# Hearing Loss in Children with Congenital Cytomegalovirus (cCMV) Infection: Natural History and Antiviral Treatment

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# Disclaimer and Disclosure

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

- I have no conflicts of interest and no disclosures to make.

# Learner Outcomes

- Describe the prevalence and natural history of sensorineural hearing loss among children with cCMV infection identified as symptomatic or asymptomatic at birth.
- Discuss available evidence and knowledge gaps on short and long-term effects of antiviral treatment for children with cCMV-related sensorineural hearing loss (SNHL).

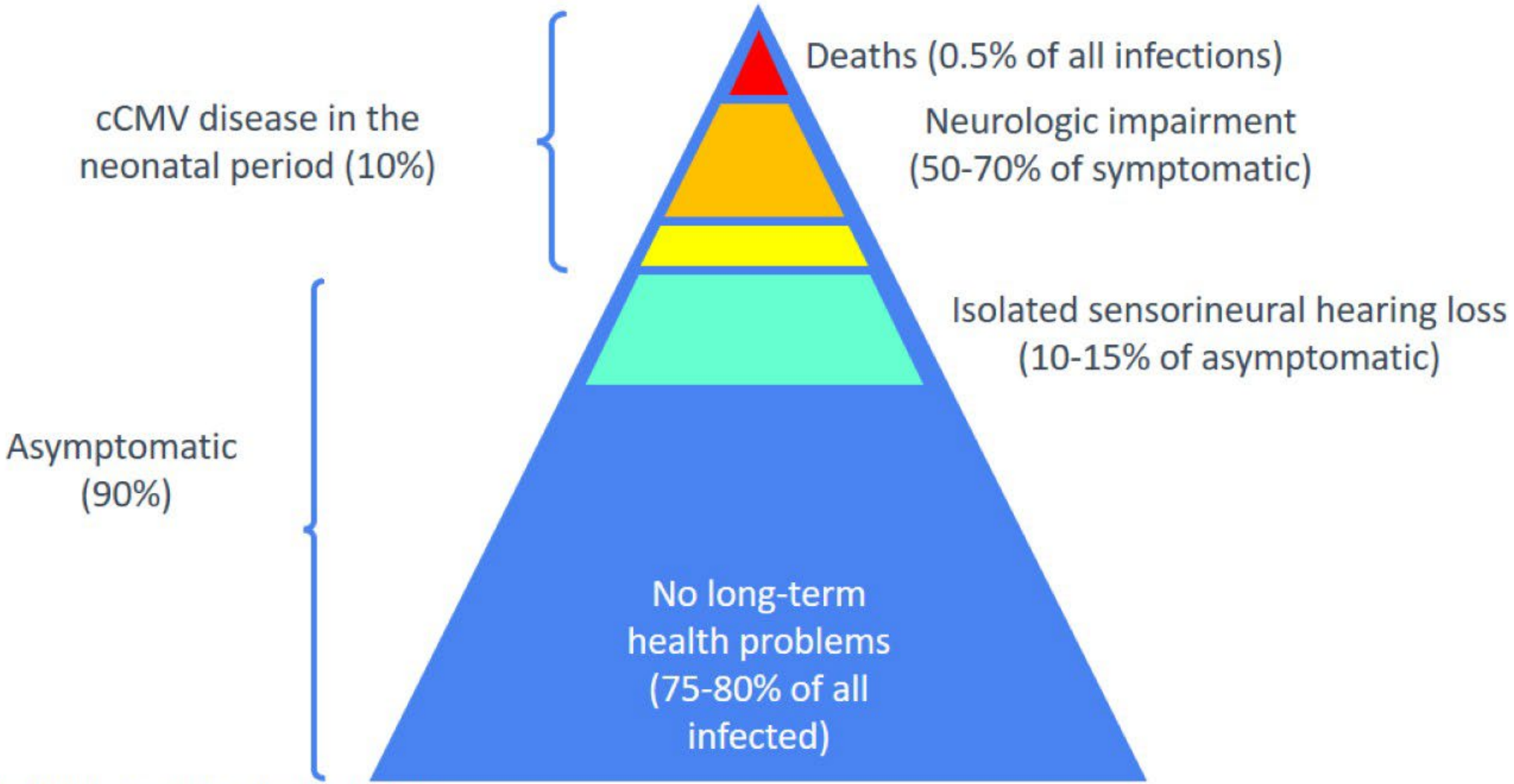
# cCMV Infection

- **Diagnosis**
  - Detection of CMV in urine, saliva, or blood in specimens collected within 21 days of life, by PCR or viral culture
  - Presence of CMV in specimens collected after 21 days of life cannot distinguish congenital from peri- or post-natal infection

# cCMV Disease

- **Neonatal signs**
  - Purpura/petechiae
  - Jaundice
  - Hepatosplenomegaly
  - Microcephaly
- **Sequelae**
  - Sensorineural hearing loss (SNHL)
  - Vision impairment
  - Intellectual disability
  - Cerebral palsy
  - Motor disability
  - Vestibular disorders

# cCMV occurs in 4.5 per 1,000 live births in the United States – 16,000 infected newborns in 2020*



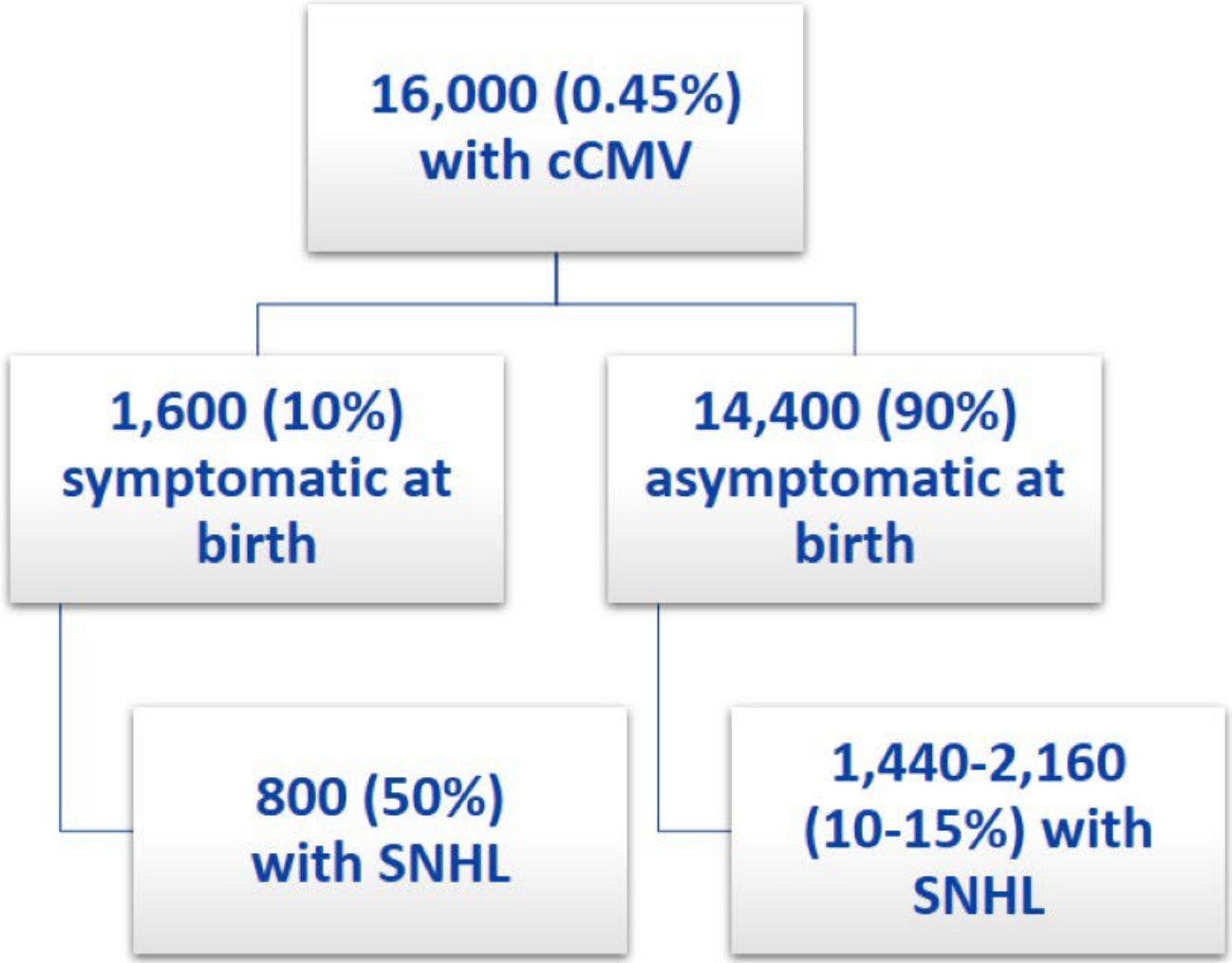

*Hypothetical cohort of 3.6 million U.S. live births

# cCMV-related sensorineural hearing loss (SNHL)

- In U.S. studies, 5-10% of cases of prelingual hearing loss attributable to cCMV
- 50% symptomatic infants
- 10-15% asymptomatic infants
- Up to half of cCMV SNHL may not be detected by newborn hearing screening

Satterfield-Nash et al. Etiology of prelingual hearing loss in the universal newborn hearing screening era: a scoping review. OTO-HNS, 2020
Lanzieri et al. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. Peds 2017

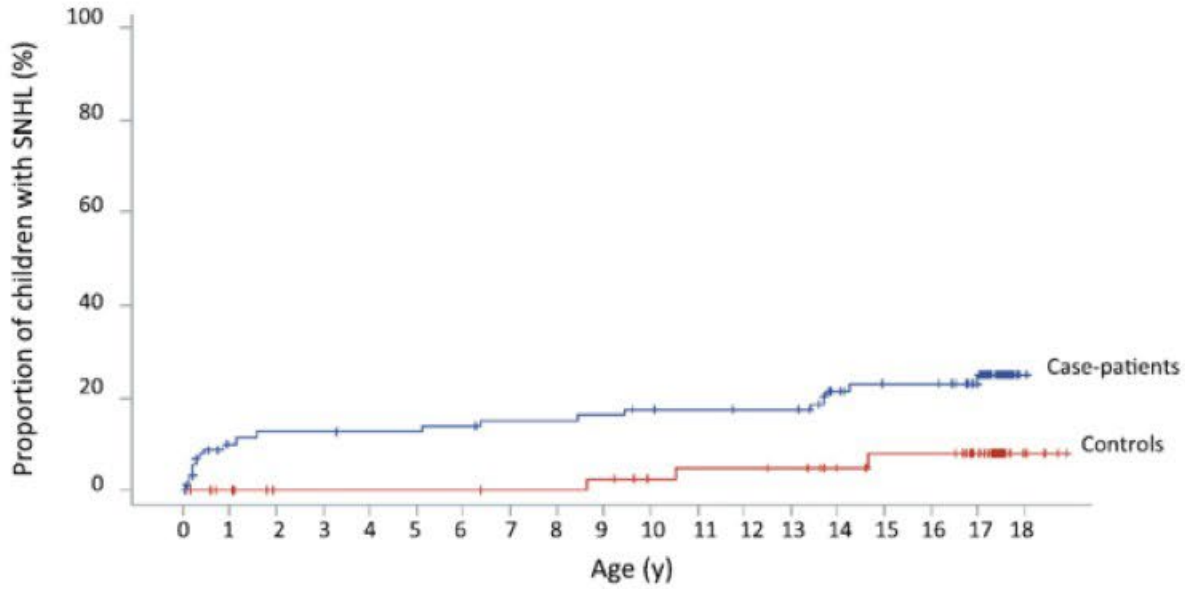
# Greater number of SNHL cases in infants with asymptomatic cCMV than symptomatic




Goderis et al. Hearing Loss and Congenital CMV Infection: A Systematic Review. Pediatrics 2014
Lanzieri et al. Hearing loss in children with asymptomatic congenital CMV infection. Pediatrics 2017

# SNHL among Children with Asymptomatic cCMV Infection and Controls

| | Probability (%) (95% CI) | | Hazard ratio (95% CI) | p-value |
|---|---|---|---|---|
| | Cases | Controls | | |
| All children | 25 (17-36) | 8 (3-22) | 4.0 (1.2-14.5) | 0.02 |
| Children with no SNHL at age 5 years | 13 (7-25) | 8 (3-22) | 1.6 (0.4-6.1) | 0.5 |

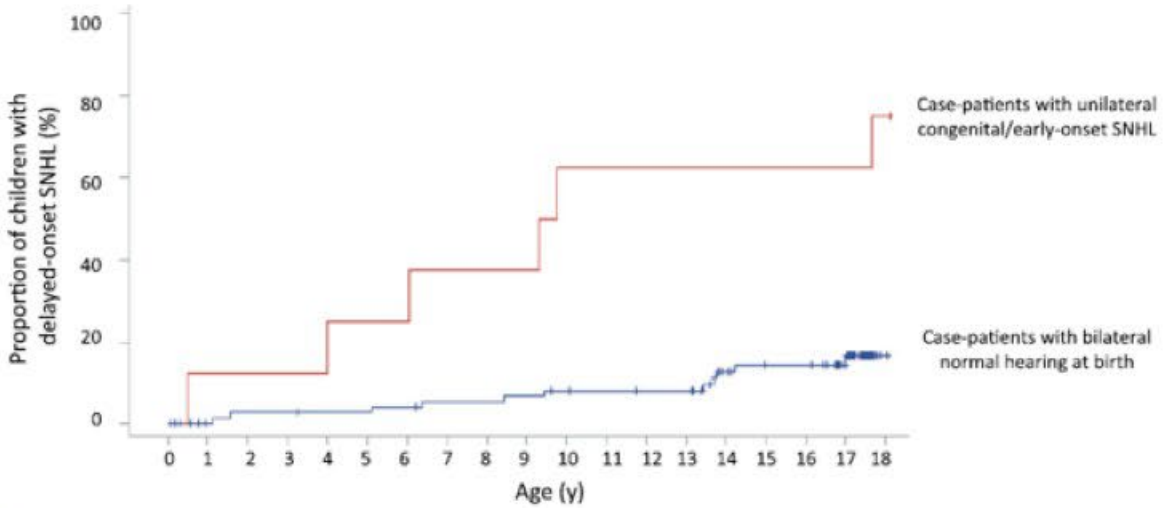



- The risk of SNHL diagnosed at any age was greater for cases than controls.
- For children with no SNHL at age 5 years, the risk of subsequently developing SNHL was not significantly greater for cases than controls.

Lanzieri et al. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. Peds 2017

# Delayed-onset SNHL among Children with Asymptomatic cCMV Infection with and without Congenital SNHL

| Initial hearing status | Probability of delayed-onset SNHL (%) (95% CI) | Hazard ratio (95% CI) | p-value |
|---|---|---|---|
| Congenital unilateral loss | 75 (44-96) | 6.9 (2.5-19.1) | <0.01 |
| No congenital loss | 16 (9-28) | | |




- The risk of delayed-onset SNHL was greater for children with congenital unilateral SNHL than those without.

Lanzieri et al. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. Peds 2017

# Estimates of Isolated SNHL Associated with cCMV, United States

| Severe to profound SNHL (≥70 dB) | Prevalence estimates* | Annual number of U.S children affected** |
|---|---|---|
| | % (95% CI) | n |
| Unilateral, by 2 years | 5 (2-12) | 700 |
| Bilateral, by 4 years | 2 (1-9) | 300 |

*Based on the Houston Congenital CMV Longitudinal Study (>30,000 newborns screened for CMV)
**Based on CMV birth prevalence of 4.5/1,000 live births, with 90% asymptomatic at birth, live birth cohort of 3.6 million (14,400 with asymptomatic cCMV). Lanzieri et al. Hearing loss in children with asymptomatic congenital CMV infection. Pediatrics 2017.

# Intelligence and Academic Achievement for Children with Asymptomatic cCMV

- **Isolated SNHL by age 2 years**
  - Lower full-scale IQ and receptive vocabulary scores
  - No differences in non-verbal intelligence, expressive language or academic achievement
- **Normal hearing by 2 years**
  - No differences in IQ, vocabulary or academic achievement scores during childhood or adolescence, compared to uninfected children

Lopez et al. Intelligence and academic achievement with asymptomatic congenital CMV infection. Pediatrics 2017

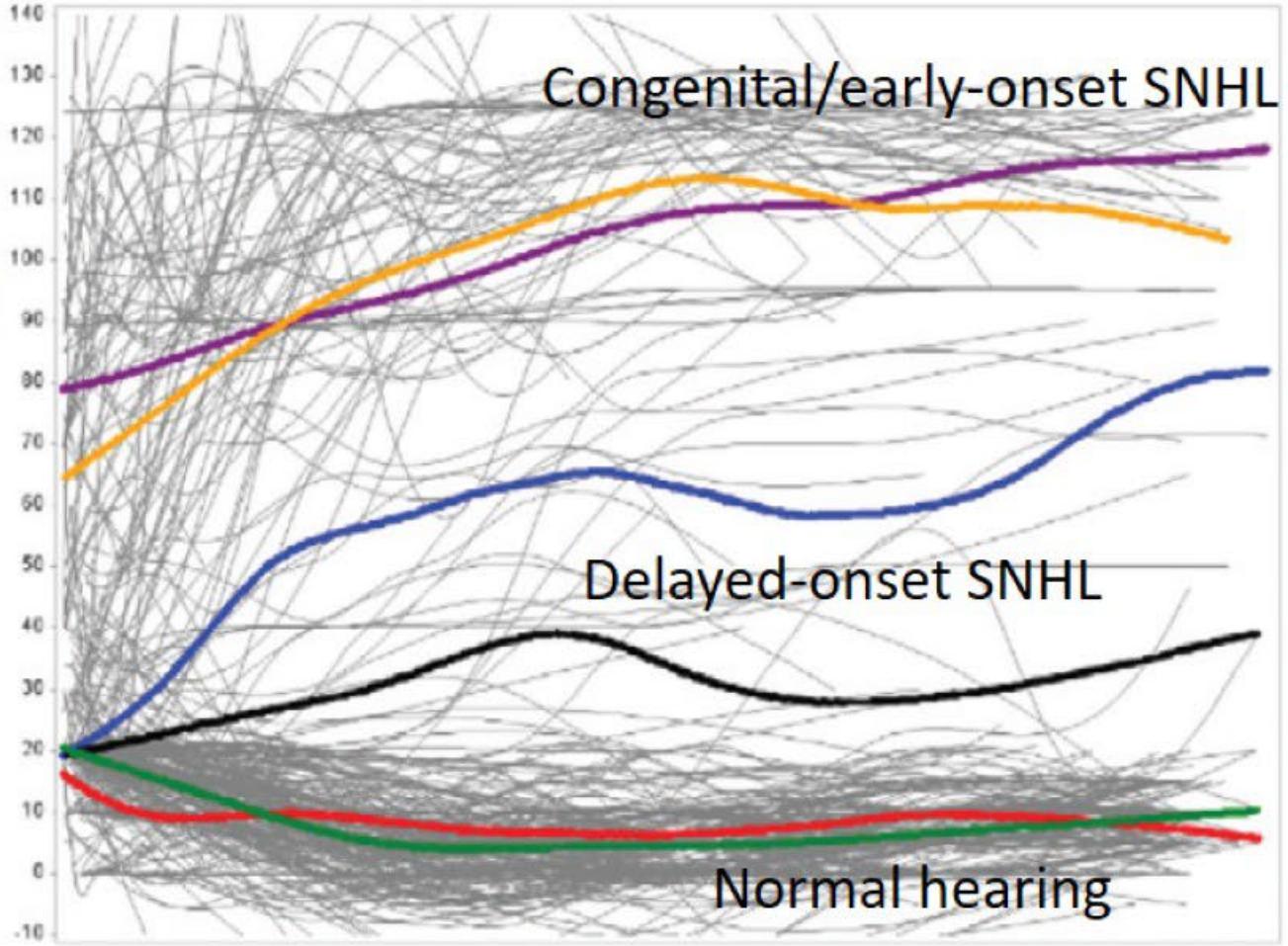
# Newborn Screening for cCMV

- **Universal newborn cCMV screening** not currently recommended
  - 2019, Ontario, Canada: expanded hearing risk factor screening program
  - 2023, Minnesota: first in the US
  - 2024, New York State: pilot study
- **Hearing-targeted screening**
  - 2013, Utah
  - Connecticut, New York, Virginia, Florida, Kentucky, and Maine
- Early intervention ⟶ Improved outcomes

# cCMV SNHL Characteristics and Risk Factors

# cCMV SNHL Characteristics – Hearing Levels Trajectory, Age 0-18 Years

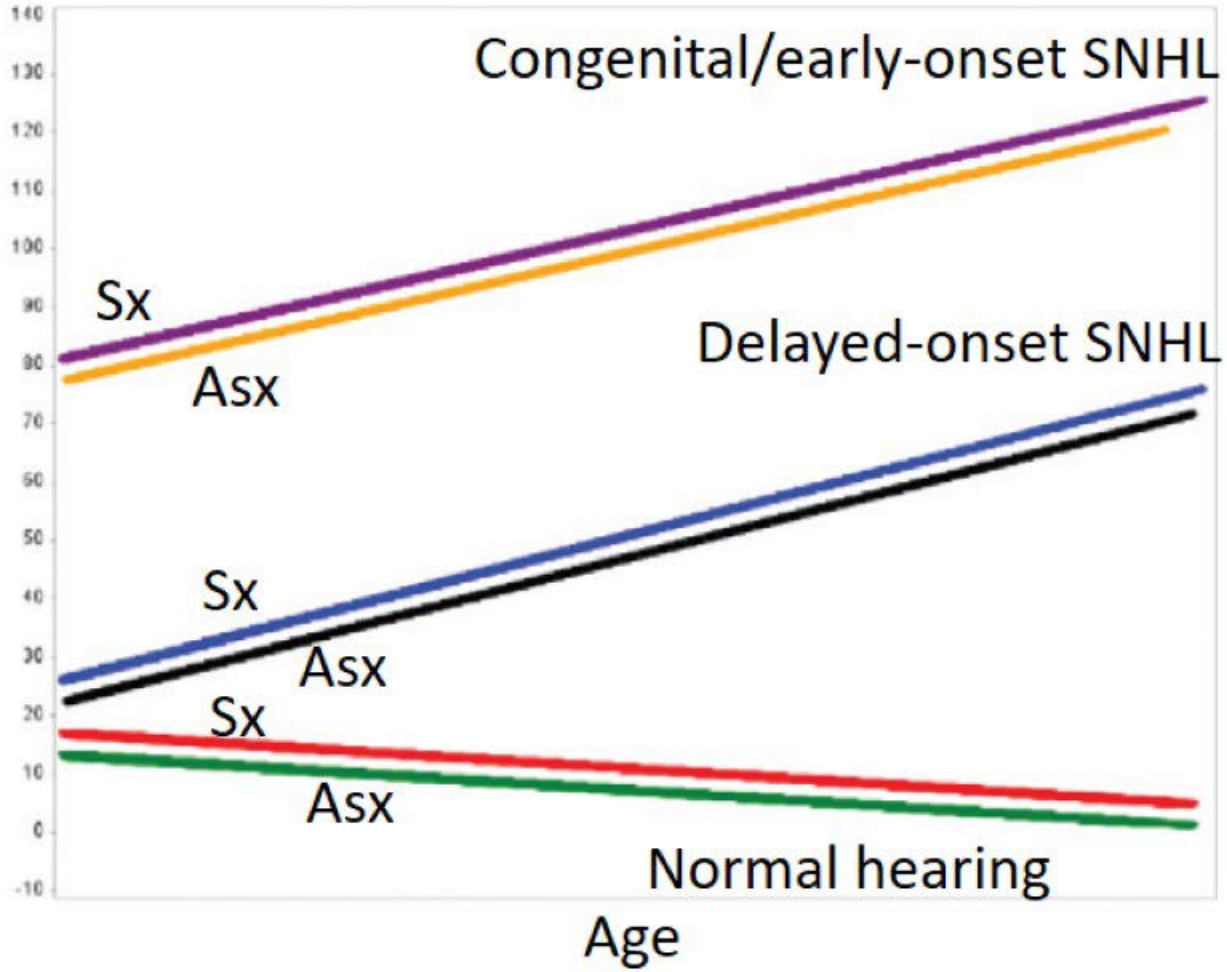
- Growth curve modeling
- Frequency-specific hearing thresholds by age (0.5 to 8 kHz)
- Ears categorized based on:
  - Child cCMV status: symptomatic vs. asymptomatic
  - SNHL status:
    - Congenital/early-onset SNHL
    - Delayed-onset SNHL
    - Normal hearing




Lanzieri et al. Hearing Trajectory in Children with Congenital Cytomegalovirus Infection. Otol HNS 20018

# cCMV SNHL Characteristics – Hearing Levels Trajectory, Age 0-18 Years

- Smoothing the spaghetti plots
- Progressive SNHL
- Similar across frequencies (4 kHz shown)
- Similar symptomatic vs. asymptomatic cCMV status




Lanzieri et al. Hearing Trajectory in Children with Congenital Cytomegalovirus Infection. Otol HNS 20018

# Risk factors for SNHL in Infants with Symptomatic cCMV

| | *HR (95% CI)* | *P-value* |
|---|---|---|
| *Model 1 (clinical signs at birth)* | (*n* = 70) | |
| Petechiae/purpura | 0.4 (0.2–0.8) | 0.011 |
| Jaundice or hyperbilirubinemia | 1.0 (0.5–1.8) | 0.987 |
| Hepatosplenomegaly | 3.4 (1.6–7.3) | 0.002 |
| Microcephaly at birth[a] | 2.6 (1.4–5.0) | 0.004 |
| Small for gestational age[b] | 1.1 (0.6–2.2) | 0.759 |
| Preterm birth[c] | 1.0 (0.5–1.7) | 0.902 |
| *Model 2 (head computed tomography scan findings within 4 months of age)* | (*n* = 73) | |
| Tissue destruction | 2.2 (1.1–4.3) | 0.024 |
| Attenuated growth | 1.6 (0.8–2.9) | 0.154 |
| Dysplastic growth | 2.4 (1.0–5.8) | 0.042 |

Lanzieri et al. Long-term outcomes of children with symptomatic congenital cytomegalovirus disease. J Perinatol 2018

# Risk factors for SNHL in Infants with Asymptomatic cCMV

| | Congenital/Early-Onset SNHL | | | | SNHL by Age 5 y | | | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | | HR | *P* Value | n (%) | | HR | *P* Value |
| Brain Abnormality | Yes | No | (95% CI) | | Yes | No | (95% CI) | |
| Intracranial calcifications | | | | | | | | |
| Yes | 1 (20) | 4 (80) | 4 | .151 | 1 (25) | 3 (75) | 3.1 | .216 |
| No | 6 (7) | 76 (93) | (0.6-26.9) | | 9 (12) | 66 (88) | (0.5-19.1) | |
| White matter lucency | | | | | | | | |
| Yes | 2 (18) | 9 (82) | 3.1 | .164 | 4 (36) | 7 (64) | 4.4 | .021 |
| No | 5 (7) | 70 (93) | (0.6-15.4) | | 6 (9) | 61 (91) | (1.3-15.6) | |
| Tissue destruction | | | | | | | | |
| Yes | 3 (17) | 15 (83) | 3 | .147 | 5 (29) | 12 (71) | 3.8 | .035 |
| No | 4 (6) | 65 (94) | (0.7-13.5) | | 5 (8) | 57 (92) | (1.1-13.1) | |

Lanzieri et al. Hearing Trajectory in Children with Congenital Cytomegalovirus Infection. Otol HNS 20018

# Antiviral Treatment of Infants with cCMV

- History
- Recommendations
- Trends
- Evidence
- Unanswered questions

# History of Antiviral Treatment of Infants with cCMV

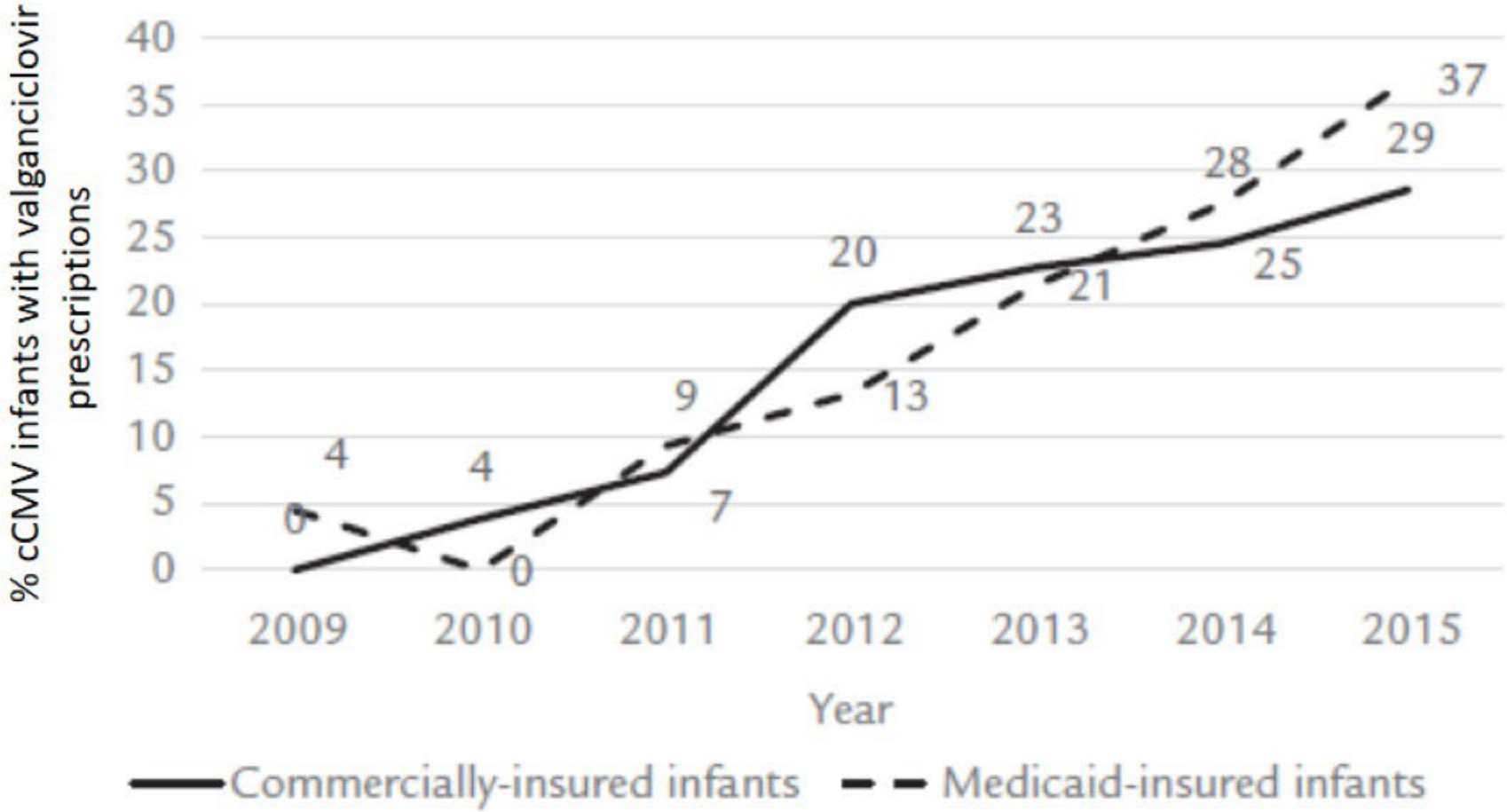
- Over 20 years since first studies of IV ganciclovir
- 2015 - Phase III trial: 6-mo vs. 6-wk valganciclovir therapy published
- Clinical trials assessing safety and efficacy of valganciclovir therapy in children with isolated SNHL
- The risk-benefit of antiviral therapy is still debated due to risk of toxicity and possible carcinogenicity

# Recommendations for Antiviral Treatment of Infants with cCMV

- American Academy of Pediatrics
  - Only infants with moderately to severely symptomatic cCMV disease who can start treatment within the first month of life
  - Not recommended for infants with isolated SNHL or asymptomatic

- European Guidelines
  - Infants with severely symptomatic cCMV disease involving the central nervous system
  - Most European experts classify infants with isolated SNHL as having severely symptomatic cCMV disease and recommend antiviral treatment, but consensus was lacking

# Valganciclovir Use Among Commercially and Medicaid-insured Infants with Congenital CMV, United States, 2009–2015




- ~90% infants had ≥1 CMV-associated condition and/or hearing loss
- ~5% infants had hearing loss without any other CMV-associated condition

Leung et al. Valganciclovir use among commercially and Medicaid-insured infants with congenital CMV infection in the United States, 2009-2015. Clin Ther 2018

# Increase in Antiviral Treatment of Infants with cCMV without Clinical Signs, United States, 2009-2015 and 2016-2019

| | 2009-2015 | | 2016-2019 | | Comparison by period | |
|---|---|---|---|---|---|---|
| | cCMV cases No. (%)* N = 3963 | Treated No. (%) N = 653 | cCMV cases No. (%)* N = 2810 | Treated No. (%) N = 1015 | Difference in proportion treated (95% CI) | Relative increase |
| Infants with Medicaid† | | | | | | |
| With cCMV-related signs (symptomatic) | 1966 (50) | 505 (26) | 1465 (52) | 719 (49) | 23 (20-27) | 1.9 |
| Moderately-to-severely symptomatic cCMV‡ | 993 (25) | 311 (31) | 771 (27) | 434 (56) | 25 (20-30) | 1.8 |
| Mildly symptomatic cCMV§ | 973 (25) | 194 (20) | 694 (25) | 285 (41) | 21 (17-26) | 2.1 |
| With HL | 342 (9) | 163 (48) | 190 (7) | 155 (82) | 34 (26-42) | 1.7 |
| Without HL | 1624 (41) | 342 (21) | 1275 (45) | 564 (44) | 23 (20-27) | 2.1 |
| With no cCMV-related signs | 1997 (50) | 148 (7) | 1345 (48) | 296 (22) | 15 (12-17) | 3.0 |
| With HL | 120 (3) | 36 (30) | 101 (4) | 55 (54) | 24 (11-37) | 1.8 |
| Without HL | 1877 (47) | 112 (6) | 1244 (44) | 241 (19) | 13 (11-16) | 3.2 |

Leung et al. Changes in Valganciclovir Use Among Infants with Congenital Cytomegalovirus Diagnosis in the United States, 2009-2015 and 2016-2019. J Peds 2022

# Initiation and Duration of Antiviral Treatment in Infants with cCMV, United States, 2010-2021

| | Ganciclovir only (n=29) | Ganciclovir and Valganciclovir (n=85) | Valganciclovir only (n=228) |
|---|---|---|---|
| **Start within 30 days of life, n (%)** | 22 (76) | 67 (79) | 99 (43) |
| **Duration of treatment, median (IQR)** | 8 (5-14) | 166 (38-211) | 171 (70-233) |

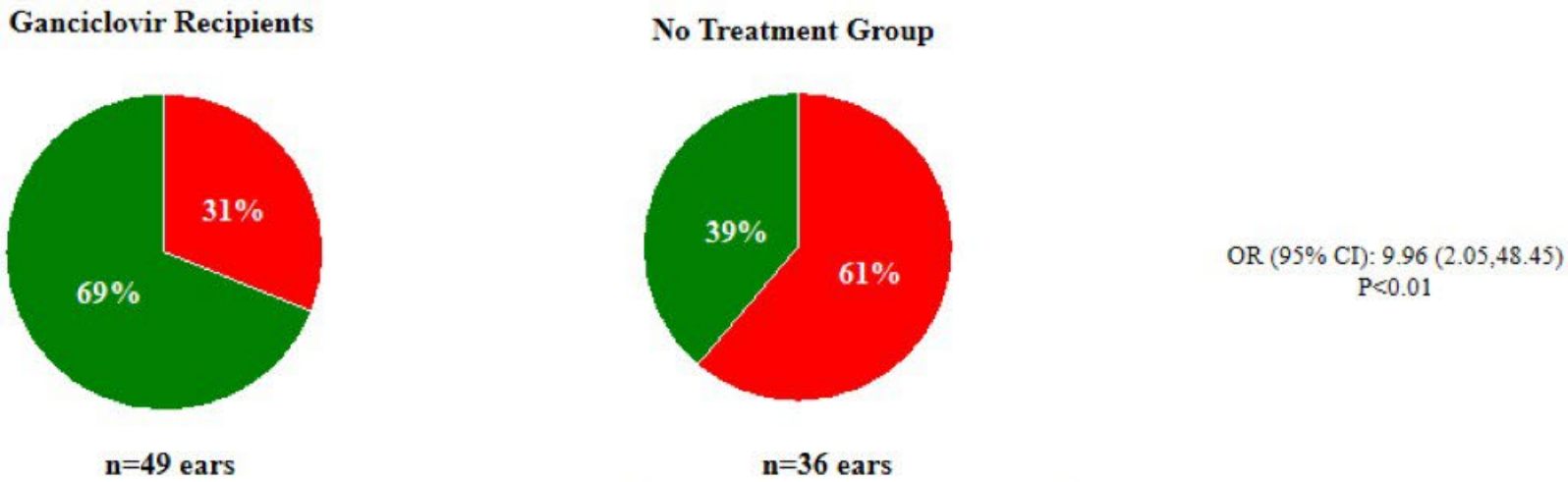
Leung et al. Ganciclovir and Valganciclovir Use Among Infants With Congenital Cytomegalovirus: Data From a Multicenter Electronic Health Record Dataset in the United States. JPIDS 2022

# Effects of Antiviral Treatment

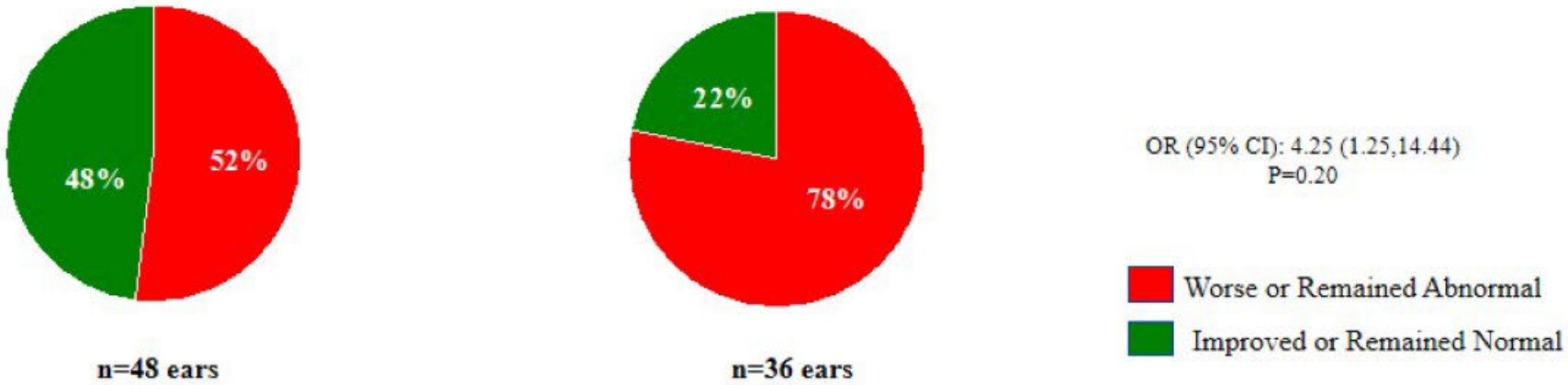
- Two clinical trials by the Collaborative Antiviral Study Group (CASG):
  1. 6-week IV ganciclovir vs. placebo
  2. 6-month vs. 6-week oral valganciclovir
     - Started within the first month of life
     - Improved hearing and developmental outcomes modestly up to 24-months of age for infants with symptomatic cCMV with central nervous system involvement
     - Risk of neutropenia

# CASG Phase III Intravenous Ganciclovir Study

## Change in Hearing Between Birth and 6 months



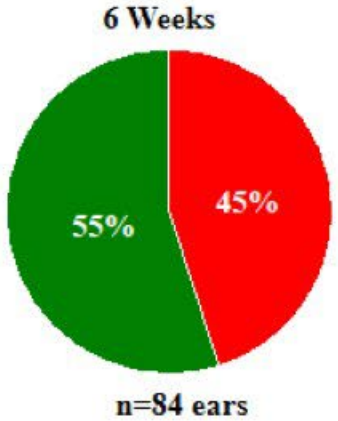

## Change in Hearing Between Birth and ≥ 12 months

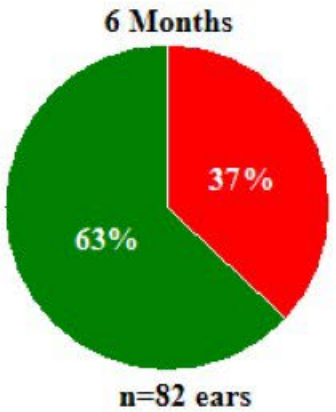



Kimberlin et al. J Pediatr 2003;143:16-25

# 6 Weeks vs. 6 Months Oral Valganciclovir

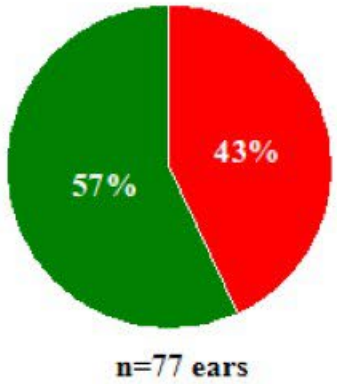
## 6 Months:

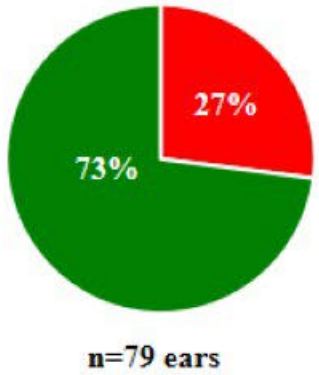



aOR* (95% CI): 1.69 (0.76,3.73)
P=0.20

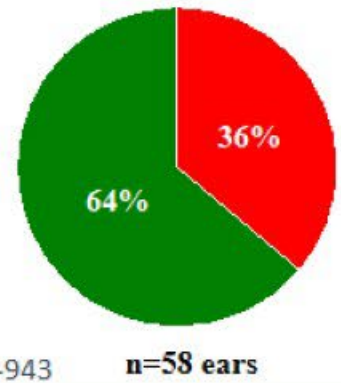
## 12 Months:

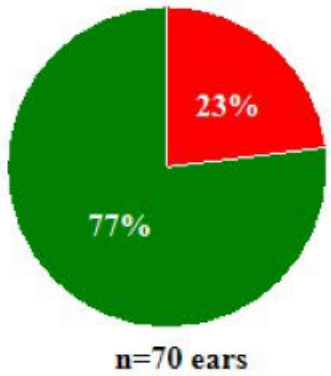



aOR* (95% CI): 3.04 (1.26,7.35)
P= 0.01

## 24 Months:




aOR* (95% CI): 2.61 (1.05,7.6.43)
P= 0.04

Worse or Remained Abnormal
Improved or Remained Normal

Kimberlin et al. N Engl J Med 2015;372(10):933-943

* CNS (a priori)

# Remaining Questions on the Effect of Antivirals

1. Is antiviral treatment protective against hearing deterioration when initiated after the first month of life, as is common practice?

2. Do improvements in hearing associated with antiviral treatment initiated in the neonatal period persist beyond early childhood?

3. Are infants with symptomatic cCMV who have normal hearing and receive antiviral treatment at lower risk of developing hearing loss?

4. Is there evidence for recommending antiviral treatment for infants with asymptomatic cCMV or isolated SNHL?

# 1. Is antiviral treatment protective against hearing deterioration when initiated after the first month of life, as is common practice?

- One placebo-controlled trial of valganciclovir:
  - Children with delayed-onset SNHL
  - Started treatment between 1 month and 3 years of age

U.S. National Library of Medicine. Valganciclovir therapy in infants and children with congenital CMV infection and hearing loss. ClinicalTrialsGov. https://www.clinicaltrials.gov/ct2/show/results/NCT01649869?cond=congenital+cytomegalovirus&draw=2&rank=27.

# Change in Total Ear Hearing at 6 Months Relative to Baseline – Primary Endpoint

| | Valganciclovir (N=26) | Placebo (N=28) |
|---|---|---|
| Improved | 0 (0.0%) | 0 (0.0%) |
| No Change (Normal to Normal) | 6 (23.1%) | 9 (32.1%) |
| No Change (Abnormal to Abnormal) | 14 (53.9%) | 18 (64.3%) |
| Worsened | 6 (23.1%) | 1 (3.6%) |

U.S. National Library of Medicine. Valganciclovir therapy in infants and children with congenital CMV infection and hearing loss. ClinicalTrialsGov. https://www.clinicaltrials.gov/ct2/show/results/NCT01649869?cond=congenital+cytomegalovirus&draw=2&rank=27.



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# 2. Do improvements in hearing associated with antiviral treatment initiated in the neonatal period persist beyond early childhood?

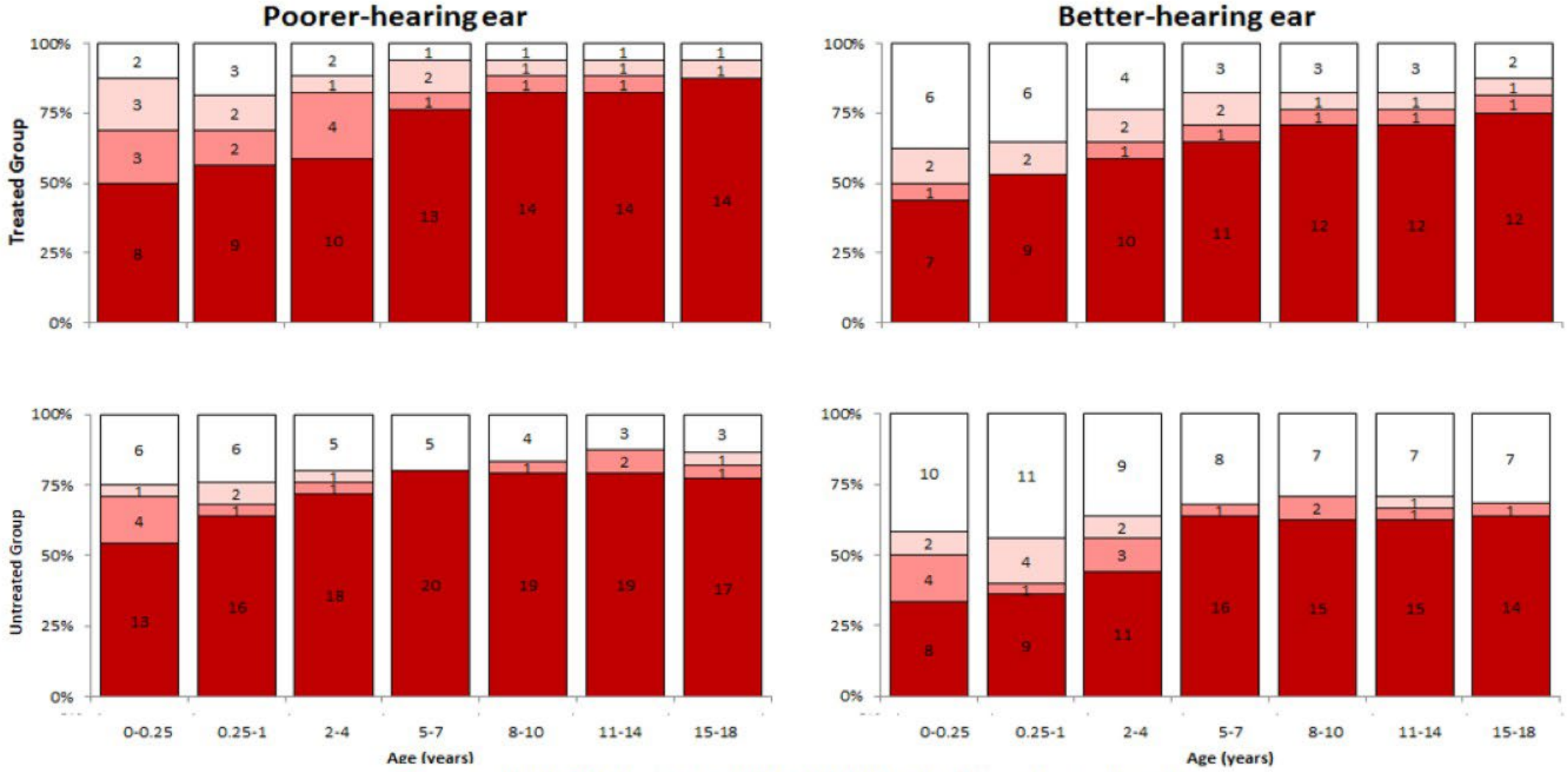
- Only one observational study:
  - The Houston Congenital CMV Longitudinal Study
    - Hearing outcomes at ≥12 years of age, post-hoc analysis
    - Children with symptomatic cCMV with and without 6-week IV ganciclovir therapy

# The Houston Congenital CMV Longitudinal Study, Post-Hoc Analysis of Infants with and without 6-week IV Ganciclovir Therapy

| Patient's characteristics | Treated* (n=17) n (%) | Untreated (n=27) n (%) |
|---|---|---|
| Participated in ganciclovir studies | 11 (65) | 4 (15) |
| Microcephaly | 14 (82) | 20 (74) |
| Other neurological abnormalities[c] | 7 (41) | 9 (33) |
| Congenital SNHL | 11 (65) | 15 (56) |
| SNHL at last assessment, median age | 16 (94), 13 years | 24 (89), 11 years |

*median 39 (range: 11-44) days

# Hearing Loss Progression among Infants with and without 6-week Intravenous Ganciclovir Therapy, Houston Cohort



# 3. Are infants with symptomatic cCMV who have normal hearing and receive antiviral treatment at lower risk of developing hearing loss?

**In normal hearing ears, SNHL diagnosed between baseline and…**

| 1st Trial | 6 wk IV Ganciclovir | Placebo |
|---|---|---|
| ≥12 mo (average 24 mo) | 6/17 (35%) | 9/17 (53%) |
| **2nd Trial** | **6 mo Vangaciclovir** | **6 wk Valganciclovir** |
| 6 mo | 9/55 (16%) | 6/55 (13%) |
| 12 mo | 2/54 (4%) | 7/47 (15%) |
| 24 mo | 5/53 (9%) | 3/38 (8%) |

# 4. Is there evidence for recommending antiviral treatment for infants with asymptomatic cCMV or isolated SNHL?

- An open-label trial to assess valganciclovir treatment for hearing loss prevention in infants with asymptomatic cCMV was recently suspended due to safety concerns
- A randomized trial to assess valganciclovir treatment in infants with isolated SNHL was stopped due to low enrolment
- A study in the Netherlands assessed whether 6-week valganciclovir therapy prevented hearing deterioration by 1 year of age among infants with cCMV and isolated SNHL compared with no treatment, but results are not yet available

# Summary

- Most SNHL cases in cCMV occur in infants that appear asymptomatic at birth
- SNHL may be progressive and require monitoring and interventions
- To treat with antivirals or not?
  - Recommended only infants with moderately to severely symptomatic cCMV who can start within the first month of life
  - Not recommended for infants with isolated SNHL or asymptomatic cCMV as evidence is lacking
  - Shared decision-making and realistic expectations as some neurological changes that have already occurred in utero may not be reversible with antiviral treatment
- If antiviral treatment delays the onset or progression of SNHL in the prelingual period, could children potentially experience improved speech and language outcomes?
- Broad approach to clinical management including anticipatory guidance, social support, hearing and developmental monitoring, and early intervention therapies

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# Thank you!

For more information, contact CDC
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