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## Congenital Cytomegalovirus (CMV) Update: Diagnosis & Management

**Planners and Content Reviewers for this activity:**

Did provide disclosure information.

Dr. Suresh Boppana discloses a financial relationship with Merck, Inc. for consulting as a member of the CMV Vaccine Advisory Committee.

Dr. Shannon Ross discloses a financial relationship with Merck as a consultant related to Congenital CMV.

All others have no relevant financial arrangements or affiliations with commercial interests.

***Commercial Support:***

This activity received no commercial support.

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Congenital Cytomegalovirus (CMV) Update: Diagnosis & Management

**Speakers: Karen Fowler, DrPH, Rebecca Oldham and Jasmine Webster**

Do not intend to discuss commercial products or services.

Do not intend to discuss non-FDA approved uses of products/providers of services.

Dr. Fowler discloses a financial relationship with Merck as a consultant related to Congenital CMV and with Meridian and Natus for webinars on Congenital CMV.

All other speakers have nothing to disclose.

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# Congenital Cytomegalovirus (CMV) Update:

## Diagnosis & Management

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Placeholder slide for parent #1

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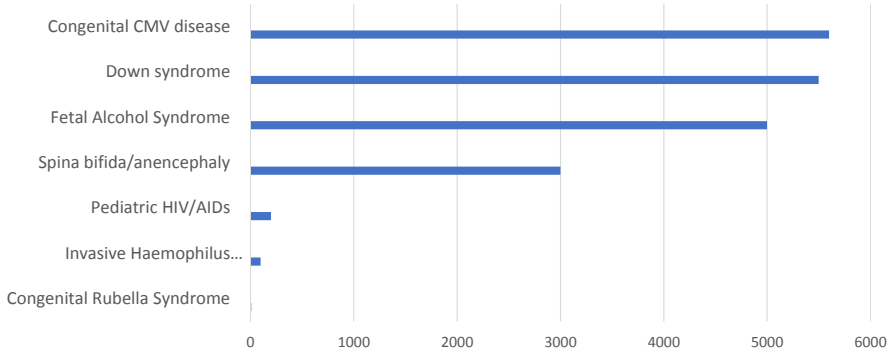
## Disease burden of congenital CMV infection




**Annual Number of US Children with Long-term Sequelae**

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The cost of congenital CMV infection is more than $1 billion in direct medical care each year in the US

(Institute of Medicine, 2000)

Leading cause of non-genetic hearing loss

**Sequelae:**

- Neurodevelopmental delay
- Motor delay
- Vision loss
- Seizures
- Cerebral palsy
- Fetal or infant death

## CMV Facts

- Common
- Herpes family
- Over 50% seroprevalence in women of child-bearing age
- Seroprevalence increases with age
- Seroprevalence close to 100% in developing countries

**High seroprevalence associated with:**

- Caring for young children
- Crowded living conditions
- Low socioeconomic level
- Sexual activity

## Transmission

- Saliva
- Nasal secretions
- tears
- Urine
- Blood
- Semen/ vaginal fluids
- Breastmilk

Exposure is mainly through contact with young children or sexual activity.

Most Healthy children and adults do not experience symptoms when infected with CMV.

When they do have symptoms:

- Influenza-like
- Fever
- Myalgia
- Pharyngitis

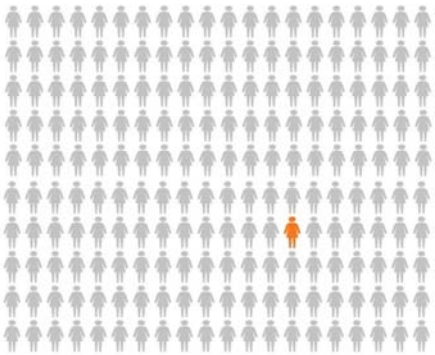
For immunocompromised & the developing fetus, CMV can be life-threatening.

## Prevalence of congenital CMV: 1 in 200 live births

**1 in 5 neonates with congenital CMV are symptomatic**

**Symptomatic infants:**

- **Much higher risk for adverse long-term outcomes**
  - **50% will develop one or more of:**
  - **Sensorineural hearing loss (SNHL)**
    - **Cognitive disability**
    - **Motor delays or disability**



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10 -15% of newborns with **asymptomatic** congenital CMV **will** develop long-term sequelae

10 % will develop SNHL

5% will have delays & motor defects

2% will have visual disturbances

Since there are no predictors of outcome, monitor & follow-up all CMV-positive newborns

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Overall prevalence of congenital CMV infection = 4.5 per 1000 live births (95% CI, 4.1 – 4.9/1000)

| CHIMES Study | N | Congenital CMV Infection (/1000) |
|---|---|---|
| Black Infants | 24,100 | 9.5/1000 |
| Non-Hispanic White Infants | 37,219 | 2.7/1000 |
| Hispanic White Infants | 32,310 | 3.0/1000 |
| Asian Infants | 4,166 | 1.0/1000 |
| Multiracial Infants | 2,436 | 7.8/1000 |

*Data from the NIDCD-funded CHIMES Study*
*Fowler et al. Racial and Ethnic Differences in the Prevalence of Congenital Cytomegalovirus Infection J Peds 2018*

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## Prevalence of Congenital CMV Infection

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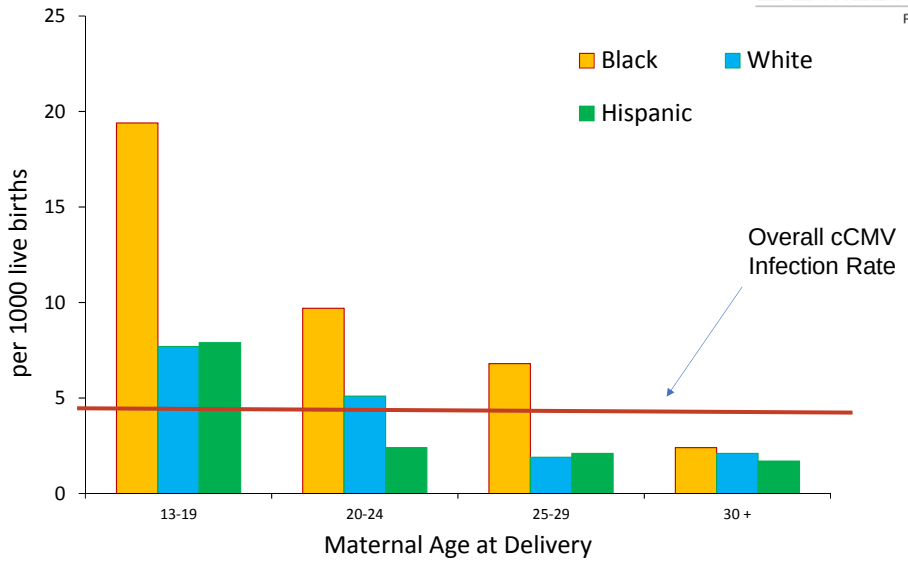


The CHIMES Study

*Data from the NIDCD-funded CHIMES Study &*
*Fowler et al. Racial and Ethnic Differences in the Prevalence of Congenital Cytomegalovirus Infection J Peds 2018*

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## Prevalence of Congenital CMV Infection

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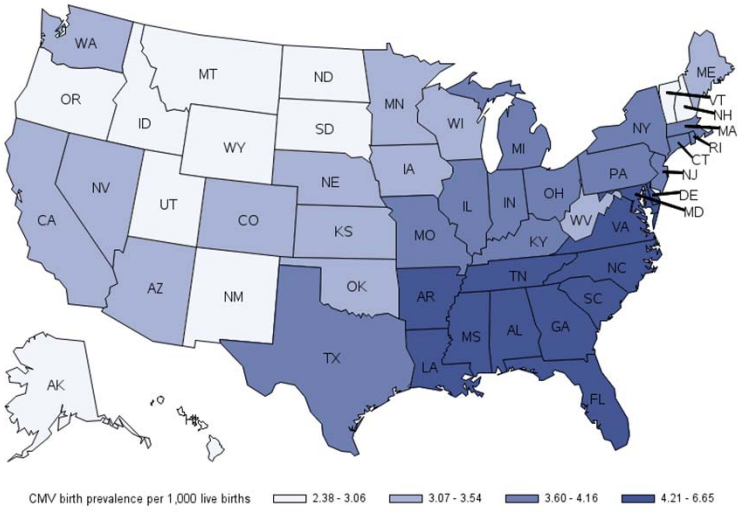


*Fowler et al. Racial and Ethnic Differences in the Prevalence of Congenital Cytomegalovirus Infection J Peds 2018 combined with state birth rates (developed by Dr. Tatiana Lanzieri)*

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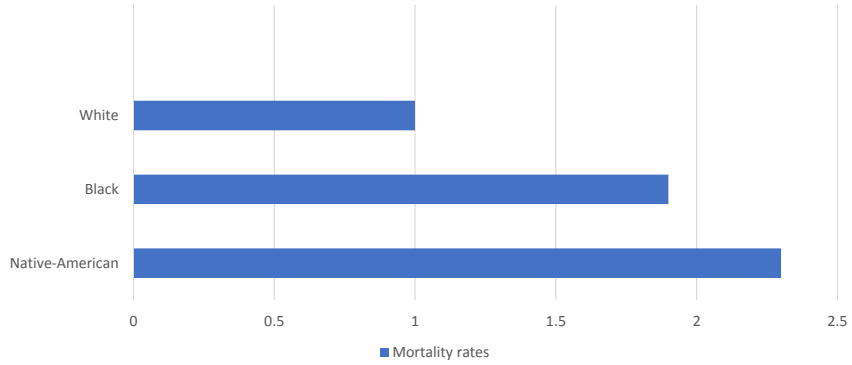
## Infant mortality due to congenital CMV

**Approximately 400 infants die annually from CMV**

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## Maternal Infection & Intrauterine Transmission

- Primary infection- first exposure to CMV
- Non-primary- recurrence or reinfection from a different strain of the virus in a woman with a previous CMV infection

- Infants born to mothers with primary infection are most at risk of transmission
- 75% of all c CMV cases are infants born to mothers with non-primary infections

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## Maternal Infection & Intrauterine Transmission

- 30% vertical transmission rate following primary infection
- No difference between primary and non-primary infection for:
  - Frequency of symptomatic infection
  - Rate of sensorineural hearing loss

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## At-risk Population

- ❑ Women who care for young children under 3 years of age:
  - Women with toddlers especially those attending daycare
  - Women working in childcare centers
  - Anyone in close contact with someone recently infected with CMV

- 30% of children < 3 years are infected with CMV
- Virus in urine & saliva in high concentrations up to 24 months

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# Approximately 30,000 infants are born with congenital CMV annually in the US

10-15% symptomatic (about 4000 infants)

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## Congenital CMV infection in the Newborn

No Clinical Manifestations → ~ 90% Asymptomatic

Disseminated Disease
- Generalized petechial rash
- Purpuric rash
- Jaundice
- Hepatosplenomegaly
- Lethargy

CNS Abnormalities
- Seizures
- Microcephaly (< 5%tile)
- Retinitis / optic atrophy
- Other focal or generalized neurologic deficits

→ ~10% Symptomatic

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## Infants with Symptomatic Congenital CMV

- 50 % are small for gestational age
  30% are premature

### Laboratory findings

- Elevated transaminases
- Hyperbilirubinemia
- Thrombocytopenia

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## Infants with Symptomatic Congenital CMV

**Radiographic findings**

❖ Intracranial calcifications
❖ Ventricular dilatation
❖ Cysts
❖ Vasculopathy

Symptomatic neonates are at higher risk for adverse neurodevelopmental sequelae

Mortality rate for symptomatic newborns is between 5 & 10%

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# CMV Diagnosis of the Newborn

PCR of saliva, urine, or both
Must be done within **3 weeks** of birth.

Saliva is the preferred method due to ease of collection

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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## Saliva Specimens for Newborn Screening

- Saliva- easy to collect
- Breastfeeding does not contribute to false-positive results (in first wks of life)
- Overall false-positive rate of <0.03% in the CHIMES study so unlikely breast feeding impacted saliva results (*Ross et al. J Infect Dis 2018*).
- However, all positive saliva PCR results should be confirmed by 3 weeks of age by urine PCR.

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# Prevention of Vertical Transmission and Treatment of the Fetus

- Possibly years before efficacious vaccine is available
- Routine use of hyperimmunoglobulin to treat pregnant women with primary CMV is NOT recommended.
- Routine use of antiviral therapy to treat or prevent fetal CMV infection is
- NOT recommended

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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## Definitions of congenital CMV infection and disease

### I. Moderate to severely symptomatic cCMV

- Multiple manifestations: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin) or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cCMV disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), chorioretinitis.

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

## Definitions of congenital CMV infection and disease

**II. Mildly symptomatic cCMV**

- Might occur with one or two isolated manifestations of cCMV 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, they can occur in isolation.

**III. Asymptomatic cCMV with isolated sensorineural hearing loss**

- No apparent abnormalities to suggest cCMV, but SNHL (≥21 decibels)

**IV. Asymptomatic cCMV**

- No apparent abnormalities to suggest cCMV, and normal hearing

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

## Consensus Recommendations for Treatment of cCMV

- **Newborns with moderate to severe symptomatic congenital CMV disease**
  - Only group recommended for treatment (at this time) 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
  - Treatment duration not to exceed 6 months

❖ The goal of treatment is to improve audiological or developmental outcomes

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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## Monitor laboratory values during treatment

- Absolute neutrophil count followed weekly for 6 weeks, then at 8 weeks, then monthly for the duration of treatment
- Transaminase monitored monthly throughout treatment
- Viral load monitoring not indicated (no correlation with treatment effect or clinical outcome)

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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Antiviral therapy NOT routinely recommended for asymptomatic newborns with isolated SNHL or newborns with mild or transient symptomatic congenital CMV infections

NCT03107871 Randomized Controlled Trial of Valganciclovir for Cytomegalovirus Infected Hearing Impaired Infants: ValEAR Trial – Albert Park MD, PI, University of Utah, funded by the National Institute on Deafness and Other Communication Disorders (NIDCD); expected end date July 2024

Antiviral therapy should NOT be administered to newborns with asymptomatic infection

NCT03301415 A Phase II, Single Stage, Single-Arm Investigation of Oral Valganciclovir Therapy in Infants with Asymptomatic Congenital Cytomegalovirus Infection – David Kimberlin MD, PI, University of Alabama at Birmingham, funded by the National Institute of Allergy and Infectious Diseases (NIAID); expected end date December, 2024

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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## Outcome following Congenital CMV infection

| Symptomatic Infants | Asymptomatic Infants |
|---|---|
| 40-60% permanent sequelae | 10-15% permanent sequelae |
| 40-50% Hearing Loss | 10-15% Hearing Loss |
| 20-50% Cognitive Impairment | 3-5% Cognitive Impairment |
| 5-20% Retinitis | 1-3% Retinitis |
| 5-10% Cerebral Palsy | |

*UAB Data; Pass et al. 1981; Fowler, et al. 1999; Dollard, et al. 2007*

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## SNHL in Infants with cCMV Infection

- Unilateral or Bilateral
- Ranges from isolated high frequency to profound
- Degree loss of loss can progress or fluctuate with time
- Late onset hearing loss occurs throughout childhood into adolescence (Median age for late onset hearing loss in symptomatic children is 36 mo and for asymptomatic children the median age is 44 mos)

Sensorineural hearing loss (SNHL) at birth =
8.9% (95% CI, 6.3% – 12.2%)

Total SNHL (at birth & late onset) in cohort =
12% (95% CI, 9.0% – 15.7%)

*Fowler et al. in prep*

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# SNHL in Infants with cCMV Infection

Targeted cCMV Screening

Selection of a specific group of infants who are considered at higher risk for cCMV – such as a NICU population or infants who do not pass (fail) their newborn hearing screening.

This approach only identifies a limited number of cCMV infants who may have CMV (like risk criteria based newborn hearing screening that existed before universal newborn hearing screening)

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# SNHL in Infants with cCMV Infection

Targeted cCMV Screening

**Hearing Screening Refers by CMV Status**

| CMV Screen | Hearing Refer* % (95% CI) |
|---|---|
| CMV Positive (n=443) | 7.0% (4.8 – 9.8%) |
| CMV Negative (n=99,502) | 0.9% (0.8 – 1.0%) |

P < 0.0001

*Fowler et al. Pediatrics 2017*

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# SNHL in Infants with cCMV Infection

Targeted cCMV Screening

## Congenital CMV Infection & SNHL at Birth

| | Newborn Hearing Screen | |
|---|---|---|
| | Refer | Pass |
| SNHL | 20 (65%) | 15 (3.6%) |
| NO SNHL | 11 | 397 |

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

*Fowler et al. Pediatrics 2017*

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# Importance of Early Intervention of Hearing Loss

Children with hearing loss face developmental delay in:

- Speech
- Language
- Learning

Early intervention and treatment mitigate effects of hearing loss on

- Linguistic development
- Social development
- Academic performance

Identify hearing loss early for timely diagnostic audiology follow-up and early intervention

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Offer follow up for **all** children with symptomatic and asymptomatic congenital CMV for early identification of auditory, visual or cognitive deficits

- Test hearing every 6 months the first 3 years of life
- Test hearing annually thereafter through age 19
- If hearing has changed, evaluate more frequently (every 3 months until stabilizes)
- Closely monitor children with identified hearing loss through adolescence for potential progression
- Refer children with identified hearing loss to pediatric audiology and early intervention programs

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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## Follow-up of Symptomatic Congenital CMV Children

**Vision**

- Newborns should undergo ophthalmologic examination soon after diagnosis & repeat as needed during the first year of life
- Annual ophthalmologic follow up visits through childhood

**Dental**

Encourage regular dental visits because congenital CMV is associated with hypoplasia and hypo-calcification of tooth enamel which leads to increased caries

*Demmler-Harrison, et al. Congenital cytomegalovirus infection: Management and outcome. UpToDate, 2018.*

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Placeholder slide for parent #2

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## Prevention of Congenital CMV Infection

There is some evidence that preventive measures are efficacious in reducing the risk of congenital CMV infection.

All pregnant women should be educated about congenital CMV infections and the following precautions:

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## Precautions for pregnant women & women planning to become pregnant

Messaging involves encouraging behaviors to reduce saliva sharing:

- Do not share food, drinks, or utensils used by young children.
- Do not put a child's pacifier or toothbrush in your mouth.
- Avoid contact with saliva when kissing a child.
- Thoroughly wash hands with soap and water for 20 seconds, especially after changing diapers, feeding a young child, or wiping a young child's nose or saliva.

*Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017*

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NATIONAL CMV FOUNDATION

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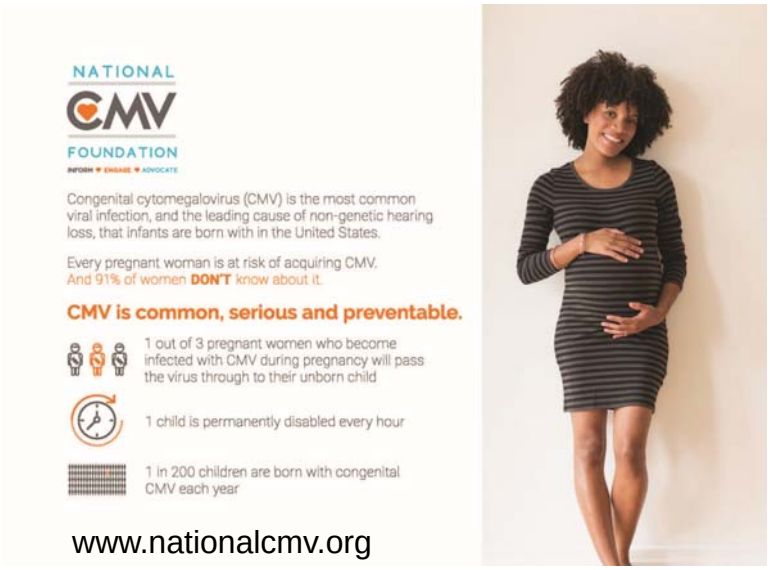
# Parent Advocacy

CMV Information/ Education

CMV Legislation



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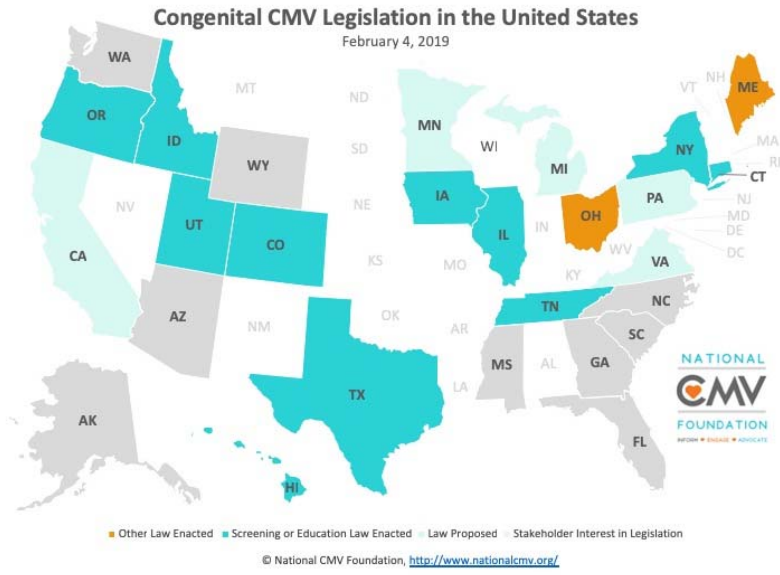
# Parent Advocacy

Legislation Components

CMV Education/ Awareness & Newborn CMV Screening



In summary, congenital CMV remains a common infection with 1 in 200 infants born with the infection in the US and over 5000 infants annually having long term sequelae following CMV infection. Recent studies on prevention, diagnosis and treatment provide newer data on identifying these infants earlier and lessening the long term effects of congenital CMV.

Thank you for viewing this CME activity.

The following slides provide useful links & additional information about congenital CMV infection.

## Useful Links & Information

- CMV Fact Sheet for Pregnant Women and Parents: https://www.cdc.gov/cmv/downloads/cmv-parents-fact-sheet-508.pdf
- The National CMV Foundation: https://www.nationalcmv.org/
- Educational downloads provided by the National CMV Foundation: https://www.nationalcmv.org/resources/educational-downloads
- Early Hearing Detection and Intervention (EHDI) information and contact information of state EHDI coordinators for children with CMV-related hearing loss: https://www.infanthearing.org/components/
- ICD-10 code for:
- 1. Congenital CMV: P35.1
- 2. Other specified hearing loss, unspecified ear: H91.8x9
- Medicaid reimbursement code- HCPCS code: 87496- Cytomeg. DNA amp probe

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## Collection & Testing for Congenital CMV Infection for Medical Providers

If you have an infant who failed their newborn hearing screening(s) for **either** ear, you should consider testing the infant for CMV. A hearing screening failure is **NOT** hearing loss but if you wait until hearing loss is confirmed later, it will be too late to evaluate whether CMV is the etiology of the hearing loss.

- Collect a sample **BEFORE** the infant is **21 days** old
  - Saliva or urine is acceptable. For a newborn still in the hospital, saliva is simpler to collect but should wait 1 to 2 hours after feeding to prevent possible breast milk contamination. Very few false positives occur with saliva in the 1st week of life. If saliva is positive it is important to repeat with urine for confirmation.
  - Before considering any treatment for an infant with congenital CMV, it is important to have more than 1 positive test.
  - Dacron swabs are used for saliva collection and may be placed in either a sterile sleeve or transport media. If using private companies for testing, they may provide the kit they prefer to use for saliva collection.

- Related CPT code **87496** (Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, amplified probe technique) if your local hospital provides PCR testing. Several private companies offer CMV PCR testing. The UAHSF Diagnostic Virology Lab offers CMV PCR testing, for more information contact: Jennifer Potter, 205 934 6750.

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## Recommended follow up for Symptomatic Infants

- 6 mos of oral valganciclovir (16 mg/kg/dose bid) with treatment initiated within first month of life for symptomatic infants with moderate to severe symptoms (evidence for treatment in infants with mild or transient symptoms is not available so not routinely recommended)
- Laboratory evaluations (CBC, LFTs)
- Neuroimaging
- Diagnostic audiologic evaluations every 6 months, until 3 years of age and annually thereafter to identify progressive or late onset hearing loss (hearing aids or cochlear implants considerations)
- Ophthalmologic Examinations
- Dental Examinations
- Early intervention enrollment for speech and hearing, physical therapy, etc.

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**Recommended follow up for Asymptomatic Infants**

- Diagnostic audiologic evaluations every 6 months, until 3 years of age and annually thereafter to identify progressive or late onset hearing loss (hearing aids and cochlear implants considerations)
- Antiviral treatment of asymptomatic infants with isolated sensorineural hearing loss is not routinely recommended. Current clinical trial underway to assess treatment in these infants (NCT03107871, estimated study completion date July 2024).
- Antiviral treatment of asymptomatic infants with normal hearing is not recommended. Current clinical trial underway to assess treatment in these infants (NCT03301415, estimated study completion date December 2024)
- Ophthalmologic Examination in the first year of life
- Early intervention enrollment for speech and language if needed
- Neuroimaging?? *(current studies ongoing)*

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