positive for each extraction method. For specimens with low viral load, CMV DNA detection ranged from 100% to 46% of samples. The top two methods for detection of CMV in DBS were thermal shock (100%) and manual Investigator (88%). The lowest detection rates were seen with M48 MagAttract and Qiagen Mini (58% and 46%, respectively), with these differences being significant (\( p < 0.01 \), student’s \( t \)-test).

For DBS specimens in the intermediate viral load category, CMV detection rates were higher with 3 methods showing 100% CMV detection and the lowest method showing 85% detection (Table 1), with this difference being significant (\( p < 0.05 \), student’s \( t \)-test). When testing DBS with high CMV loads, all extraction methods identified 100% of DBS
specimens as positive. All CMV DNA negative control samples tested negative, and there was no PCR inhibition seen with any of the extraction methods.

5. Discussion

Our study found large and consistent differences in the relative performance of six DNA extraction methods for DBS measuring yields for both genomic and viral DNA at multiple concentrations. The highest yield methods were Investigator manual and thermal shock; the lowest yield methods were Qiagen mini and M48 MagAttract. Two of the above mentioned methods, thermal shock [14–18] and Qiagen mini [6,9,11–13], have been used by several CMV studies and showed variable sensitivities for identifying CMV infection in children. But the studies varied widely, mainly regarding the sample size and the extent to which it was enriched for infants with symptomatic CMV infection. The largest CMV newborn screening study to date was the CMV and Hearing Multicenter Screening (CHIMES) study that used the M48 MagAttract method for DBS testing. DBS sensitivity observed in CHIMES was the lowest reported to date at 28–34% compared to saliva and it was concluded that DBS would not be suitable for newborn screening [9]. However, our study showed that M48 MagAttract had the lowest DNA yield of the 6 methods evaluated which was likely a contributing factor to the poor performance of DBS testing in CHIMES [9].

A major strength of the present study is the comprehensive expertise at CDC for DBS diagnostic testing. The Newborn Screening and Molecular Biology Branch at CDC manufacturers and validates quality assurance materials for all biomarkers associated with the core conditions on the Recommended Uniform Screening Panel. A second strength of the study was the use of blood from patients with CMV viremia, as opposed to the often used CMV uninfected blood spiked with laboratory strain AD169. The results of our study were consistent with those from the DBS method comparison by de Vries [10], which examined seven different extraction methods (four of which are in common with our study) and also used blood from patients with CMV viremia. Concordant with our study, the Investigator manual and thermal shock methods showed superior performance for detection of CMV. A third DBS methods comparison by Gohring [19] included four methods and showed the Qiagen Mini kit performed much better than thermal shock (referred to as heat). However the Gohring study used AD169-spiked blood instead of naturally infected blood, and their thermal shock (heat) method did not include the important pre-incubation of DBS at either 4 °C overnight [10] or at room temperature for 2 h.

Methods that are under consideration for newborn screening need to be sensitive, adaptable to automation, and cost-effective. Extraction methods used in our study that provided the best results for CMV detection from DBS (Investigator manual and thermal shock) are low throughput and thus in their current form are not suitable for newborn screening. However with sufficient market demand, these methods could potentially be developed for higher throughput and lower cost. The thermal shock protocol has the advantage of very low cost over the other methods tested but does have the disadvantage of an overnight freezing step. This will be addressed in future work.
For CMV newborn screening, it is clear DBS would offer lower analytical sensitivity than saliva or urine. However, only 15–20% of children with congenital CMV infection develop permanent disabilities [2,3] and they are largely the children born with higher viral loads [20–22]. Thus, DBS-based detection may offer adequate clinical sensitivity. Moreover, amplification methodologies continue to improve and provide increased sensitivity. Atkinson recently reported enhanced detection of CMV from DBS using a single tube nested PCR [23]. In conclusion, our study demonstrates that DBS warrant further consideration for identification of newborns at risk for disability from congenital CMV infection.

Acknowledgments

Funding

This work was supported by intramural funding from the Centers for Disease Control and Prevention.

The authors would like to express their sincere gratitude to Dr. Belinda Yin-Lieberman, Medical Director, Virology/Serology at the Cleveland Clinic Foundation for providing the de-identified CMV positive blood specimens.

References


Fig. 1.
Quantitative results for CMV DNA yield according to extraction method. Data points (circles) represent the average CMV DNA yield for each DBS specimen from triplicate extractions. Vertical lines show the full range of DNA yield per method. Mean (square) and median (diamond) viral DNA yields for the complete sample set are shown for each extraction method, with numeric values for means shown.
Fig. 2. Overall quantitative results for CMV DNA yield from six extraction methods. Average DNA yields for all specimens combined is shown for each extraction method, for low and intermediate viral load categories.
Fig. 3.
Quantitative results for extraction of total genomic DNA: the mean genomic DNA yield measured by qPCR targeting housekeeping gene RNAse P. Replica extractions quantified in duplicate were performed for all 25 blood samples.
Table 1
Qualitative assessment. Percentage of CMV-positive DBS in which CMV was detected following various extractions methods.

<table>
<thead>
<tr>
<th>Method</th>
<th>Low viral load category (n = 8) (%)</th>
<th>Intermediate viral load category (n = 11) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator – manual</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>Investigator – QIACube</td>
<td>79</td>
<td>100</td>
</tr>
<tr>
<td>Qiagen mini</td>
<td>46</td>
<td>91</td>
</tr>
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<td>Thermal shock</td>
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<td>100</td>
</tr>
<tr>
<td>Gentra puregene</td>
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<td>100</td>
</tr>
<tr>
<td>M48 MagAttract</td>
<td>58</td>
<td>85</td>
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</table>
Saliva Polymerase-Chain-Reaction Assay for Cytomegalovirus Screening in Newborns

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*Members of the CMV and Hearing Multicenter Screening (CHIMES) study group are listed in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND
Congenital cytomegalovirus (CMV) infection is an important cause of hearing loss, and most infants at risk for CMV-associated hearing loss are not identified early in life because of failure to test for the infection. The standard assay for newborn CMV screening is rapid culture performed on saliva specimens obtained at birth, but this assay cannot be automated. Two alternatives — real-time polymerase-chain-reaction (PCR)–based testing of a liquid-saliva or dried-saliva specimen obtained at birth — have been developed.

METHODS
In our prospective, multicenter screening study of newborns, we compared real-time PCR assays of liquid-saliva and dried-saliva specimens with rapid culture of saliva specimens obtained at birth.

RESULTS
A total of 177 of 34,989 infants (0.5%; 95% confidence interval [CI], 0.4 to 0.6) were positive for CMV, according to at least one of the three methods. Of 17,662 newborns screened with the use of the liquid-saliva PCR assay, 17,569 were negative for CMV, and the remaining 85 infants (0.5%; 95% CI, 0.4 to 0.6) had positive results on both culture and PCR assay. The sensitivity and specificity of the liquid-saliva PCR assay were 100% (95% CI, 95.8 to 100) and 99.9% (95% CI, 99.9 to 100), respectively, and the positive and negative predictive values were 91.4% (95% CI, 83.8 to 96.2) and 100% (95% CI, 99.9 to 100), respectively. Of 17,327 newborns screened by means of the dried-saliva PCR assay, 74 were positive for CMV, whereas 76 (0.4%; 95% CI, 0.3 to 0.5) were found to be CMV-positive on rapid culture. Sensitivity and specificity of the dried-saliva PCR assay were 97.4% (95% CI, 90.8 to 99.7) and 99.9% (95% CI, 99.9 to 100), respectively. The positive and negative predictive values were 90.2% (95% CI, 81.7 to 95.7) and 99.9% (95% CI, 99.9 to 100), respectively.

CONCLUSIONS
Real-time PCR assays of both liquid- and dried-saliva specimens showed high sensitivity and specificity for detecting CMV infection and should be considered potential screening tools for CMV in newborns. ( Funded by the National Institute on Deafness and Other Communication Disorders.)
CYTOMEGALOVIRUS (CMV) IS A FREQUENT cause of congenital infection and a leading nongenetic cause of sensorineural hearing loss.\textsuperscript{1-5} In most infants with congenital CMV infection, clinical abnormalities do not manifest at birth; rather, the infection is asymptomatic. However, sensorineural hearing loss eventually develops in approximately 10 to 15\% of CMV-positive children.\textsuperscript{3,4,6-8} in a substantial proportion who are not diagnosed by means of newborn hearing screening.\textsuperscript{7-9} Screening of newborns for CMV infection will permit early identification of at-risk congenitally infected infants for purposes of targeted monitoring and intervention during critical stages of speech and language development.\textsuperscript{10,11}

A variety of methods have been evaluated for use in the diagnosis of congenital CMV infection on the basis of saliva, urine, and dried-blood-spot specimens obtained from newborns.\textsuperscript{12-17} Culture-based testing of urine and saliva specimens has been the standard method to identify infants with congenital CMV infection.\textsuperscript{13,18,19} However, culture-based methods are not easily amenable to automation and, therefore, cannot be adapted for large-scale newborn screening.

Since dried-blood-spot specimens are obtained routinely in all infants, the usefulness of polymerase-chain-reaction (PCR) testing of dried-blood spots for the diagnosis of congenital CMV infection has been examined.\textsuperscript{15,16,20-23} In addition, our recent large-scale newborn-screening study of a dried-blood-spot PCR assay that was prospectively compared with the standard saliva rapid culture showed that real-time dried-blood-spot PCR assay fails to identify the majority of CMV-infected newborns.\textsuperscript{14} Therefore, challenges remain in achieving high sensitivity of dried-blood-spot testing to screen newborns for CMV infection.\textsuperscript{24} Urine specimens collected on filter disks have also been explored as samples for CMV screening in newborns, but urine samples are harder to collect than saliva samples; this approach has not been validated by direct comparison with culture.\textsuperscript{17,25}

Because of their ease of collection and since high titers of CMV are shed in the saliva of infected newborns, saliva specimens appear to be a better and less invasive type of sample for newborn screening.\textsuperscript{24,26,27} The current study was designed to determine the usefulness of a real-time PCR assay of saliva specimens obtained from newborns for CMV screening. During phase 1 of the study, saliva specimens were placed in transport medium and stored at 4°C before testing. PCR testing of dried-saliva specimens (those that were not placed in transport medium and remained at ambient temperature during specimen storage and transport) was examined in phase 2 of the study, since dried specimens are easier to store and transport. Finally, all PCR assays were performed without a DNA-extraction step, to test an assay that would be more practical for screening all newborns.

\section*{METHODS}

\section*{STUDY DESIGN}

Infants born at seven hospitals in the United States from June 2008 through November 2009 were enrolled prospectively in our National Institute on Deafness and Other Communication Disorders (NIDCD) CMV and Hearing Multicenter Screening (CHIMES) study. All live-born infants were eligible for participation. Infants with positive saliva-screening results (from rapid culture or PCR assay) were enrolled in the follow-up component of the study to monitor hearing outcome. Clinical decisions about evaluation and possible treatment of the CMV-infected infants were made by the physicians at each study site.

The NIDCD was the study sponsor and provided general oversight for the design and conduct of the study. However, the NIDCD had no role in the collection, management, analysis, and interpretation of the data or in the preparation, review, or approval of the manuscript. Institutional-review-board approval was obtained at each study site, and written informed consent was obtained from a parent or parents of all participating infants. The study was conducted according to the protocol (available with the full text of this article at NEJM.org). Race or ethnic group was reported by a parent. The study was designed by the CHIMES study investigators in consultation with NIDCD project officers. All authors vouch for the integrity of the data and data analyses and made the decision to submit the manuscript for publication. Members of the CHIMES study group are listed in the Supplementary Appendix, available at NEJM.org.

\section*{SPECIMEN COLLECTION}

A real-time PCR protocol developed in our laboratory was adapted to test saliva specimens from newborns.\textsuperscript{14} Saliva specimens were collected by swabbing the inside of the baby’s mouth using a
sterile polyester-fiber–tipped applicator (PurFybr) and transported to the central laboratory at the University of Alabama at Birmingham within 1 week after collection.\(^{14,19}\)

Saliva swabs were placed in transport medium, transported to the central laboratory, and tested by means of rapid culture. During phase 1 of the study (beginning in June 2008), the specimens were also tested by means of liquid-saliva PCR assay. For phase 2 of the study (March through November 2009), an additional saliva swab collected at the same time was allowed to air-dry, placed in a sterile tube without transport medium, maintained and transported at ambient temperature to the central laboratory, and tested by means of dried-saliva PCR assay. Saliva specimens from some of the infants born between June 2008 and February 2009 were tested with the use of all three methods (rapid culture, liquid-saliva PCR assay, and dried-saliva PCR assay).

### Specimen Processing and Testing

Liquid-saliva specimens were processed for rapid culture and PCR assay as described previously.\(^{14,19}\) Dried-saliva specimens were processed by adding 300 μl of PCR-grade water to the tubes containing the swabs, vortexing, and incubating for 20 minutes at room temperature. Then, 5 μl of the eluate containing saliva was used, without first undergoing DNA extraction, in the real-time PCR assay.

**Rapid-Culture Assay**

A rapid-culture assay for the detection of early-antigen fluorescent foci, involving a monoclonal antibody against the major immediate early antigen of CMV, was used to detect CMV in saliva specimens.\(^{14,18,19}\) Laboratory personnel performing the rapid culture were unaware of the results of PCR assay, and those performing the PCR assay were unaware of the results of the rapid culture.

**Real-Time PCR Assay**

A real-time PCR protocol described previously for dried-blood spots was performed to detect CMV DNA in saliva samples.\(^{14}\) A sample was considered positive if five or more copies per reaction were detected.

**Follow-up Testing**

Infants with positive rapid culture, PCR assay, or both were reevaluated to determine whether the PCR results were true or false positive results. This was done by testing saliva and urine specimens with the use of rapid culture and PCR assay (as described above).

### Statistical Analysis

The results of the liquid- and dried-saliva real-time PCR assays were compared with those of saliva rapid culture (the standard method). Sensitivity, specificity, and predictive values for the PCR assays were calculated using standard methods for proportions and exact 95% confidence limits.

Likelihood ratios are based on the ratio of sensitivity and specificity and are independent of the prevalence of congenital CMV infection in the population; therefore, likelihood ratios can be used directly to estimate the probability of congenital CMV infection at the individual level.\(^{28}\) The positive likelihood ratio was calculated as the sensitivity divided by (1 specificity), the negative likelihood ratio was calculated as (1 sensitivity) divided by the specificity, and the 95% confidence intervals were calculated according to the method described by Simel and colleagues.\(^{24}\) All statistical analyses were performed using SAS software, version 9.2 (SAS Institute).

### Results

**Study Population and Specimens**

During the study period, 34,989 infants were enrolled. The mean (±SD) age at the time of collection of saliva specimens was 1.0±1.2 days. Characteristics of the study population are shown in Table 1. Nearly all the infants (98.0%) were from well-baby nurseries. The median age at the time of collection of follow-up samples was 3.6 weeks (interquartile range, 2.6 to 6.6). Overall, 177 newborns (0.5%; 95% confidence interval [CI], 0.4 to 0.6) tested positive for CMV on screening by means of rapid culture, PCR assay, or both. No study-related adverse events were observed.

**Newborn CMV Screening with Saliva Rapid Culture and Real-Time PCR Assay**

**Rapid Culture and Liquid-Saliva PCR Assay**

During phase 1, liquid-saliva specimens were collected from 17,662 newborns and tested for CMV with the use of rapid culture and liquid-saliva real-time PCR assay. A total of 93 infants (0.5%; 95% CI, 0.4 to 0.6) tested positive for CMV by any
test (Fig. 1). All 85 infants with a positive rapid-culture result also had a positive liquid-saliva PCR assay, and the PCR assay also identified 8 additional infants as infected although their culture results were negative (Table 2). The sensitivity of liquid-saliva real-time PCR assay as compared with standard rapid culture was 100% (95% CI, 95.8 to 100) (based on 85 of 85 infants); the specificity was 99.9% (95% CI, 99.9 to 100) (based on 17,569 of 17,577 infants). The positive and negative predictive values for the saliva PCR assay were 91.4% (95% CI, 83.8 to 96.2) and 100% (95% CI, 99.9 to 100), respectively (based on 85 of 93 infants and 17,569 of 17,569 infants, respectively). The positive likelihood ratio for the liquid-saliva PCR assay was 2197 (95% CI, 1099 to 4393), and the negative likelihood ratio was 0 (95% CI, 0.0 to 0.1). Of the 93 newborns who were positive on screening, 79 (85%) were enrolled for follow-up, of whom 72 tested positive on both rapid culture and PCR assay, with 1 of the 72 found to be negative on retesting by means of rapid culture and PCR assay of both saliva and urine specimens. Of the 8 infants who tested positive on PCR assay only, 7 were enrolled in follow-up; of those, 6 were found to be negative for CMV on retesting by means of rapid culture and PCR assay of both saliva and urine specimens.

### Table 1. Baseline Characteristics of the 34,989 Study Newborns.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17,278 (49.4)</td>
</tr>
<tr>
<td>Male</td>
<td>17,711 (50.6)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1,358 (3.9)</td>
</tr>
<tr>
<td>Black</td>
<td>8,298 (23.7)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>11,356 (32.5)</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>12,833 (36.7)</td>
</tr>
<tr>
<td>Other, including &gt;1 category</td>
<td>1,142 (3.3)</td>
</tr>
<tr>
<td>Insurance for hospital stay — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>23,326 (66.7)</td>
</tr>
<tr>
<td>Public or no insurance</td>
<td>11,663 (33.3)</td>
</tr>
<tr>
<td>Hospital nursery — no. (%)</td>
<td></td>
</tr>
<tr>
<td>“Well-baby” nursery</td>
<td>34,275 (98.0)</td>
</tr>
<tr>
<td>Neonatal intensive care</td>
<td>714 (2.0)</td>
</tr>
<tr>
<td>Maternal age — yr</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.3±6.1</td>
</tr>
<tr>
<td>Median (range)</td>
<td>27 (12–52)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
† Race or ethnic group was reported by a parent.

Rapid Culture and Dried-Saliva PCR Assay

During phase 2, a dried-saliva specimen was also collected from 17,327 newborns. Of the 84 (0.5%; 95% CI, 0.3 to 0.5) newborns who were positive for CMV on either type of screening assay, 76 (90%) were positive on rapid culture (Fig. 1). The dried-saliva real-time PCR assay yielded positive results for 74 of the 76 samples that were positive on rapid culture and an additional 8 samples that were negative on rapid culture (Table 2). As compared with rapid culture, the sensitivity of the dried-saliva PCR assay was 97.4% (95% CI, 90.8 to 99.7) (based on 74 of 76 infants) and the specificity was 99.9% (95% CI, 99.9 to 100) (based on 17,245 of 17,253 infants), respectively. The positive and negative predictive values for the dried-saliva PCR assay were 90.2% (95% CI, 81.7 to 95.7) and 99.9% (95% CI, 99.9 to 100), respectively (based on 74 of 82 infants and 17,243 of 17,245 infants, respectively). The positive likelihood ratio for the dried-saliva PCR assay was 2100 (95% CI, 1049 to 4202), and the negative likelihood ratio was 0.03 (95% CI, 0.0 to 0.1) (Table 2). Of the 84 infants who were positive for CMV on either test, 74 (88%) were enrolled in follow-up. All 66 infants whose specimens were positive by means of both rapid culture and PCR assay and were enrolled in follow-up were positive for CMV on retesting. The 2 infants who were positive on rapid culture but negative on PCR assay were found to still be positive for CMV on retesting with the use of rapid culture and PCR assay. Of the 8 infants who were found to be CMV-positive on PCR assay but not rapid culture, 2 were lost to follow-up and 6 underwent retesting with the use of rapid culture: 4 were found to be CMV-negative and 2 were found to still be CMV-positive.

Liquid-Saliva vs. Dried-Saliva PCR Assay

Between June 2008 and February 2009, all three screening methods (saliva rapid culture, liquid-saliva PCR assay, and dried-saliva PCR assay) were carried out on saliva specimens obtained from 5276 newborns. There was 100% agreement between the results of the liquid-saliva and the dried-saliva PCR assays (Table 3). Both types of PCR assay confirmed the CMV-positive status of all 42 infants with positive rapid-culture results and identified 1 additional infant as being CMV-positive after re-testing.
Our large, prospective study of CMV screening in newborns shows that the real-time PCR assay of both liquid-saliva and dried-saliva samples has excellent sensitivity (>97%) and specificity (99.9%) as compared with the standard saliva rapid culture. This indicates that the saliva PCR assays, which can easily be adapted for large-scale screening of newborns, will identify most infants who have congenital CMV infection.

The majority of infants with congenital CMV infection will not be identified by means of clinical examination during the newborn period. In addition, sensorineural hearing loss can develop after birth and continue to progress during early childhood in a significant proportion of children with CMV-associated sensorineural hearing loss.\textsuperscript{6-9,20} Thus, the availability of rapid and reliable diagnostic methods that can be adapted for high-throughput screening is essential for early identification of children at risk for CMV-associated sensorineural hearing loss. Testing dried-blood-spot specimens with the use of PCR-based methods appeared to be a promising strategy for CMV screening in newborns, because several previous studies reported that dried-blood-spot PCR assay is highly sensitive in identifying infants with congenital CMV infection.\textsuperscript{15,20,21,30}

However, the results of our recent multicenter study comparing dried-blood-spot real-time PCR assays with saliva rapid culture in more than 20,000 infants revealed that dried-blood-spot PCR assays identified fewer than 40% of CMV-infected newborns.\textsuperscript{14} In addition, the performance of the dried-blood-spot PCR assay has been shown to vary according to the size of the filter-paper punch, the DNA-extraction methods, and the PCR-assay protocols used.\textsuperscript{16,22,23,31} These findings, in addition to demonstrating the challenges in developing sensitive high-throughput assays for testing dried-blood spots, suggest that many newborns with congenital CMV infection may not have detectable CMV DNA in peripheral blood. Further advances in PCR methods might improve the sensitivity of the dried-blood-spot PCR assay, however, allowing for acceptable levels of detec-
tion of infants with congenital CMV infection in the future.

The data reported here show that the same dried-blood-spot PCR protocol applied to saliva identified more than 97% of CMV-infected newborns. In addition, these findings show that saliva is a more reliable type of specimen than dried-blood spots for identifying congenital CMV infection by means of PCR assay and can be an effective tool for mass screening of newborns for CMV. Although testing of urine specimens collected on filter disks inserted into diapers of newborns was recently shown to be a promising approach for newborn CMV screening, urine specimen collection is not without challenges. Obtaining urine specimens from infants requires additional steps and time that are not needed for collecting saliva, and validation of methods of urine collection and urine PCR assay are needed before the practicality of urine-sample screening can be evaluated for large-scale CMV screening in newborns.

In 16 infants, saliva specimens were positive on screening by means of real-time PCR assay but not rapid culture. To determine whether these PCR results were false positives, retesting was performed with the use of PCR assay of saliva and rapid culture of saliva and urine specimens obtained at the time of enrollment into the follow-up study. If these tests were negative, we considered the screening results to be false positives. Three infants who were found to be CMV-positive only at birth, one by means of liquid-saliva PCR assay and two by means of dried-saliva PCR assay, had positive results on rapid culture and PCR assay during follow-up. These findings indicate that PCR assays identified additional CMV-infected newborns missed when tested with the use of rapid culture.

In 10 infants who had negative rapid culture results but positive PCR results (6 on liquid-saliva PCR assay and 4 on dried-saliva PCR assay), retesting yielded false positive PCR results: the follow-up saliva and urine specimens were negative for CMV. As CMV is occasionally shed in the genital tract secretions of seropositive women at delivery and in the breast milk of most seropositive mothers, these false positive results could be due to CMV-containing maternal secretions present in the infants’ saliva samples. Although false positive saliva PCR results could lead to unwarranted parental anxiety and additional testing in infants to confirm or rule out congenital CMV infection, the overall frequency of false positive results for both liquid-saliva and dried-saliva PCR assays was less than 0.03%. In addition, the small negative likelihood ratios for both saliva PCR assays indicate that a negative result on these assays does rule out congenital CMV infection (Table 2).

The dried-saliva PCR assay failed to detect CMV infection in two newborns, leading to slightly lower sensitivity (97.4%; 95% CI, 90.8 to 99.7) than for the liquid-saliva PCR assay. Nevertheless, the simplified procedures for specimen collection, storage, and transport, combined with the high

<table>
<thead>
<tr>
<th>Rapid Culture</th>
<th>Liquid-Saliva PCR Assay</th>
<th>Dried-Saliva PCR Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>17,569</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>17,569</td>
</tr>
<tr>
<td>Sensitivity (95% CI) — %</td>
<td>100 (95.8–100)</td>
<td>97.4 (90.8–99.7)</td>
</tr>
<tr>
<td>Specificity (95% CI) — %</td>
<td>99.9 (99.9–100)</td>
<td>99.9 (99.9–100)</td>
</tr>
<tr>
<td>Positive likelihood ratio (95% CI)</td>
<td>2197 (1099–4393)</td>
<td>2100 (1049–4202)</td>
</tr>
<tr>
<td>Negative likelihood ratio (95% CI)</td>
<td>0 (0.0–0.1)</td>
<td>0.01 (0.0–0.1)</td>
</tr>
<tr>
<td>Positive predictive value (95% CI) — %</td>
<td>91.4 (83.8–96.2)</td>
<td>90.2 (81.7–95.7)</td>
</tr>
<tr>
<td>Negative predictive value (95% CI) — %</td>
<td>100 (99.9–100)</td>
<td>99.9 (99.9–100)</td>
</tr>
</tbody>
</table>
sensitivity, support dried-saliva PCR assay as a reasonable approach to CMV screening in newborns. Although the need for collection of an additional specimen adds to the complexity of the existing newborn-screening programs, the saliva PCR assays described in this study have four main advantages for CMV screening in newborns. These are reasonable sensitivity and specificity, noninvasive specimen collection, elimination of the DNA-extraction step (which simplifies the laboratory procedures, thus providing considerable cost savings), and the fact that dried-saliva specimens can be stored and transported at room temperature, further simplifying specimen handling and transport.

A limitation of this study is that the 34,812 infants found to be CMV-negative on both rapid culture and PCR assay of saliva samples obtained at the screening visit were not enrolled in follow-up to definitively exclude congenital CMV infection (by retesting with the use of rapid culture of saliva or urine). Therefore, it is possible that CMV-infected newborns may have been missed by the rapid culture, affecting our determination of the sensitivity and specificity of saliva PCR assay. However, we believe this possibility is quite low, since the saliva rapid culture has been shown to have a sensitivity of at least 98%.14,19 At present, although imperfect, rapid culture of saliva or urine specimens remains the most widely accepted standard method for identification of infants with congenital CMV infection.14,19,27

In summary, the usefulness of saliva specimens for identification of CMV by means of PCR assay was shown. The screening methods have been further simplified, with the use of dried specimens and processing that does not require a DNA-extraction step, without significant loss of sensitivity or specificity. This strategy appears to be suitable for a high-throughput assay for large-scale screening to identify newborns with congenital CMV infection.

Supported by a grant (N01 DC50008) from the National Institute on Deafness and Other Communication Disorders. Presented in part at the 47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, October 29–November 1, 2009, and at the 21st Annual Meeting of the Pediatric Academic Societies, Vancouver, BC, Canada, May 1–4, 2010.

Dr. Boppana reports receiving consulting fees from GlaxoSmithKline; Dr. Palmer, grant support from Roche; Dr. Ahmed, manuscript preparation fees from Mead Johnson; Dr. Berstein, consulting fees from Vical and Novartis; and Dr. Fowler, consulting fees from GlaxoSmithKline and Merck. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.


<table>
<thead>
<tr>
<th>Rapid Culture</th>
<th>Liquid-Saliva PCR Assay</th>
<th>Dried-Saliva PCR Assay</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>42</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>5233</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>5233</td>
<td>43</td>
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10. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: principles and


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Detection of Congenital Cytomegalovirus Infection by Real-Time Polymerase Chain Reaction Analysis of Saliva or Urine Specimens

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Viral culture of urine or saliva has been the gold standard technique for the diagnosis of congenital cytomegalovirus (CMV) infection. Results of rapid culture and polymerase chain reaction (PCR) analysis of urine and saliva specimens from 80 children were compared to determine the clinical utility of a real-time PCR assay for diagnosis of congenital CMV infection. Results of urine PCR were positive in 98.8% of specimens. Three PCR-positive urine samples were culture negative. Results of saliva PCR and culture were concordant in 78 specimens (97.5%). Two PCR-positive saliva samples were culture negative. These findings demonstrate that PCR performs as well as rapid culture of urine or saliva specimens for diagnosing congenital CMV infection and saliva specimens are easier to collect. Because PCR also offers more rapid turnaround, is unlikely to be affected by storage and transport conditions, has lower cost, and may be adapted to high-throughput situations, it is well suited for targeted testing and large-scale screening for CMV.

Keywords. Diagnosis; viral culture; congenital CMV; PCR; saliva; Urine.

Cytomegalovirus (CMV) is a leading cause of congenital infection worldwide, occurring in 0.2%–2.2% of live births [1]. Congenital CMV infection is also a leading nongenetic cause of sensorineural hearing loss and other neurodevelopmental disabilities [1]. Early diagnosis of congenital CMV infection will permit timely identification of infants at risk of poor neurodevelopmental outcomes and will allow targeted monitoring and intervention.

The confirmation of congenital CMV infection can only be made with certainty before the third week of life. After this, it is difficult to distinguish congenital infection from infection acquired in the postnatal period. The gold standard for the diagnosis of congenital CMV infection in newborns has traditionally been viral culture of urine or saliva specimens. However, this method is expensive and laborious, and, even with use of rapid culture assays, results may be delayed several days. Polymerase chain reaction (PCR) amplification is being used more frequently for the diagnosis of viral infections because of its enhanced sensitivity and rapid turnaround. The clinical utility of PCR assays for the diagnosis of congenital CMV infection is being explored but has yet to be validated.

We recently demonstrated high sensitivity and specificity of a real-time PCR screening assay to detect congenital CMV infection in saliva specimens obtained from infants as part of the National Institute on Deafness and Other Communication Disorders (NIDCD) CMV and Hearing Multicenter Screening (CHIMES) study [2]. Newborns positive for CMV by screening were enrolled for follow-up evaluation to confirm congenital CMV infection, and, as part of the confirmatory testing, saliva and urine samples were analyzed by both real-time PCR and rapid culture. Here, we compare the results of these tests to determine whether our real-time PCR assay, shown to be useful for screening newborns, demonstrates clinical utility for the diagnosis of congenital CMV infection. In addition, this study aims to determine whether this PCR assay performs equally well in both urine and saliva samples.

METHODS

From March 2007 through March 2012, 100 332 infants born at 7 US medical centers were screened for congenital CMV infection as part of the NIDCD CHIMES study [2, 3]. Infants with positive screening results by CMV PCR or by rapid culture of
saliva were presumed to have congenital CMV infection and were enrolled in a follow-up study to confirm congenital infection and to monitor hearing function. During the study period, 497 infants were found to be CMV positive on screening, and of those, 462 were enrolled in the follow-up component of the study. From March 2007 through February 2009, 4 of the study sites used sterile cotton balls placed in the diaper for collection of urine specimens; these 4 sites then switched to urine bags for sample collection for the remainder of the study period. For infants from whom urine specimens were collected using cotton balls, the rate of CMV-positive rapid cultures was substantially lower (56.1% for cotton vs 93.4% for bag; \( P < .0001 \)); these 66 infants were excluded from the analysis. Of the remaining 396 with confirmed congenital infection, 80 had both saliva and urine samples obtained within the first 3 weeks of life, and these constituted the study population. Written informed consent was obtained from a parent of all participating infants.

The saliva samples were collected as described elsewhere [2, 3]. Urine samples were collected in sterile urine bags, and samples were transported and stored at 4°C until tested.

The presence of CMV in saliva and urine specimens was identified using a rapid culture method as described previously [3–5]. Samples were run in duplicate, and the presence of at least 1 fluorescent focus in 1 well was defined as a positive result. For PCR, urine or saliva samples were briefly centrifuged to remove debris. A 5-µL aliquot of the urine or saliva sample in transport medium was used directly as a template, without a DNA extraction step, in a real-time PCR assay to amplify 2 conserved regions, using primers, probes, and TaqMan reagents as described elsewhere [2, 3]. A sample was considered positive for CMV if \( \geq 1 \) International Unit (IU) per reaction was detected. The detection limit of this PCR assay was determined to be 116 IU per mL of the sample (1.72 ge/mL = 1 IU/mL).

The results of rapid culture and PCR were compared for both saliva and urine samples, using exact confidence intervals (CIs) and the McNemar test, where appropriate.

## RESULTS

The distribution of race/ethnicity in the study population was 31.3% black (25/80), 32.5% white non-Hispanic (26/80), and 31.3% Hispanic (25/80). Nearly half (47.5%; 38/80) of the participating infants were female, and 71.3% (57/80) had public insurance or were uninsured. The majority of the infants (93.8%) were from the well-baby nursery, the mean gestational age (±SD) at birth was 38.6±1.63, and the mean birth weight (±SD) was 3232±632.3 g. Urine and saliva samples were obtained from the study subjects at a median of 16 days of life (range, 2–20 days). Seven subjects received antiviral therapy, but urine and saliva samples were obtained prior to the initiation of treatment.

Results of PCR were positive in 79 of 80 urine samples (98.8%; 95% CI, 93.2%–100.0%), compared with positive culture results in 76 of 80 urine samples (95% CI, 87.8%–98.6%). PCR and culture results were concordant in 76 specimens (96.3%). Discordance of results was observed in 3 samples, which were positive by PCR but negative by culture (\( P = .688 \)). One urine specimen was negative by both culture and PCR (Table 1).

Results of rapid culture of saliva specimens for detection of CMV were positive for 78 of 80 subjects (97.5%; 95% CI, 91.3%–99.7%), whereas results of real-time PCR were positive for all 80 subjects (100%; 95% CI, 95.5%–100%). Concordant positive results were observed for both assays in 78 subjects (97.5%). PCR identified CMV in saliva specimens from 2 infants that tested negative by rapid culture (Table 1).

As urine is considered by many to be the optimal sample for detection of CMV in newborns, a comparison of PCR and rapid culture of saliva and urine specimens was performed. Results of urine PCR for CMV were positive in 79 of 80 infants (98.8%;

<table>
<thead>
<tr>
<th>Table 1. Comparison of Urine Real-Time Polymerase Chain Reaction (PCR) and Urine Rapid Culture and Saliva Real-Time PCR and Saliva Rapid Culture for the Diagnosis of Congenital Cytomegalovirus Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Result, by Test</strong></td>
</tr>
<tr>
<td>Urine rapid culture</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Saliva PCR</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* \( P = .688 \) for discordant results.

<table>
<thead>
<tr>
<th>Table 2. Comparison of Urine and Saliva Real-Time Polymerase Chain Reaction (PCR) and Urine and Saliva Rapid Culture for the Diagnosis of Congenital Cytomegalovirus Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Result, by Test</strong></td>
</tr>
<tr>
<td>Saliva PCR</td>
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</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Saliva rapid culture</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* \( P = .688 \) for discordant results.
95% CI, 93.2%–100%), whereas results of saliva PCR were positive in all 80 infants (100%; 95% CI, 95.5%–100%). PCR identified CMV in a saliva specimen from 1 infant whose urine specimen was CMV negative by PCR (Table 2). A similar comparison was done for rapid culture of saliva versus urine specimens. Results of saliva culture were positive in 78 of 80 subjects (97.5%; 95% CI, 91.3%–99.7%), whereas results of urine culture were positive in 76 of 80 (95.0%; 95% CI, 87.8%–98.6%). Results of saliva rapid culture were positive in 4 subjects for whom the urine culture was CMV negative, and urine culture identified CMV in specimens from 2 infants for whom results of saliva culture were negative (P = .688; Table 2).

**DISCUSSION**

PCR is widely available, rapid, and sensitive method of viral detection. The PCR assay is routinely used for the diagnosis of CMV infection in immunocompromised hosts at risk for severe disease, such as solid organ and hematopoietic stem cell transplant recipients. For the diagnosis of congenital CMV infection, PCR has not been universally adopted, and viral culture remains the accepted standard. We recently demonstrated that a real-time PCR assay developed in our laboratory has excellent sensitivity and specificity when compared with rapid culture of saliva specimens for screening of newborns for congenital CMV infection. In the current study, we evaluated the clinical utility of the same PCR assay for the diagnosis of congenital CMV infection. Using urine and saliva specimens from a large cohort of infants with congenital CMV infection, we demonstrated that PCR performs as well as rapid culture for the detection of virus in both urine and saliva samples.

Comparison of urine PCR with urine culture for the diagnosis of congenital CMV infection has not been well studied. The few studies that have investigated the role of urine PCR for the diagnosis of congenital CMV report sensitivities ranging from 93% to 100% [6–8]. In the current study, by use of urine specimens from infants known to be infected with CMV, detection of CMV was consistently achieved using the real-time PCR assay when compared with culture. Similarly, there are few studies comparing PCR to culture for the detection of CMV in saliva samples. Warren et al demonstrated that PCR of saliva specimens detected virus in 89% of 160 samples, compared with 90% detected by rapid culture [9]. Using saliva samples from infants known to have congenital infection, we demonstrated higher detection rates of CMV by use of PCR, compared with rapid culture.

Concordance between PCR and culture results was high for both urine (95%) and saliva (98%) samples. Discordant samples positive by PCR but negative by rapid culture may be interpreted as false-positive PCR results or false-negative culture results. Since PCR is generally a more sensitive method of pathogen detection than culture, false-positive results may be observed with PCR. False-positive saliva PCR results could be due to contamination by genital tract secretions or breast milk [10, 11]. However, CMV is rarely detected in breast milk before 2 weeks postpartum, with CMV DNA levels peaking at a month after delivery [11]. Specimen storage and transport, as well as the interval between specimen collection and processing, can lead to a significant decrease in the titer of infectious virus, resulting in a lower yield for culture-based assays, compared with PCR [12].

Of the 2 saliva samples that were negative by rapid culture but positive by PCR, both were positive by urine PCR and by urine culture. Similarly, urine specimens from 3 infants had discordant test results, with all testing positive by PCR but negative by rapid culture. All 3 of these subjects were confirmed to be positive for CMV by PCR and culture of saliva. Since all of the study infants had positive results of newborn screening and the culture-negative specimens obtained for confirmation of congenital CMV infection were positive by PCR, the discordance between results of PCR and results of rapid culture in our study more likely represents false-negative rapid culture results rather than false-positive PCR results.

Infants with congenital CMV infection shed large amounts of virus in saliva and urine, making both specimens ideally suited for detection of virus, but urine has traditionally been the more frequently used sample. Limited data exist on the comparison of the 2 specimen types for the diagnosis of congenital CMV. In 28 infants with congenital CMV infection, Yamamoto et al found that saliva PCR identified 24 cases (86%), compared with 26 (93%) detected by urine PCR [13]. With a larger sample size, findings from the current study indicate that the likelihood of detection, either by culture or PCR amplification, is as high or slightly higher for saliva specimens (Table 1). Results of saliva culture were positive in a higher proportion of samples, compared with urine culture (97.5% vs 95.0%), although the difference is not significant. Results of PCR were positive for all saliva samples, compared with only 98.8% of urine PCR results. In addition to offering improved detection of CMV, saliva specimens are more easily collected than urine specimens, making them better suited for either targeted testing or large-scale screening for congenital CMV infection.

This study does have limitations. PCR protocols for CMV have not been well standardized across different laboratories; thus, there can be variability in the performance of different PCR protocols. The incorporation of recently developed international standards in CMV PCR assays is expected to decrease the variability of the assay performance between and within laboratories [14]. The primers used for this study have been validated with the current international standards, and the results were reported as IUs to allow comparison with other studies.

We demonstrated that PCR amplification is equivalent to rapid culture for the diagnosis of congenital CMV infection, using either urine or saliva specimens. Saliva samples are more easily collected than urine specimens. Compared with culture,
PCR amplification offers more rapid turnaround, is unlikely to be affected by storage and transport conditions, has lower cost, and may be adapted to high-throughput situations, making it well suited for targeted testing and large-scale screening.

Notes

Acknowledgment. We dedicate this article to the memory of Dr Bob Tolan, for his dedication and support of the CHIMES study.

Financial support. This work was supported by the National Institutes of Health (grants R01-HD061959 to W. J. B.; RO1-DC012661 to S. A. R.; NO1-DC50008, R01-HD061959 to S. B. B.; U01-PO000177, U01-DD-12-005, RO1-HD61959, U01-AI103401-01, RO1-DC012661, and NO1-DC50008 to K. B. F.; NO1-DC50008 to A. A.; NO1-DC50008 to A. L. P.; NO1-DC50008 to M. G. M.; NO1-DC50008 to P. J. S.; and NO1-DC50008 to D. I. B.).

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection

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IMPORTANCE Congenital cytomegalovirus (cCMV) infection is a major cause of childhood deafness. Most cCMV infections are not diagnosed without newborn screening, resulting in missed opportunities for directed care.

OBJECTIVE To estimate the cost-effectiveness of universal and targeted newborn cCMV screening programs compared with no cCMV screening.

DESIGN, SETTING, AND PARTICIPANTS Models were constructed using rates and outcomes from prospective cohort studies of newborn cCMV screening in US postpartum care and early hearing programs. Costs of laboratory testing, treatment, and hearing loss were drawn from Medicaid data and published estimates. The benefits of cCMV screening were assumed to come from antiviral therapy for affected newborns to reduce hearing loss and from earlier identification of hearing loss with postnatal onset. Analyses were performed from July 2014 to March 2016.

INTERVENTIONS Models compared universal or targeted cCMV screening of newborns with a failed hearing screen, with standard care for cCMV infection.

MAIN OUTCOMES AND MEASURES The incremental costs of identifying 1 cCMV infection, identifying 1 case of cCMV-related hearing loss, and preventing 1 cochlear implant; the incremental reduction in cases of severe to profound hearing loss; and the differences in costs per infant screened by universal or targeted strategies under different assumptions about the effectiveness of antiviral treatment.

RESULTS Among all infants born in the United States, identification of 1 case of cCMV infection by universal screening was estimated to cost $2000 to $10 000; by targeted screening, $566 to $2832. The cost of identifying 1 case of hearing loss due to cCMV was as little as $27 460 by universal screening or $975 by targeted screening. Assuming a modest benefit of antiviral treatment, screening programs were estimated to reduce severe to profound hearing loss by 4.2% to 13% and result in direct costs of $10.86 per newborn screened. However, savings of up to $37.97 per newborn screened were estimated when costs related to functionality were included.

CONCLUSIONS AND RELEVANCE Newborn screening for cCMV infection appears to be cost-effective under a wide range of assumptions. Universal screening offers larger net savings and the greatest opportunity to provide directed care. Targeted screening also appears to be cost-effective and requires testing for fewer newborns. These findings suggest that implementation of newborn cCMV screening programs is warranted.
Cost-effectiveness of Newborn Screening for Congenital Cytomegalovirus Infection

Cytomegalovirus (CMV) is the most common congenital infection and a leading cause of childhood hearing loss, cognitive deficits, and visual impairment. The prevalence of congenital CMV (cCMV) infection has been estimated to be 0.64% at birth, which translates into more than 20,000 neonates with congenital infection born annually in the United States. Of these neonates, at least 3000 are estimated to develop permanent neurologic disabilities each year due to cCMV infection. Approximately 10% to 25% of all childhood sensorineural hearing loss (SNHL) can be attributed to cCMV infection. With an estimated annual cost of up to $4 billion in the United States, cCMV infection is an enormous public health concern.

A minority of newborns with cCMV infection have clinically evident manifestations of disease at birth, which are largely nonspecific. As many as 50% of these symptomatic infants will experience neurologic sequelae, including SNHL. An additional 10% to 15% of the asymptomatic newborns will experience SNHL due to cCMV infection that can be present at birth or appear years later. A definite diagnosis of cCMV requires direct viral detection in saliva, urine, or blood samples during the first 2 to 3 weeks of life; if detected later, postnatal CMV infection cannot be excluded. Polymerase chain reaction (PCR) analysis for CMV in saliva samples is sensitive, convenient, and amenable to large-scale screening. At present, diagnosis of cCMV infection depends largely on clinical suspicion. However, only a small proportion of symptomatic cCMV infections (and essentially none of the asymptomatic ones) are diagnosed using this approach. All infants with cCMV infection, symptomatic or asymptomatic, may benefit from early diagnosis for anticipatory guidance, early identification of late-onset hearing impairment, and appropriate support. Treatment of newborns with symptomatic cCMV infection with the antiviral drug valganciclovir hydrochloride for 6 months also aimed at high-risk newborns have been evaluated, most commonly targeting infants with a failed newborn hearing screen. Targeted cCMV screening based on failed newborn hearing screens would not capture infections that result in late-onset hearing loss. Although estimates have been calculated for the benefits of universal screening and the cost of targeted screening programs, formal cost-effectiveness analyses have not been performed for either strategy.

Methods

Model Structure
We constructed the following 2 models to estimate the effect of cCMV screening programs on hearing loss and costs compared with standard care for most newborns (no screening): one to evaluate universal newborn screening and one for targeted screening (eFigure in the Supplement). Because this study used only secondary data in aggregate, it was exempted from human subjects protection review by the University of British Columbia.

Key Points

Question: Is newborn screening for congenital cytomegalovirus (cCMV) infection cost-effective?

Findings: In a cost-effectiveness study that compared universal (for all newborns) or targeted cCMV screening (newborns with a failed universal newborn hearing screen) with no screening under a wide range of assumptions regarding the US costs of testing, treatment, and hearing loss related to cCMV infection, universal and targeted cCMV screening were relatively low cost, or cost saving if costs related to lost productivity were included.

Meaning: Universal and targeted newborn screening programs for cCMV infection in the United States appear to be cost-effective.
of $10 to $50 per newborn undergoing testing,\textsuperscript{19,20} which includes the oral swab and CMV PCR analysis and a confirmatory urine PCR analysis for any newborns with a positive test result.\textsuperscript{23} We did not include administrative costs; we acknowledge that start-up costs to add CMV screening to existing programs might increase costs, but these are expected to be one time and modest given the assumption that infrastructure already in place for newborn screening would be used. For example, all US states have established universal newborn screening programs for hearing loss by audiometry and for genetic diseases using dried blood spots.

Infants with confirmed cCMV infection were assumed to undergo a medical evaluation. Those with a failed hearing screen were also assumed to have an expedited comprehensive audiologic evaluation within the first month of life (rather than by 3 months\textsuperscript{24}) to guide the use of antiviral treatment. All cCMV-infected children without hearing loss at birth were assumed to have audiologic testing every 6 months to monitor for late-onset hearing impairment;\textsuperscript{24} this follow-up was assumed to lead to earlier identification of hearing loss by a mean of 24 months. These follow-up costs end at the sixth birthday or when hearing loss is discovered. For infants with asymptomatic infection who have no hearing loss at birth, antiviral treatment is not recommended and no consensus exists on testing. For infants with symptomatic infections at birth, with or without hearing loss, antiviral treatment with valganciclovir is indicated given evidence of improved hearing outcomes.\textsuperscript{15} All infected newborns with symptoms and/or hearing loss at birth were also assumed to undergo basic laboratory testing, cranial ultrasonography, and ophthalmologic examination. We assumed that all infants with an abnormal finding on ultrasonography or on a neurologic examination would undergo brain magnetic resonance imaging and that these results would represent 20% of symptomatic and 1% of asymptomatic infants identified as a result of CMV screening. Identification of cCMV infection through screening was assumed to save the costs of testing for other common causes of hearing loss.\textsuperscript{25}

For infants with infection and hearing loss at birth but no other apparent disease, equipoise exists among experts about whether antiviral therapy is indicated.\textsuperscript{18,19,26,27} As such, the universal and targeted screening were modeled with and without antiviral treatment of this group. Costs of drugs and monitoring for toxic effects were included for all children treated with valganciclovir. Costs savings were based on a recent trial\textsuperscript{26} that found improved outcomes at 24 months in 77% of newborns treated with 6 months vs 6 weeks of valganciclovir. Because approximately 22% of infants were observed to improve without treatment in an earlier trial,\textsuperscript{28} we estimated that the current standard treatment improves hearing in approximately half of symptomatic infants. We therefore modeled the effect of antiviral treatment so that 50% of children in each hearing loss category were assumed to improve by 1 hearing loss category; that is, 50% of children who would have had profound hearing loss had severe hearing loss; 50% who would have had severe hearing loss had moderate hearing loss; 50% who would have had moderate hearing loss had mild hearing loss; and 50% who would have had mild hearing loss had normal hearing. We assumed that benefits are permanent and that this treatment has no effect on hearing loss with onset after 24 months. We applied this effect to all cases of hearing loss that developed within 2 years of birth for children with symptomatic infection. We assumed the same antiviral benefits if given to children who had hearing loss at birth but were otherwise asymptomatic. Although valganciclovir treatment of symptomatic cCMV infection may also result in improved neurocognitive outcomes,\textsuperscript{26} these outcomes were not included owing to insufficient data to estimate the associated benefits and costs. We also modeled the cost-effectiveness of cCMV screening using higher and lower antiviral effectiveness and in the absence of antiviral treatment for any child.

Cost savings for children with asymptomatic cCMV infection without hearing loss at birth and for symptomatic children with onset of hearing loss beyond 24 months are assumed to result from earlier identification of hearing loss by virtue of repeated follow-up audiologic evaluations. Early identification has been found to reduce the functional impairments resulting from hearing loss.\textsuperscript{29} Kennedy et al\textsuperscript{30} found that early identification of hearing loss resulting from newborn hearing screens was associated with a 24% improvement in receptive language compared with no screening. We assumed that the impact of early intervention for late-onset hearing loss was one-half that for hearing loss present at birth, which is consistent with other estimates.\textsuperscript{31} As such, we estimated a 12% reduction in the costs associated with any category of hearing loss owing to the earlier identification of hearing loss that results from cCMV screening and audiologic follow-up.

Once hearing loss was identified, costs of care were broken down into the following 4 categories: (1) medical, (2) audiologic, (3) equipment, and (4) therapy and special education programs. We assumed that only 50% of cases of bilateral profound hearing loss receive a cochlear implant\textsuperscript{32-34} at a cost of $100,000.\textsuperscript{20} We also estimated the costs related to loss of productivity as an adult. We assumed no loss of productivity for adults with mild or moderate hearing loss. For severe and profound hearing loss, the loss of productivity was estimated to be $926,000 in 2016 US dollars.\textsuperscript{20} Life expectancy was assumed to be 79 years. Modeling estimates were generated using Excel software (version 2010; Microsoft Corp).

### Results

The net financial impact of universal or targeted cCMV screening was calculated as the sum of the screening-related costs (Table 1) and the difference between the hearing loss–related costs derived from the Special Education Expenditure Project\textsuperscript{36} (Table 2) with and without screening. We assumed the following 2 screening effects: (1) an improvement in hearing owing to antiviral therapy for infants with clinical manifestations of cCMV infection at birth and (2) benefits resulting from earlier identification of hearing loss and earlier interventions. The proportion of infants with cCMV infection who developed hearing loss, categorized as mild to moderate or severe to profound, at a given age is shown in Table 3. The total proportion of symptomatic infections in this cohort was 14%, which is
similar to the mean proportion from published screening studies. Among all 551 children with cCMV infection, 22 (4.0%) had hearing loss at birth (consistent with cCMV infection accounting for approximately 2 cases of SNHL per 10,000 population or 13.3% of all SNHL at birth), and 71 (12.9%) developed hearing loss at any time, which is again consistent with published estimates.

The total costs to identify 1 case of cCMV infection and 1 case of cCMV-related hearing loss using the universal and targeted screening models and with a range of testing costs are shown in Table 4. The cost to prevent cochlear implantation for 1 child was estimated to be as little as $39,401, assuming antiviral treatment of symptomatic infants identified by targeted screening with a moderately inexpensive test. However, we estimated a cost ranging from $4,064,157 to $12,620,277 to prevent cochlear implantation for 1 child through universal screening depending on the cost of the test used.

Depending on assumptions related to antiviral treatment, the results of the universal and targeted screening models ranged from modest direct costs of $10.86 (sensitivity analysis, $6.97 to $14.73) to net savings of $37.97 (sensitivity analysis, $14.60 to $61.34) per newborn undergoing screening (Table 5). Both screening approaches were more cost-effective if antiviral therapy was assumed to be given and effective for isolated hearing loss at birth rather than just to newborns with clinically evident symptoms of cCMV infection. Even in the absence of any antiviral treatment, the direct costs of screening were modest, ranging from $2.01 per newborn undergoing targeted screening to $14.16 per newborn undergoing universal screening. Without treatment, the benefits of screening were derived exclusively from early identification of late-onset hearing loss. Under all assumptions, universal screening was slightly more cost-effective than targeted screening when the total lifetime functional cost of hearing loss was included.

Discussion

Newborn cCMV screening strategies have been increasingly recognized for their potential medical benefits. Debate about these programs has increased as a result of recent advances in diagnosis and treatment. Convenient, accurate, and inexpensive testing for cCMV in newborns with the use of oral swabs is now available. Available evidence indicates that current approaches to identification of newborns with cCMV-related disease are inadequate, and most infants with a cCMV infection will not receive timely and appropriate care in the absence of some type of screening program.

Targeted cCMV screening, triggered by suspected newborn hearing loss, has been shown to be feasible in the United States and United Kingdom. Notably, offering cCMV testing for newborns with hearing loss is mandated by law in some US states. Preliminary reports of the cost of these programs are comparable to those of other screening programs. Although universal newborn screening could benefit thousands of children per year in the United States, it has not been adopted for cCMV infection, in part because of questions regarding cost-effectiveness. We find that universal and targeted screening programs appear to reduce total costs under most assumptions.

The major strength of this study is a comprehensive analysis of all the costs related to newborn cCMV screening using data derived from large prospective cohorts. Net savings from universal screening were estimated to be greater than those from targeted screening, although screening costs are higher. Savings from screening strategies are derived from improved hearing with antiviral treatment of affected newborns but also from earlier detection of late-onset hearing loss. One impor-

Table 1. Cost Assumptions Associated With Newborn cCMV Screeninga

<table>
<thead>
<tr>
<th>Screening Item</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>All screened newborns</td>
<td></td>
</tr>
<tr>
<td>Collection and CMV PCR testing of oral swab</td>
<td>10-50 per test</td>
</tr>
<tr>
<td>All newborns with cCMV infection</td>
<td></td>
</tr>
<tr>
<td>Medical evaluation</td>
<td>150.38</td>
</tr>
<tr>
<td>Symptomatic newborns with cCMV infection and/or hearing loss at birth</td>
<td></td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>23</td>
</tr>
<tr>
<td>Cranial ultrasonography</td>
<td>82.03</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>560.00</td>
</tr>
<tr>
<td>Ophthalmology examination</td>
<td>115.44</td>
</tr>
<tr>
<td>All newborns with cCMV infection without hearing loss at birth</td>
<td></td>
</tr>
<tr>
<td>Audiologic follow-up</td>
<td>152.76 per visit</td>
</tr>
<tr>
<td>All treated newborns</td>
<td></td>
</tr>
<tr>
<td>Valganciclovir hydrochloride</td>
<td>4400</td>
</tr>
<tr>
<td>Laboratory monitoring</td>
<td>385</td>
</tr>
</tbody>
</table>

Abbreviations: CBC, complete blood cell; cCMV, congenital cytomegalovirus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

a All costs are in current US dollars. Costs that would be incurred even in the absence of cCMV screening (eg, newborn hearing screening studies) are not included.

b The range of costs for CMV PCR is conservatively high and includes confirmation of positive swab results with a urine PCR analysis according to current estimates.

c Late-onset hearing loss due to cCMV infection rarely occurs after 6 years of age; children older than 6 years are expected to receive routine hearing screening for school-aged children.

d Different indications for treatment (eg, symptoms at birth or symptoms and/or hearing loss at birth) were modeled given the equipoise among experts.

Table 5

<table>
<thead>
<tr>
<th>Screening Item</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory monitoring</td>
<td>385</td>
</tr>
</tbody>
</table>

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Table 2. Annual Cost Assumptions for Care of Children With Hearing Loss Due to cCMV Infection

<table>
<thead>
<tr>
<th>Age Group by Severity of Hearing Loss</th>
<th>Service and Cost Medicala</th>
<th>Audiologyb</th>
<th>Equipmentc</th>
<th>Therapyd</th>
<th>Total Cost per Infant, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>From identification of hearing loss to &lt;6 y</td>
<td>ENT yearly ($100 first visit; $66 each subsequent visit)</td>
<td>OAE, tympanometry, and VRA every 6 mo ($305.52)</td>
<td>Hearing aids ($1144), FM system ($334)</td>
<td>0</td>
<td>$1850 ($1884 the first year)</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>ENT yearly ($100 first visit; $66 each subsequent visit)</td>
<td>OAE, tympanometry, and VRA every 6 mo ($305.52)</td>
<td>Hearing aids ($858), FM system ($668)</td>
<td>$6907</td>
<td>$8805 ($8839 the first year)</td>
</tr>
<tr>
<td>Severe to profound</td>
<td>ENT yearly ($100 first visit; $66 each subsequent visit)</td>
<td>OAE, tympanometry, and VRA every 6 mo ($305.52)</td>
<td>Hearing aids ($858), FM system ($668)</td>
<td>$6907</td>
<td>$8805 ($8839 the first year)</td>
</tr>
<tr>
<td>6 to &lt;13 y</td>
<td>ENT every 2 y ($22 per year)</td>
<td>OAE, tympanometry, and play audiometry yearly ($178.55)</td>
<td>Hearing aids ($1001), FM system ($334)</td>
<td>0</td>
<td>$1536</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>ENT every 2 y ($22 per year)</td>
<td>OAE, tympanometry, and play audiometry yearly ($178.55)</td>
<td>Hearing aids ($751), FM system ($668)</td>
<td>$19151</td>
<td>$20771</td>
</tr>
<tr>
<td>Severe to profound</td>
<td>ENT every 2 y ($22 per year)</td>
<td>OAE, tympanometry, and play audiometry yearly ($178.55)</td>
<td>Hearing aids ($751), FM system ($668)</td>
<td>$19151</td>
<td>$20771</td>
</tr>
<tr>
<td>13 to &lt;18 y</td>
<td>ENT once ($13.20)</td>
<td>OAE, tympanometry, and conventional audiometry yearly ($178.55)</td>
<td>Hearing aids ($1001), FM system ($334)</td>
<td>0</td>
<td>$1527</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>ENT once ($13.20)</td>
<td>OAE, tympanometry, and conventional audiometry yearly ($178.55)</td>
<td>Hearing aids ($751), FM system ($668)</td>
<td>$19151</td>
<td>$20762</td>
</tr>
<tr>
<td>Severe to profound</td>
<td>ENT once ($13.20)</td>
<td>OAE, tympanometry, and conventional audiometry yearly ($178.55)</td>
<td>Hearing aids ($751), FM system ($668)</td>
<td>$19151</td>
<td>$20762</td>
</tr>
<tr>
<td>≥18 y</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>$948</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>$948</td>
</tr>
<tr>
<td>Severe to profound</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>$948</td>
</tr>
</tbody>
</table>

Abbreviations: cCMV, congenital cytomegalovirus; ENT, ear, nose, and throat; FM, frequency modulation; OAE, otoacoustic emissions; VRA, visual reinforcement audiometry.

*All costs are in 2016 US dollars. All hearing loss due to cCMV infection is assumed to occur by 6 years of age.

*Otolaryngology (ENT) visits are estimated to occur at the frequency shown to evaluate changing hearing loss or other issues identified by audiologic follow-up. Visits are expected to be rare beyond 18 years of age and are therefore excluded.

*Costs include audiologist time. The cost of auditory brainstem response required to confirm audiometry results for a small minority of children is excluded.

*We assumed that 50% of children with mild to moderate and all with severe to profound hearing loss receive FM systems; that all children with hearing loss receive hearing aids; and that 50% of children with severe to profound hearing loss receive cochlear implants at a 1-time cost of $100 000, after which they no longer incur hearing aid costs. The yearly cost for FM systems have been calculated based on binaural fitting with replacement every 5 years, including estimated costs for maintenance, repair, and replacement parts using a representative retail price. The yearly costs for hearing aids have been calculated based on binaural amplification with replacement every 4 years, including ear molds, batteries, and fitting fees.

*For those younger than 6 years, includes any program designed to optimize the development of language, speech, and communication for preschoolers. Therapy for school-aged children includes speech therapy and assistance with schooling, such as note taking. Costs are derived from the Special Education Expenditure Project.39

The impact of earlier identification of late-onset hearing loss due to cCMV infection is also not well defined, and different estimates would affect the cost-effectiveness of screening, particularly using the universal approach. We did not estimate the effects of screening or treatment on cognitive outcomes owing to insufficient information on which to base costs and effect despite evidence that antiviral therapy appears to improve developmental outcomes.41 If antiviral treatment does reduce intellectual disability, cost savings of cCMV screening would likely increase dramatically.42 Other limitations include our estimates of the costs of screening, costs associated with hearing loss, and assumptions about the impact of early intervention. As such, we evaluated a range of CMV PCR costs that include recent estimates.19,20 Even if testing costs were as high as $50, universal screening would still be roughly cost neutral under some scenarios in our model. These estimates are highly conservative given experience with per-sample PCR costs of less than $10 in other newborn screening programs.43 Newborn PCR-based screening programs for other diseases have already demonstrated the possibility for cost savings,43,44 and the costs of high-throughput molecular diagnostics will likely continue to decrease. Other efficiencies might further increase savings. For example, improving the specificity of screening for hearing or timeliness of confirmatory audiologic evaluation could reduce the number of CMV tests using a targeted screening strategy. Identification of infants with cCMV infection could result in costs for use of health care resources that exceed our estimates (eg, excessive use of magnetic resonance imaging of the brain), which would reduce the savings associated with screening. On the other hand, although we assumed some cost savings from...
### Table 3. Timing and Severity of Hearing Loss Among Children With cCMV Infection

<table>
<thead>
<tr>
<th>Timing of Onset by Severity of Hearing Loss&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All Children With cCMV Infection, No. (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Asymptomatic</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>At birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>4 (0.7)</td>
<td>6 (1.1)</td>
<td>10 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>6 (1.1)</td>
<td>6 (1.1)</td>
<td>12 (2.2)</td>
<td></td>
</tr>
<tr>
<td>≤12 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>3 (0.5)</td>
<td>6 (1.1)</td>
<td>9 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>5 (0.9)</td>
<td>8 (1.5)</td>
<td>13 (2.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 to 24 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;24 to 36 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;36 to 48 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>0</td>
<td>5 (0.9)</td>
<td>5 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;48 to 60 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>0</td>
<td>3 (0.5)</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;60 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>5 (0.9)</td>
<td>5 (0.9)</td>
<td>10 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Severe to profound</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>None identified</td>
<td>49 (8.9)</td>
<td>431 (78.2)</td>
<td>480 (87.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77 (14.0)</td>
<td>474 (86.0)</td>
<td>551 (100)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Mild to moderate severity indicates greater than 20 to 70 dB; severe to profound severity, greater than 70 dB (based on worst ear).

<sup>b</sup> Indicates symptoms at birth, not including hearing loss.

Abbreviation: cCMV, congenital cytomegalovirus.

### Table 4. Estimated Mean Incremental Costs per Newborn to Identify Cases of cCMV Infection and Related Hearing Loss

<table>
<thead>
<tr>
<th>Cost</th>
<th>Screening Strategy, $&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Universal</td>
<td>10/Test</td>
<td>50/Test</td>
<td></td>
</tr>
<tr>
<td>Cost to identify 1 cCMV infection</td>
<td>2000</td>
<td>10 000</td>
<td></td>
<td>566</td>
</tr>
<tr>
<td>Cost to identify 1 cCMV-related hearing loss</td>
<td>27 460</td>
<td>90 038</td>
<td></td>
<td>975</td>
</tr>
<tr>
<td>Cost to prevent 1 cochlear implant&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 064 157</td>
<td>12 620 277</td>
<td></td>
<td>39 401</td>
</tr>
</tbody>
</table>

Abbreviation: cCMV, congenital cytomegalovirus.

<sup>a</sup> All costs are in 2016 US dollars.

<sup>b</sup> Assumes valganciclovir hydrochloride treatment of only symptomatic newborns, calculated as the number of newborns who needed to be screened to prevent 1 cochlear implant case multiplied by the incremental cost of screening, follow-up, and valganciclovir per newborn screened.

### Table 5. Estimated Mean Savings of Newborn cCMV Screening Strategies<sup>a</sup>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Screening Strategy&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Universal</td>
<td>Treat cCMV-Infected Symptomatic Newborns Only</td>
<td>Treat cCMV-Infected Symptomatic Newborns With Hearing Loss at Birth</td>
<td>No Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 (2.5 to 12.6)</td>
<td>13 (5.3 to 21)</td>
<td>NA</td>
</tr>
<tr>
<td>Reduction in severe to profound cases enabled by screening, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs/savings per newborn excluding loss-of-productivity costs, $</td>
<td></td>
<td>−10.86 (−14.73 to −6.97)</td>
<td>−6.83 (−12.98 to −0.68)</td>
<td>−14.16 (−18.63 to −9.71)</td>
</tr>
<tr>
<td>Net costs/savings per newborn including loss-of-productivity costs, $</td>
<td></td>
<td>21.34 (6.54 to 36.17)</td>
<td>37.97 (14.60 to 61.34)</td>
<td>1.67</td>
</tr>
</tbody>
</table>

Abbreviations: cCMV, congenital cytomegalovirus; NA, not applicable.

<sup>a</sup> Assumes a screening test cost of $10 per newborn. All costs/savings are in 2016 US dollars.

<sup>b</sup> Treatment consists of valganciclovir hydrochloride. Values shown are derived using the estimated benefit of valganciclovir on hearing loss as described in the Methods section, with a sensitivity analysis shown in parentheses in which the estimated benefit is 50% lower or higher.
decreased use of diagnostic testing for other common causes of hearing loss among newborns diagnosed with cCMV infection, other costs might be saved by avoiding “the diagnostic odyssey.” The true proportion of newborn hearing loss due to cCMV infection is also uncertain but has implications for the cost-effectiveness of targeted CMV screening.

Limited information is available about the costs associated with hearing loss. We estimated total lifetime costs of $280,000 for children with severe or profound hearing loss, plus an estimated productivity loss of $926,000, for a total cost of approximately $1.2 million, which is consistent with other estimates. We also provide results with and without costs related to the loss of productivity. A major contributor to these costs is educational assistance. Our estimate of the cost of educational assistance for severe and profound hearing loss with onset before age 6 years is approximately $230,000. Although estimates vary in other studies from about $135,000 to $290,000, using the extremes of this range of educational assistance cost does not have a major effect on the model. For example, if educational assistance costs of $135,000 are used, the savings estimate of universal cCMV screening with antiviral treatment for symptomatic newborns and for newborns with hearing loss at birth falls from $37.97 per newborn to approximately $30. Because hearing loss has lifetime effects, the discount rate used in calculations is an important consideration. Varying the discount rate from 1% to 3% increases the present value net cost estimate by approximately $3 per newborn for universal screening and by approximately $1.50 per newborn for targeted screening.

Conclusions

We found that screening newborns for cCMV infection is generally associated with cost savings, or is essentially cost neutral from the perspective of net public spending, across a wide range of assumptions. These results, combined with the reported clinical benefits and high parental acceptance, appear to satisfy accepted criteria for newborn screening. Thus, in the absence of a vaccine or other effective methods to prevent cCMV infection, newborn cCMV screening appears warranted in the United States.


The Utah Cytomegalovirus (CMV) Mandate:

A Five Year Review

Jill Boettger, M.S., CCC-A
CMV Data Coordinator

Stephanie Browning McVicar, Au.D., CCC-A
Early Hearing Detection & Intervention (EHDI) Director

September 2018
The Utah Department of Health’s mission is to protect the public’s health through preventing avoidable illness, injury, disability, and premature death; assuring access to affordable, quality health care; and promoting healthy lifestyles.

Our vision is for Utah to be a place where all people can enjoy the best health possible, where all can live and thrive in healthy and safe communities.
STRATEGIC PRIORITIES

Healthiest People – The people of Utah will be among the healthiest in the country.

Optimize Medicaid – Utah Medicaid will be a respected innovator in employing health care delivery and payment reforms that improve the health of Medicaid members and keep expenditure growth at a sustainable level.

A Great Organization – The UDOH will be recognized as a leader in government and public health for its excellent performance. The organization will continue to grow its ability to attract, retain, and value the best professionals and public servants.
Learning Objective 1: Describe issues that can arise with non-universal CMV testing mandates

Learning Objective 2: Identify preliminary outcomes of the Utah CMV mandate

Learning Objective 3: Create strategies for successful CMV testing programs
26-10-10 UCA, “Cytomegalovirus (CMV) Public Education and Testing”

- **UDOH establish and conduct a public education program** to inform *pregnant women and women who may become pregnant* about CMV (incidence, transmission, birth defects, diagnostic methods, preventative measures)

- Provide information to: *child care providers, school nurses, health educators, health care providers, religious organizations offering children’s programs as part of worship services*
Do you know about the risks of CYTOMEGALOVIRUS during pregnancy?

1 of every 5 children born with CYTOMEGALOVIRUS (CMV) will have PERMANENT DISABILITIES.

And yet,

MOST WOMEN ARE UNAWARE that CMV during pregnancy can harm their baby.

Know the Facts. Protect your baby.

Learn more at:
HEALTH.UTAH.GOV/CMV

or FACEBOOK.COM/CMVUtah

Cytomegalovirus (CMV) Can Cause Birth Defects.
1 OF EVERY 5 children born with CYTOMEGALOVIRUS (CMV) will have PERMANENT DISABILITIES.

And yet,

MOST WOMEN ARE UNAWARE that CMV during pregnancy can harm their baby.

Know the facts. Protect your baby.

LEARN MORE AT: HEALTH.UTAH.GOV/CMV OR FIND US AT: FACEBOOK.COM/CMVUtah

Do you know about the risks of cytomegalovirus (CMV) during pregnancy?

1 of every 5 children born with CMV will have permanent disabilities.

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@CMVUtah

Know the facts. Protect your baby.

Do U know about the risks of cytomegalovirus during pregnancy?

1 of every 5 children born with cytomegalovirus (CMV) will have permanent disabilities.

Learn more at: health.utah.gov/cmv

Know the facts. Protect your baby.
26-10-10 UCA, “Cytomegalovirus (CMV) Public Education and Testing”

If a newborn infant fails the newborn hearing screening test(s)……

Medical Practitioner shall:
Test the newborn infant for CMV before 21 days of age…unless the parent objects;

And provide to the parents information re: birth defects caused by congenital CMV and available methods of treatment.
26-10-10 UCA, “Cytomegalovirus (CMV) Public Education and Testing”

(continued)

**UDOH** shall:

- *Provide information to the family and the medical practitioner (if known)* information re: the *testing requirements* when providing results indicating that an infant has failed the newborn hearing screening test(s).
R398-4-3. Clarification of when a newborn fails a hearing screen.

- The newborn **must fail both hearing screens**, the initial hearing screen routinely done at birth **and** the subsequent follow-up screen,

**OR**

- if/when the initial failed hearing screen is obtained **after 14 days of age** before the medical practitioner is required to test for CMV.
Utah Newborn Hearing Screening

INPATIENT

Hospital
10-12 hrs.

Before Discharge
24 hrs.

OUTPATIENT

7-10 Days
Utah Newborn Hearing Screening

**Outpatient Screening**

- **Pass**
- **Refer**

**Pediatric Audiologist**

- Monitor Development:
  - Hearing
  - Speech/Language

- Auditory Brainstem Response (ABR) Testing

**Lab**

- CMV PCR Testing

*2 hours or more after feeding

**Medical Home**

**< 14 Days**

**< 21 Days**
R398-4-4. Special populations of newborns.

- In special populations of newborns where newborn hearing screening(s) cannot be accomplished prior to 21 days of age, **testing for CMV is left to the discretion of the medical practitioner(s) caring for the newborn.**

- Special population of newborns may include, but are not limited to, premature or medically fragile newborns or newborns receiving on-going medical care.
R398-4-5. Reporting Requirements.
Medical practitioners are required to submit results of the CMV testing to UDOH for each newborn under their care who is referred for CMV testing within 10 days of receiving results.
Completion of Diagnostics by 90 Days Before the CMV Mandate, 18 Months and 4 and 5 Years After the Mandate

- 2 years prior to the Mandate 7/1/11 to 6/30/13
- 18 months after the Mandate 7/1/13 to 12/31/14
- 4 years after the Mandate 1/1/17 to 6/30/17
- 5 years after the Mandate 7/1/17 to 12/31/17
Number of Babies with 2nd OP Screens
First 5 Years of the Mandate

Number of infants

Year 1  Year 2  Year 3  Year 4  Year 5

0 10 20 30 40 50 60 70 80 90 100
Percent of Babies with CMV Testing Who Passed the Second OP Screen

- 7/13 to 12/14: 15%
- 1/15 to 6/15: 31%
- 7/15 to 12/15: 33%
- 1/16 to 6/16: 51%
- 7/16 to 12/16: 61%
- 1/17 to 7/17: 61%
- 7/17 to 12/17: 87%
- 1/18 to 6/18: 87%
Percent of CMV Testing for Special Populations NICU Babies

It is therefore recommended that strong consideration be given to testing NICU infants with any (even if only 1 is noted) of the following signs for congenital CMV infection in the first 3 weeks of life, even if alternative explanations are possible or even probable:

1) Abnormal head size (microcephaly [<10th %ile] OR macrocephaly [>90th %ile]) at birth
2) Intrauterine growth restriction (weight <10th %ile for gestational age) at birth
3) Hydrops
4) Intracranial OR intraabdominal calcifications on first imaging exam
5) Hepatomegaly OR splenomegaly (>1 cm below the right or left costal margin) in first 72 hours
6) AST or ALT >100 U/L OR direct bilirubin >1.0 mg/dL in first 72 hours
7) Petechiae at any time OR thrombocytopenia (<100,000/mm³) on ≥2 occasions in first 72 hours
8) ‘Blueberry muffin’ appearance
9) Neuronal migration disorders (e.g., polymicrogyria, lissencephaly, pachygyria, schizencephaly) on first imaging exam
10) Unexplained brain lesions or neurologic findings
Challenges

Percent Tested for CMV by 21 Days for Hearing Targeted Eligible Infants

7/13 - 6/15: 74.5%
7/15 - 12/15: 80%
1/16 - 6/16: 84%
7/16 - 12/16: 89%
1/17 - 6/17: 84%
7/17 - 12/17: 89%
1/18 to 6/18: 88%

UDOH Assist
Challenges

All Infants Tested for CMV by 21 Days vs. UDOH Assist (UDOHA) >21 Days Taken Out

- 93% tested by 21 days
- 89% tested by 21 days - UDOHA
- 94% tested by 21 days
- 88% tested by 21 days - UDOHA

% Tested by 21 days

% Tested by 21 days - UDOHA

1/17 - 6/17 7/17 - 12/17 1/18 - 6/18
## Challenges

### CMV Testing within One Week of 21 days

<table>
<thead>
<tr>
<th></th>
<th>Total % Tested by Day 21</th>
<th>Day 22</th>
<th>Day 23</th>
<th>Day 24</th>
<th>Day 25</th>
<th>Day 26</th>
<th>Day 27</th>
<th>Day 28</th>
<th>% w/in 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/16 to 12/16</td>
<td>89%</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>7/14 = 50%</td>
</tr>
<tr>
<td>1/17 to 6/17</td>
<td>84%</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12/25 = 48%</td>
</tr>
<tr>
<td>7/17 to 12/17</td>
<td>89%</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7/14 = 50%</td>
</tr>
<tr>
<td>1/18 to 12/18</td>
<td>88%</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7/16 = 44%</td>
</tr>
<tr>
<td>Totals</td>
<td>X=87.5%</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>X=48%</td>
</tr>
</tbody>
</table>

- About 50% of the late CMV testing occurred within 1 week of 21 days.
- **23/30 or 77%** of late testing for CMV occurred within 4 days of 21 days.
Challenges

Percent of Out of Hospitals Births Tested for CMV

- 3% tested 7/13 to 12/14
- 13% tested 1/15 to 6/15
- 0% tested 7/15 to 12/15
- 25% tested 1/16 to 6/16
- 27% tested 7/16 to 12/16
- 20% tested 1/17 to 6/17
- 24% tested 7/17 to 12/17
- 55% tested 1/18 to 6/18
- 90% for NBHS

HEALTHIEST PEOPLE | OPTIMIZE MEDICAID | A GREAT ORGANIZATION
First Lab Specimen Types Over 5 Years

- Saliva: 48%
- Blood: 3.5%
- Urine: 48.5%

N=530
N=521
N=39
Comparison of % Tested for Eligibility Groups Over Five Years
Percent of Eligible Infants Tested for CMV
5 Years of Testing since the Mandate

<table>
<thead>
<tr>
<th>Date</th>
<th>% Tested for CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>July-Dec 2013</td>
<td>36%</td>
</tr>
<tr>
<td>Jan-June 2014</td>
<td>56%</td>
</tr>
<tr>
<td>July-Dec 2014</td>
<td>51%</td>
</tr>
<tr>
<td>Jan-June 2015</td>
<td>59%</td>
</tr>
<tr>
<td>July-Dec 2015</td>
<td>69%</td>
</tr>
<tr>
<td>Jan-June 2016</td>
<td>72%</td>
</tr>
<tr>
<td>July-Dec 2016</td>
<td>74%</td>
</tr>
<tr>
<td>Jan-June 2017</td>
<td>91%</td>
</tr>
<tr>
<td>July-Dec 2017</td>
<td>96%</td>
</tr>
<tr>
<td>Jan-June 2018</td>
<td>96%</td>
</tr>
</tbody>
</table>

6 months Intervals

Utah Data
Percent of Eligible Babies Tested for CMV
With Corresponding Improvement Events

- 36% (7/13 to 12/13)
- 56% (1/14 to 6/14)
- 51% (7/14 to 12/14)
- 59% (1/15 to 6/15)
- 69% (7/15 to 12/15)
- 72% (1/16 to 6/16)
- 74% (7/16 to 12/16)
- 91% (1/17 to 6/17)
- 96% (7/17 to 12/17)
- 96% (1/18 to 6/18)

Key Events:
- Timely PCP Follow-up Calls
- UDOH Assist
- CMV Data Coordinator
- CMV Report Cards
- CMV Standing Order
- CMV Reporting Module
- CMV Mandate Starts
**Utah CMV Testing Order**

**Cytomegalovirus & Auditory Brainstem Response**

**Testing Orders**

**NOTE: NO ACTION REQUIRED BY PROVIDER, order has been placed.**

Parents, Your baby did not pass the second newborn hearing screening and Utah law requires lab testing be completed for a common virus, Cytomegalovirus (CMV), which can be associated with hearing loss. CMV testing is painless requiring a urine sample (preferred) or a saliva sample. *A saliva sample should be obtained at least 2 hours after breastfeeding.* It is vital that this CMV lab test is done before your baby is 21 days of age. Your baby also requires a more detailed hearing test known as ABR (Auditory Brainstem Response), which should be scheduled as soon as possible. Results of both the CMV and ABR tests will be reported to your primary care provider and the State Early Hearing Detection and Intervention (EHDI) Program which is responsible for the newborn hearing screening and CMV testing mandates.

<table>
<thead>
<tr>
<th>Field</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant’s Full Name</td>
<td>DOB: Birth Location:</td>
</tr>
<tr>
<td>Mother’s Full Name:</td>
<td>Phone #:</td>
</tr>
<tr>
<td>Primary Care Provider (PCP):</td>
<td>Location:</td>
</tr>
<tr>
<td>PCP Phone #:</td>
<td>PCP Fax #:</td>
</tr>
</tbody>
</table>

1. **Diagnostic ABR Testing**
   - **CPT code**: 92505 [Diagnosis Code: H91.90 (sensorineural hearing loss)]
   - Lab testing should include at least click and frequency-specific stimuli, bilaterally.
   - ABR test date: Location: ____________________________

2. **CMV Qualitative PCR Lab Testing Order**
   - **CPT code**: 87865 [Diagnosis Code: H91.90 (sensorineural hearing loss)]
   - *If available, BMV would be acceptable.*

**Urine** (preferred specimen):
- **Name**: Cytomegalovirus by Qualitative PCR (CMV/PCR)
- **Specimen Collection**: collect and submit 1 ml
- **Stability of specimen**: Ambient; 24 hrs; Refrigerated: 24 hrs; Freeze: 3 months
- **Required**: 1-5 days

**Saliva** (cheek swab with ORACollect OC-100 kit) **Should be obtained 2 hours after breastfeeding**
- **Name**: Cytomegalovirus by Qualitative PCR, Saliva (CMV/PCR Lab)
- **Specimen Collection**: Collect and submit saliva in ORACollect OC-100 kit
- **Specimen Collection**: DNA extraction
- **To obtain ORACollect OC-100 kit**: ARUP Client Services: 801-587-2787
- **Specimen Handling**: Ambient: 7 days; Refrigerated: 7 days; Freeze: 3 months
- **Required**: 1-5 days

**Results come to UDOH directly from the lab.**

**Questions?** Please call 801-584-8715**

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**HEALTHIEST PEOPLE | OPTIMIZE MEDICAID | A GREAT ORGANIZATION**
CMV Report Cards

- PCP felt testing was not needed (Pediatrician, MD) – 0
- Doctor did not receive Fax requesting CMV testing although sent to him -0
- PCP unaware of 21 day deadline for CMV testing (Pediatrician, DO) – 0
- Wrong PCP notified by fax -1 (Correct pediatric practice, wrong doctor)
- Parent refused testing -1
- Babies with comorbidities including otitis media, cleft lip and palate and Down’s syndrome were not referred for testing by PCP - 0

Comments and Recommendations

1. Overall, a great job with 80% of the babies being tested when deleting the one whose parents refused testing. This is a 34% increase from the previous 6 months!
2. All CMV tests were completed by the 21 day cut off!
3. Two of the babies who were not tested, passed their OP screen but still qualified for testing because their first test was after 14 days.
4. One baby who was not tested passed the second OP screen but should have been referred for testing after the initial failed OP screen.
5. For the parent who refused testing further education maybe helpful. The CMV brochures, *Congenital CMV and Hearing Loss* and *What Women Need to Know about CMV*, available in English and Spanish, are useful tools to educate parents. Brochures templates are available on the CSHCN website, [http://www.health.utah.gov/cshcn/programs/cmv.html](http://www.health.utah.gov/cshcn/programs/cmv.html), or we can send some if you need them!
6. Congratulations April and Kevin. You are one of the top three hospitals in Utah for the percent of eligible babies being tested for CMV! Keep up the exemplary work!
CMV Testing Over Time
This graph shows the progress of CMV testing at your hospital since the beginning of the mandate in 2013. The number of babies eligible for CMV testing for each time period from left to right was as follows: 46, 15, 9, 18, 23 & 18.

Test Results (FYI)
- CMV Positive - 1
- CMV Negative – 33
- False Positive – 1
- Refused Testing – 2
- Tested by Saliva – 9, Urine – 26, Blood – 1 Dried blood spot, Multiple tests – 1

Reasons Found for Not Testing Eligible Infants
- Fax forms were not received by the PCP - 4
- Parent did not follow through with testing – 1 (PCP wrote a lab order but parent did not follow through, parent reported she had no recall of CMV testing.)
- PCP chose not to test after baby passed the second OP screen – 1

Comments and Recommendations
1. Nice job getting 91% of the CMV testing for 34 babies completed by 21 days.
2. We are hoping the new CMV order will help with old problems such as the PCP not receiving the fax requesting testing. If possible walking the parents to the lab immediately after failure of the first OP screen will help with parents with following through with testing.
3. Keep up the great work. IMC has the most babies eligible for CMV testing so there is a lot to keep us with!
Number of Known* CMV Tests Over 5 years with Corresponding CMV Lab Result Access

- CMV Mandate Starts – Lab Results Faxed
- Searching Medical Records - iCentra
- CMV – Reportable Condition
- cHIE Access
- cHIE Access Interrupt
- Electronic Lab Reporting Exports

*Not just Hearing Targeted testing
Percent of Eligible Infants Tested for CMV
Aggregate Data for IHC Birthing Facilities
July 2013 to December 2017
Utah Five Years

• 255,190 births in Utah
• 1932 were eligible for CMV testing
• 273 Special Populations were excluded (no NBHS before 21 days)
• 3 IP initial screens on Day 14 were excluded
• 1656 babies were then eligible for testing = 6.5/1000 births
• 50 babies declined testing (3%)
• 1100 babies were tested for CMV
• 30 “hearing-targeted” infants were identified with cCMV = 2.7%
• An additional 8 were inconclusive (+ but tested after 21 days and no other abnormalities) = 3.5%
Utah Five Years

About Infants Tested per

3

CONGENITAL

VERMONT

100
Benefits of our HT CMV Mandate:

• cCMV now a qualifying diagnosis for EI
• Any CMV testing for infants < 1 year of age, direct reporting to UDOH (Division of Disease Control and Prevention)
• Increased overall awareness of cCMV in the medical community, e.g. NICU testing
• Improvement in EHDI 3 month dx milestone attainment
• Significantly more infants had completed dx by 6 mos than pre-mandate
• Discovered multiple OP rescreening protocol (which has decreased)
Continued:

• Formation of “cCMV Clinic” with community partners and testing/referral protocols
• Standing CMV/ABR order facilitating quick and easy testing for families and providers
• cCMV testing precipitated by failed NBHS allowed for further diagnostic testing which informed treatment options (e.g. abnormal imaging)
• Dedicated CMV Data and Follow-Up Coordinator essential
Goals for the Sixth Year:

• Survey parents who refused CMV testing to better understand reasons for the refusal
• Investigate possible money sources to help parents with no insurance afford CMV testing
• Continue to develop CMV Registry
• Reach out to parents of cCMV babies with normal hearing to see if testing has been completed and get results. If hearing testing has not been completed then facilitate testing.
• Create early intervention for cCMV children protocol
Conflict of Interest Disclosure Form

Note: A potential or actual conflict of interest exists when commitments and obligations are likely to be compromised by the nominator(s)' other material interests, or relationships (especially economic), particularly if those interests or commitments are not disclosed.

This Conflict of Interest Form should indicate whether the nominator(s) has an economic interest in, or acts as an officer or a director of, any outside entity whose financial interests would reasonably appear to be affected by the addition of the nominated condition to the newborn screening panel. The nominator(s) should also disclose any personal, business, or volunteer affiliations that may give rise to a real or apparent conflict of interest. Relevant Federally and organizationally established regulations and guidelines in financial conflicts must be abided by. Individuals with a conflict of interest should refrain from nominating a condition for screening.

Date: 03/27/2019

Name: Sara Menlove Doutre

Position: Chair, Scientific Advisory Committee, National CMV

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☑ I have no conflict of interest to report.

☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. _______________________________________________________________________

2. _______________________________________________________________________

3. _______________________________________________________________________

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: 

Date: 03/27/2019
Conflicts of Interest Disclosure Form

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Date: 03/27/2019

Name: Janelle Greelee

Position: Chair, RUSP Nomination Committee, National CMV

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

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1. 

2. 

3. 

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Signature: 

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Date: 03/27/2019
Name: Kristen Hutchinson Spytek
Position: President & CEO, National CMV Foundation

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.
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1. 

2. 

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: ____________________________
Date: 03/27/2019
DATE: August 27, 2018

TO: Advisory Committee on Heritable Disorders in Newborns and Children

SUBJECT: Nomination of congenital Cytomegalovirus for review as part of the Recommended Uniform Screening Panel

On behalf of Merck, I am writing to express my support for the review of congenital cytomegalovirus (cCMV) screening by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) as a part of the Recommended Uniform Screening Panel (RUSP). For more than a century, Merck has been inventing medicines and vaccines for many of the world’s most challenging diseases. Merck’s mission is to discover, develop, and provide innovative products and services that save and improve lives around the world. We are committed to finding solutions to the world’s greatest health challenges and discovering smart, sustainable ways to expand global access to healthcare.

Awareness of CMV remains low despite it having long been recognized as the leading cause of congenital sensorineural hearing loss. Each year in the United States, approximately 1 in 200 babies are born with cCMV and 1 in 5 of these children will have long term health problems. Beyond hearing loss which can sometimes appear years after birth, other health problems can include vision loss, intellectual disability, seizures, and more.

Currently, there is no uniform recommendation for screening newborns for cCMV in the United States. The limited time window following birth to determine if an infant has cCMV requires a standardized approach. Screening, detection, and early diagnosis could aid in early multi-disciplinary interventions for newborns and lead to improved long term developmental outcomes. Screening could also enable better surveillance and reporting allowing researchers to gain a more complete view of cCMV to further understand the true burden of congenital CMV disease and support the scientific development of new technologies addressing this disease.

Currently, a few states in the U.S. have passed legislation requiring targeted testing for cCMV based on failed newborn hearing screens; however this approach could miss diagnosing cCMV in affected infants. Evidence suggests that newborn screening is cost-effective under a wide set of assumptions and universal screening offers a larger savings opportunity and the opportunity to direct care.  (Gantt, JAMA Pediatr. 2016;170(12):1173-1180).

A review of the evidence by the ACHDNC and a systematic assessment of the impacts of different approaches for cCMV screening on individuals and health systems is timely to conduct now. The assessment will provide important direction for a subsequent RUSP recommendation and will provide a universal standard that states can adopt and allow for early diagnosis of cCMV.

Sincerely,

Roy D. Baynes, MD, PhD
SVP & Head Global Clinical Development,
Chief Medical Officer
Conflict of Interest Disclosure Form

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Date: 08/30/2018

Name: Roy D. Baynes, MD, PhD

Position: SVP & Head Global Clinical Development, CMO

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☑ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. Merck Chief Medical Officer - overseeing development of a CMV vaccine

2. Merck Product - Letemovir for CMV sero+ allogeneic stem cell transplant patients

3. Board of Directors for Atara Inc. Therapy for CMV disease in stem cell transplant

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: ____________________________

Date: 08/30/2018
Genetic Services Branch  
Division of Services for Children with Special Health Needs  
Maternal and Child Health Bureau  
Health Resources and Services Administration  
5600 Fishers Lane, Room 18W-68  
Rockville, MD 20857

September 10, 2018

Dear Advisory Committee on Heritable Disorders in Newborns and Children:

We are writing to provide our support for the nomination of congenital CMV (cytomegalovirus) for consideration by the Committee for the Recommended Uniform Screening Panel (RUSP). We fully support the nomination of this condition for inclusion in the Uniform Screening Panel.

We as pediatricians and scientists at the University of Alabama at Birmingham in the Division of Pediatric Infectious Diseases have a long standing commitment to caring for children with congenital CMV and to advance our understanding of congenital CMV infection. Our congenital CMV research has been supported by the National Institutes of Health, Centers for Disease Control, various foundations and other extramural funding agencies. Over the years, we have collaboratively and individually contributed to the scientific knowledge in the understanding of the pathogenesis and transmission mechanisms of congenital CMV, predictors of adverse outcomes, mechanisms of hearing loss, and therapy and vaccine development.

UAB has been in the forefront of screening and identifying infants with congenital CMV, with over 60,000 infants screened at University Hospital since 1980. In addition, the recent CHIMES study led by Drs. Suresh Boppana and Karen Fowler screened over 100,000 infants for congenital CMV infection and established a scalable molecular diagnostic assay that could be used for universal screening for CMV. Also, the recent randomized antiviral treatment trial led by Drs. David Kimberlin and Rich Whitley have provided further evidence for antiviral therapy in children with congenital CMV infection.

Congenital CMV infection occurs in 4 to 5 per 1000 live births in the United States and one in every six children born with congenital CMV will develop permanent health problems. Without CMV screening, early intervention and antiviral therapy are missed opportunities that would provide benefits for many of the infants with congenital CMV infection.
We are fully supportive of this initiative and we thank the committee for its consideration of congenital CMV for the RUSP panel.

Sincerely,

Suresh B. Boppana, MD
Hugh Dillon, MD Endowed Professor of Pediatrics

William J. Britt, MD
Charles A. Alford Endowed Chair in Pediatric Infectious Diseases

Karen B. Fowler DrPH
Professor

David W. Kimberlin, MD
Co-Director, Division of Pediatric Infectious Diseases
Sergio Stagno MD Endowed Chair in Infectious Diseases

Shannon A. Ross, MD
Associate Professor

Richard J. Whitley, MD
Co-Director, Division of Pediatric Infectious Diseases
Loeb Eminent Scholar Chair in Pediatrics
Distinguished Professor
Conflict of Interest Disclosure Form

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Date: 09/18/2018

Name: Suresh Boppana, MD

Position: Professor of Pediatrics, UAB School of Medicine

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☑ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. Board Member, National CMV Foundation

2. Merck, Consultant, CMV Vaccine Program

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: [Signature]

Date: 09/18/2018
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Date: 09/18/2018

Name: Karen B Fowler

Position: Professor

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

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☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. 

2. 

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: Karen B Fowler

Date: 09/18/2018
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Date: 09/18/2018

Name: David Kimberlin, MD

Position: Professor of Pediatrics, University of Alabama at Birmingham

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☑ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. Editor, American Academy of Pediatrics Red Book

2. 

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature:

Date: 09/18/2018
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Date: 09/19/2018

Name: Shannon Ross, MD

Position: Associate Professor of Pediatrics

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. 

2. 

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: ________________________________

Date: 09/19/2018
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Date: 09/18/2018

Name: Richard J. Whitley

Position: Distinguished Professor

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☑ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. Gilead Sciences - Member of Board of Directors and Health Policy Advisory Board

2. GlaxoSmithKline - Member of the Data Safety and Management Board

3. Merck - Member of the Data Safety and Management Board

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature:

Richard J. Whitley

Date: 09/18/2018
May 31, 2018

Dear Advisory Committee on Heritable Disorders in Newborns and Children,

Through this letter, I provide my enthusiastic support for the nomination of congenital cytomegalovirus (CMV) for consideration by the Committee for the Recommended Uniform Screening Panel (RUSP).

As a pediatric infectious diseases expert and as a CMV specialist, with over 35 years experience in research, clinical management, diagnosis and prevention of congenital CMV, I have documented the long term effects of childhood survivors of CMV, I have developed novel assays for the diagnosis of congenital CMV in newborns, I have participated in antiviral clinical trials for treatment of congenital CMV, and I have advocated for prevention strategies for congenital CMV.

I know very well the importance of congenital CMV to the public health, and the importance of the short diagnostic window of opportunity (first 3 weeks of life) to establish, with certainty, the diagnosis of congenital CMV in a newborn infant. Early diagnosis of congenital CMV, through inclusion on the RUSP, will allow newborns to benefit from appropriate anticipatory guidance to monitor for hearing loss, vision loss, and neurodevelopmental disabilities, and allow physicians to make appropriate management decisions, such as antiviral therapy, that have been shown to reduce morbidity and improve quality of life.

I wholeheartedly and enthusiastically support the addition of congenital CMV to the RUSP.

I thank the Committee for your consideration of this important request.

Sincerely,

[Signature]

Gail J. Demmler Harrison MD
Professor Pediatrics
Baylor College of Medicine
Attending Physician, Infectious Diseases Service
Texas Children’s Hospital
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Date: 05/31/2018

Name: Gail J Demmler-Harrison MD

Position: Professor of Pediatrics, Section Infectious Diseases

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1.

2.

3.

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: [Signature]  
Date: 05/31/2018
October 3, 2018

Dear Advisory Committee on Heritable Disorders in Newborns and Children,

We, the Board of Directors of the Directors of Speech and Hearing Programs in State Health and Welfare Agencies (DSHPSHWA) are writing to provide our support for the nomination of congenital cytomegalovirus (cCMV) for consideration by the Committee for the Recommended Uniform Screening Panel (RUSP).

DSHPSHWA largely represents Early Hearing Detection and Intervention (EHDI) stakeholders in programs nationwide. Our membership is primarily made up of state EHDI Coordinators who are charged with developing a comprehensive and coordinated statewide Early Hearing Detection and Intervention (EHDI) system of care to ensure infants receive appropriate and timely services. Therefore, we are acutely aware of the impact of cCMV on the families with whom we work. We have observed families that are provided little to no information regarding cCMV and are not aware of the need for screening after birth. Our families desperately need the screening and related information to provide adequate care for their children in a timely manner. From an EHDI perspective, cCMV is the greatest non-syndromic cause of hearing loss and is often the cause of progressive and/or delayed-onset hearing loss. Failure to diagnose the cCMV infection can lead to a delayed diagnosis of hearing loss, impacting the child’s language development and educational progression.

DSHPSHWA, and specifically EHDI programs, have 20 years of experience with point of care newborn hearing screening and follow-up. EHDI programs also have experience with population health data collection related to hearing screening and children who are deaf or hard of hearing. While a system to monitor children who test positive for cCMV is not currently in place, it is feasible to develop given that most states already track cCMV as a potential risk factor for hearing loss.

Thank you for your consideration of adding cCMV to the RUSP.

Sincerely,

Marcia Fort, Au.D., CCC-A
Past-President, DSHPSHWA
Genetics and Newborn Screening Unit Manager and EHDI Coordinator
Conflict of Interest Disclosure Form

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Date: 10/08/2018

Name: Marcia Fort

Position: Genetics and Newborn Screening Unit Manager

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☑️ I have no conflict of interest to report.

☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. 

2. 

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: Marcia Fort

Date: 10/08/2018
Dear Advisory Committee on Heritable Disorders in Newborns and Children,

We write to provide support for the nomination of congenital CMV (cytomegalovirus) infection for consideration by the Committee for the Recommended Uniform Screening Panel (RUSP).

Vaccine Research and Development, Pfizer Inc., is currently exploring the potential for development of a vaccine that could be given to women, either before or during pregnancy, to reduce the risk of congenital CMV infection and disease. This goal is driven by the important health burden of this disease:1 Congenital CMV infection is estimated to occur in ~0.5 to 0.7% of all live births; 10% of those infected will be symptomatic at birth, with 50% of these manifesting neurodevelopmental disabilities including sensorineural hearing loss; 90% are asymptomatic at birth but 10-15% of these will develop sensorineural hearing loss. Approximately 20% of all hearing loss at birth and 25% of all hearing loss at 4 years of age is attributable to congenital CMV infection.2 Disabilities after congenital CMV infection are now more common in the United States than recognized conditions of Down syndrome, fetal alcohol syndrome, or spina bifida.1 In the absence of a vaccine to prevent the disease, prompt diagnosis and valganciclovir treatment of symptomatic congenital CMV infection has been associated with improved audiologic outcomes and neurodevelopmental outcomes; prompt diagnosis would facilitate early identification of hearing loss so that other interventions could also be applied early to facilitate hearing and child development. In addition, routine screening would better identify the burden of disease that could be prevented by a vaccine, facilitating vaccine development and recommendations. Testing for CMV in saliva, urine, or both, at the time of birth, optimally distinguishes congenital disease from postnatally acquired disease, which can occur within 3 weeks after birth and typically has a more benign course. Hence, testing for congenital CMV infection is particularly well suited for the RUSP.

We, therefore, recommend that the Advisory Committee on Heritable Disorders in Newborns and Children add congenital CMV infection to the RUSP, and thank the committee for their consideration.

Sincerely,

William C. Gruber, M.D., FAAP, FIDSA
SVP Vaccine Clinical Research and Development, Pfizer, Inc.

Kathrin U. Jansen, PhD
SVP and Head Vaccine Research and Development, Pfizer, Inc.

1. Please see references as cited in the ACHDNC form for nomination of a condition in the RUSP.
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Date: 09/14/2018

Name: William C. Gruber, M.D.

Position: SVP Vaccine Clinical R&D, Pfizer Inc

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☑ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. Employee of Pfizer Inc with salary, stock, and stock options

2.

3.

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: [Signature] SVP, Vaccine Clinical R&D

Date: 09/14/2018
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Date: 09/23/2018

Name: Kathrin U. Jansen

Position: SVP and Head Vaccine R&D, Pfizer Inc

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

☒ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

1. Employee of Pfizer Inc with salary, stock, stock options

2.

3.

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: ____________________________  SVP and Head of Vaccine R&D

Date: 09/23/2018
May 29, 2018

Advisory Committee on Heritable Disorders in Newborns and Children

To The Honorable Committee Members,

As a representative of the California State Assembly, I urge you to support the nomination of congenital cytomegalovirus (CMV) to the Recommended Universal Screening Panel (RUSP).

In 2017, constituents from California’s San Fernando Valley asked me to help address the lack of knowledge about and screening for congenital CMV. In response to the compelling stories of families affected by CMV and the numerous studies on the importance of early identification of children infected with congenital CMV, I authored Assembly Bill 1801. This bill would require the California State Department of Health Care Services to establish a commission to review issues surrounding CMV exposure in California. If the commission deems it appropriate, they could develop recommendations to help combat this serious virus.

Each year in California, 3,000 children are born with CMV and may develop hearing loss, vision loss, cerebral palsy, mental and physical disabilities, behavior issues, and seizures. It is my goal that the commission proposed under this bill would contribute to the research needed for the RUSP to determine whether or not CMV is worthy to be added to newborn screening programs. Likewise, the recommendations of your committee will be very important to our proposed commission and will help inform how we move forward to better increase knowledge and identification of congenital CMV in California.

The decision of your committee—along with the commission proposed under my legislation—has the capacity to improve the long-term health of our state, both fiscally and that of our children. Thank you for your careful consideration and I respectfully ask for your approval on this important matter.

Sincerely,

ADRIN NAZARIAN
Member, Assembly District 46th
Conflict of Interest Disclosure Form

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Date: 05/29/2018

Name: Adrin Nazarian

Position: California State Assembly Member

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

✓ I have no conflict of interest to report.

☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

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I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: ___________________________

Date: 05/29/2018
May 23, 2018

NEONATAL CMV SCREENING

To whom this may concern:

I am a pediatric infectious diseases specialist who has been long interested in congenital cytomegalovirus (CMV) infection. CMV is the most important cause of congenital abnormalities because it infects women during pregnancy and frequently passes to the fetus. Infected newborns may have serious disease or may develop problems later in childhood. It is therefore important to identify infected infants at birth, so that they may be offered services or even have antiviral treatment of their infections.

Therefore, I strongly support testing of all infants at birth by a simple test of their saliva for the presence of CMV. This would be a first step in the eventual control of the disease by education and vaccination of women to prevent congenital CMV disease.

Yours truly,

Stanley A. Plotkin, MD

4650 Wismer Road, Doylestown, PA 18902
Conflict of Interest Disclosure Form

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Date: May 26, 2018

Name: Stanley A. Plotkin, MD

Position: Professor Emeritus of Pediatrics, University of Pennsylvania

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☐ I have no conflict of interest to report.

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I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: 

Date: 25 May, 2018
June 8, 2018

Dear Advisory Committee on Heritable Disorders in Newborns and Children,

I am writing to provide my complete and unwavering support for the nomination of congenital cytomegalovirus (CMV) infection for inclusion on the Recommended Uniform Screening Panel (RUSP). I am a board-certified neonatologist and pediatric infectious diseases specialist with a longstanding interest in clinical and translational research focused on perinatal and neonatal infections such as congenital CMV infection. I am the Principal Investigator (PI) for the NICHD Neonatal Research Network (NRN) at Nationwide Children’s Hospital (NCH) – The Ohio State University (OSU) College of Medicine, and previously had the same position at the University of Texas (UT) Southwestern Medical Center, Dallas from 4/2006 to 7/2013, when I moved to Columbus, OH and became the Director of Clinical & Translational Research in Neonatology at NCH–OSU.

Congenital CMV infection is the most common congenital viral infection worldwide and the leading nongenetic cause of hearing loss in newborns. Since 1995, I have worked with the NIAID Collaborative Antiviral Study Group (CASG; University of Alabama at Birmingham) on ganciclovir and then valganciclovir treatment of neonates with symptomatic congenital CMV infection, and have shown that treatment significantly improves hearing outcomes. This has resulted in a major shift in the management of these infants. Importantly, it has resulted in the need for newborn CMV screening. In 1997 when Texas mandated universal newborn hearing screening, I implemented targeted CMV screening for infants who did not pass the hearing screen at Parkland Memorial Hospital, and detected a 6% incidence of congenital CMV infection in these infants. At the same time, we also implemented targeted screening of infants born to HIV-infected mothers and found a 3% prevalence of congenital CMV infection. In addition, I was the UT Southwestern site PI for the NIDCD multicenter study of The Natural History of CMV-Related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in Newborns (CHIMES study). This study showed that newborn dried blood spots lacked sensitivity for universal CMV screening, but established saliva as the preferred and sensitive newborn screening method for congenital CMV infection.

I feel strongly that the time for universal CMV screening is NOW! Although both targeted and universal CMV screening has been shown to be cost-effective, universal screening provides larger net savings and the greatest opportunity for directed care. The prevalence of congenital CMV infection, its associated sequelae, the availability of a simple saliva screening tool, available antiviral treatment, and directed therapies for hearing impairment mandate that we act now to make universal screening a reality!
Thank you for your consideration of congenital CMV infection as part of universal newborn screening. Please let me know if there is any further information that I could provide to make this happen.

Sincerely,

Pablo J. Sánchez, M.D.
Professor of Pediatrics
Nationwide Children's Hospital - The Ohio State University
Divisions of Neonatal-Perinatal Medicine and Pediatric Infectious Diseases
Director, Clinical & Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, RB3, WB5245
Columbus, Ohio 43205-2664
614-355-6638 (phone)
614.355.5899 (fax)
Pablo.sanchez@nationwidechildrens.org
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Date: 06/08/2018

Name: Pablo J Sanchez

Position: Professor of Pediatrics

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

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I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: Pablo J Sanchez

Date: 06/08/2018
Dear Advisory Committee on Heritable Disorders in Newborns and Children,

I am writing to provide my support for the nomination of congenital CMV (cytomegalovirus) for consideration by the Committee for the Recommended Uniform Screening Panel (RUSP). I fully support nomination of this condition for inclusion in the Uniform Screening Panel.

I am a pediatrician and physician-scientist at the University of Minnesota in the Division of Pediatric Infectious Diseases and Immunology. I have been studying cytomegalovirus biology and infection for over thirty years. My laboratory is supported by the National Institutes of Health, March of Dimes Birth Defects Foundation, and other extramural funding agencies. Most significantly, I maintain a clinical practice which includes many infants with congenital CMV infection. My laboratory is piloting a universal newborn screening study in Minnesota. We have identified many infants through universal screening and have found that the program is well-accepted by primary care physicians, parents, and public health officials. The ability to identify infants at high risk for hearing loss has allowed us to follow these children closely and, in settings where hearing loss emerges after the newborn period, has allowed us to intervene early. Selected infants are treated with antiviral therapy, but it is important to consider in this context that therapy entails much more than the mere prescription of an antiviral drug. Congenital CMV screening has clear, tangible benefits for newborns and it belongs on the RUSP panel!

I am fully supportive of this initiative and I thank the committee for its consideration of congenital CMV for the RUSP panel.

Sincerely,

Mark R. Schleiss, MD
American Legion and Auxiliary Heart Research Foundation Chair
Professor, Division of Pediatric Infectious Diseases and Immunology
University of Minnesota Medical School
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Date: 06/09/2018

Name: Mark R. Schleiss MD

Position: Professor of Pediatrics

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☑️ I have no conflict of interest to report.

☐ I have the following conflict of interest to report (please specify other nonprofit and for-profit boards you (and your spouse) sit on, any for-profit businesses for which you or an immediate family member are an officer or director, or a majority shareholder, and the name of your employer and any businesses you or a family member own:

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I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: _____________________________

Date: 06/09/2018
Dear Advisory Committee on Heritable Disorders in Newborns and Children,

I am writing to express my support for the inclusion of congenital cytomegalovirus (cCMV) as a part of the Recommended Uniform Screening Panel (RUSP). I am Professor of Psychology at Utah State University and the founding Director of the National Center for Hearing Assessment and Management (NCHAM). NCHAM has been funded since 1994 by HRSA’s Maternal and Child Health Bureau to be the National Technical Resource Center for Newborn Hearing Screening and Intervention Programs. In that capacity we work closely with all state-based Early Hearing Detection and Intervention (EHDI) programs in providing support, training, and technical assistance for the operation and improvement. We have extensive experience on issues and evidence related to implementing and improving the efficacy of EHDI programs. Because of my work for the past 30 years in the implementation and refinement of newborn hearing screening programs, I am very familiar the newborn screening procedures. I have seen the benefits of appropriate screening and the negative consequences of inappropriate screening. I was the principal investigator for the Rhode Island Hearing Assessment Project which figured prominently in the recommendation of the National Institutes of Health Consensus Development Conference on Early Identification of Hearing Impairment in Infants and Young Children. Based on that experience, I understand the importance of having evidence about costs and outcomes before recommending population-based screening for any condition.

However, it is also important to recognize that there are many different types of useful evidence. At the time that NIH recommended in 1993 that all newborns be screened for hearing loss, there were no randomized controlled trials and there were not many programs actually doing universal newborn hearing screening. But there was enough experience with newborn hearing screening procedures and enough knowledge about the natural course of childhood hearing loss to be confident that newborn hearing screening was feasible and could be done cost-efficiently. There was also a wealth of experienced and clinical judgement that substantial benefits were associated with earlier identification of congenital hearing loss.

As more and more programs began implementing newborn hearing screening programs based on the NIH recommendations in 1993, the methods and procedures became more efficient and effective, and the evidence for benefits became more compelling. Some people still argued that it was inappropriate to recommend universal newborn hearing screening until randomized trials could be completed so that the evidence would be more definitive. However, it is clear in retrospect that there was already sufficient evidence about the feasibility and benefits to justify moving forward and that the progress of the next 15 years happened largely because more and more programs began implement newborn hearing screening programs.

I believe we are at a similar point in time with cCMV. Even though only a few programs have implemented cCMV screening programs, there is enough evidence about the success of those programs, coupled with data about consequences of not identifying cCMV early, that it is clear that newborn cCMV screening programs will have substantial benefits for children and families. Although cCMV contributes to many other negative outcomes, the benefit associated with being able to identify many more children with hearing loss (particularly late-onset hearing loss) are enough to justify the inclusion of cCMV on the RUSP. I hope you will give serious consideration to including cCMV as a part of the RUSP.

Sincerely,

Karl R. White
Director, National Center for Hearing Assessment and Management
Emma Eccles Jones Endowed Chair in Early Childhood Education
Professor of Psychology
Utah State University
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Date: 06/11/2018

Name: Karl White

Position: Director, NCHAM

Please describe below any relationships, transactions, positions you hold (volunteer or otherwise), or circumstances that you believe could contribute to a conflict of interest:

☑️ I have no conflict of interest to report.

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1. 

2. 

3. 

I hereby certify that the information set forth above is true and complete to the best of my knowledge.

Signature: Karl White

Date: 06/11/2018