cCMV positive, what is next? Are we prepared?

Suresh Boppana
University of Alabama at Birmingham

CMV Public Health and Policy Conference
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DISCLOSURES

Research support from GSK biologics

Do not intend to discuss unlabeled or commercial products other than issues related to treatment of infants with congenital CMV infection
# The CHIMES study Investigators and Personnel

**Sponsor:** NIDCD

**Children and their families**

<table>
<thead>
<tr>
<th>University of Alabama at Birmingham</th>
<th>University of Mississippi Medical Center</th>
<th>Cincinnati Children’s Medical Center</th>
<th>University of Texas Southwestern Medical Center</th>
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<tbody>
<tr>
<td>Suresh Boppana</td>
<td>April Palmer</td>
<td>David Bernstein</td>
<td>Pablo Sanchez</td>
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<td>Karen Fowler</td>
<td>Kathy Irving</td>
<td>Dan Choo</td>
<td>Gregory L. Jackson</td>
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<td>William Britt</td>
<td>Delia Owens</td>
<td>Kurt Schibler</td>
<td>Asuncion Mejias</td>
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<td>Mirjam Kempf</td>
<td>Suzanne Roark</td>
<td>Kate Catalanotto</td>
<td>Peter S. Roland</td>
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<td>David Kimberlin</td>
<td>Mindy Ware</td>
<td>Linda Jamison</td>
<td>Oscar Rosado</td>
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<td>Faye McCollister</td>
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<td>Patty Kern</td>
<td>Angela G. Shoup</td>
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<td>Shannon Ross</td>
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<td>Maureen Sullivan-Mahoney</td>
<td>Elizabeth K. Stehel</td>
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<td>Masako Shimamura</td>
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<td>Stacie Wethington</td>
<td>Audra Stewart</td>
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<td>Nitin Arora</td>
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<td>Cathy Boatman</td>
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<td>Amita Bey</td>
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<td>Jessica Esquivel</td>
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<td>Belinda Blackstone</td>
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<td>Kathy Katz-Gaynor</td>
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<td>Valisa Brown</td>
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<td>April Liehr</td>
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<td>Alice Brumbach</td>
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<td>Kristine E. Owen</td>
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<td>Nazma Chowdhury</td>
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<td>David Sosa</td>
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<td>Steven Febres-Cordero</td>
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<td>Lizette Torres</td>
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<td>Noelle Le Lievre</td>
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<td>Emily Mixon</td>
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<td>Zdenek Novak</td>
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<td>Misty Purser</td>
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<td>Julie Woodruff</td>
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**St Peters University Hospital**
- Robert Tolan
- Kristina Feja
- Maria Class
- Marci Schwab

**Carolinas Medical Center**
- Amina Ahmed
- Edie Cox
- Julie Courtney
- Nubia Flores
- Molly Ricart
- Lisa Schneider
- Jennifer West

**Pittsburgh Children’s Hospital**
- Marian Michaels
- Diane Sabo
- Jena Colaberardino
- Noreen Jeffrey
- Anne Maracek
- Gretchen E. Probst
- Cheryl Rosenberg
Agenda

• Safest and most appropriate course of treatment for babies diagnosed with CMV

• How to build the capacity of providers to diagnose and care for infants with cCMV?
Treatment and interventions for CMV-infected infants

- Early intervention for hearing loss
  - Amplification and/or cochlear implantation

- Other individualized interventions and treatments for children with significant neurologic involvement
  - Evaluation and management in a multidisciplinary clinic

- Antiviral therapy
  - Only studied in symptomatic infants
  - Treatment trials planned in infants with asymptomatic infection
Early intervention for hearing loss

• Undetected hearing loss (even mild or unilateral) has serious negative consequences on speech, language, social & academic development

• Dramatic benefits associated with early identification of hearing loss (Vohr et al. 2008; Yoshinaga-Itano et al, 1998)

• Families of infants with all degrees of HL should be offered Early Intervention

• Amplification can be provided as early as 1 month of age

www.infanthearing.org
Effects of age of identification on language development

- Prospective, longitudinal study of early-identified infants

- 30 children with mild-profound hearing loss (HL) compared to 96 normal hearing (NH) controls

- Children identified $< 3$ months and treated had stronger language development at 12-16 months than those identified $> 3$ months

Vohr et al., 2008
Early identification on language development

Language Quotients at Three Years of Age by Age of Identification Category

Ages of Identification

Language Quotient Score

Average range

Yoshinaga-Itano et al. 1998
Antiviral treatment

• Most common sequela is hearing loss
  • 10-15% of infants with asymptomatic infection
  • 40-50% of infants with symptomatic infection

• Other sequelae
  • Cognitive, motor, and visual deficits, seizures, and neurodevelopmental delay

• Controlled trials of antiviral therapy
  • Only performed in infants with SYMPTOMATIC infection
  • Primary outcome - improvement in hearing

• Ganciclovir or oral equivalent valganciclovir
Treatment of congenital CMV infection

A Phase III, Randomized, Placebo-Controlled, Blinded Investigation of Six Weeks vs. Six Months of Oral Valganciclovir Therapy in Infants with Symptomatic Congenital Cytomegalovirus Infection

• To compare the impact on hearing outcomes
• To compare the impact on neurologic outcomes
• To compare the safety profile of six weeks versus six months of antiviral therapy with valganciclovir
• To correlate change in whole blood viral load with hearing and neurologic outcomes

• 109 subjects enrolled
• All subjects received 6 weeks of open-label oral valganciclovir therapy, after which time they were randomized to continued oral valganciclovir for the next four and a half months or to a matching placebo.

Kimberlin et al., NEJM 2015;372:933-43
Valganciclovir treatment trial
6 weeks vs 6 months in symptomatic cCMV

Kimberlin et al., NEJM 2015;372:933-43
Valganciclovir Treatment Study
6 weeks vs. 6 months in symptomatic congenital CMV

- Trend towards improved developmental outcomes in 6 month treatment group
- Grade 3-4 neutropenia less frequent than with IV ganciclovir (21%)
- ALT and AST elevations seen at months 4 and 5

Kimberlin et al. NEJM, 2015
### Definition of symptomatic cCMV

**CASG Studies:**
- Thrombocytopenia
- Petechiae
- Hepatomegaly
- Splenomegaly
- IUGR
- Hepatitis (elevated transaminases and/or direct bilirubin)
- CNS involvement
  - Microcephaly, radiographic abnormalities, abnormal CSF indices, chorioretinitis, hearing deficits by ABR

**CHIMES Study:**
- Generalized petechiae
- Purpura
- Hepatomegaly
- Splenomegaly
- Jaundice with Direct Bilirubin >3
- CNS abnormalities
  - Microcephaly, seizures, focal or generalized neurological deficits
  - Chorioretinitis
Symptomatic congenital CMV is a spectrum

- Hearing loss risk increases with increasing severity of symptoms
- Asymptomatic (10-15%) < Petechiae only (22%) < Transient (37%) < Neurologic (60%)
Symptomatic congenital CMV
- Moderate to severe symptomatic disease
- Readily identified by clinical exam, typically have >1 symptom
- Thrombocytopenia, petechiae, hepatomegaly, splenomegaly, IUGR, hepatitis, and/or CNS involvement

Mildly symptomatic congenital CMV
- One or two manifestations of disease and findings mild in scope
- e.g. mild hepatomegaly, mild thrombocytopenia, isolated petechiae

Asymptomatic congenital CMV with isolated SNHL
- No abnormalities to suggest congenital infection
- SNHL- confirmed by diagnostic testing (NOT failed NBHS)

Asymptomatic congenital CMV
- No abnormalities to suggest congenital infection and normal hearing at birth
Consensus recommendations for treatment of congenital CMV

- Symptomatic congenital CMV disease (Moderate to severe disease)
  - Only group recommended because it is the only population in which there is randomized, controlled data proving benefit

- 6 month of oral valganciclovir 16mg/kg/DOSE bid
- Treatment should be initiated within the first month of life
- Monitor neutrophil counts and transaminases regularly
- Viral load monitoring not indicated (no correlation with treatment effect or clinical outcome)
- Treatment duration - 6 months
Consensus Recommendations for Treatment of Congenital CMV

- Antiviral therapy NOT routinely recommended for mildly symptomatic congenital CMV disease
- Antiviral therapy NOT routinely recommended for asymptomatic congenital CMV with isolated SNHL
- Antiviral therapy NOT recommended for babies with asymptomatic congenital CMV
- Antiviral therapy NOT routinely recommended in infants <32 weeks gestational age
Evaluation and follow-up of infants with symptomatic cCMV

At Birth
- Thorough physical exam to assess for growth parameters, HSM, petechiae, purpura
- CBC, LFTs
- Neuroimaging - sonography or MRI
- Ophthalmologic examination
- Hearing testing-age appropriate (NOT hearing screen)

Follow-up
- Hearing testing every 6 months until age 3, then annually until adolescence
- Developmental assessments in some children
Evaluation and follow-up of infants with asymptomatic cCMV
## Asymptomatic cCMV

<table>
<thead>
<tr>
<th>Lab/Neuroimaging</th>
<th># abnormal (%, Exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt;100,000*</td>
<td>7/105 (6.7%, 2.7 – 13.2)</td>
</tr>
<tr>
<td>ALT &gt;80 U/L</td>
<td>0/55 (0%)</td>
</tr>
<tr>
<td>Direct Bilirubin &gt;3.0mg/dL</td>
<td>0/149 (0%)</td>
</tr>
<tr>
<td>CNS Calcifications**</td>
<td>7/104 (6.7%, 2.8 – 13.4)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>0/77 (0%)</td>
</tr>
</tbody>
</table>

*Among the infants with Platelets<100,000, 7/7 were in the NICU with a mean gestation age of 32.7 wks (±4.6), all < 2500 g

**3 < 37 wks; 2 with petechial rash only on face
Asymptomatic cCMV
Association between calcifications and SNHL

<table>
<thead>
<tr>
<th></th>
<th>SNHL</th>
<th>Normal hearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcifications</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>No Calcifications</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>94</td>
</tr>
</tbody>
</table>

P=0.14 Fisher’s exact test

HL – 35 wk, 2170 g; 39 wk, 2809 g
## Eye abnormalities in infants with cCMV

<table>
<thead>
<tr>
<th>Eye Abnormality</th>
<th>Symptomatic (n=42)</th>
<th>Asymptomatic (n=83)</th>
<th>Control (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral Optic Atrophy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral Optic Atrophy</td>
<td>3 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unilateral Macular Scar</td>
<td>3 (7%)</td>
<td>2 (2.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral Macular Scar</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unilateral Peripheral Retinal Scar</td>
<td>3 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral Peripheral Retinal Scar</td>
<td>3 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total with retinal scars</td>
<td>9 (21%)</td>
<td>2 (2%)*</td>
<td>0</td>
</tr>
<tr>
<td>Mod to severe visual impairment</td>
<td>9 (21%)</td>
<td>0*</td>
<td>0</td>
</tr>
</tbody>
</table>

One patient with active chorioretinitis - Symptomatic

“screening of asymptomatic patients at birth may not be necessary”

*Coats et al JAAPPOS, 2000 Apr;4(2):110-6*
Evaluation and follow-up of infants with asymptomatic cCMV

At Birth
- Thorough physical exam to assess for symptoms
- Diagnostic audiological testing (OAE and ABR)
- Ophthalmologic examination (at some point)
- Laboratory evaluation (CBC, LFTs)?
- Neuroimaging?
Identification of infants with cCMV

- Based on clinical findings – a proportion of symptomatic infants will be identified.

- Targeted Screening – testing of infants referred on NHS for CMV.

- Universal CMV screening.
CMV Legislation

### CHIMES Study

**Targeted Approach to CMV Screening**

#### Hearing Screening Refers by CMV Status

<table>
<thead>
<tr>
<th>CMV Screen</th>
<th>Hearing Refer* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMV Positive (n=443)</strong></td>
<td>7.0% (4.8 – 9.8%)</td>
</tr>
<tr>
<td><strong>CMV Negative (n=99,500)</strong></td>
<td>0.9% (0.9 – 1.0%)</td>
</tr>
</tbody>
</table>

*P < 0.0001

*Fowler et al. manuscript under review*
# CHIMES Study

## Targeted Approach

Hearing Screening Refers by CMV Status & Nursery

### WBN

<table>
<thead>
<tr>
<th>CMV Screen</th>
<th>Hearing Refer* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV Positive (n=400)</td>
<td>5.5% (3.5 – 8.2%)</td>
</tr>
<tr>
<td>CMV Negative (n=96,151)</td>
<td>0.8% (0.7 – 0.9%)</td>
</tr>
</tbody>
</table>

P < 0.0001

### NICU

<table>
<thead>
<tr>
<th>CMV Screen</th>
<th>Hearing Refer* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV Positive (n=43)</td>
<td>20.9% (10.0 – 36.0%)</td>
</tr>
<tr>
<td>CMV Negative (n=3,166)</td>
<td>5.1% (4.4 – 5.9%)</td>
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</table>

P < 0.0001
### CHIMES Study
Possible Targeted Approach

<table>
<thead>
<tr>
<th>Congenital CMV Infection &amp; SNHL at Birth</th>
<th>Newborn Hearing Screen</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Refer</td>
</tr>
<tr>
<td>SNHL</td>
<td>20</td>
</tr>
<tr>
<td>NO SNHL</td>
<td>11</td>
</tr>
</tbody>
</table>
### CHIMES Study

#### Possible Targeted Approach

**Congenital CMV Infection & SNHL at Birth**

<table>
<thead>
<tr>
<th></th>
<th>Refer</th>
<th>Pass</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNHL</strong></td>
<td>20 (65%)</td>
<td>15 (3.6%)</td>
</tr>
<tr>
<td><strong>NO SNHL</strong></td>
<td>11</td>
<td>397</td>
</tr>
</tbody>
</table>

Newborn hearing screening identified 57% (95% CI, 39% - 74%) of CMV-Related SNHL in the newborn period.
Universal newborn CMV screening

- Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (chartered in 2003)
  - Evidence review evaluated based on key questions of 3 broad categories
    - Natural history, case definition, incidence/prevalence known?
    - Screening test or test algorithm for the condition with sufficient analytic validity?
    - Has the clinical validity of screening test in combination with diagnostic test been determined?
    - What is the clinical utility of the screening test (benefits/harms)?
    - Is there direct evidence that screening leads to improved outcome?
    - How cost effective is the screening, diagnosis and treatment?

Genet Med, 2010
Universal newborn CMV screening

Screening test or test algorithm for the condition with sufficient analytic validity?

Diagnosis in newborn DBS testing

- **Interest in DBS**
  - Collected from all newborns
  - Easier to integrate into existing screening programs
  - Many initial studies showed high sensitivity

- **Potential problems**
  - Viral load in blood is low and variable
  - Chronic intrauterine infection
  - Negative blood PCR in some symptomatic infants
  - Amount of available DBS may be limited
20,448 Newborns screened

11,422 Screened by Saliva rapid culture and single-primer DBS PCR

11,341 Negative No further testing

81 CMV Positive
71 Rapid culture
26 DBS Positive

60 CMV positive
59 Rapid culture
17 DBS PCR

9026 screened by Saliva rapid culture and 2-primer DBS PCR

8983 Negative No further testing

43 CMV Positive
43 Rapid culture
14 DBS PCR

32 CMV positive
32 Rapid culture
11 DBS PCR

3 CMV negative
3 Rapid culture
1 DBS PCR

Boppana et al. JAMA 2010;303:1375-1382
Congenital CMV infection
Diagnosis in newborns

- Saliva PCR
  - Large amounts of virus shed in saliva
  - Saliva rapid culture considered the gold standard
  - Easy and noninvasive sample collection
  - No need for DNA extraction
  - Dried saliva specimens are easier to store and transport
## Table 2. Real-Time Polymerase-Chain-Reaction (PCR) Assays of Liquid- and Dried-Saliva Specimens, vs. Rapid Culture, Used to Screen for Congenital Cytomegalovirus Infection.

<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>0.03 (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>

Universal newborn screening for cCMV

Has the clinical validity of screening test in combination with diagnostic test been determined?

“...ability of the screening test to detect as many as possible affected individuals... and to minimize the occurrence of false positives.”

## Screening Saliva False Positives by Race & Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th># False Pos.</th>
<th>N</th>
<th>False Pos %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>6</td>
<td>23,857</td>
<td>0.03%</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>5</td>
<td>32,189</td>
<td>0.02%</td>
</tr>
<tr>
<td>White, Non-Hispanic</td>
<td>10</td>
<td>36,962</td>
<td>0.03%</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>4,150</td>
<td>0.02%</td>
</tr>
<tr>
<td>Multiracial</td>
<td>1</td>
<td>2,408</td>
<td>0.04%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>23</strong></td>
<td><strong>99,622</strong></td>
<td><strong>0.02%</strong></td>
</tr>
</tbody>
</table>

From CDC breastfeeding webpage: 2008 racial and ethnic disparities in breastfeeding in the U.S.

Breastfeeding rates: 58.9% for blacks, 75.2% for whites, 80.0% for Hispanics

*Accessed April 10, 2015 http://www.cdc.gov/breastfeeding/resources/breastfeeding-trends.htm*

False Positive: confirmed cases **cCMV- 1:17**
False Positive: confirmed cases **metabolic disorders 56:1**

Cost-effectiveness of newborn CMV screening

Soren Gantt, Francois Dionne, Fred Kozak, Oran Goshen, David Goldfarb, Albert Park, Suresh Boppana, and Karen Fowler
Estimated costs and savings from cCMV screening*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Targeted screening</th>
<th>Universal screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat if symptoms at birth only</td>
<td>Treat if symptoms or SNHL at birth</td>
</tr>
<tr>
<td>Direct (costs) savings</td>
<td>$0.90</td>
<td>$4.95</td>
</tr>
<tr>
<td>Net (costs) savings**</td>
<td>$10.66</td>
<td>$27.31</td>
</tr>
</tbody>
</table>

* Assuming $10/test
** Includes loss of productivity due to hearing loss
Cost-effectiveness of newborn CMV screening

Summary

• Newborn cCMV screening appears cost-effective under a wide range of assumptions

• Even assuming no antiviral treatment, screening is essentially cost-neutral when costs related to loss of productivity are included
  • Substantial savings due to earlier identification and directed care for late-onset hearing loss

• When modestly effective antiviral treatment is assumed, screening results in cost savings

• Universal screening incurs greater direct costs, but greater net savings, than targeted screening under all scenarios
Cost-effectiveness of newborn CMV screening

Limitations

- Sensitivity analyses performed for selected parameters but assumptions may be inaccurate
- Costs might be higher if health care utilization due to screening is greater than expected
  - Indiscriminate testing (e.g., brain MRI) or treatment
- Savings might be substantially higher
  - If costs related to cognitive impairment or other cCMV-related morbidity were included
  - If antiviral treatment is found to be effective for late-onset SNHL
  - As the cost of molecular diagnostic assays decrease

Universal newborn CMV screening

1. Natural history, case definition, incidence/prevalence known? ✓
2. Screening test or test algorithm for the condition with sufficient analytic validity? ✓
3. Has the clinical validity of screening test in combination with diagnostic test been determined? ✓
4. What is the clinical utility of the screening test (benefits/harms)? ±
5. Is there direct evidence that screening leads to improved outcome? ±
6. How cost effective is the screening, diagnosis and treatment? ✓
Awareness of CMV
Building capacity

- Increased awareness of maternal and congenital CMV

- Develop standard guidelines for the evaluation of infants with asymptomatic cCMV

- Generate data to provide evidence for antiviral treatment of infants with isolated SNHL

- Resources to care for the increased number of children with cCMV identified on targeted or universal screening