U.S. FOOD & DRUG ADMINISTRATION

Drug Development Considerations for the Treatment of Neonatal Enterovirus Infection and Congenital Cytomegalovirus Infection

May 7-8, 2024

Day 2

Workshop Overview

Day 1	Morning	General Principals of Pediatric and Neonatal Drug Development
		Enterovirus: Epidemiology and Disease Background
	Afternoon	Enterovirus Trial Design Challenges: Panel Discussion
Day 2	Morning	Congenital CMV Infection Epidemiology and Clinical Overview
		Congenital CMV Infection Drug Development Considerations
	Afternoon	Congenital CMV Infection: Trial Design Challenges- Panel Discussion

Housekeeping

- This meeting is being recorded. Speaker slides, transcripts, and recordings will be available on the meeting's webpage in the coming weeks- please check this page regularly for updates.
- Speaker and panelist affiliations and disclosures are available on the meeting's webpage under "Meeting Materials".

- For the general audience:
  - Your microphone and video are automatically turned off.
  - Submit questions using the "**Q&A**" feature at the bottom center of your screen in Zoom.

- **If you are experiencing technical Zoom difficulties, please reach out to Corey.Farley@fda.hhs.gov or Marcus.Washington@fda.hhs.gov**

Session 1:
Congenital CMV Infection Epidemiology and Clinical Overview

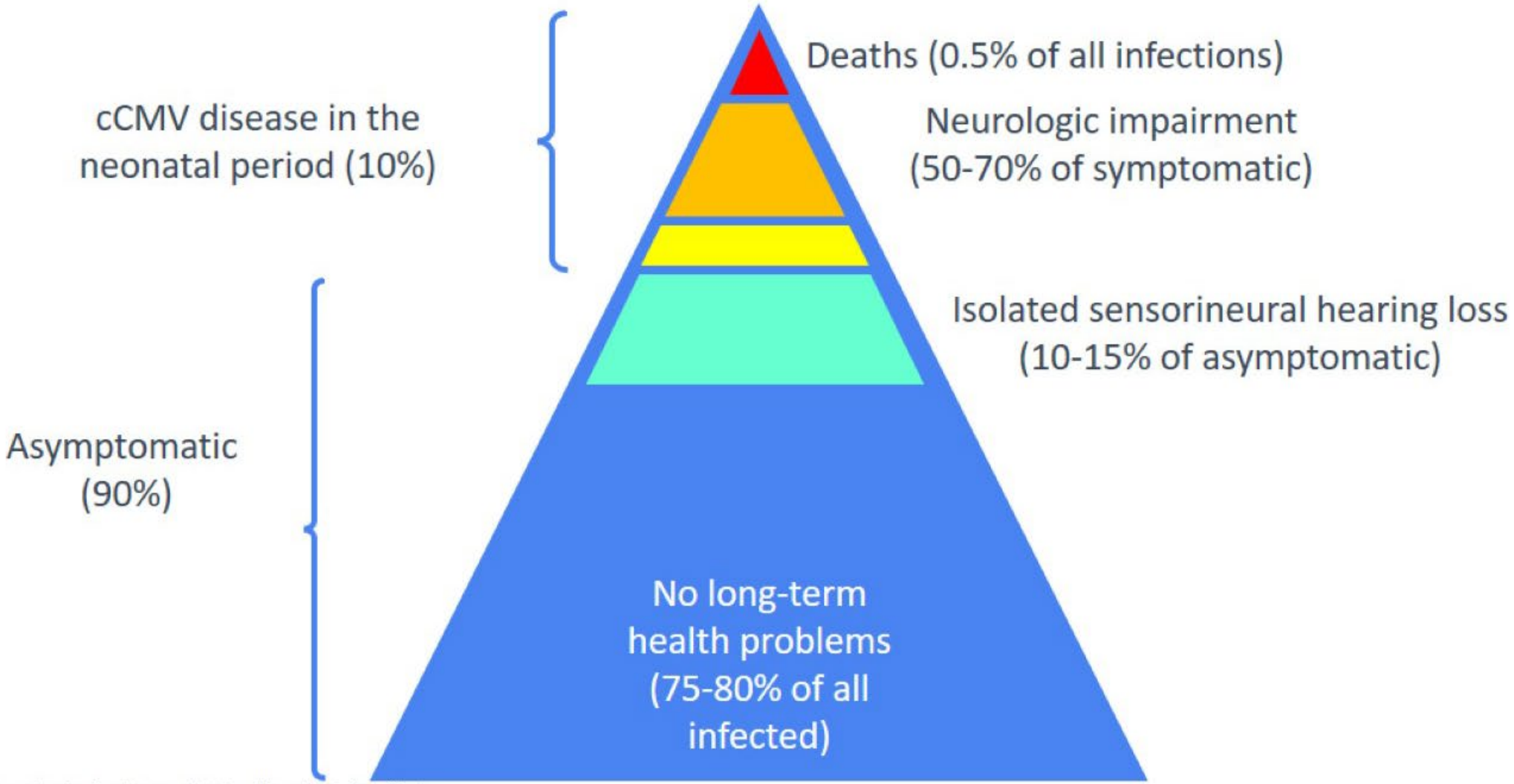
- **Surveillance and Epidemiology of cCMV in the United States**
  - Tatiana Lanzieri, MD, MPH; CDC
- **CMV and the Maternal-Fetal Dyad: Whom to Screen, How to Screen, and When to Treat?**
  - Mark Schleiss, MD; University of Minnesota Medical School
- **cCMV Clinical Overview**
  - Roberta DeBiasi, MD, MS; Children's National Hospital and Research Institute
- **Living with Congenital CMV: Parent Perspectives**
  - Megan Pesch, MD, MS; University of Michigan/Michigan Medicine

Surveillance and Epidemiology of Congenital Cytomegalovirus (cCMV) in the United States

Tatiana M. Lanzieri, MD, MPH

Measles, Rubella and CMV Epidemiology Team
Viral Vaccine Preventable Diseases Branch
Division of Viral Diseases

Congenital CMV infection occurs in 4.5 per 1,000 live births in the United States – 16,000 newborns in 2020*



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

Congenital CMV-related sensorineural hearing loss (SNHL)

- In U.S. studies, 5-10% of hearing loss in children aged ≤2 years attributable to cCMV
- 50% of symptomatic and 10-15% of asymptomatic infants will have sensorineural hearing loss
- Up to half of cCMV sensorineural hearing loss may not be detected by newborn hearing screening

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

Children with Congenital CMV Infection and Isolated Sensorineural Hearing Loss

- Progressive hearing loss is common
  - Require audiology monitoring
- Children initially with unilateral hearing loss have a higher risk of developing bilateral loss
- By age 2 years, 3 in 5 of these children have severe to profound hearing loss, unilateral or bilateral
  - Candidates for cochlear implant

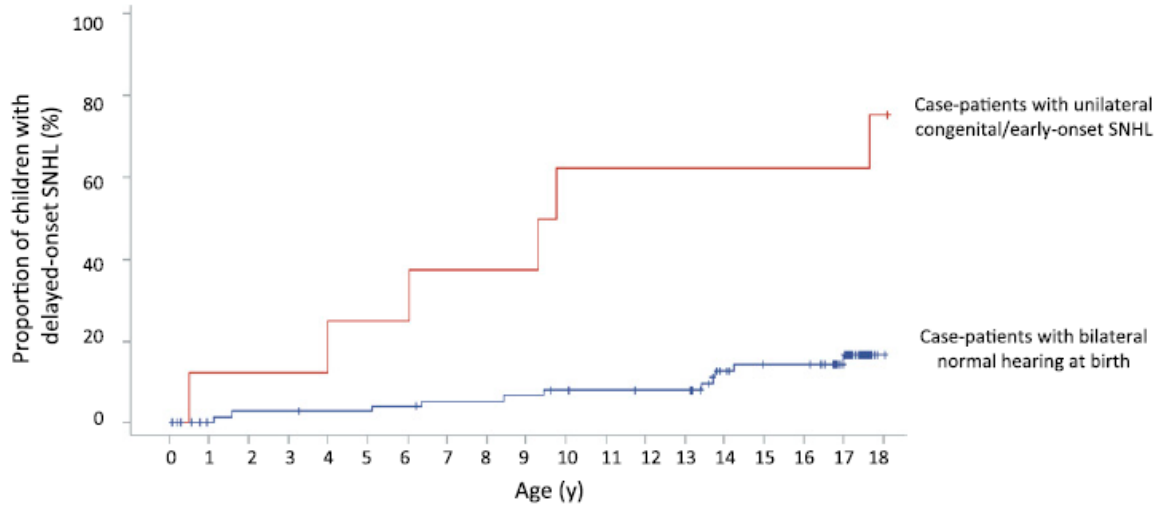


FIGURE 2
Delayed-onset SNHL among children with asymptomatic congenital CMV infection with and without unilateral congenital/early-onset hearing loss.

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

Newborn Screening and Surveillance for Congenital CMV in the United States

Newborn Screening for cCMV in the United States

2013 – Hearing-targeted screening in Utah, followed by several other states and hospital networks

2023 – Universal screening in Minnesota

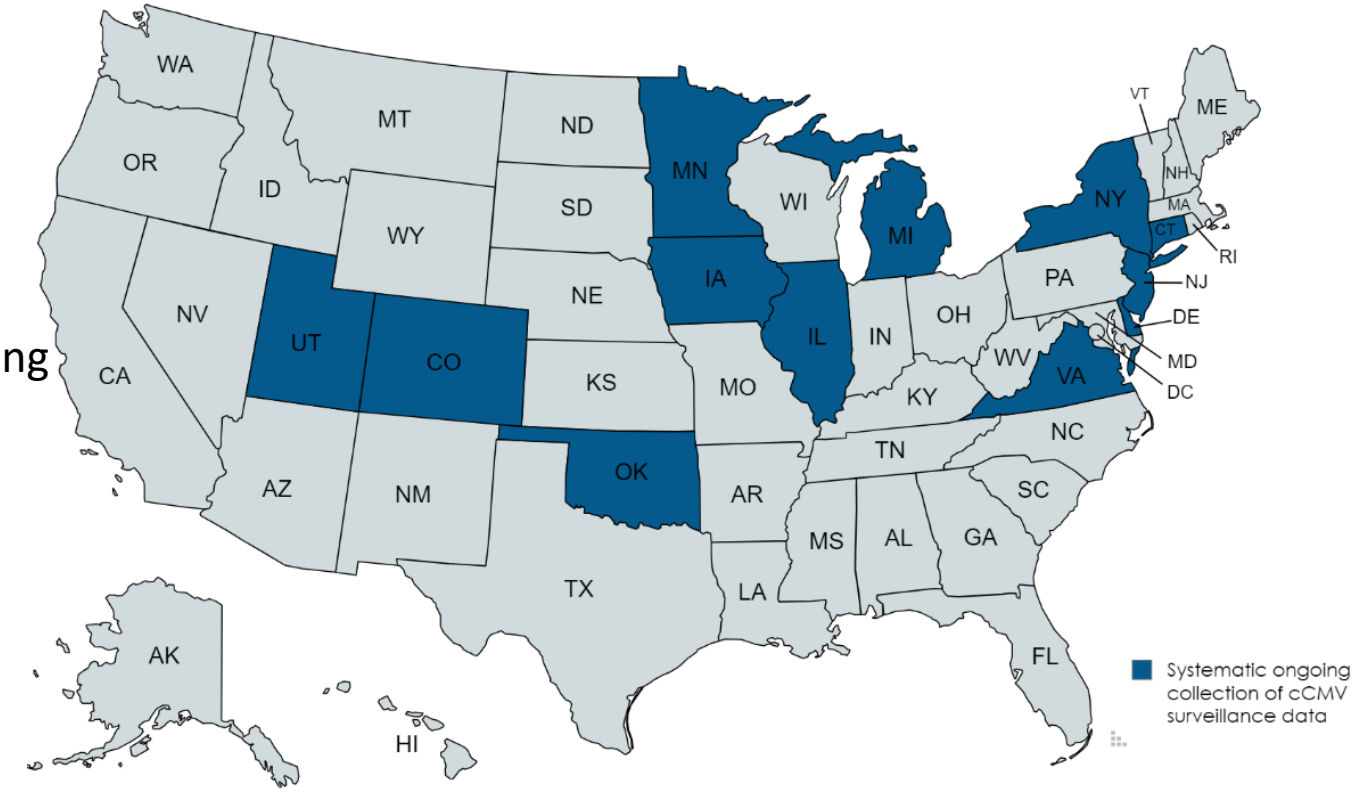
- Pilot in New York, and approved legislation in Connecticut and New Jersey*

Not part of the recommended universal screening panel

Minnesota | SF1698 | 2021-2022 | Vivian Act
New Jersey | S3975 | 2020-2021 | cCMV Screening and Public Awareness Campaign, pending inclusion in the recommended universal screening panel
Connecticut | HB 6821 | 2023 | An Act Concerning Cytomegalovirus, pending implementation
Advisory Committee on Heritable Disorders in Newborns and Children. Chair Letter to cCMV Nominators

Status of cCMV Surveillance in the United States

- cCMV is not a nationally notifiable condition
- Standardized case definitions of cCMV infection and disease
  - Approved by the Council of State and Territorial Epidemiologists in 2023
- At least twelve states have initiated efforts to conduct cCMV surveillance
  - Monitor trends in disease prevalence
  - Connect families to resources and services
  - Track compliance to hearing-targeted screening
- Case ascertainment methods vary
  - Universal, hearing-targeted, high-risk infant screening
  - Administrative data or clinical reports
- Data collection variable across states
  - Demographics, clinical signs, laboratory and treatment data, long-term outcomes



23-ID-02_Standardized Surveillance Case Definitions for Congenital Cytomegalovirus Infection and Disease

Raines et al. Congenital Cytomegalovirus Surveillance in the United States. Birth Defects Res, 2023.

Ongoing cCMV Surveillance Projects

- Surveillance for Emerging Threats to Pregnant People and Infants Network (SET-NET)
  - Health departments: Minnesota, Utah, New York, New Jersey & Iowa (Year 1) + Virginia & Illinois (Year 2)
- Maternal and Infant Clinical Network (MAT-LINK)
  - University of Minnesota, University of Rochester, University of South Florida, and Baylor College of Medicine
- Goal of the projects:
  - Identify and evaluate cCMV surveillance methods
  - Assess feasibility of longitudinal data collection for infants with cCMV through 3 years of age

Tong et al. Population-Based linked longitudinal surveillance of pregnant people and their infants: A critical resource for emerging, re-emerging, and persistent threats. J Women Health, 2023.
Surveillance for Emerging Threats to Mothers and Babies (SET-NET) | CDC
Maternal and Infant Network (MAT-LINK) | CDC

cCMV Surveillance

Goals

- Inform clinical guidance, vaccination and newborn screening policy

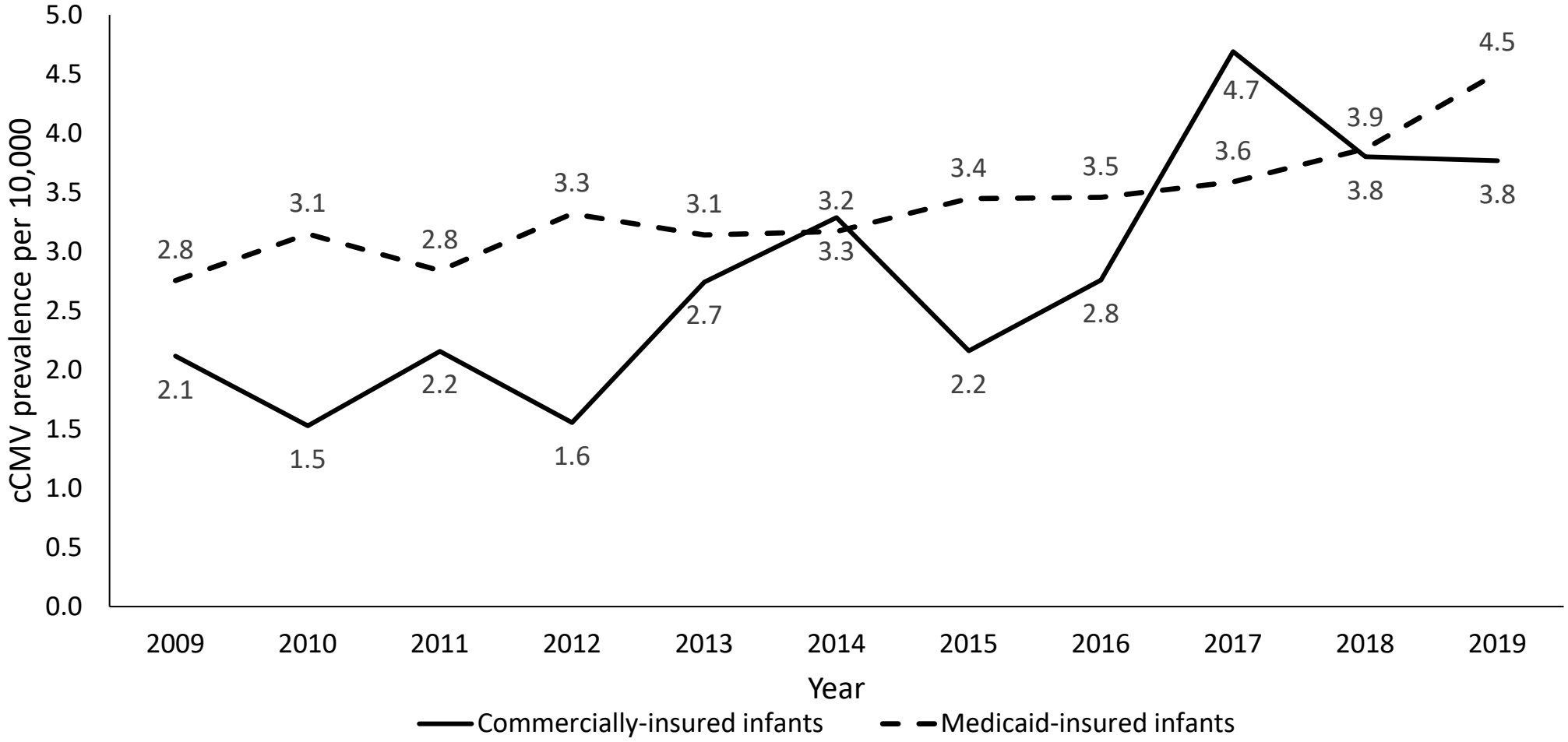
Objectives

- Monitor trends and identify groups at higher risk of cCMV
- Characterize clinical spectrum of disease, long-term outcomes and access to services
- Monitor trends in use of antivirals
    - Equity and whether in line with recommendations
    - Real-world effectiveness

Trends in Prevalence and Antiviral Use for Infants with Congenital CMV in the United States

Analyses of Administrative Data

Prevalence of cCMV Disease* among Commercially- and Medicaid-insured Infants, 2009–2019



* ICD-9-CM or ICD-10-CM code for congenital CMV infection or CMV disease within 45 days of life

Leung et al. Changes in Valganciclovir use among infants with congenital cytomegalovirus diagnosed in the United States, 2009-2015 and 2016-2019. Pediatrics, 2022.

Antiviral Treatment Recommendations

- Infants with moderate to severely symptomatic cCMV disease (i.e., multiple signs or central nervous system involvement)
  - 6 months oral valganciclovir therapy, starting within first month of life
  - Intravenous ganciclovir may be used initially
- Infants with isolated sensorineural hearing loss
  - Antiviral therapy not recommended in the United States
  - Evolving recommendations in Europe
    - 6-months → 6-weeks oral valganciclovir therapy
- Limited data on efficacy of antivirals on preserving hearing in the long-term

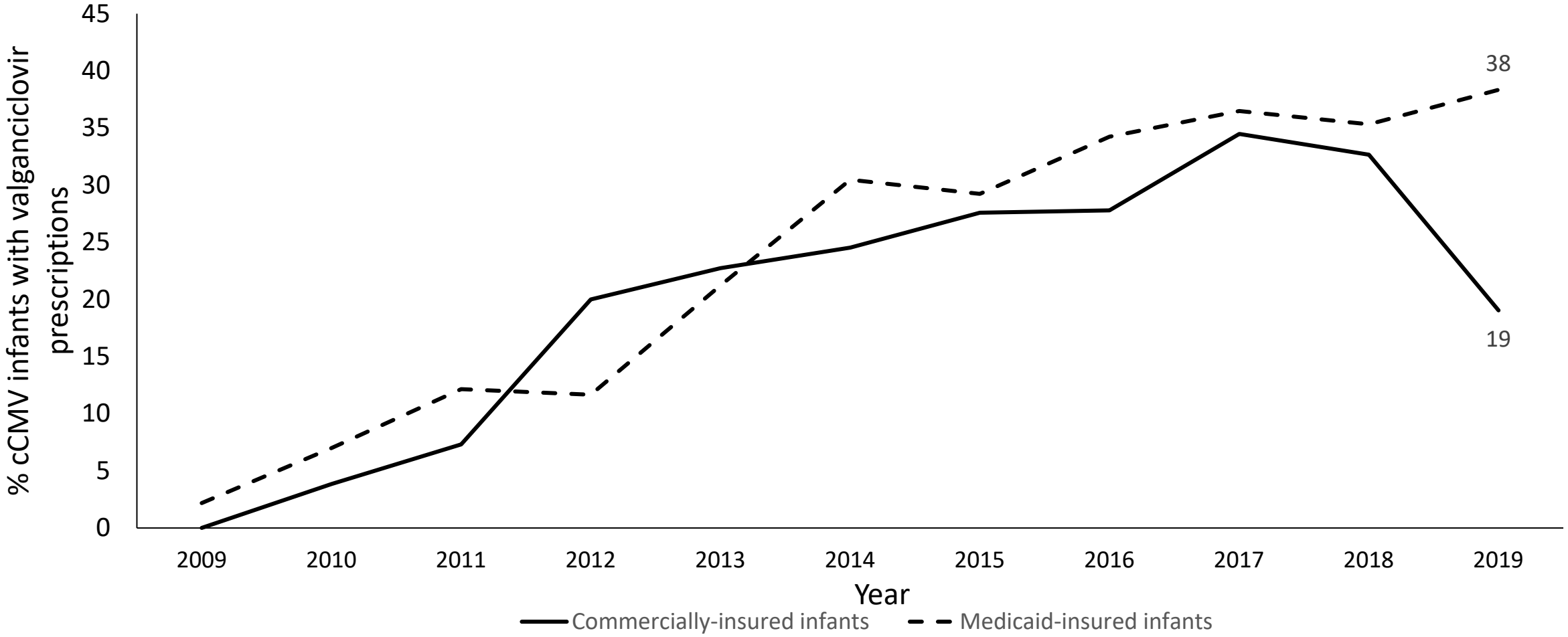
Kimberlin et al. Cytomegalovirus Infection. Redbook: Report of the Committee of Infectious Diseases, 2021-2024.
Rawlinson et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. The Lancet Infectious Diseases, 2017
Luck et al. Congenital Cytomegalovirus: A European Expert Consensus Statement on Diagnosis and Management. Pediatr Infect Dis J, 2017.
Lereuz-Ville et al. Consensus Recommendation for prenatal, neonatal, and postnatal management of congenital cytomegalovirus infection from the European congenital infection initative. Lancet Reg Heath Eur, 2024.
Chung et al. Valganciclovir in Infants with Hearing Loss and Clinically Inapparent Congenital Cytomegalovirus Infection: A Nonrandomized Controlled Trial. J Pediatr, 2024.
Lanzieri et al. Considering Antiviral Treatment to Preserve Hearing in Congenital CMV. Pediatrics, 2023.

Ganciclovir and Valganciclovir Use Among Infants with cCMV–U.S. Multicenter Electronic Health Record Dataset, 2010–2021

Antiviral	n (%)	Start of Treatment in Days (Median, Q1-Q3)	Duration of Treatment in Days (Median, Q1-Q3)	Neutropenia n (%)
Ganciclovir only	29 (4)	13 (5-29)	8 (5-14)	6 (21)
Valganciclovir only	228 (33)	45 (19-99)	171 (70-233)	39 (17)
Both	85 (12)	G: 16 (5-47) V: 49 (21-90)	G: 8 (4-19) V: 160 (30-201)	22 (26)
None	347 (50)	-	-	22 (6)

Leung et al. Ganciclovir and Valganciclovir use among infants with congenital cytomegalovirus: Data from a multicenter electronic health record dataset in the United States. J Pediatr Infect Dis Soc, 2022.

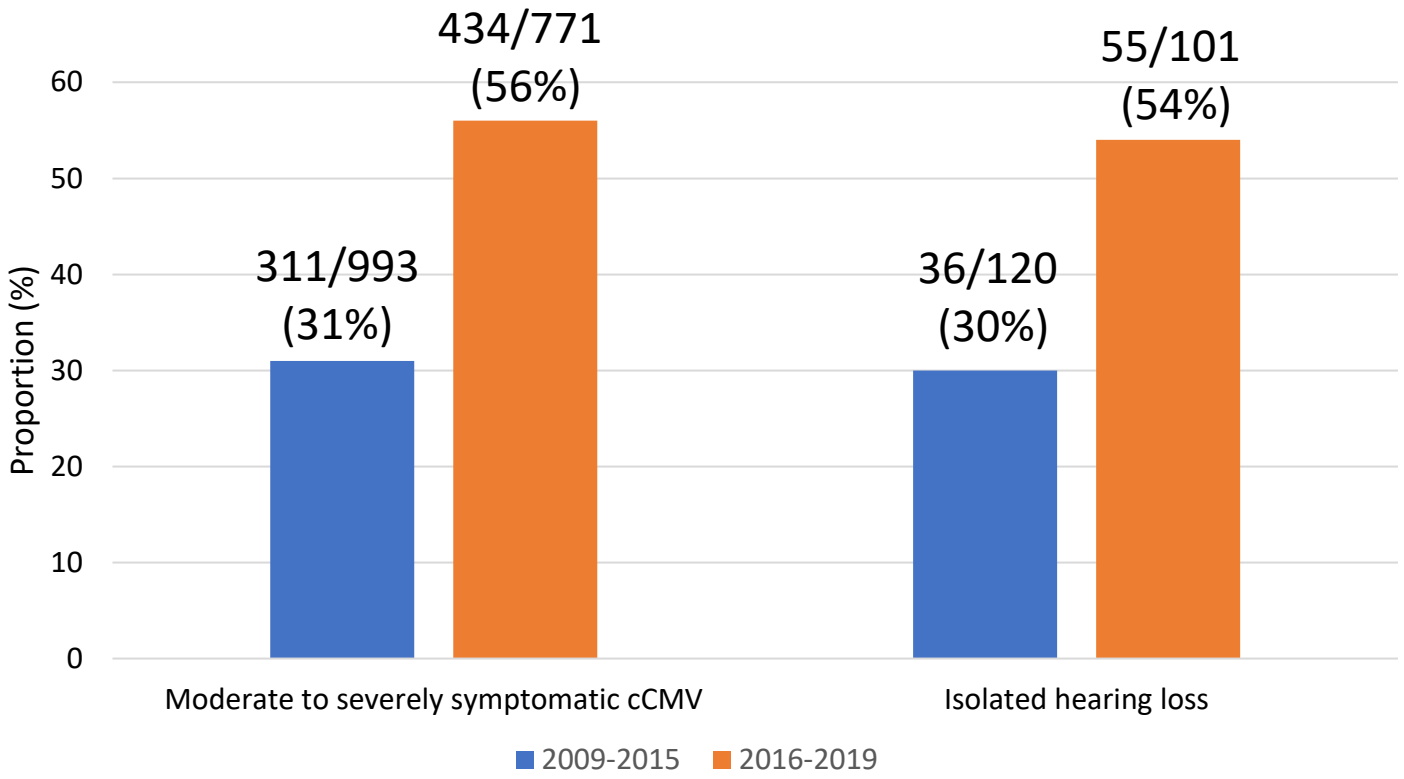
Valganciclovir Use Among Commercially and Medicaid-insured Infants with cCMV Diagnosis, United States, 2009–2019



*Database include only outpatient drug prescriptions, thus data on use of intravenous ganciclovir not available.

Leung et al. Changes in Valganciclovir use among infants with congenital cytomegalovirus diagnosed in the United States, 2009-2015 and 2016-2019. Pediatrics, 2022.

From 2009-2015 to 2016-2019, the proportion of infants with cCMV treated with valganciclovir increased for all cCMV disease categories* CMS Medicaid Database



*Data for mildly symptomatic and asymptomatic cCMV not shown.

Leung et al. Changes in Valganciclovir use among infants with congenital cytomegalovirus diagnosed in the United States, 2009-2015 and 2016-2019. Pediatrics, 2022.

Summary

- Dynamic landscape on U.S. newborn screening, surveillance and treatment recommendations for cCMV
- Increase identification of infants with cCMV infection and disease
- Increasing use of antivirals since 2010
  - Mostly in line with prior recommendations but also for infants with isolated sensorineural hearing loss
- Need for increasing provider education and shared clinical decision-making given limited data on enduring benefits of antivirals
- Need for assessing real-world effectiveness of antivirals recommended off label and for developing new drugs

Acknowledgments

Jessica Leung
Kelley Raines
Ashrita Rau
David Sugerman
Van Tong
Kate Woodworth
Mark Schleiss
All SET-NET and MAT-LINK collaborators

Thank you!

Please feel free to contact me (uyk4@cdc.gov) with any questions

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

CMV and the Maternal-Fetal Dyad: Whom to Screen, How to Screen, and When to Treat?

Mark R. Schleiss, MD

American Legion and Auxiliary Heart Research Foundation Professor

Department of Pediatrics

University of Minnesota Medical School

May 8, 2024

9:25-9:40 AM

MEDICAL SCHOOL
UNIVERSITY OF MINNESOTA

FDA Workshop: Drug Development Considerations for the Treatment of Neonatal Enterovirus Infection and Congenital Cytomegalovirus Infection

CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE
UNIVERSITY OF MINNESOTA

UNIVERSITY OF MINNESOTA
Driven to Discover℠

Maternal Screening for CMV

No recommendation for routine maternal CMV antibody screening from ACOG

Among women of childbearing age (15–44 years), CMV seroprevalence was 58.3% in one analysis (https://doi.org/10.1086/508173; 95% CI, 55.3%–61.4%)

Reinfections with transmission can occur in seropositive women

Combination of IgG serology, IgM serology, and avidity index

Antiviral therapy consideration based on study in Israel (DOI: 10.1016/S0140-6736(20)31868-7

Society of Obstetricians and Gynaecologists of Canada (SOGC) guideline

SOGC Guideline 420 (DOI: 10.1016/j.jogc.2021.05.015)

In provinces where CMV IgG avidity testing is available, screening for CMV primary infection in the first trimester (using IgG and IgM antibodies followed by IgG avidity testing if the patient is IgM-positive) can be offered, especially in women at high risk (those who have a child under 3 years at home)

Reinfections with transmission can occur in seropositive women

Society of Obstetricians and Gynaecologists of Canada (SOGC) guideline (cont)

The available evidence is insufficient to recommend routine maternal antiviral therapy for fetal infection.

A double-blind, randomized controlled trial reported on 90 pregnant patients with primary CMV infection acquired during the periconceptional period or the first trimester of pregnancy; either oral valacyclovir (**8 g per day**) or placebo. Fetal infection in 29.8% in the placebo group and 11.1% in valacyclovir group (OR 0.29; 95% CI 0.09–0.9).

Benefit was limited to those with infection acquired during the first trimester; there was no significant difference in fetal infection among patients with periconceptional infection.

DOI: 10.1016/j.jogc.2021.05.015

Multicenter Italian Observational Study

The inclusion criterion was the diagnosis of cytomegalovirus primary infection occurring in the periconceptional period or up to 24 weeks of gestation. The primary outcome was the transmission by the time of amniocentesis. The secondary outcomes were termination of pregnancy, transmission at birth, symptomatic infection at birth, and a composite outcome (termination of pregnancy or transmission at birth).

Valacyclovir significantly reduced the rate of cCMV diagnosis at the time of amniocentesis and termination of pregnancy and appeared to reduce rate pf symptomatic cCMV.

DOI: https://doi.org/10.1016/j.ajogmf.2023.101101

Congenital CMV Screening

Targeted screening (”Hearing-Targeted” Screening)

Universal screening

The CHIMES Study

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,[d] Julie L. Woodruff, AuD,[e] 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

Pediatrics, 139(2)

What about Asymptomatic cCMV infants who do not refer on UNHS?

What about Asymptomatic cCMV infants who do not refer on UNHS?

- Fowler et al, 2017

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

	Did Not Pass Hearing Screen, No. (%)	Passed Hearing Screen, No. (%)	Total, No. (%)
Unilateral loss	8 (40)	8 (53)	16 (46)
Bilateral loss	12 (60)	7 (47)	19 (54)
Mild loss (21–40 dB HL)	7 (35)	9 (60)	16 (46)
Moderate or greater loss (>40 dB HL)	13 (65)	6 (40)	19 (54)
Total SNHL	20 (57)	15 (43)	35 (100)

Should We Include cCMV in the Recommended Uniform Screening Panel (RUSP)

YES

Diagnostic evaluation

Anticipatory monitoring

Hearing loss may be delayed, progressive in nature

Antiviral therapy

Neurodevelopmental evaluation

NO

Most infants asymptomatic

Overuse of antivirals

Undue parental anxiety

Cost issues (though is cost-effective)

Ethical concerns

Does not fit RUSP paradigm

Advisory Committee on Heritable Disorders in Newborns and Children

Advisory Committee on Heritable Disorders in Newborns and Children
5600 Fishers Lane, Room 18W68
Rockville, Maryland 20857
301-443-2521– Phone
www.hrsa.gov/advisory-committees/heritable-disorders

The Committee recognizes cCMV as a medically serious condition, with a CLIA-approved confirmatory test and available treatment modalities.

However, the Nomination and Prioritization Workgroup concluded that they had insufficient information to move the nomination forward in the process. One of the key requirements for all nominations is a prospective population-based pilot study. In order to make a decision as to whether to advance the nomination to the next step of evidence review, the Committee will require additional information in the following areas:

1. Pilot study
2. Case definition
3. Screening test.
4. Clinical utility.
5. Treatment.

Universal Congenital CMV Screening

- Importance of timing of specimen acquisition
- **WHAT** to Use for Screening?
  - Dried blood spots (DBS)
  - Urine
  - Saliva
- CHIMES study
  - DBS PCR **insufficient sensitivity** (20,448 subjects; range 28-34%)
  - Saliva PCR **high sensitivity** (34,989 subjects; 97-100%)
- Saliva-based PCR has been focal point of policy discussions in newborns
  - False positives
  - Cost

Improved Extraction and DNA Recovery

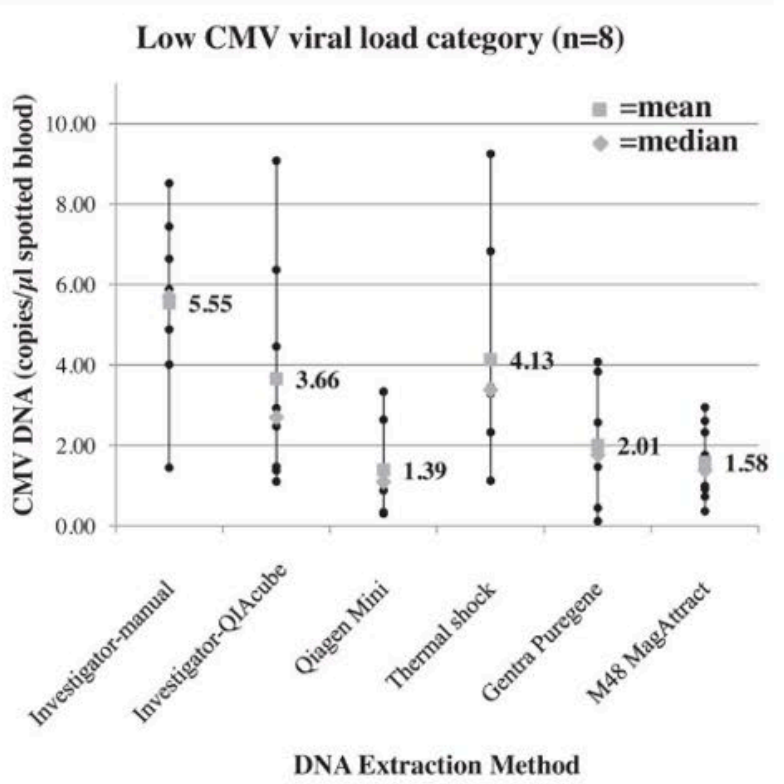
Improved DNA recovery methodologies

DOI: 10.1016/j.jviromet.2019.01.005

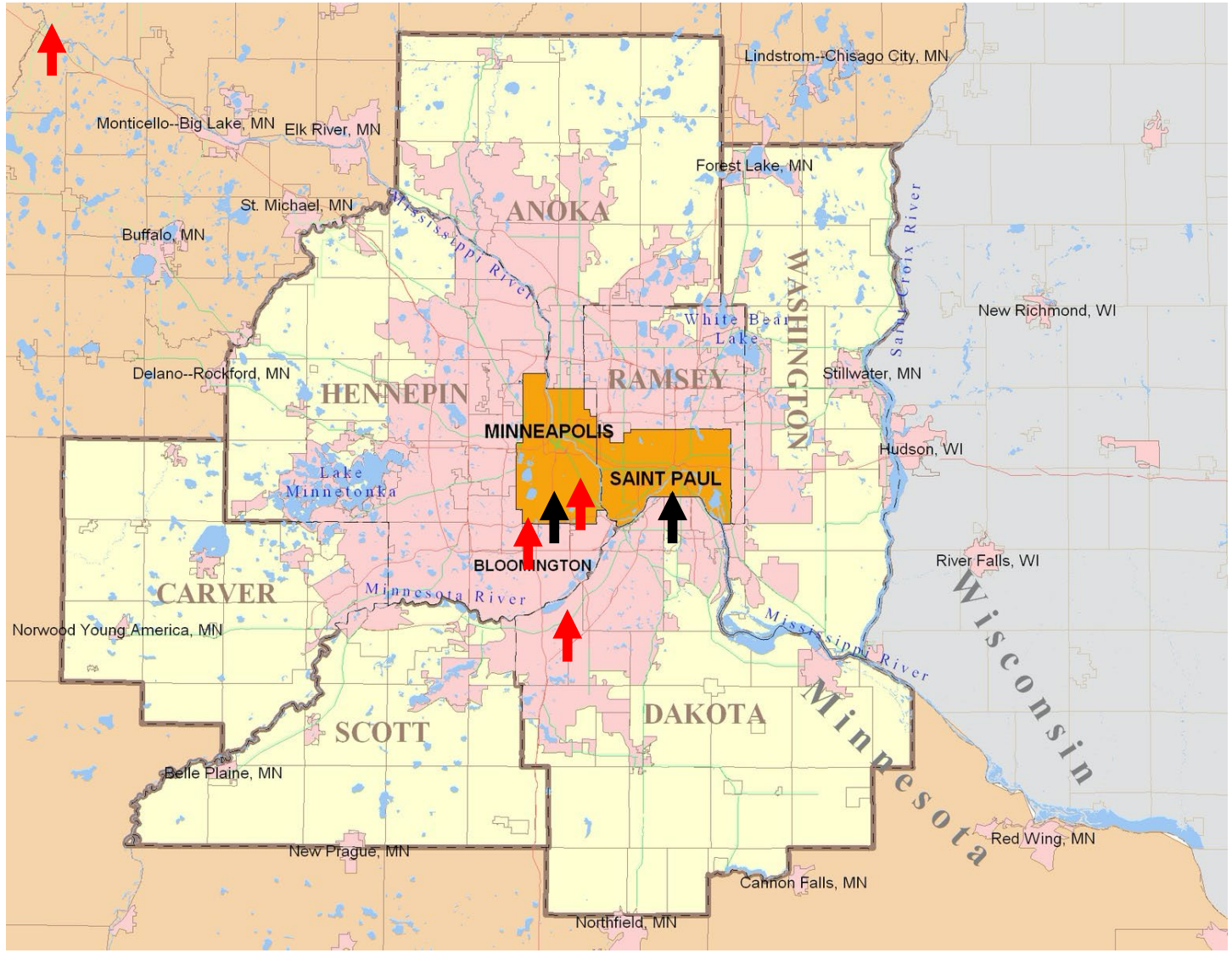
DOI: 10.1016/j.jcv.2015.03.015

Improved extraction buffers

DOI: 10.1007/s10875-011-9609-4



Increased sensitivity of PCR techniques/platforms



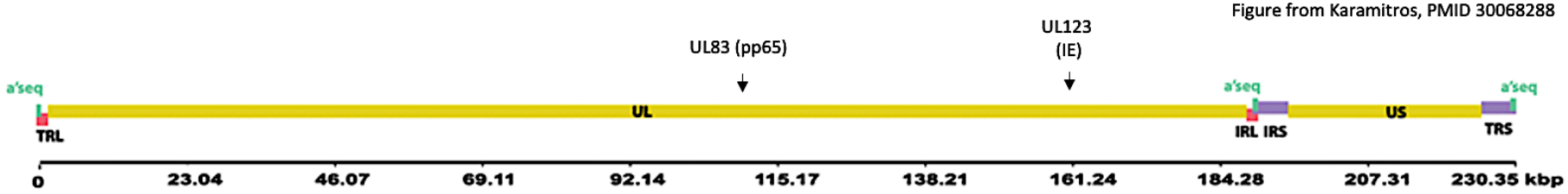
https://www.nationsonline.org/oneworld/map/USA/minnesota_map.htm
https://jogh.org/2022/jogh-12-03027

Universal Screening Study 2017-2023

23,644 consented from 2017-2023

DBS		Saliva	
Three 3 mm DBS punches CDC Lab	DBS	Three 3 mm DBS punches UMN Lab	Saliva	Saliva Swab UMN Lab
Wash with 200 µL Extracta DBS- Spin at 3500 rpm for 5 min		240 µL 90% ATL + 10% proteinase K Incubation ON 400 rpm at 56°C		300 µL Extraction Reagent
50µL Extracta DBS 95°C for 25 min		QIAamp 96 DNA QIAcube HT kit		95°C, 30 min, 300 rpm
Rapid cooling		qPCR for UL83 (virus) and NRAS (host)		Rapid cold down
qPCR for UL123 (virus) and Exogenous Internal Positive Control				qPCR for UL83 (virus) and NRAS (host)

Figure from Karamitros, PMID 30068288



Follow-up of Screen-Positive Infants: What's Next?

Confirmation of diagnosis

Audiology referral

CBC, LFTs

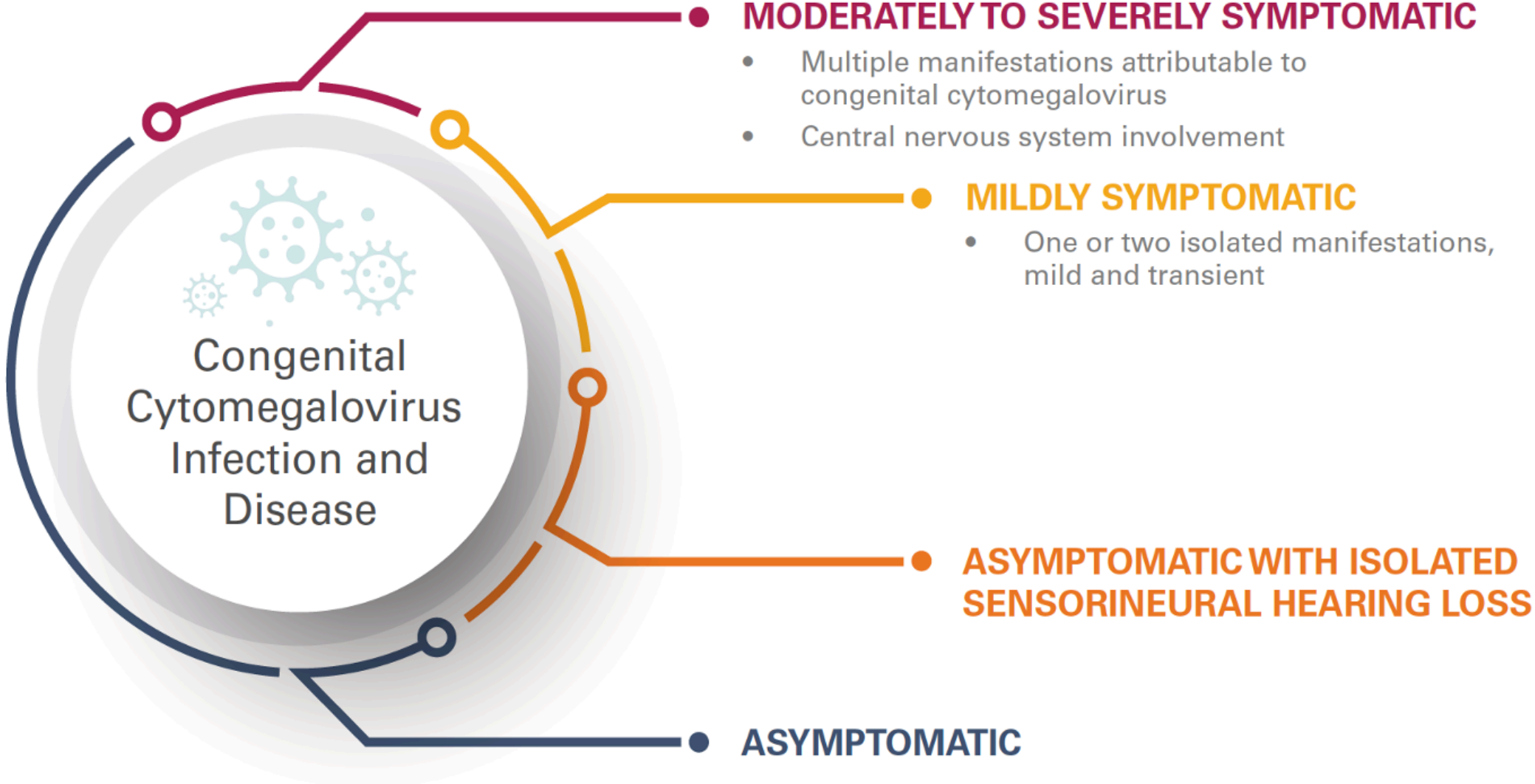
Ophthalmology

Head ultrasonography

Define disease category

- Asymptomatic
- Asymptomatic except for SNHL
- Mildly symptomatic
- Moderately to severely symptomatic

Rawlinson et al., http://dx.doi.org/10.1016/S1473-3099(17)30143-3



Shoup & Kettler (2023). Audiologist role in congenital cytomegalovirus. Audiology Today, 35(1): p.37.
Adapted from Rawlinson et al, 2017. cCMV infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis and therapy. Lancet ID 17:e177-88

JAMA Pediatrics | Original Investigation

Sensitivity of Dried Blood Spot Testing for Detection of Congenital Cytomegalovirus Infection

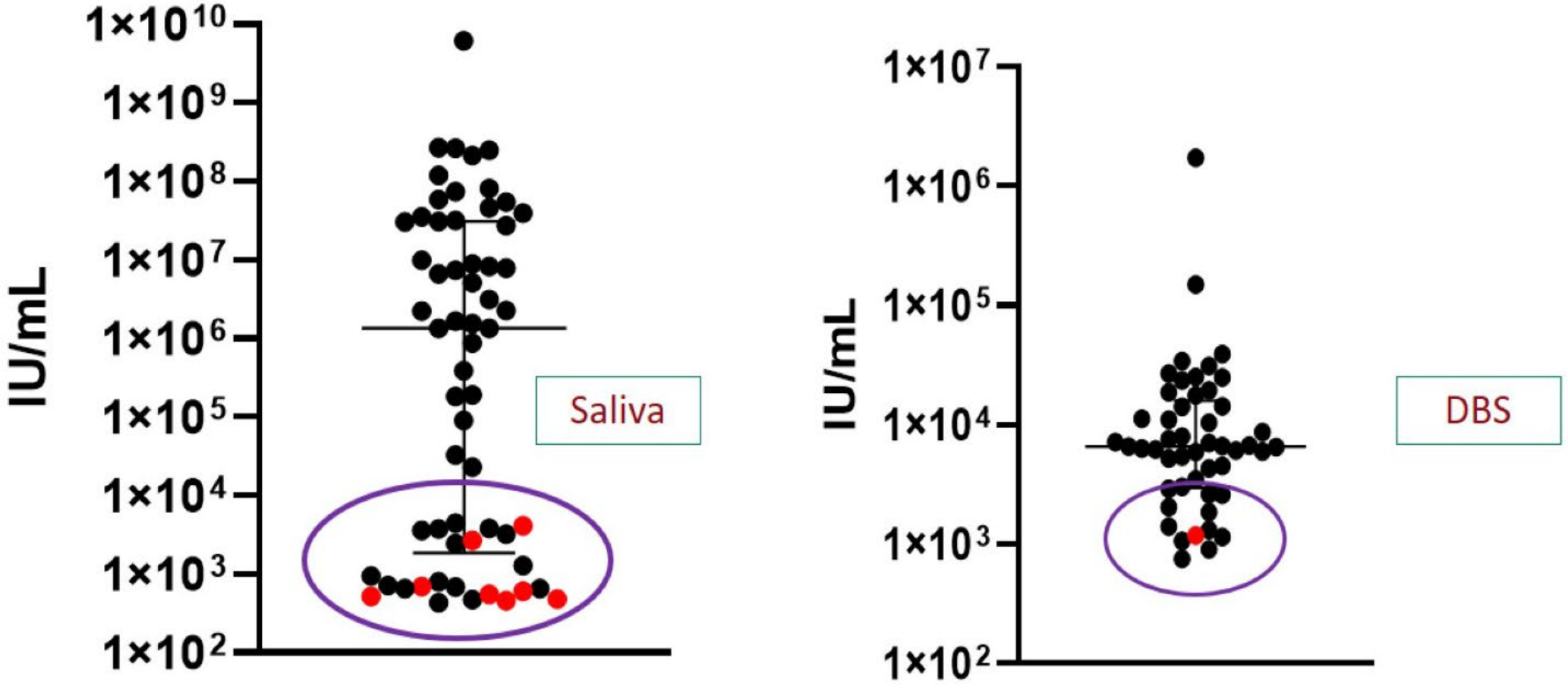
Sheila C. Dollard, PhD; Maggie Dreon, MS; Nelmary Hernandez-Alvarado, MS; Minal M. Amin, MPH; Phili Wong, MS; Tatiana M. Lanzieri, MD, MPH; Erin A. Osterholm, MD; Abbey Sidebottom, PhD; Sondra Rosendahl, MS; Mark T. McCann, BA; Mark R. Schleiss, MD

Table 2. Performance of DBS and Saliva Polymerase Chain Reaction Testing for Identifying Newborns with Congenital CMV Infection (N = 12 554)

	Saliva		DBS combined		DBS UMN		DBS CDC	
Congenital CMV infection[a]	Yes	No	Yes	No	Yes	No	Yes	No
Positive screen, No. (%)	52 (0.4)	8 (0.1)	48 (0.4)	1 (0)	41 (0.3)	0 (0)	43 (0.3)	1 (0)
Negative screen, No. (%)	4 (0)	12 490 (99.5)	8 (0.1)	12 497 (99.5)	15 (0.1)	12 498 (99.6)	13 (0.1)	12 497 (99.5)
Parameter, % (95% CI)	**Saliva**		**DBS combined**		**DBS UMN**		**DBS CDC**	
Sensitivity	92.9 (83.0-97.2)		85.7 (74.3-92.6)		73.2 (60.4-83.0)		76.8 (64.2-85.9)	
False negative	7.1 (2.8-17.0)		14.3 (7.4-25.7)		26.8 (17.0-39.6)		23.2 (14.1-35.8)	
Specificity	99.9 (99.9-100)		100.0 (100-100)		100.0 (100-100)		100.0 (100-100)	
PPV	86.7 (75.8-93.1)		98.0 (89.3-99.6)		100.0 (91.4-100)		97.7 (88.2-99.6)	
False positive	13.3 (6.9-24.2)		2.0 (0.4-10.7)		0.0 (0.0-8.6)		2.3 (0.4-11.8)	
NPV	100 (99.9-100)		99.9 (99.9-100)		99.9 (99.8-99.9)		99.9 (99.8-99.9)	

doi: 10.1001/jamapediatrics.2020.5441

Viral Load Distribution in Saliva and DBS Positives



doi: 10.1001/jamapediatrics.2020.5441

Data Overview from Screening Study

23,644 final number consented

87 confirmed cases of cCMV (3.7/thousand)

13/87 confirmed cases of cCMV only had a positive saliva

6/87 confirmed cases of cCMV were based only on DBS (2 CDC, 1 UMN, 3 both)

68/98 confirmed cases of cCMV had both a positive saliva and positive DBS

- 9 with positive saliva and CDC DBS only
- 4 with positive saliva and UMN DBS only
- 55 with positive saliva and both CDC and UMN DBS positive

https://doi.org/10.1093/ofid/ofad500.2462

Parameter	Saliva	DBS UMN	DBS CDC	DBS combined
Sensitivity	93%	72%	79%	85%
Specificity	99%	99%	99%	99%

https://doi.org/10.1093/ofid/ofad500.2462

87 infants identified with cCMV out of 23,644 total screened (prevalence of 3.7 per 1,000)

68 infants classified as asymptomatic

4 infants classified as asymptomatic with isolated SNHL

15 infants classified as symptomatic

9 infants classified as mildly symptomatic

6 infants classified as moderately-to-severly symptomatic

- 2 with delayed hearing loss
- 2 with hearing loss at initial diagnosis

2 Infants with late onset SNHL

- Asymptomatic 78%
- Symptomatic 17%
- Asymptomatic with SNHL 4.6%

In total 10/87 infants to date have demonstrated variable degrees of SNHL (11.5%)

https://doi.org/10.1093/ofid/ofad500.2462

Clinical Sensitivity

21 infants with symptomatic CMV disease at birth and/or isolated SNHL

Clinical sensitivity of saliva testing -> 20/21 = 95%

Clinical sensitivity of DBS testing (UMN) -> 17/21 = 81%

Clinical sensitivity of DBS testing (CDC) -> 19/21 = 90%

18 were treated with valganciclovir

https://doi.org/10.1093/ofid/ofad500.2462

Antiviral Therapy for cCMV

Moderate-to-Severe Symptomatic Disease Including CNS Involvement

- Six months oral valganciclovir
- Monitor for toxicity
- Improved neurodevelopmental and audiological outcomes

Isolated SNHL

- Six weeks of oral valganciclovir

Therapy should be commenced within 13 weeks of age

doi: 10.1016/j.jpeds.2024.113945
doi: 10.1016/j.jpeds.2024.113934

EDITORIAL

'Vivian Act' takes aim at underrecognized virus in babies

Minnesota could pioneer screening for congenital cytomegalovirus.

By Editorial Board | JULY 15, 2021 — 5:30PM

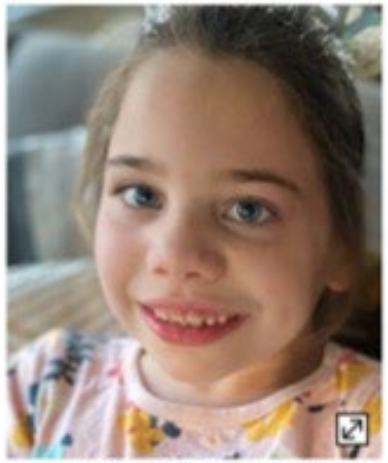


PHOTO COURTESY OF LEAH HENRIKSON

Vivian Henrikson

Seven years ago, the Henrikson family was minutes away from taking newborn Vivian home from the hospital. Then, an astute physician doing a final check on the two-day-old infant called a halt to the discharge.

"Things just kind of aren't adding up," Leah Henrikson remembers him saying. Leading up to that, Vivian had a constellation of symptoms — some jaundice, a rash called petechiae and had failed a hearing screening — but nothing that said, "Oh my gosh, we have a really sick baby on our hands."

KARE 11

News Weather Sports

Credit: Steidl Family

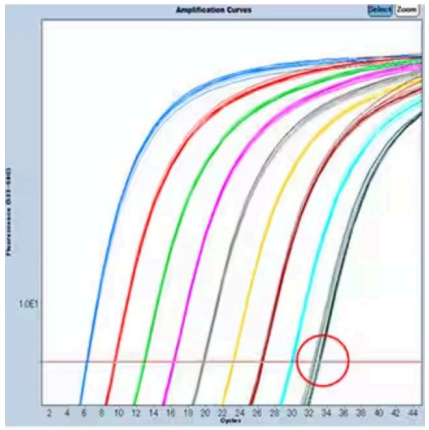
Hank Steidl was born with CMV, which caused a blind spot in one of his eyes.

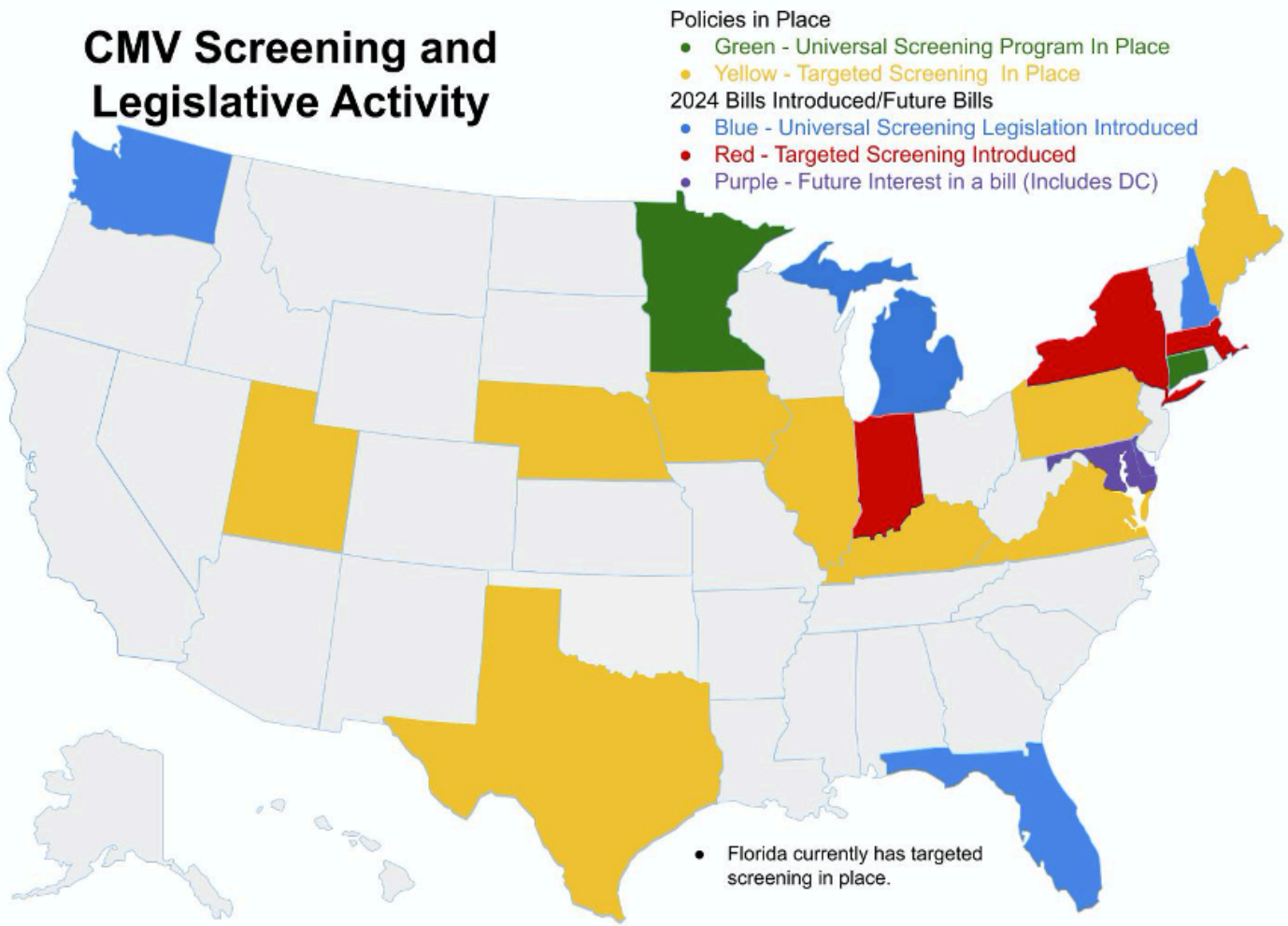
U of M researcher develops new way to screen for virus impacting babies in utero

CMV is common and usually not harmful, unless you get it while you're pregnant.

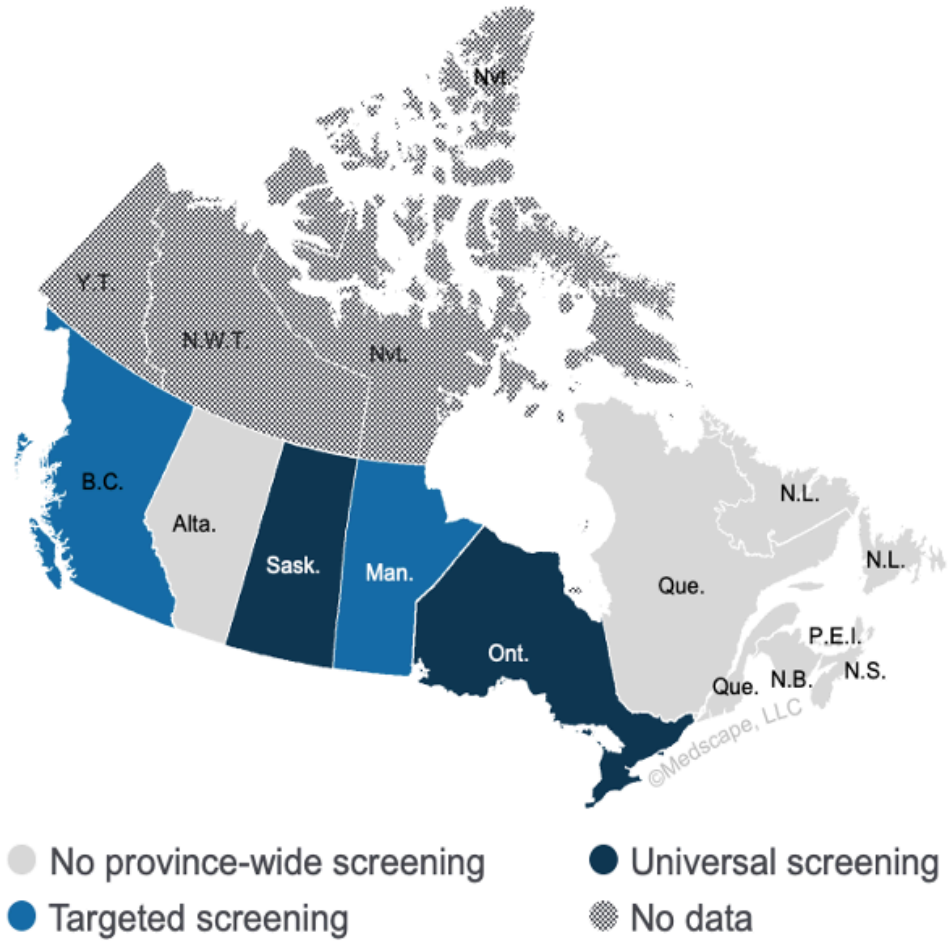
Author: **Jennifer Austin**
Published: **8:30 AM CST February 23, 2021**
Updated: **8:30 AM CST February 23, 2021**

Minnesota Newborn Screening Program Commences DBS CMV Screening on 2/8/2023





Congenital CMV Policies in Canada



www.acialliance.org/page/CMVandHearingLoss

HEALTH
University of Minnesota
Masonic Children's Hospital

Universal newborn congenital cytomegalovirus (cCMV) screening

FEBRUARY 19, 2024

It is estimated that 1 in every 200 US newborns have congenital cytomegalovirus (cCMV). Delayed identification of cCMV in newborns precludes timely intervention to mitigate sequelae of the infection such as hearing loss and other neurological complications. Newborn testing for cCMV enables appropriate diagnosis and intervention by multidisciplinary teams to properly manage the immediate consequences of cCMV, avoid unnecessary additional testing that can result from delayed diagnosis, and monitor for future complications. It is the position of the American Academy of Otolaryngology – Head and Neck Surgery that universal newborn cCMV screening is necessary to best accomplish these goals.

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY®

https://www.entnet.org/resource/universal-newborn-congenital-cytomegalovirus-ccmv-screening/

Universal Screening: Controversies and Uncertainties

CNS Imaging Findings

- Subependymal cysts
- LSV
- MRI – on which infants?

Ophthalmology evaluations

Antiviral therapy

CDC

Sheila Dollard, PhD
Tatiana Lanzieri, MD, MPH
Minal M. Amin MPH
Phili Wong MS

MDH

Ruth Lynfield, MD
Richard Danila, PhD
Maggie Dreon, MS
Sondra Rosendahl, MS
Mark T. McCann, BA
Kirsten Coverstone
Trenna.Lapacinski
Gina Liverseed
Tory Kaye

Allina Health

Abbey Sidebottom, PhD
Whitney Wunderlich, MA (lead)
Dimpho Orionzi, MS
Sirri Ngwa, MS

Children's MN

Emily Harrison, MD
Abby Meyer, MD
Tim Lander, MD
Sarah Shefelbine, MD

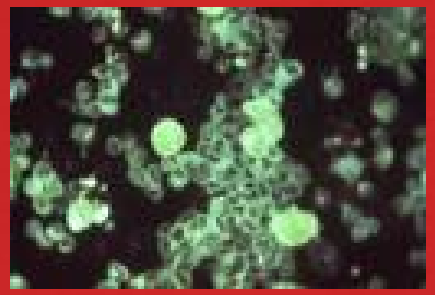
Advocates

Leah Henrikson
Stephanie Steidl
Abby Stahowiak
Kelly Fenton
Karin Housley
Michelle Benson
Dan Wolgamott

UMN

Nelmary Hernandez-Alvarado, MS
Erin Osterholm, MD
Emily Graupmann, BA (lead)
Amy Ash, BA
Kristin Chu, BS
Jensina Ericksen, RN BSN
Brittany Faanes, MPS CCRP
Amy Hanson, CCRC
Michelle Huggett, BS
Ashley Kemp, BA
Mary Pat Osborne, RN, BSN
Loralie Peterson, MPH
Angela Tipp, BS
Jenna Wassenaar, BS CCRP
Rebecca Kruc, MS
Amanda Galster, MPH
Jennifer Goldfarb
Michael Georgieff, MD
Damian Fair, MD
Jed Elison, PhD
Sally Stoyell, PhD
Igor Nestrasil, MD, PhD
Hannah Herd, AuD
Kristi Gravel, AuD
Tina Huang, MD
Alisha Olson, RN
Cecelia Mullin
Amy Kodet
Allie Forsythe
Peggy Nelson, PhD
Monica Bondy
Andres Gomez, PhD
Mark Herzberg, PhD
Craig Bierle, PhD
Tim Griffin, PhD
Joseph Neglia, MD
Adam Recknor
Elizabeth Hedin

New Horizons in Clinical Diagnosis and Treatment of Congenital CMV



Roberta L. DeBiasi, MD, MS
Chief, Division of Pediatric Infectious Diseases
Children's National Medical Center/ Children's Research Institute
Professor of Pediatrics and Microbiology/ Immunology/Tropical Medicine
George Washington University School of Medicine

Objectives

- Briefly review physical examination, laboratory and radiographic findings of congenital CMV infection
- Discuss current and prenatal and postnatal diagnostics for congenital CMV infection
- Discuss features of Symptomatic Congenital CMV infection
- Discuss current prenatal and postnatal treatments for congenital CMV
- Brief overview of clinical trials focused on maternal and infant screening, prevention, diagnosis and treatment of congenital CMV

Congenital CMV: Clinical Significance

- Symptomatic at birth (10% of infected infants)
  - 40-60% with severe neurologic sequelae
    - Sensorineural deafness (progressive)
    - Seizures
    - Intellectual Disability
    - Chorioretinitis, Optic neuritis, Microphthalmia
    - Microcephaly (Birth HC <3%), Polymicrogyria
  - 10% fatal in early infancy
- Asymptomatic at birth (90% of infected infants)
  - 10-15% present later with neurological sequelae
    - Developmental Delay
    - Progressive sensorineuronal hearing loss

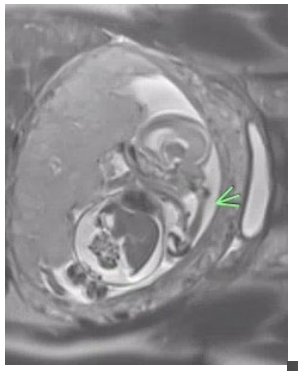
- Congenital CMV responsible for 20-25% of all hearing loss in young children

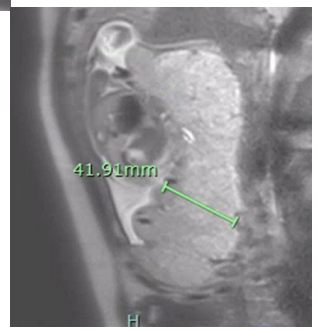
Clinical Manifestations

Prenatal Findings suggestive of Congenital CMV Infection

Ultrasound markers suggestive of fetal CMV

- **Brain**
  - Periventricular calcifications
  - Cerebral ventriculomegaly
  - Microcephaly
  - Pseudocysts: periventricular or adjacent occipital horn
  - Polymicrogyria
  - Cerebellar hypoplasia
  - Large cisterna magna
- **GI System**
  - Hyperechogenic fetal bowel
  - Ascites
  - Hepatosplenomegaly
  - Hepatic calcifications
- **Fetal growth restriction**
- **Pleural and/or pericardial effusion**
- **Amniotic fluid abnormalities** (oligo or poly)
- **Hydrops**
- **Placental abnormalities:** thickening, enlargement, heterogeneous, calcifications





Prenatal Follow-up

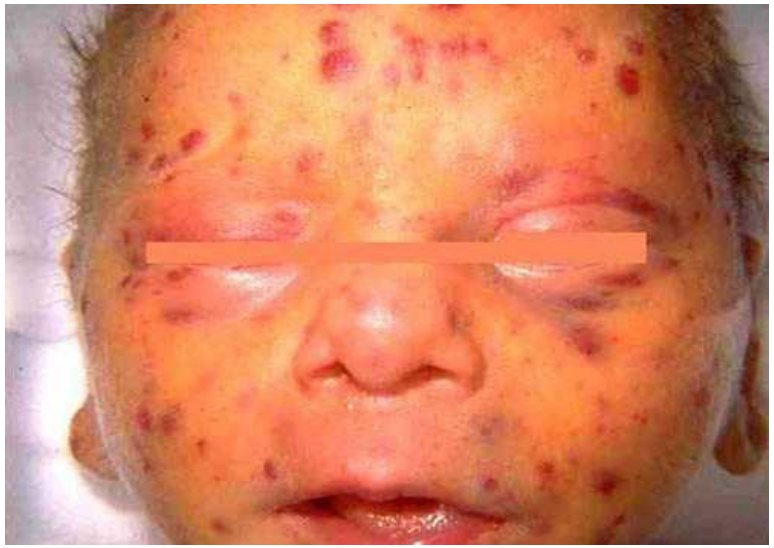
- In infected fetuses, **serial U/S** q2-4 weeks useful to detect development of abnormalities.
  - **U/S abnormalities can appear ≥12 weeks after maternal infection**
- **Fetal MRI** can diagnosis CNS findings not seen by US
- If fetus infected and U/S normal amniotic fluid **viral load has been studied to** distinguish risk of symptomatic or asymptomatic infection at birth

Children's National

Postnatal Clinical Manifestations of Congenital CMV Infection

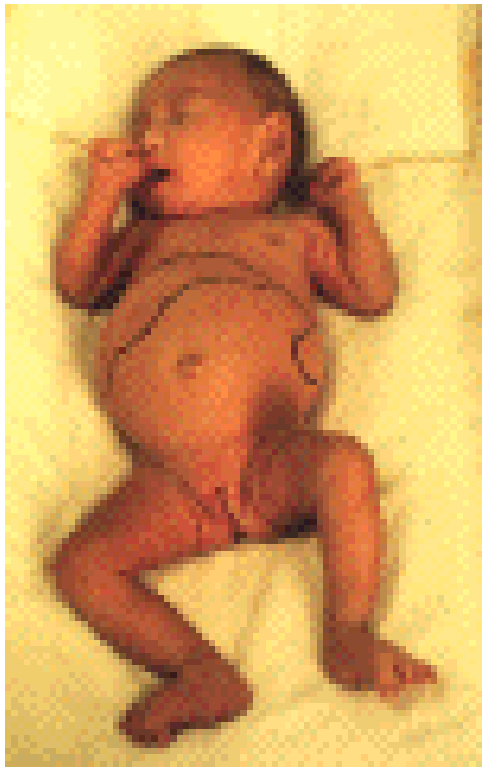
- Small for Gestational Age (<2 SD)
- Jaundice (Usually direct hyperbilirubinemia)

- Blueberry Muffin" rash:
  Extramedullary Hematopoiesis



- Petechiae, Purpura

- Hepatosplenomegaly



AAP RedBook

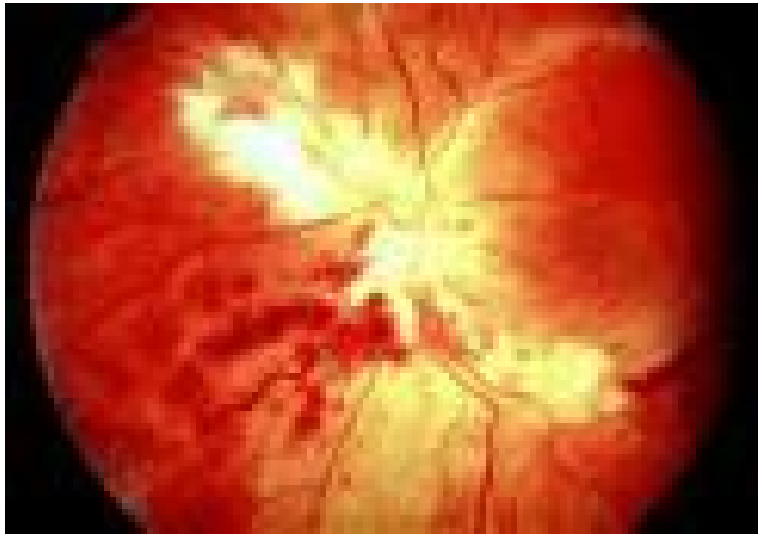
CNS Infection with Congenital CMV

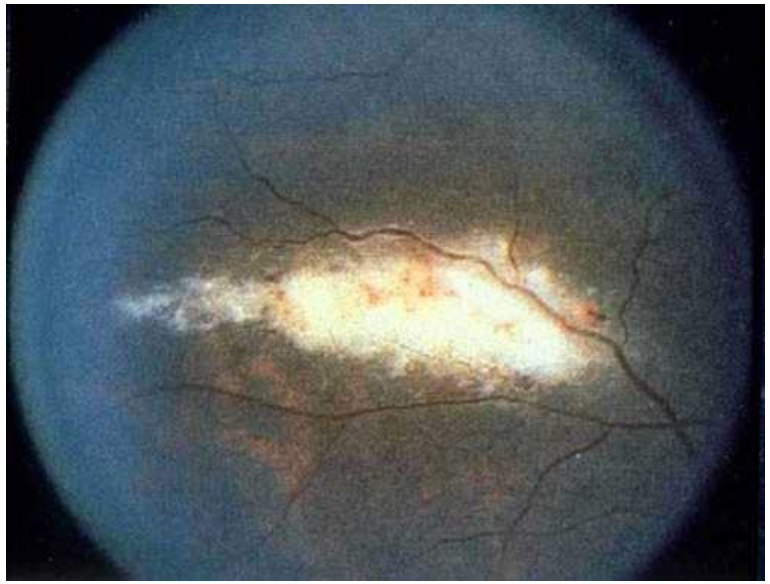
- **If CMV enters CNS early in development, significant structural damage can ensue**
  - **Unclear why** fetal/newborn brains are susceptible to CMV compared to adult brain
  - Developing cells susceptible to **lytic or apoptotic effects**
  - Structural abnormalities depend on **fetal gestational age** at infection

- **Pathogenic spectrum**
  - Lytic infection of neuronal progenitor cells in subventricular zone
  - Vasculitis- loss of supporting vessels in the developing brain
  - Meningoencephalitis- release of inflammatory mediators
- Extravasation of blood from damaged microvasculature- **calcifications**

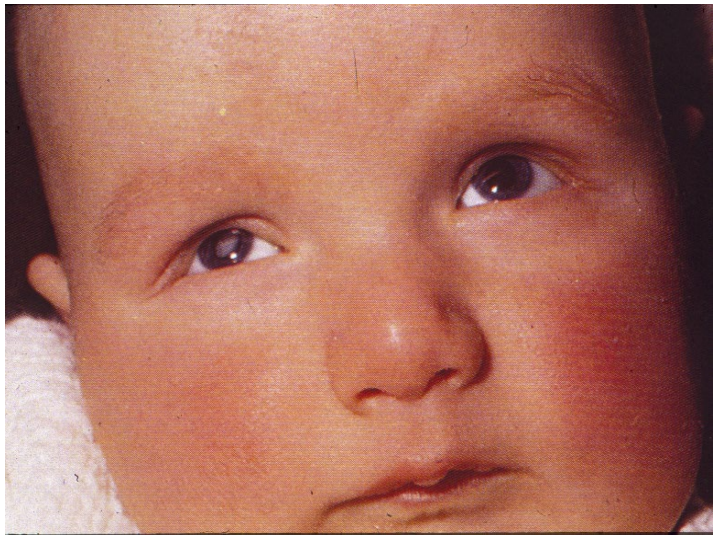
Ocular Manifestations of Congenital CMV

Chorioretinitis





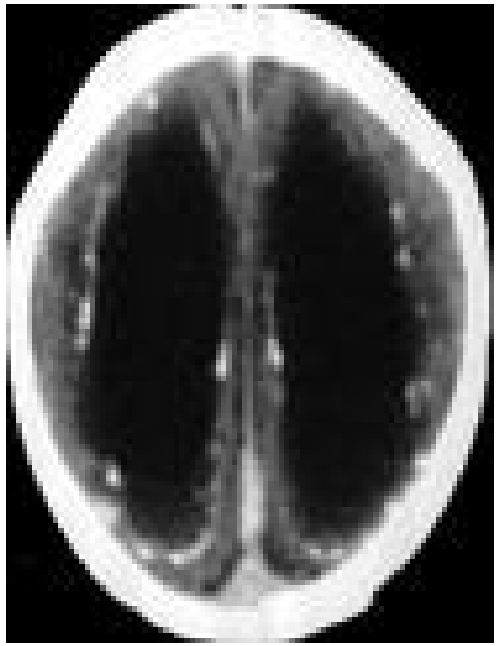
Cataract



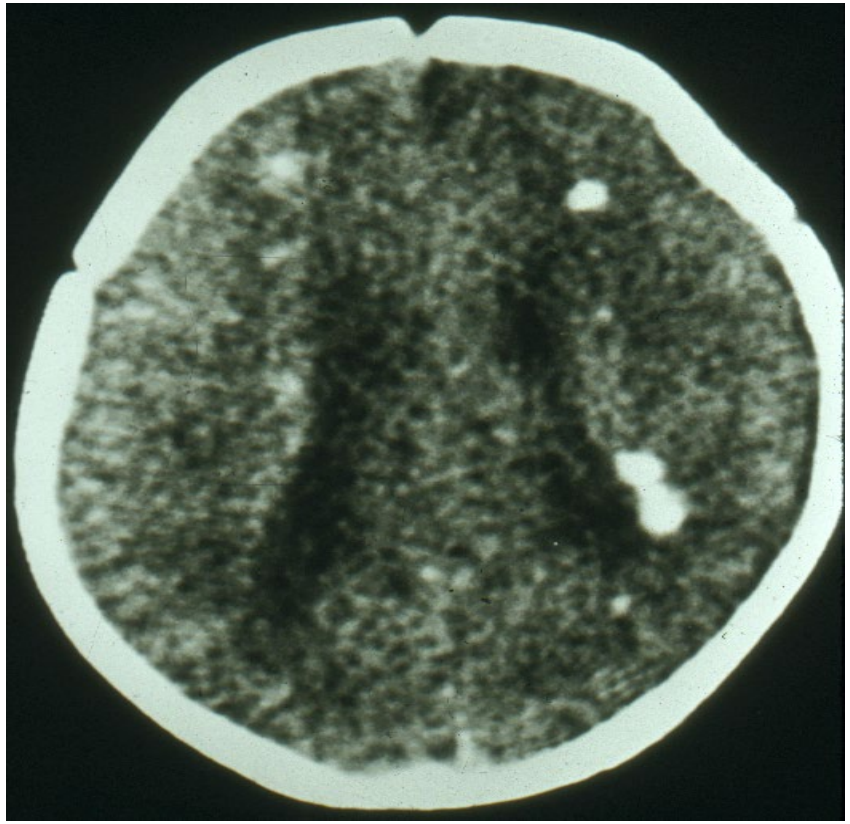
AAP RedBook

CNS Manifestations of Congenital CMV Infection

- Lethargy, Poor Suck, Hypotonia
- Hydrocephalus



- Periventricular Calcifications



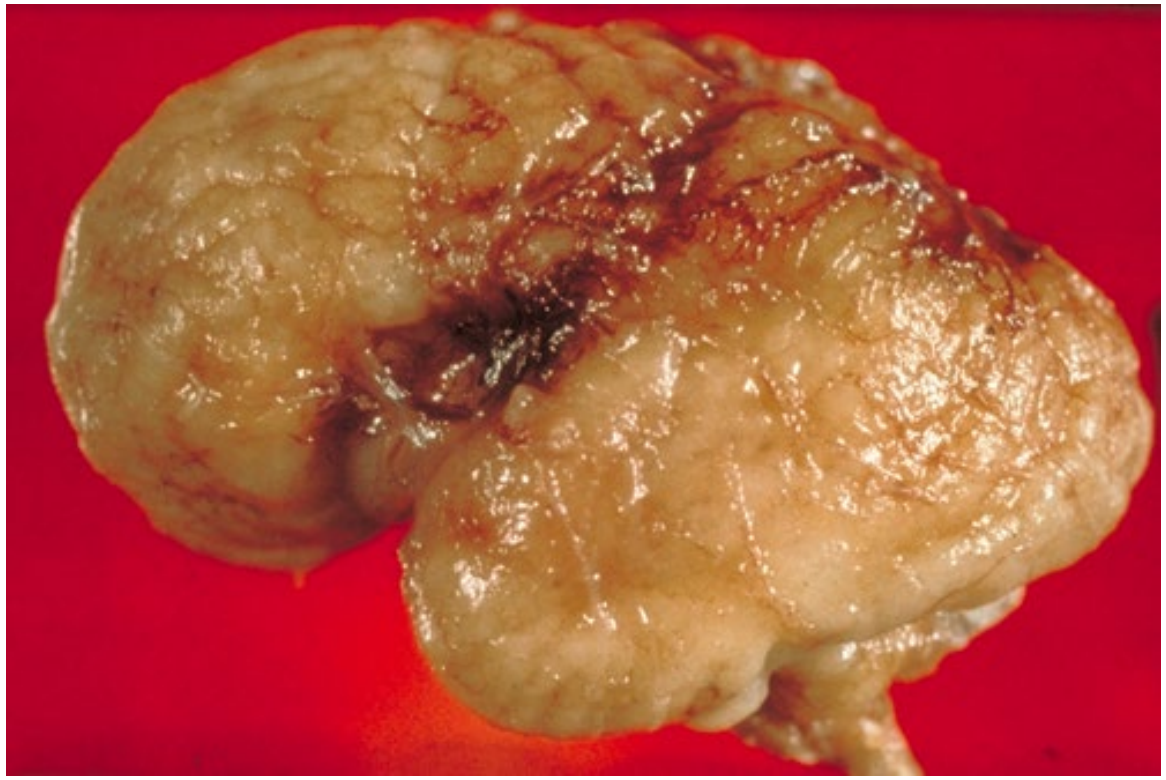
- Periventricular Cysts, Subependymal pseudocysts
- White matter abnormalities
- Cortical atrophy, Migration disorders

AAP RedBook

CNS Manifestations of Congenital CMV

- Most critical period for malformations and disruptions is the 3rd-8th week of gestation
  - Microcephaly (HC <2 SD)
  - Polymicrogyria

- CMV infection in the third trimester can cause encephalitis



Microcephaly, abnormal gyral pattern

AAP RedBook

Atrophic cortex, dilated ventricles, periventricular calcifications

AAP RedBook

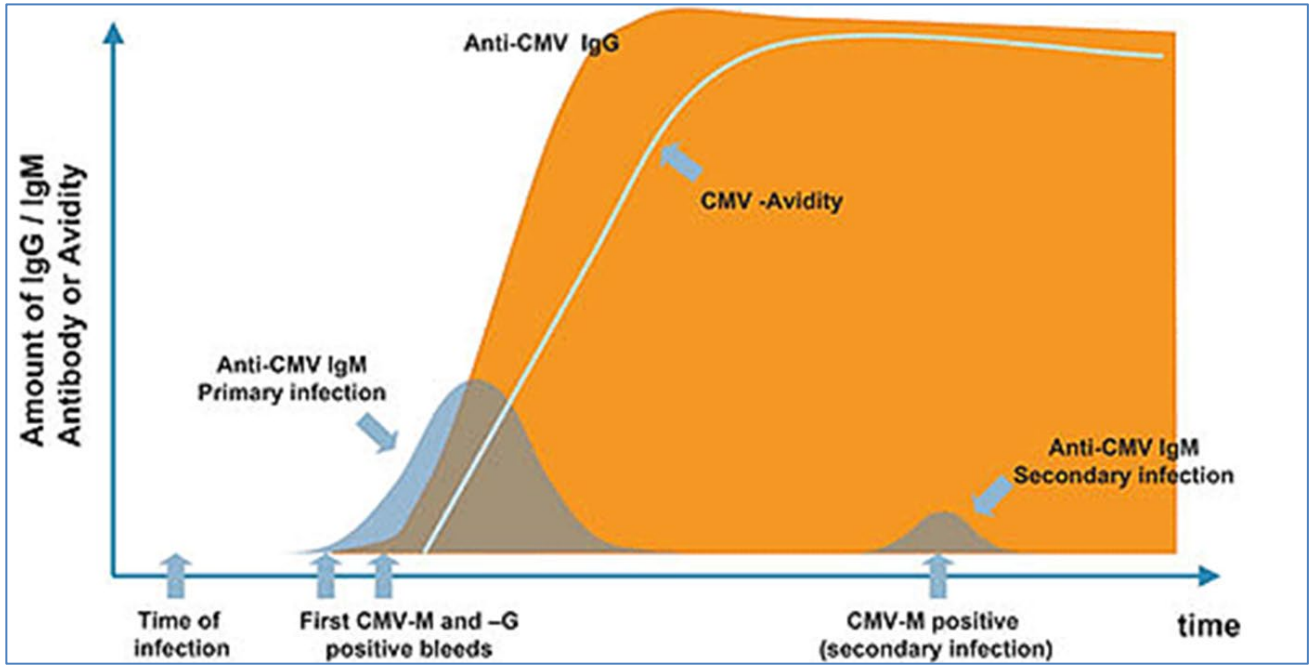
Hearing Loss in Congenital CMV

- **Hearing loss- most common long-term sequelae**
  - Pathogenesis poorly understood
  - Variable: Mild to Profound; Unilateral or Bilateral
  - Can progress after perinatal period
- Incidence 10-15% overall:
  - Majority of bilateral hearing loss in symptomatic
  - Majority unilateral in asymptomatic group (Goderis et al)
- **Lack understanding of mechanisms** for viral-induced damage to developing auditory system
- Some **fetopsy studies have shown** inflammatory cell infiltrate and involvement of vestibular system
- Animal models show **virus + inflammation necessary** for ear pathology
- Treatments currently target viral replication – some studies proposed to target host inflammatory responses

Diagnosis

Prenatal Serologic Diagnosis of CMV in Mother

- Ideally, serostatus known prior to pregnancy
- If CMV IgG and IgM both negative
  - identifies seronegative mother at risk
- If CMV IgG and IgM both positive
  - either primary infection or reactivated disease
- **IgG Avidity** can help sort out:
  - Low avidity IgG = acute or recent infection
  - High avidity IgG = infection in past
    - If high avidity IgG Ab present in first trimester (first 12-16 weeks gestation), risk of CMV transmission to fetus is low
- If only CMV IgG positive; IgM negative
  - Prior infection likely
  - But if obtained for first time from pregnant mother with symptoms or abnormalities on prenatal imaging, avidity may assist



Amniotic Fluid CMV PCR

- Sensitivity 90-98% ; Specificity 92-98%

- **Must be done >6 weeks after symptom onset and >22 weeks gestation**

- Research Question:
  - Are their threshold AF CMV viral loads predictive of symptomatic disease? Not known; conflicting results:
  - Lazzarotto et al
    - $\geq 10^3$ copies/mL; 100% risk for congenital infection
    - $\geq 10^5$ copies/mL; predictive of symptomatic congenital infection
    - <500 copies/mL; unlikely symptomatic congenital infection
  - Other groups
    - No Clear cutoffs; considerable overlap
    - If negative, infection unlikely, but not ruled out

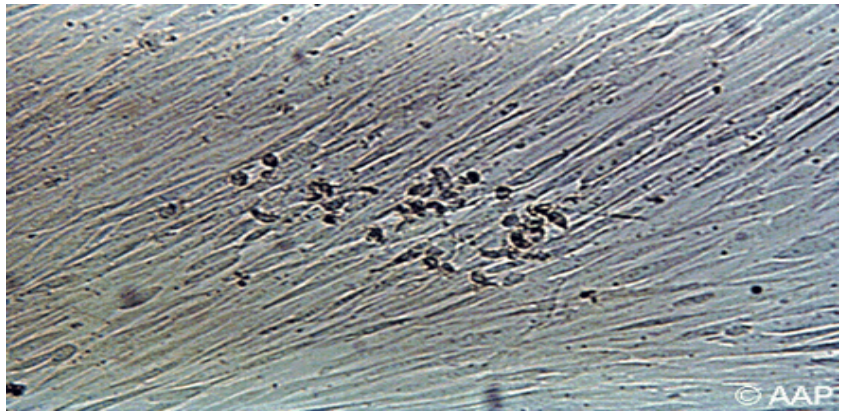
Lazzarotto, JPeds, 2000
Goegebuer, J Clin Microbio, 2009

Postnatal Laboratory Diagnosis of Congenital CMV

- Must be diagnosed in first 3 weeks of life

- CMV PCR (has largely replaced culture)
  - Urine
  - Saliva
  - Neonatal Blood Spot
    - Lower sensitivity: 40-50%
  - Blood
  - CSF

- Serology- less of a role
  - CMV IgG (maternal transfer)
  - CMV IgM (unreliable)



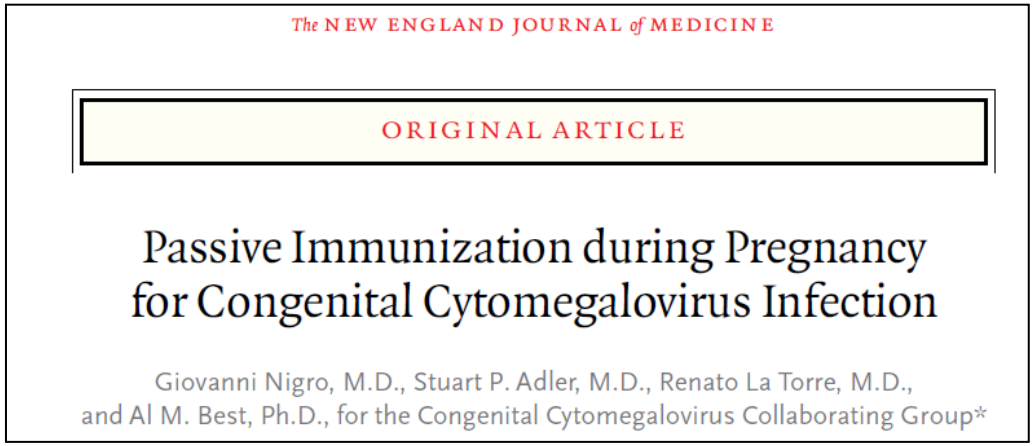
Postnatal Evaluation to Identify Symptomatic Congenital CMV Infection

- Growth parameters (HC, Weight, Length) to identify nonsymmetric SGA
- Careful physical exam: Liver, Spleen, Skin, Eyes
- CBC with Differential (Anemia, Thrombocytopenia)
- Liver Panel (ALT, Total and Direct Bilirubin)
- Head Ultrasound (and/or MRI)
- Ophthalmologic Exam to evaluate for retinitis
- Newborn Hearing Screen, repeated if failed, BAER if consistently failed

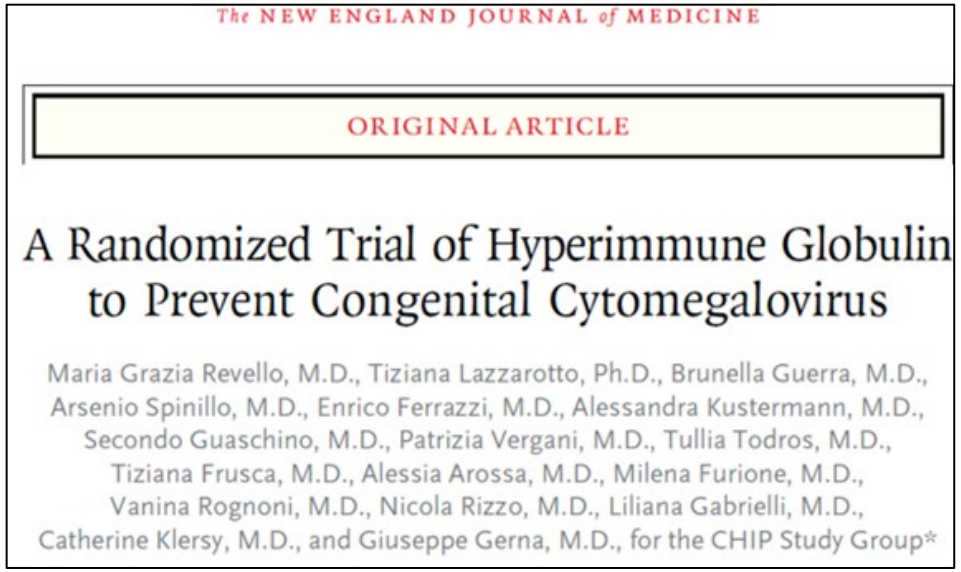
Treatment

Prenatal Treatment:
Hyperimmune CMV Immunoglobulin Not Recommended

- 2005: **Uncontrolled** clinical trial (Nigro)
  - Protective vs. symptomatic disease in Treatment and Preventative Groups
  - Significantly increased CMV-specific IgG concentrations and avidity
  - No adverse effects
  - Raised enthusiasm for controlled clinical trial

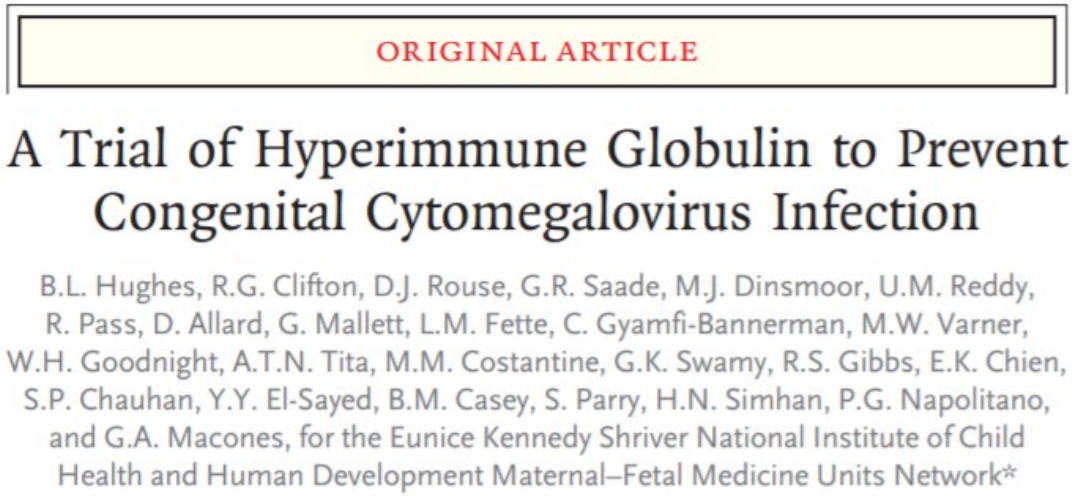


- 2014: **Randomized Controlled Trial** (Revello)
  - No differences in incidence of congenital infection
  - No difference in clinical outcome of congenital infection
  - No differences in virus-specific antibodies, T cell response, viral DNA blood
  - Adverse events higher in treated vs. placebo



Prenatal Treatment: 2021 Randomized Trial Hyperimmune CMV globulin

- Randomized, double blinded,
- Recruitment 2012-2018,
- 399 women with primary CMV infection in pregnancy dx prior to 23 weeks gestation
- **Trial stopped early for futility**
- No differences in:
  - Infection of the Fetus or Neonate
  - Death
  - Preterm Birth
  - Birthweight <5th percentile
- Adverse Events in Treatment Group
  - Severe allergic reaction
  - Higher incidence Headache, Shaking Chills .



ORIGINAL ARTICLE

A Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus Infection

B.L. Hughes, R.G. Clifton, D.J. Rouse, G.R. Saade, M.J. Dinsmoor, U.M. Reddy, R. Pass, D. Allard, G. Mallett, L.M. Fette, C. Gyamfi-Bannerman, M.W. Varner, W.H. Goodnight, A.T.N. Tita, M.M. Costantine, G.K. Swamy, R.S. Gibbs, E.K. Chien, S.P. Chauhan, Y.Y. El-Sayed, B.M. Casey, S. Parry, H.N. Simhan, P.G. Napolitano, and G.A. Macones, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

Hughes et al, NEJM, 2021

Prenatal Treatment: Antiviral Intervention

Ganciclovir: Cannot use ganciclovir in utero (mutagenic, gonadotoxic)

Valacyclovir: Oral, high dose 8 grams/day

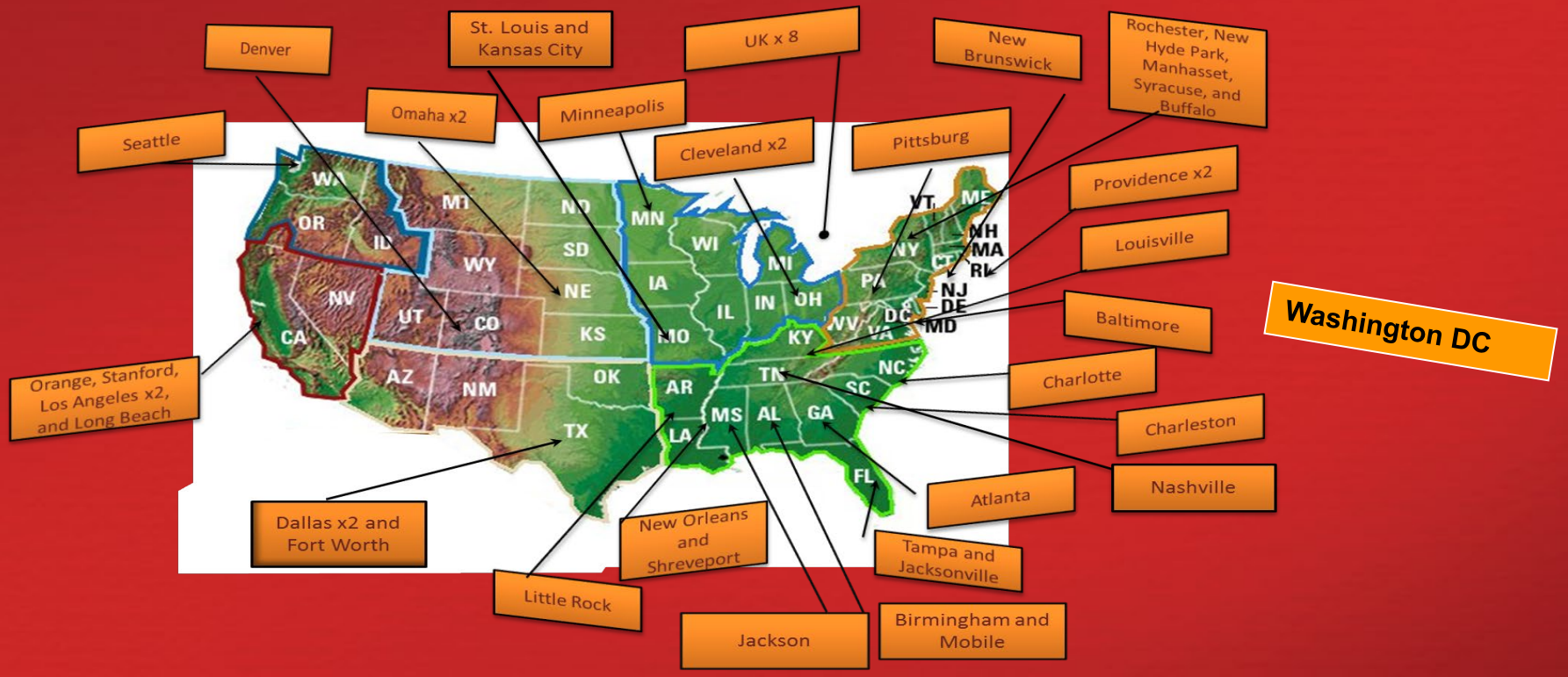
- **Shahar- Nissan–** Randomized double blind/placebo/controlled trial to prevent vertical transmission in a known positive mom (Lancet)
  - 100 women; 8 grams/day divided BID
  - No safety issues
  - Reduction in amniocentesis PCR positivity in treated compared to non treated women

- **Jacquemard–** Observational study of pregnancies affected by CMV with confirmed fetal infection
  - 20 women; 8 grams/day dose
    - No safety issues
    - Demonstrated decreased circulating fetal viral load

- **Leruez-Ville (2016)–** In utero treatment of congenital CMV (babies with + amnio PCR) - open label phase II.
  - 43 women; 8 grams/day divided QID
    - No safety issues identified
    - 82% infants asymptomatic vs. 43% symptomatic historical comparison cohort
    - Fetal Viral Loads decreased on treatment

Postnatal Antiviral Treatment Trials to Define Standard of Care for Infants with Congenital CMV

NIH/NIAID Collaborative Antiviral Study Group (CASG)
NIH/NIAID Congenital and Perinatal Infections Consortium (CPIC) - 2019



Pivotal Postnatal Antiviral Treatment Studies

- **CASG 102: 1991-1999**
  - Randomized to 6 weeks intravenous ganciclovir 6 mg/kg q12 or no treatment for symptomatic CNS Disease
  - Treatment group OR 5.03 for normal or improved hearing in best ear at baseline and 6 months
  - Untreated group much more likely to have hearing loss at 6 months (OR 21.1) and 1 year (OR 10.26)
    - Kimberlin et al, *J Peds 2003*

- Follow-on neurodevelopmental study of same patients
  - Treated had fewer number of delays on Denver Developmental Inventory at 6 months, 1 year of age
    - Oliver et al, *J Clin Virol* 2,009

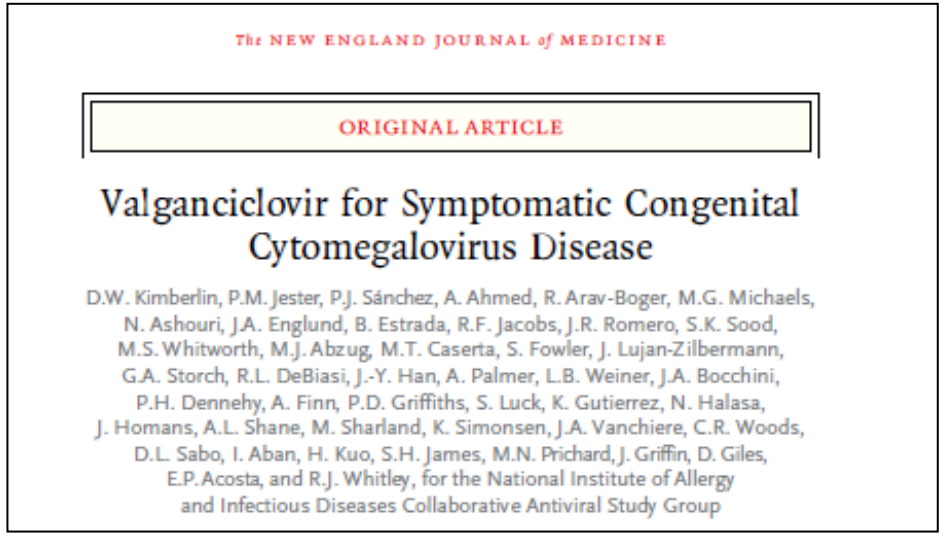
- Drawbacks:
  - Requirement for prolonged PICC line
  - Neutropenia
  - Potential nephrotoxicity, cancer risk, gonadal toxicity

- Other Observations and Rationale for Subsequent Trials
  - Viremia suppressed while on ganciclovir but…viral load rebounded after discontinuing therapy
  - Sensorineuronal hearing loss is known to be progressive over first years of life
  - Suggested that more prolonged suppression of viral load could be beneficial to hearing and neurodevelopment

CASG 112:
A Phase III, Randomized, Placebo-Controlled, Blinded Investigation of 6 Weeks vs. 6 Months of Oral Valganciclovir Therapy in Infants with Symptomatic Congenital Cytomegalovirus Infection

- Objectives
  - To compare impact on hearing of six weeks versus six months of oral valganciclovir 16 mg/kg bid in infants with symptomatic congenital CMV disease
  - To compare safety profiles
  - To compare impact on neurodevelopmental outcomes at 1 and 2 yrs of age

- Results
  - At 6 months:
    - No Differences in best ear hearing between groups
  - At 1 and 2 years:
    - Hearing more likely to improve or stabilize in the 6 month vs. 6 week treatment group
  - Neurodevelopmental: Improved Bayley Language Composite and Receptive Communication Scales
    - Less toxicities compared to IV therapy


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease

D.W. Kimberlin, P.M. Jester, P.J. Sánchez, A. Ahmed, R. Arav-Boger, M.G. Michaels, N. Ashouri, J.A. Englund, B. Estrada, R.F. Jacobs, J.R. Romero, S.K. Sood, M.S. Whitworth, M.J. Abzug, M.T. Caserta, S. Fowler, J. Lujan-Zilbermann, G.A. Storch, R.L. DeBiasi, J.-Y. Han, A. Palmer, L.B. Weiner, J.A. Bocchini, P.H. Dennehy, A. Finn, P.D. Griffiths, S. Luck, K. Gutierrez, N. Halasa, J. Homans, A.L. Shane, M. Sharland, K. Simonsen, J.A. Vanchiere, C.R. Woods, D.L. Sabo, I. Aban, H. Kuo, S.H. James, M.N. Prichard, J. Griffin, D. Giles, E.P. Acosta, and R.J. Whitley, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

Kimberlin et al , *NEJM,* 2015

Symptomatic cCMV and Treatment Decisions : Congenital Cytomegalovirus: A European Expert Consensus Statement

Disease Manifestation	Treatment Recommendation	Level of Evidence
Consensus		
CNS disease Microcephaly, CNS calcification, chorioretinitis White matter changes (or other abnormalities on MRI consistent with CMV disease)†	Ganciclovir/valganciclovir: duration 6 months*	Treatment: Quality A, Strength 1 (to treat) Duration: Quality B, Strength 2
Other "severe" disease (includes life-threatening or severe single-organ or multiorgan non-CNS disease)	Ganciclovir/valganciclovir: minimum of 6 weeks, up to 6 months*‡	Treatment: Quality B, Strength 1 Duration: Quality B, Strength 2
"Mild" disease: isolated or transient disease (eg, jaundice, Petechiae, SGA in isolation; max 2 abnormalities)	No treatment	Treatment: Quality C, Strength 2 (for no treatment)
No clinical or biochemical findings of disease (± detectable CMV viremia)	No treatment	Treatment: Quality D, Strength 1 (for no treatment)
Majority opinion: but not consensus		
Isolated hearing deficit*§	Ganciclovir/valganciclovir: Duration 6 months*	Treatment: Quality C, Strength 1 Duration: Quality C, Strength 2
"Moderate" disease (see text for definition; eg, multiple minor findings consistent with CMV disease)*	Consider treatment after discussion with specialist Duration: Minimum of 6 weeks and up to 6 months*	Treatment: Quality C, Strength 2 Duration: Quality B, Strength 2

There is currently only evidence for starting treatment in the first month of life.

*Limited evidence without full consensus: see text for further description.

†In the case of isolated, nonspecific MRI findings that are not consistent with cCMV disease, it was agreed that treatment is not necessarily indicated.

‡It was suggested (without consensus) that treatment might continue in this group until the underlying clinical manifestation of disease (eg, hepatitis) resolved because benefit of 6 months treatment is unclear.

§No studies address this particular group, although they were included in eligibility criteria for treatment in both published RCTs of treatment.

Luck et al, PIDJ 2017

Other Recommended Interventions for cCMV Infants

- Dose Adjustment and Toxicity Monitoring while on Oral Valganciclovir
- Audiologic Evaluations 6 months for first 5 years of life then annually until 8 years of life
- Early Intervention Programs
- Neurologic and Neurodevelopmental assessments every 6 month to 1 year – ASQ
- Followup with ID annually through school age
- PT/OT as needed

The Future: Active Congenital CMV Research - 1

- ClinicalTrials.gov:
  - 61 Trials (US and International) focusing on Congenital CMV

<u>Targeting Prenatal Period</u>:

- Identification of Prenatal/fetal biomarkers
  - Maternal viral load, cytokines, genetics
  - Proteomics

- Prenatal Intervention/Treatment
  - Prevention with behavioral modification (hygiene) to avoid infection in seronegative moms
  - Prevention with vaccine
  - Prevention with passive immunity
  - **Prevention using antiviral therapy: valacyclovir, letermovir**

The Future: Active Congenital CMV Research – 2

Targeting Postnatal Period:

- **Postnatal Universal and Targeted Screening**
  - Screen (PCR) all newborns
  - Screen (PCR) subset of newborns who fail newborn hearing screen, or other abnormal parameters

- **Postnatal Treatment**
  - Monoclonals
  - Cytotoxic T Lymphocyte therapy
  - Newer antiviral agents – **Letermovir: CPIC study as adjunctive therapy starting now!**
  - Expansion of valganciclovir treatment to asymptomatic infants
  - Expansion of treatment to beyond the neonatal period
    - **CASG 204 complete: Screened and treated subset of infants (1 month-4 years of age) who developed postnatal sensorineuronal hearing loss**
      - **Neonatal blood spot PCR for retroactive dx of congenital CMV**
      - **Randomized to treatment with valganciclovir for 6 weeks vs. placebo**
      - **Results: No differences in hearing outcomes, but small N**
        - ***Kimberlin et al, JPeds 2024***

Children's National Congenital Infection Program

Program Highlights

- Multidisciplinary
- Innovative research.
- Seamless process, support services
- Advanced fetal-neonatal imaging

Roberts DeBiasi
Co-Director,
Congenital Infection Program
Division Chief
Infectious Disease

Sarah Mulkey
Co-Director,
Congenital Infection Program
Prenatal-Neonatal Neurologist

Adre DuPlessis
Division Chief,
Prenatal Pediatrics Institute

Congenital Infections

- Chagas
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Enterovirus
- Herpes simplex virus (HSV)
- HIV/AIDS
- Lyme disease
- Lymphocytic choriomeningitis virus (LCMV)
- Malaria
- New emerging threats, SARS CoV-2
- Parvovirus B19
- Rubella
- Serious bacterial infection or other viral infection in the mother, including seasonal influenza
- Syphilis
- Toxoplasmosis
- Zika virus (ZIKV)

https://childrensnational.org/departments/congenital-infection-program

Children's National

Living with Congenital Cytomegalovirus: Parent Perspectives

Megan H. Pesch, MD, MS
Clinical Assistant Professor
Developmental and Behavioral Pediatrics
University of Michigan

Disclosures

Immediate Past President of the National CMV Foundation
Consultant for Moderna and MedScape
Research funding NICHD

Table of Contents


STOP
ALL WAY
1
2
3

Therapies

- Early Intervention
- Speech therapy
- Occupational therapy
- Physical therapy
- Parent coaching

Specialists

- Otolaryngology
- Audiology
- Ophthalmology
- Physical Medicine and Rehabilitation
- Developmental Pediatrics
- Infectious Diseases
- Immunology


National CMV Foundation
CMV is...
SERIOUS
COMMON

Ann Arbor Michigan → St Louis Missouri

St Louis, Missouri → Michigan

Pregnancy

- Most women not counseled
- Findings on imaging
- Many doctors misinformed (antibodies)
- Specialist referrals with limited options

Treatment in pregnancy

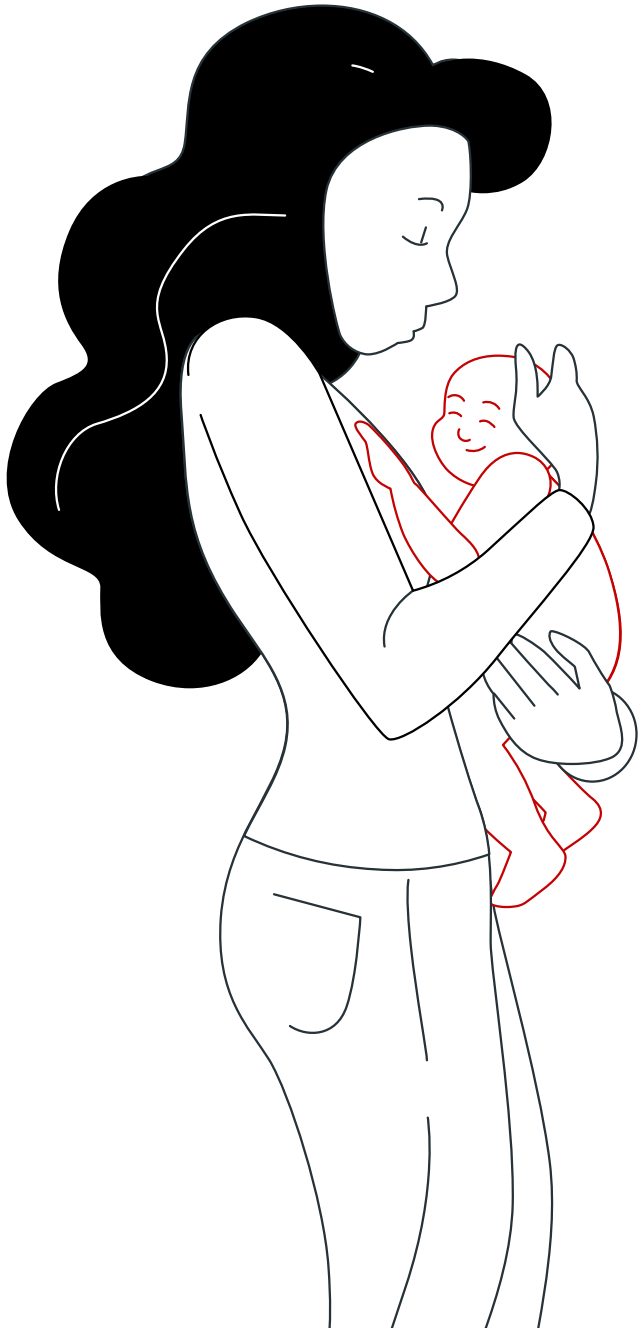
- In the US antivirals not recommended
- Mothers supporting other mothers online
- Traveling to providers who will take a chance
- Termination may be offered before antivirals

Treatment in pregnancy

"I'm so thankful for this online community. There is such a depth of knowledge from this group I am just really thankful for. None of the doctors know what to do. I am the one bringing them ideas from this group!"

"My doctor said we can't do antivirals. I'm so scared about what's going to happen. Does anyone know any MFMs in XXXX who will at least talk to me about antivirals?"

* Quotes paraphrased from social media



Diagnostic odyssey

Infancy

- Unexpected role as a medical parent
  - Anger, feeling of betrayal
  - Precious moments lost

Living with cCMV

"The hardest thing is the lack of awareness and knowing that (we) were not given the knowledge to prevent this"

"(We) were robbed of the ability to try to reduce the risk of (cCMV in pregnancy)"

* Quotes summarized from FDA Parent Listening session

Diagnostic odyssey

"By the time we found out about her CMV it was too late for treatment"

"We saw so many specialists, (he) got so many tests. We were told that he probably had a fatal genetic condition. No one ever mentioned CMV."

* Quotes paraphrased from social media

Misinformation and discrimination

“ The nurse literally ran out of our room when she found out (our baby) had CMV. She said she was expecting and couldn’t risk taking care of our baby”

“ My infectious disease doctor told me I should keep away from other people. She was wearing a full Tyvek suit when we was talking to me. I walked away from that appointment thinking I had serious infectious disease and was a risk to her and other people ”

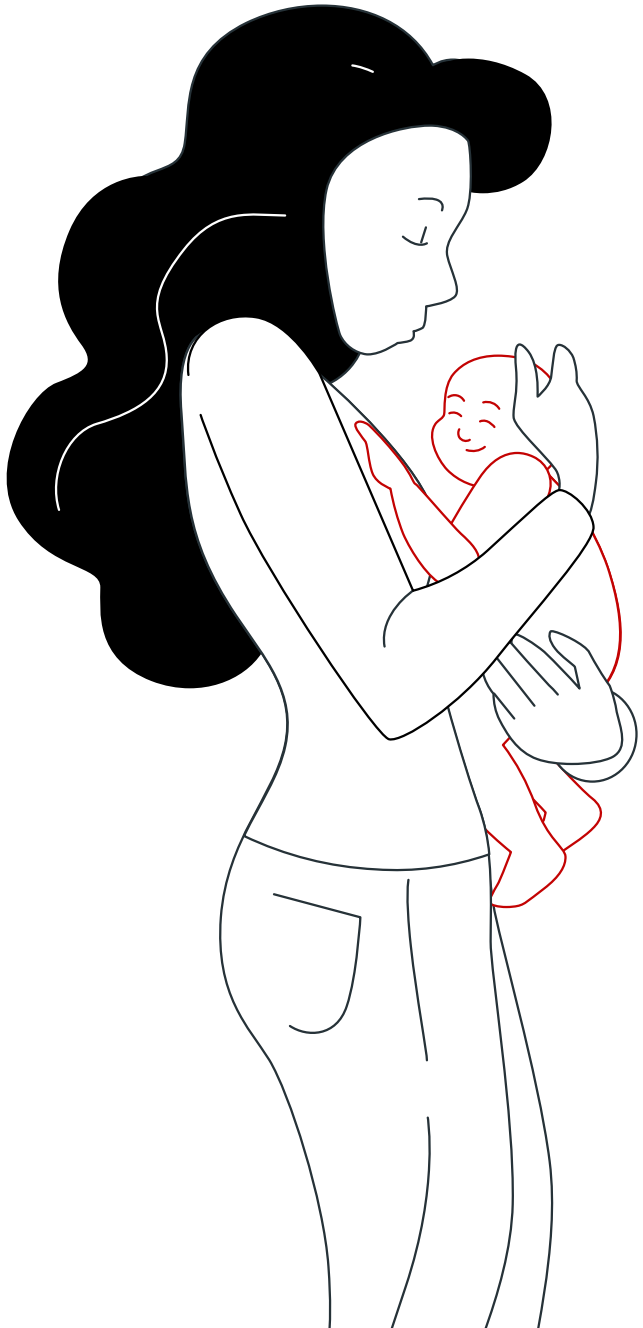
* Quotes summarized from parents on Instagram

Misinformation and discrimination

“ My son was kicked out of daycare before he even started. The daycare director called the State Health Dept, and they told her that my baby was a risk to their staff”

“ We don’t tell anyone about (his) diagnosis anymore. We’ve been shunned too many times. I want to be open but I do not want him or my older child excluded from activities or social opportunities”

* Quotes summarized from parents on Instagram



Family life

- “Educating by just existing”
- “Every single part of (our) lives has been affected. There are so many little things”
- Leaving or changing employment, stress on marriage, siblings feeling left out

Zappas et al, 2023; quotes from FDA PLS

Early Childhood and Beyond

- Anticipatory grief
- CMV Warriors
- Comparisons to peers can be painful
- Growing family is a complicated decision and planning for the future is challenging

Zappas et al, 2023

Fear of the Unknown

“We live with anticipatory fear, wondering what else will happen. When will her hearing get worse, will there be a point when we can’t control her seizures? What will life be like for her when we are no longer around. In some ways I hope I outlive her”

* Quotes summarized from parents on Instagram

Life after loss – Dakota's story

"If we had known about the CMV earlier we could have made decisions as parents for her. But the medical system made those decisions for us. We both worked in healthcare and we had a 2 year old at home. No one said anything."

"I'm still mad because we were at a large medical center in XXX. There's lots of resources. And it seemed everyone just didn't want to liability of treating a pregnant woman…. We are both pharmacists, we understand the risks better than anyone"

Life after loss – Dakota's story

"When she was born we were told she had a 1/3 chance of being deaf. No one told us the whole truth about how bad CMV could be. And Dakota had the worst case scenario"

"I felt like the whole 34 days she was in the NICU (until she passed away) no one was ever completely honest with us"

Life after loss – Dakota's story

"We recently passed a law in Washington State. I'm willing to answer any questions you have. I just want to continue being a parent to my daughter even though she's not here. I will help however I can. "

Summary

- CMV is the worst but our kids are the best
- We need more awareness
- Families deserve answers and treatment
- Lives are lost to lack of knowledge and lack of treatment

Thank you

pesch@umich.edu

@DrCMVMom

@MeganPeschMD

Megan H Pesch, MD, MS

@Megan.PeschMDMS

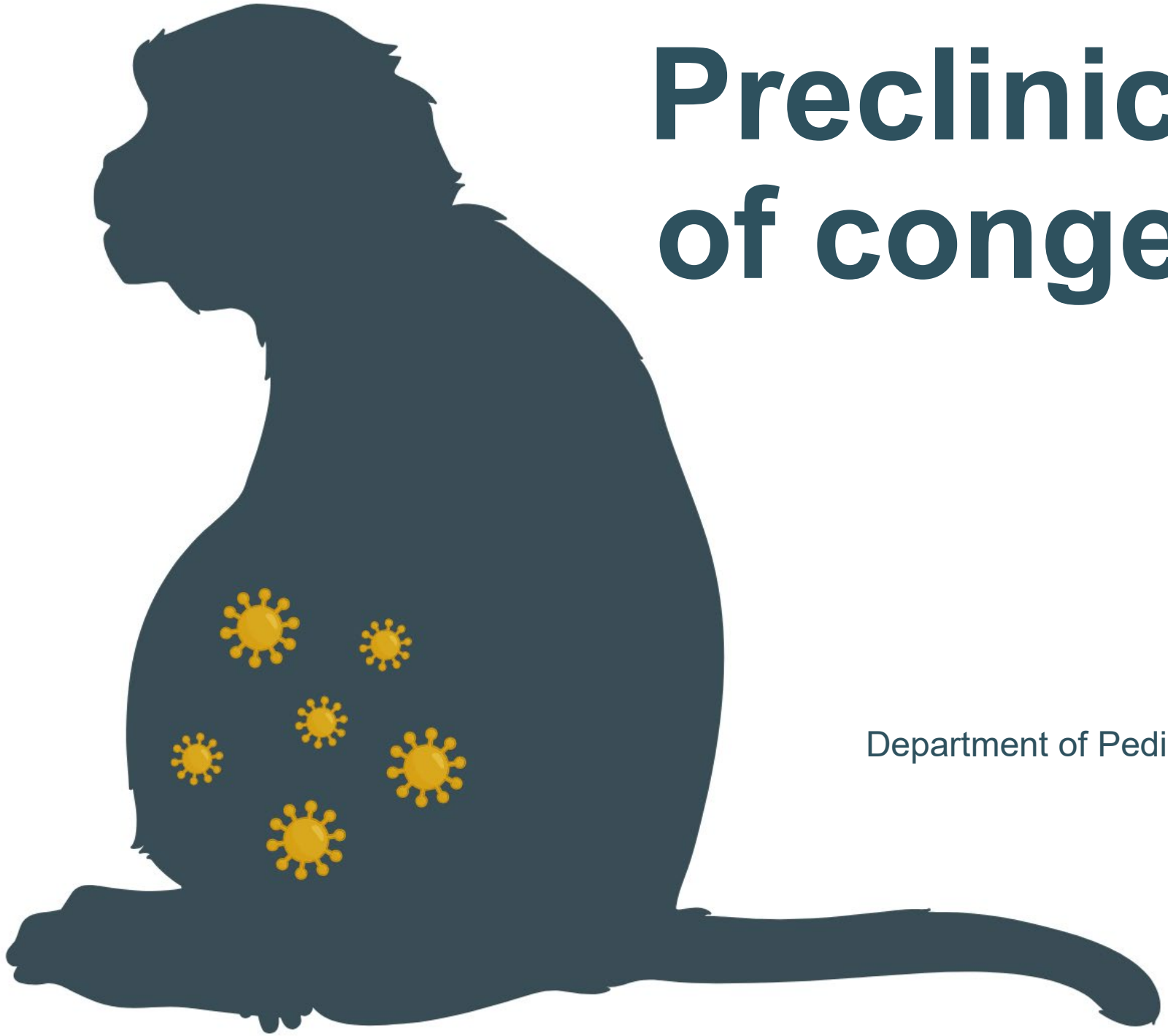
U.S. FOOD & DRUG ADMINISTRATION

Clarifying Questions and Answers

U.S. FOOD & DRUG ADMINISTRATION

Session 2:
Congenital CMV Infection Drug Development Considerations

- **cCMV Preclinical Models**
  - Emma Mohr, MD, PhD; University of Wisconsin- Madison
- **cCMV and Hearing Loss: Study Design Considerations**
  - Lindsay DeVries, AuD, PhD; FDA
- **Alternative Routes of Drug Administration**
  - Ryan Kau, MD; FDA
- **Neurodevelopmental Outcomes of Children with cCMV: A Wide Spectrum**
  - Megan Pesch, MD, MS; University of Michigan/Michigan Medicine
- **cCMV Drug Development: Where do we go from here? Experience of the Pediatric Trials Network**
  - Rachel Greenberg, MD, MB, MHS; Duke University School of Medicine



Preclinical models of congenital CMV infection

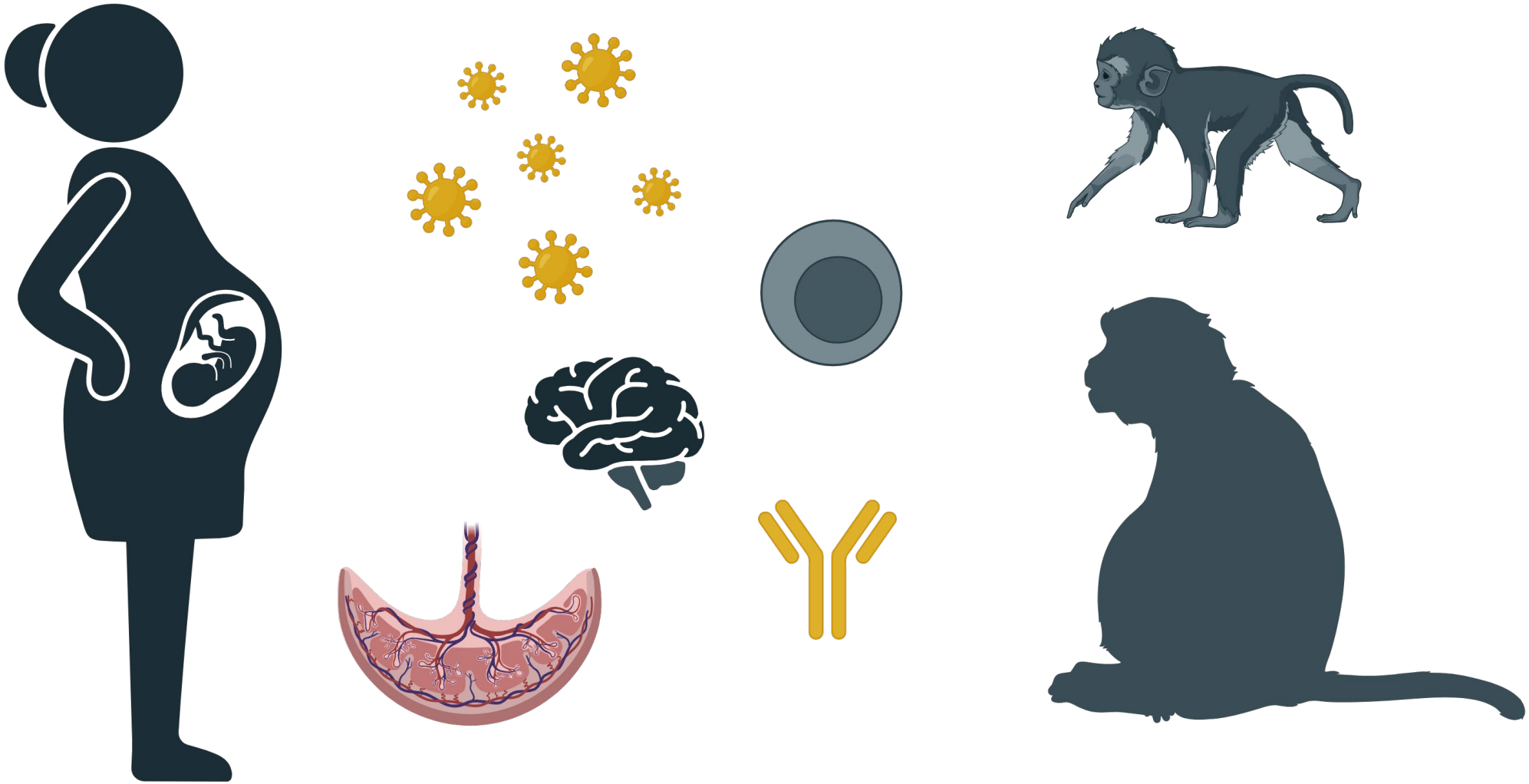
Emma Mohr, MD PhD

University of Wisconsin-Madison

Department of Pediatrics, University of Wisconsin-Madison

May 8, 2024

Rhesus macaques are a model of human pregnancy and congenital CMV infection



Images from Biorender

Roark HK et al. 2020

Early work with RhCMV established rhesus macaques as a preclinical model of congenital infection

Fetal intracerebral inoculation in the 2nd trimester with RhCMV resulted in ventricular dilatation and leptomeningitis

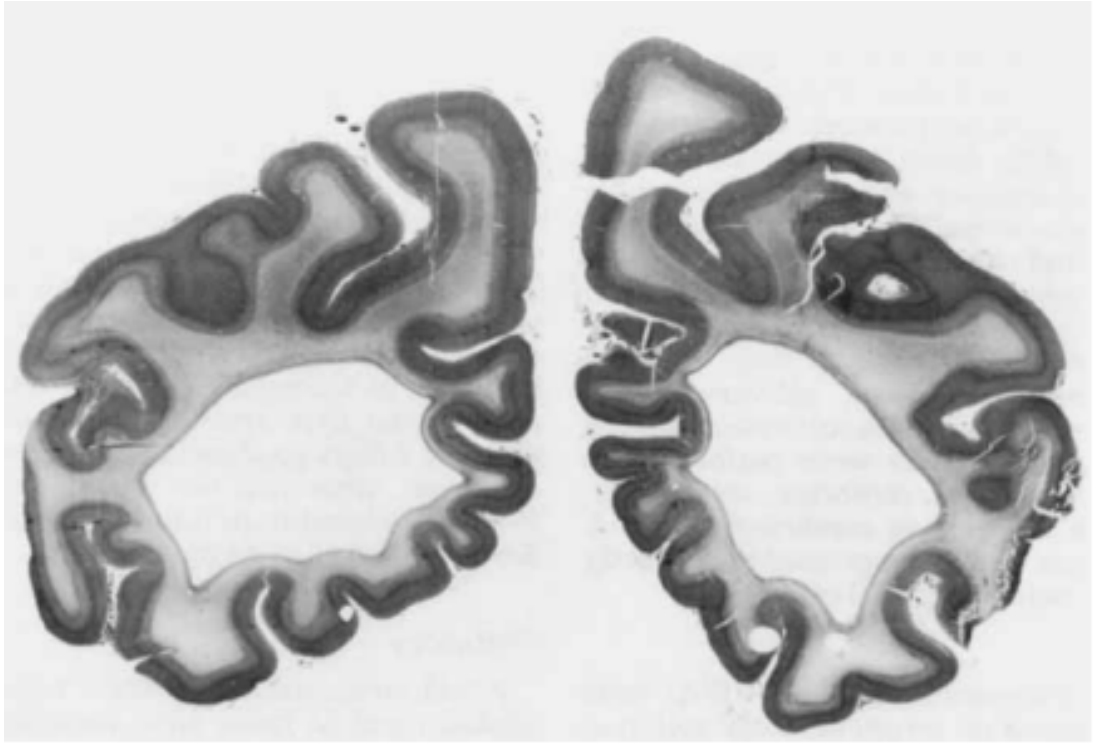
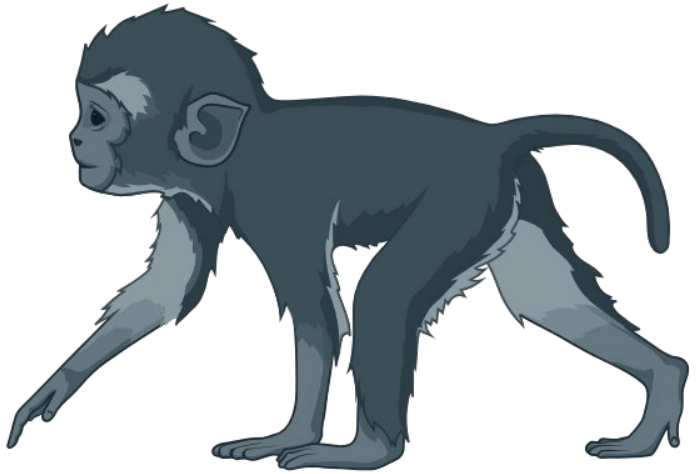


Fig. 2. Coronal section of the cerebral hemisphere of a monkey fetus inoculated intracerebrally at 80 days gestation. There is severe dilatation of both occipital horns. Hematoxylin and eosin, ×2.5.

London WT et al. 1986

- Model congenital CMV infection in pregnancy
- Study postnatal CMV transmission
- No studies of infant outcomes following prenatal infection



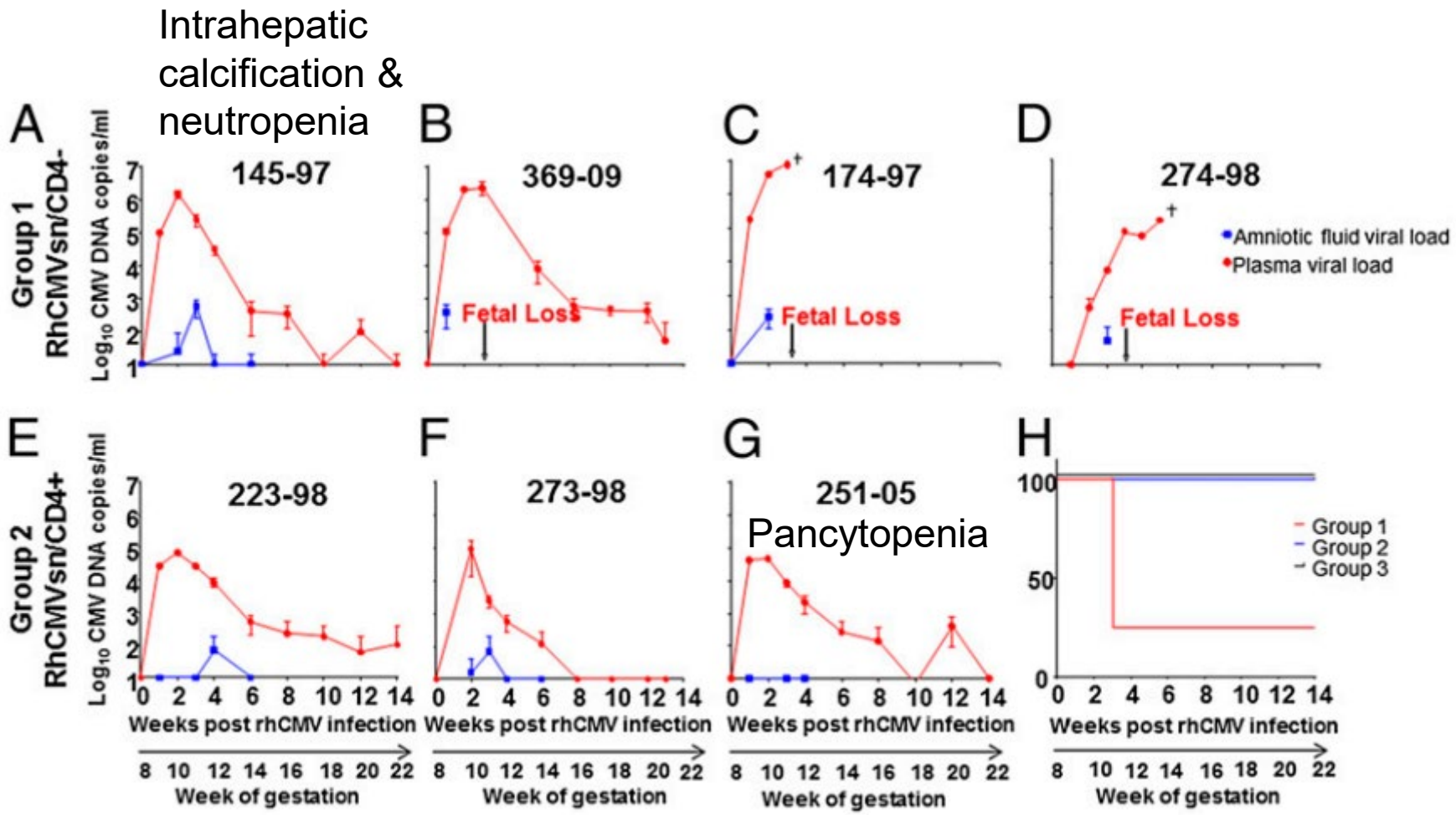
Images from Biorender

Maternal CD4+ T cells protect against severe congenital disease

Higher vertical transmission rate and more fetal loss in the T cell depleted group

Group 1: Treated with recombinant rhesus anti-CD4+ T cell depleting antibody before intravenous rhCMV inoculation

Group 2: Immunocompetent

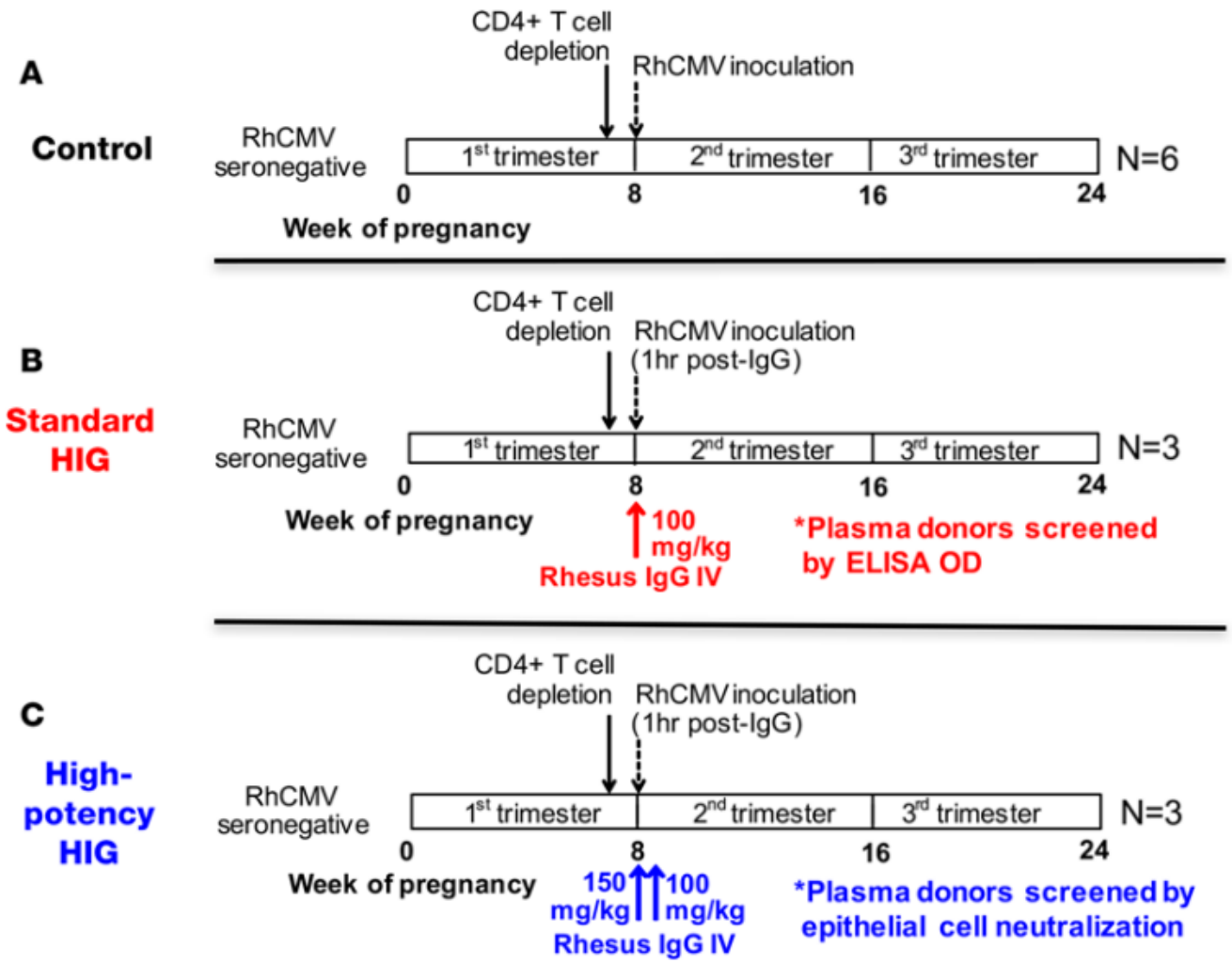


Fetus/infant evaluation: fetal ultrasound, viral load, and CBC

Bialas KM et al. 2015

Pre-existing antibodies protect again congenital infection

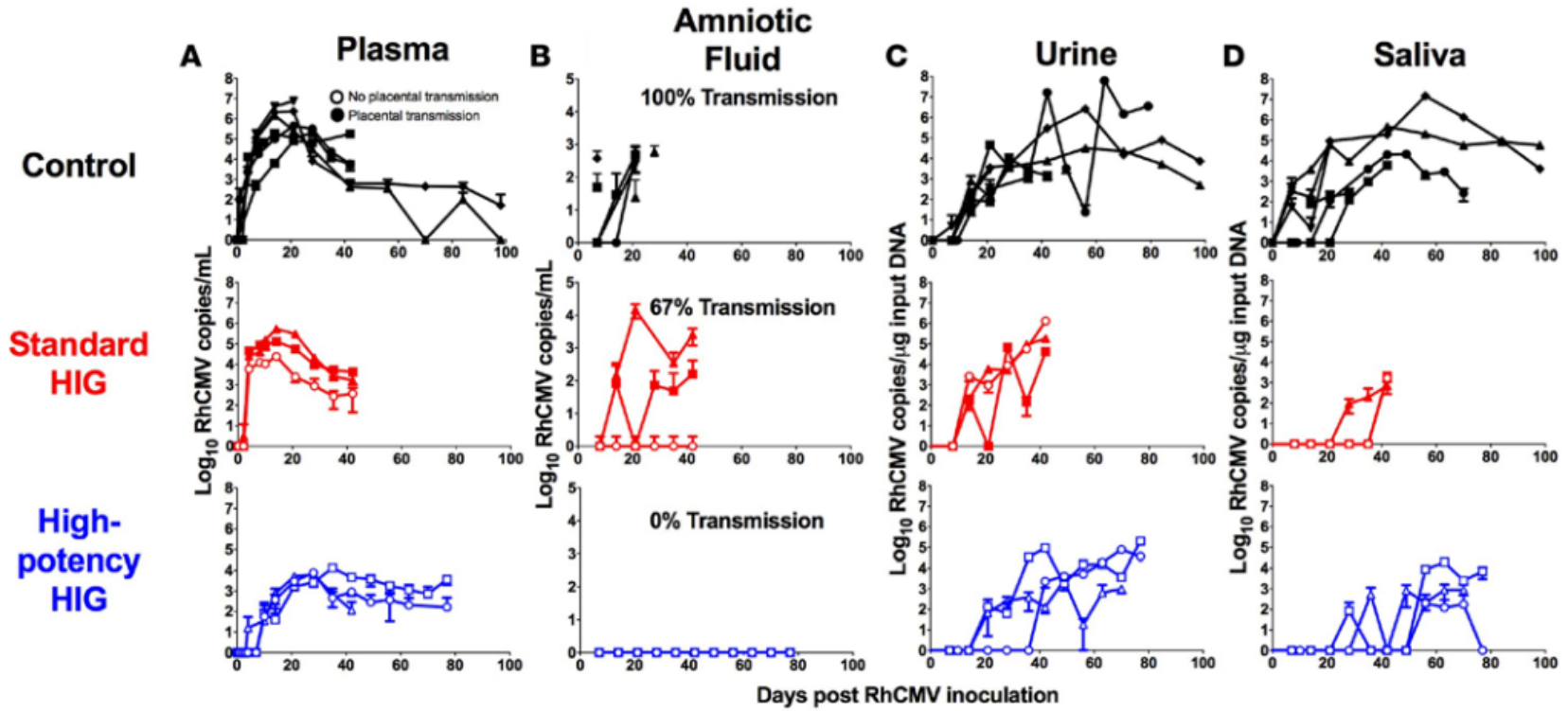
Experimental design: does hyperimmunoglobulin improve pregnancy outcomes in this severe phenotype?



HIG: hyperimmunoglobulin

Nelson CS et al. 2017

Pre-existing antibodies protect again congenital infection

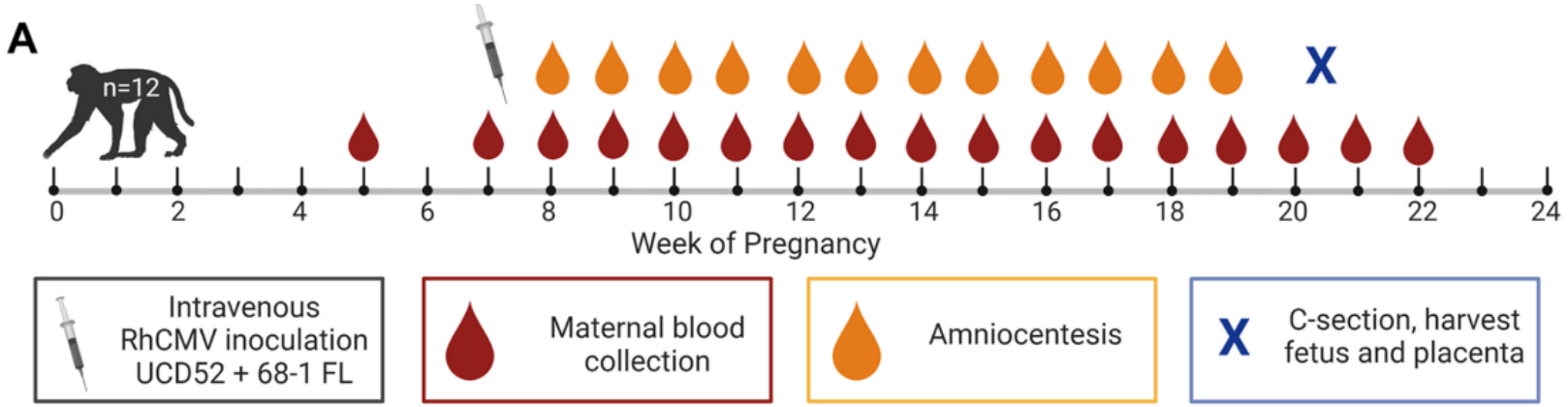


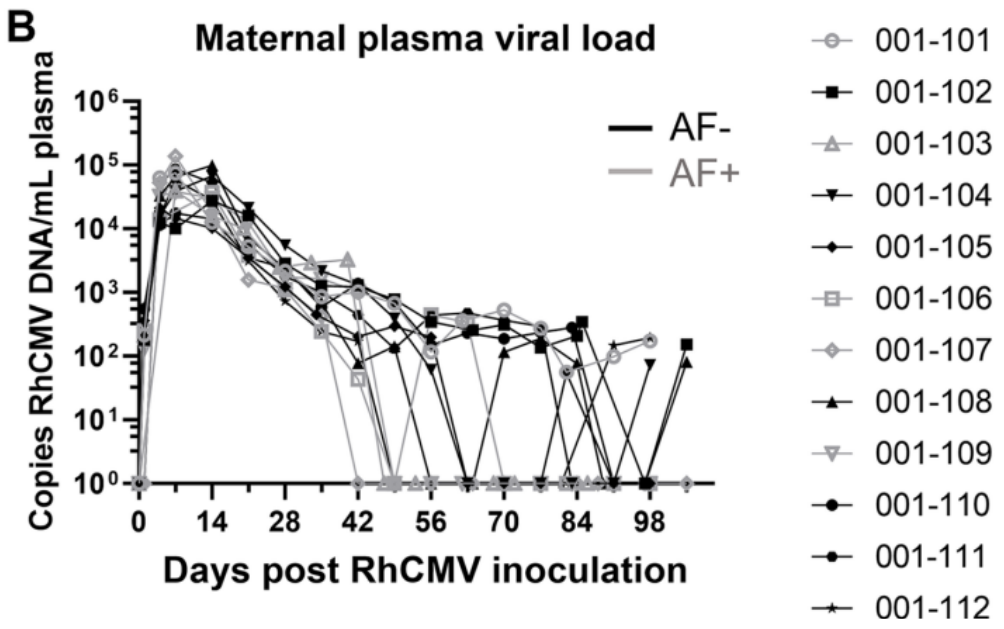
Pretreatment with high potency HIG reduces plasma viral load and prevents vertical transmission

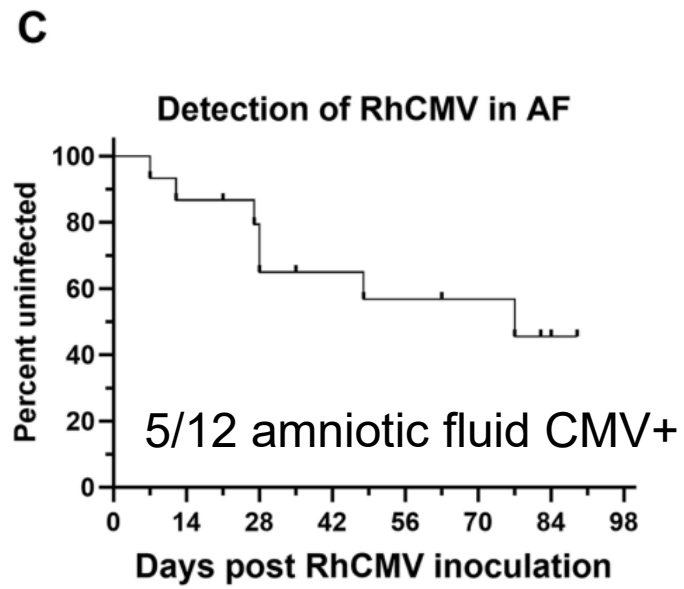
Nelson CS et al. 2017

Vertical transmission occurs in <50% of immunocompetent pregnant macaques

Maternal plasma viral loads are similar between dams with and without viral loads in the amniotic fluid

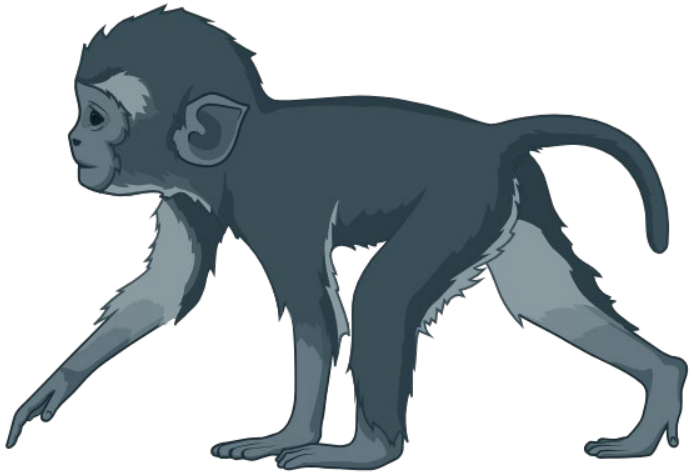






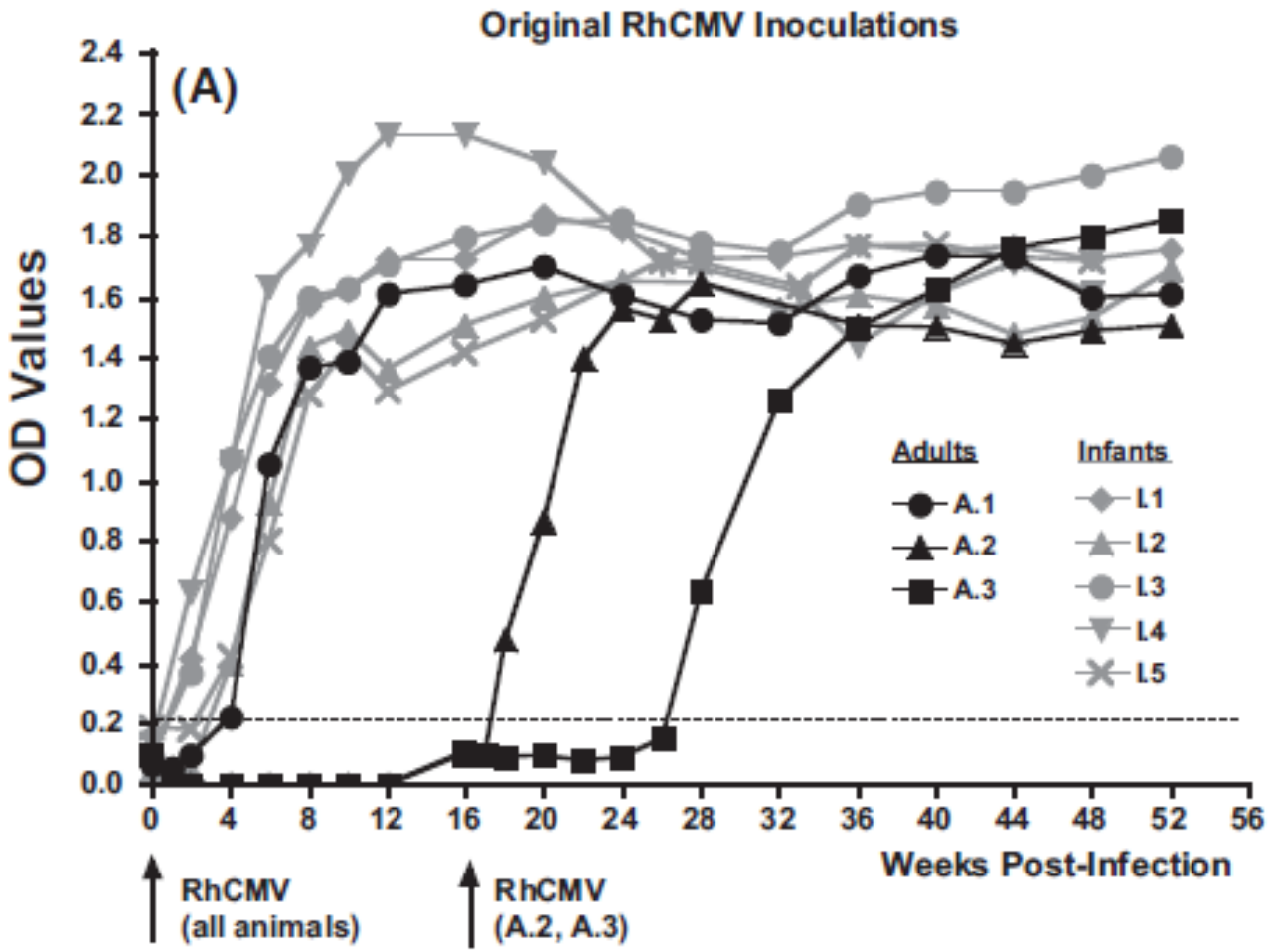
Otero CE et al. 2023

The infant rhesus macaque model has focused on postnatal CMV acquisition and transmission, not on antiviral treatment of prenatal CMV infection



Infant macaques can be infected with CMV via oral route

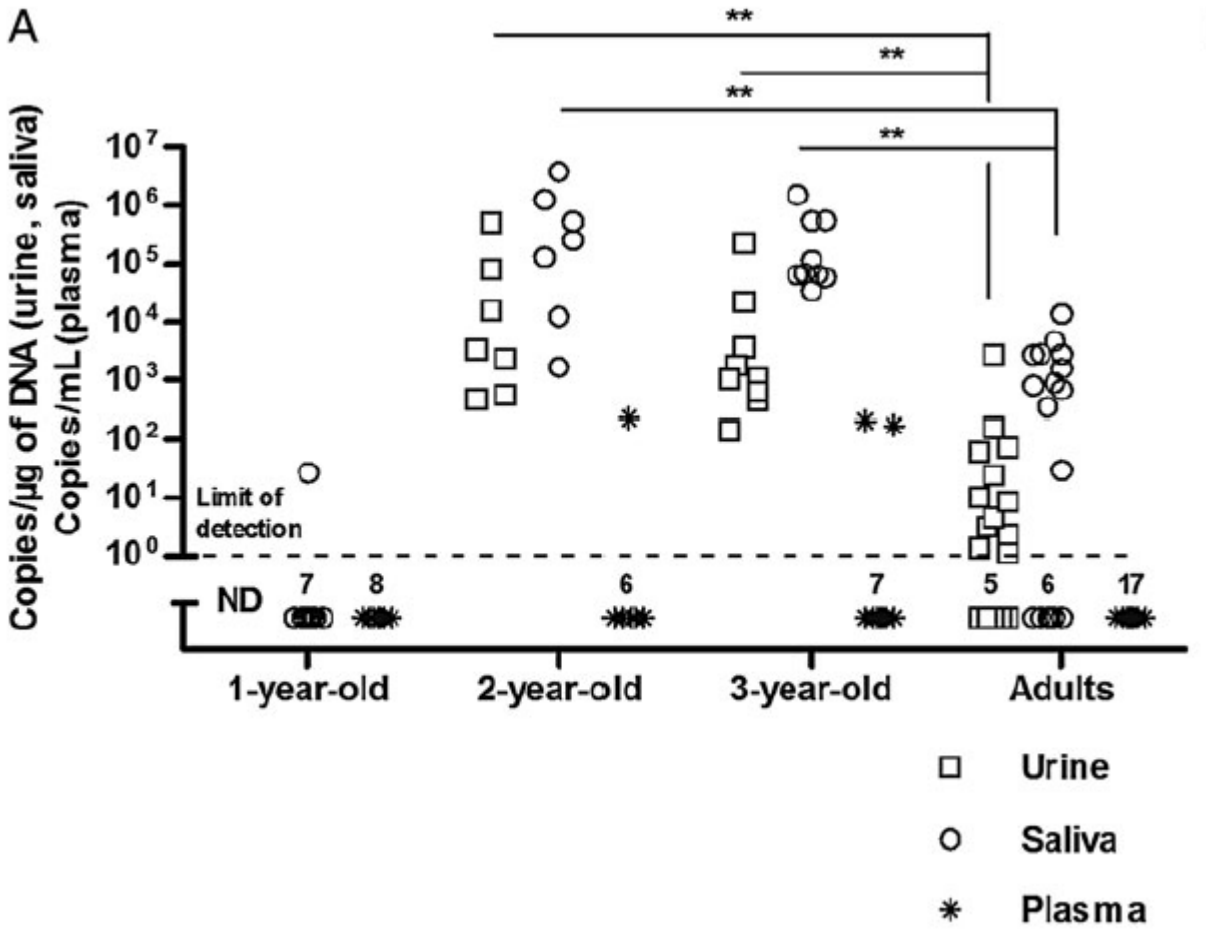
Young infant macaques develop CMV infection after oral inoculation more commonly than adult macaques



Dela Pena MG et al. 2012

Macaques acquire natural CMV infection after a year of age

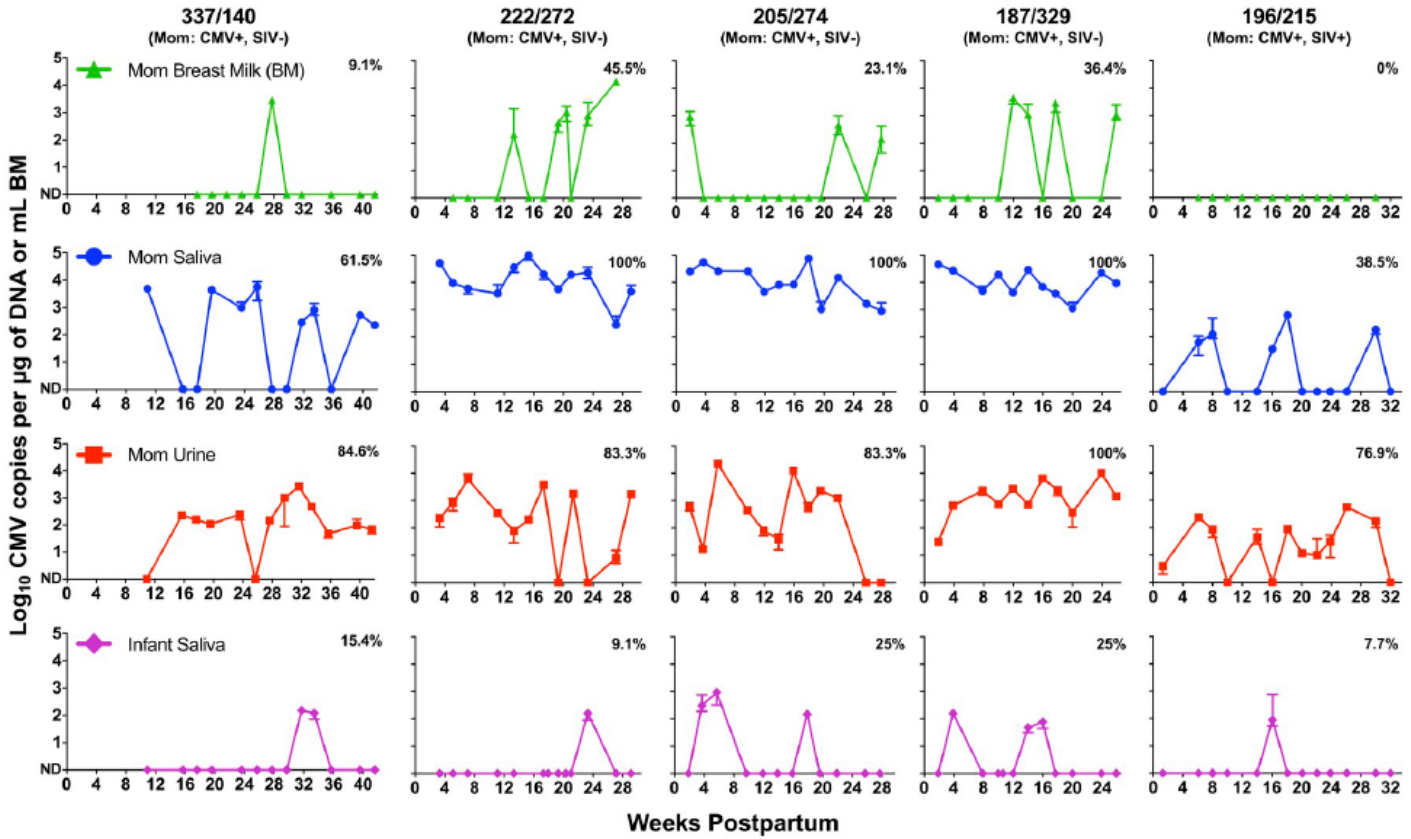
CMV viral loads were measured in 1-, 2-, and 3-year old and adult macaques



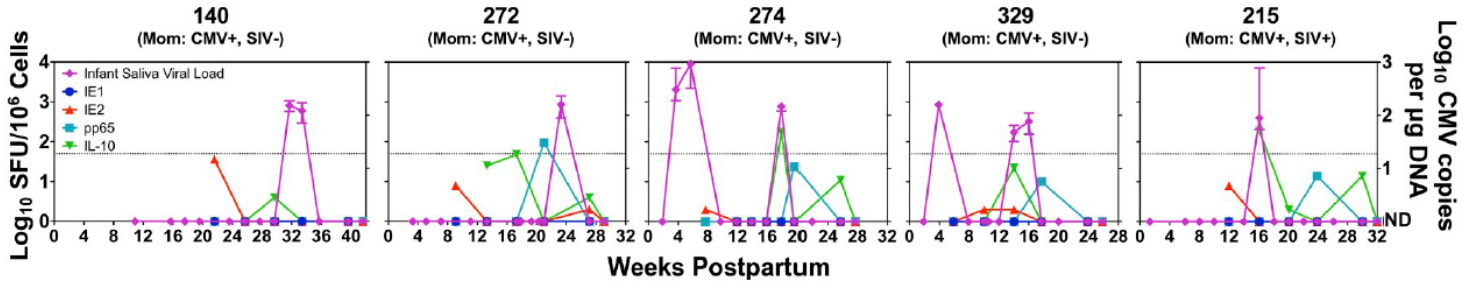
Dela Pena MG et al. 2012

Infant macaques are not a good model for breastfeeding transmission of postnatal CMV infection

Mother and infant CMV viral loads before weaning



Infant T cell responses

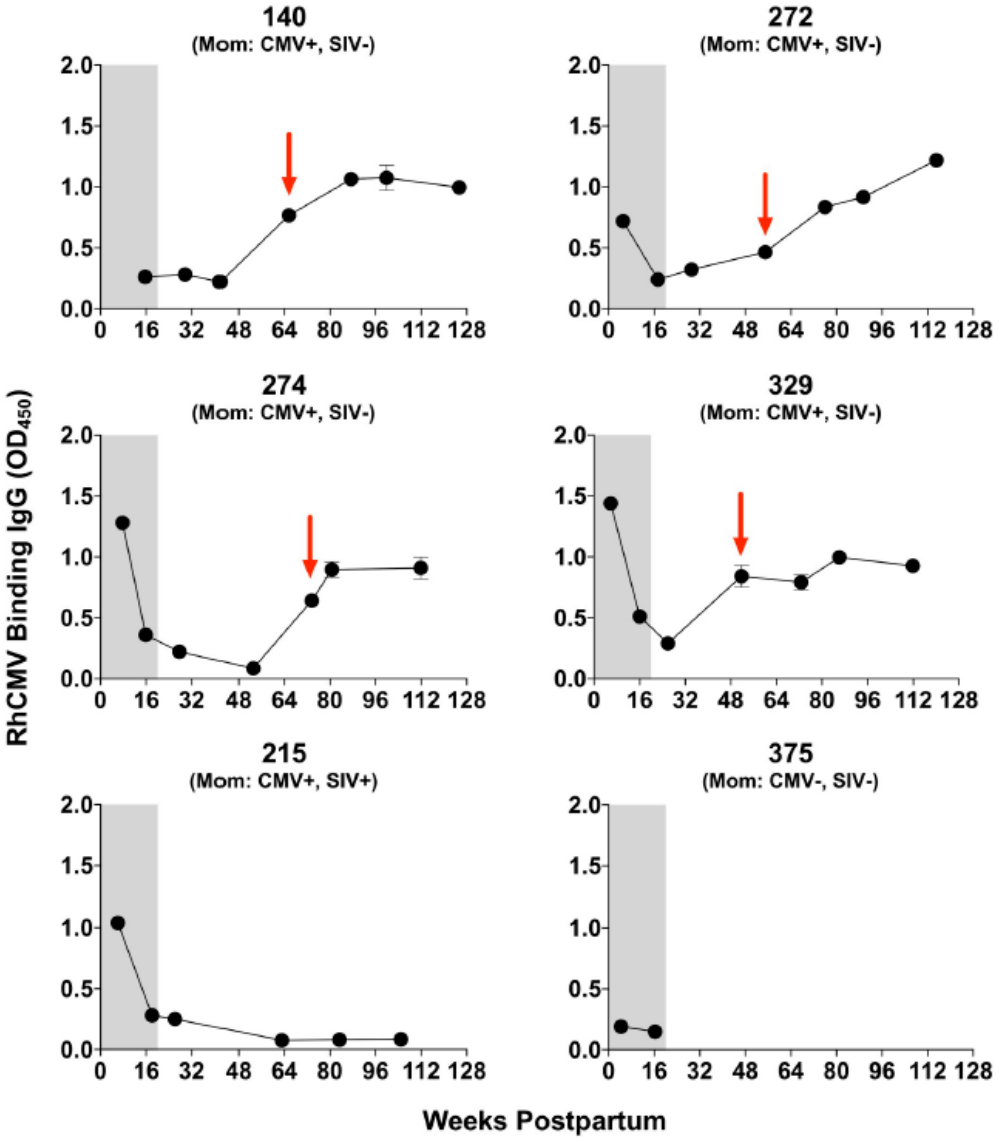


Infant macaques have infrequent oral shedding in the first year of life, not established CMV infection

Kaur A et al. 2018

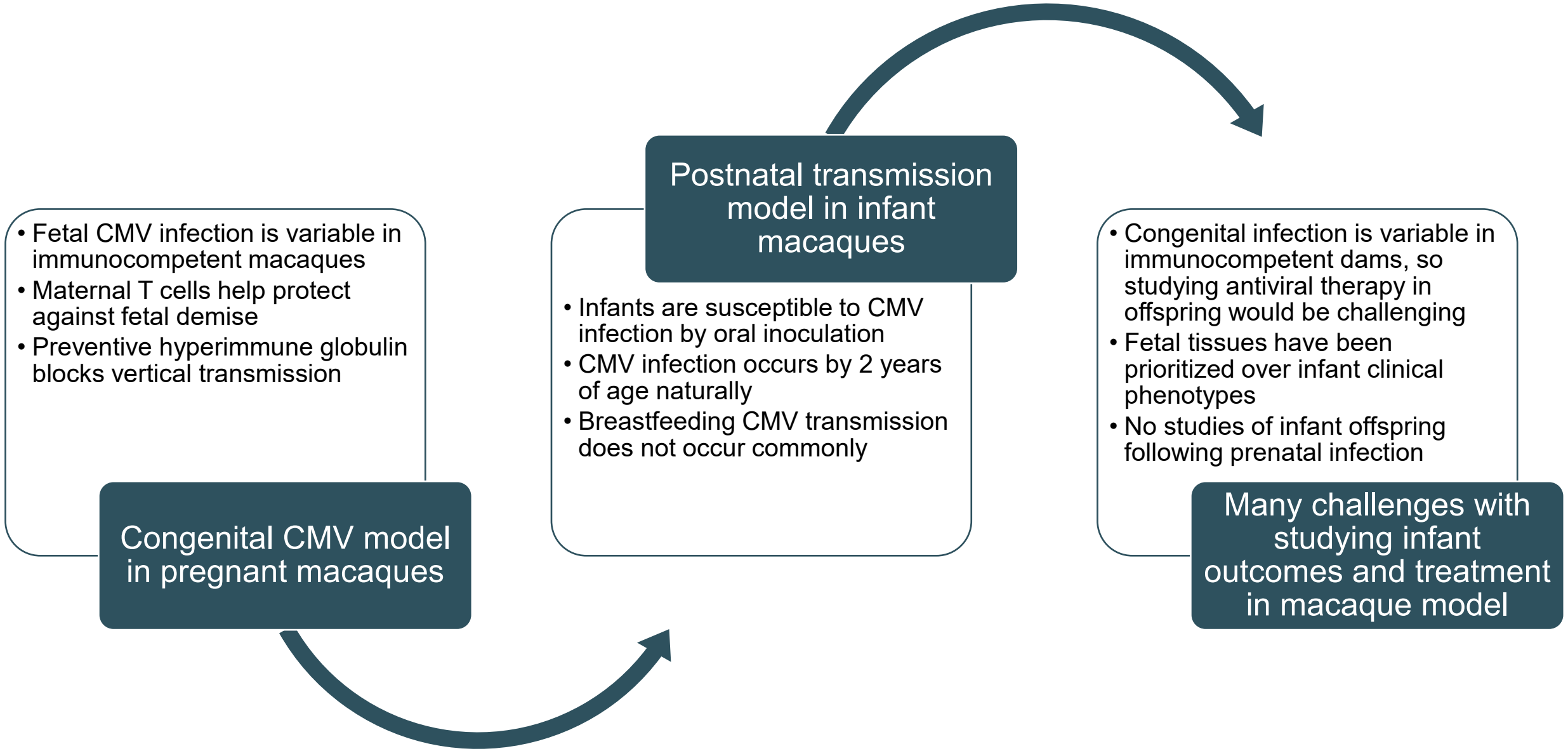
Infant macaques are not a good model for breastfeeding transmission of postnatal CMV infection

Infant macaques developed CMV-specific antibody responses after ~12 months of age, after being weaned



Kaur A et al. 2018

Conclusions and research goals



Congenital CMV and Hearing Loss: Study Design Considerations

Lindsay DeVries, Au.D., Ph.D.
OHT1/DHT1B/ENT Devices Team
Center for Devices and Radiological Health

Outline

- Characteristics of Hearing loss
  - The Basics
  - Congenital CMV
- Hearing Assessment in the Pediatric Population
  - Testing modalities across age range
  - Current protocols for children with congenital CMV
- Considerations for study design/endpoints
  - General considerations
  - Endpoint timepoints

U.S. FOOD & DRUG ADMINISTRATION

Hearing Loss and the Audiogram

Hearing Loss: The Basics

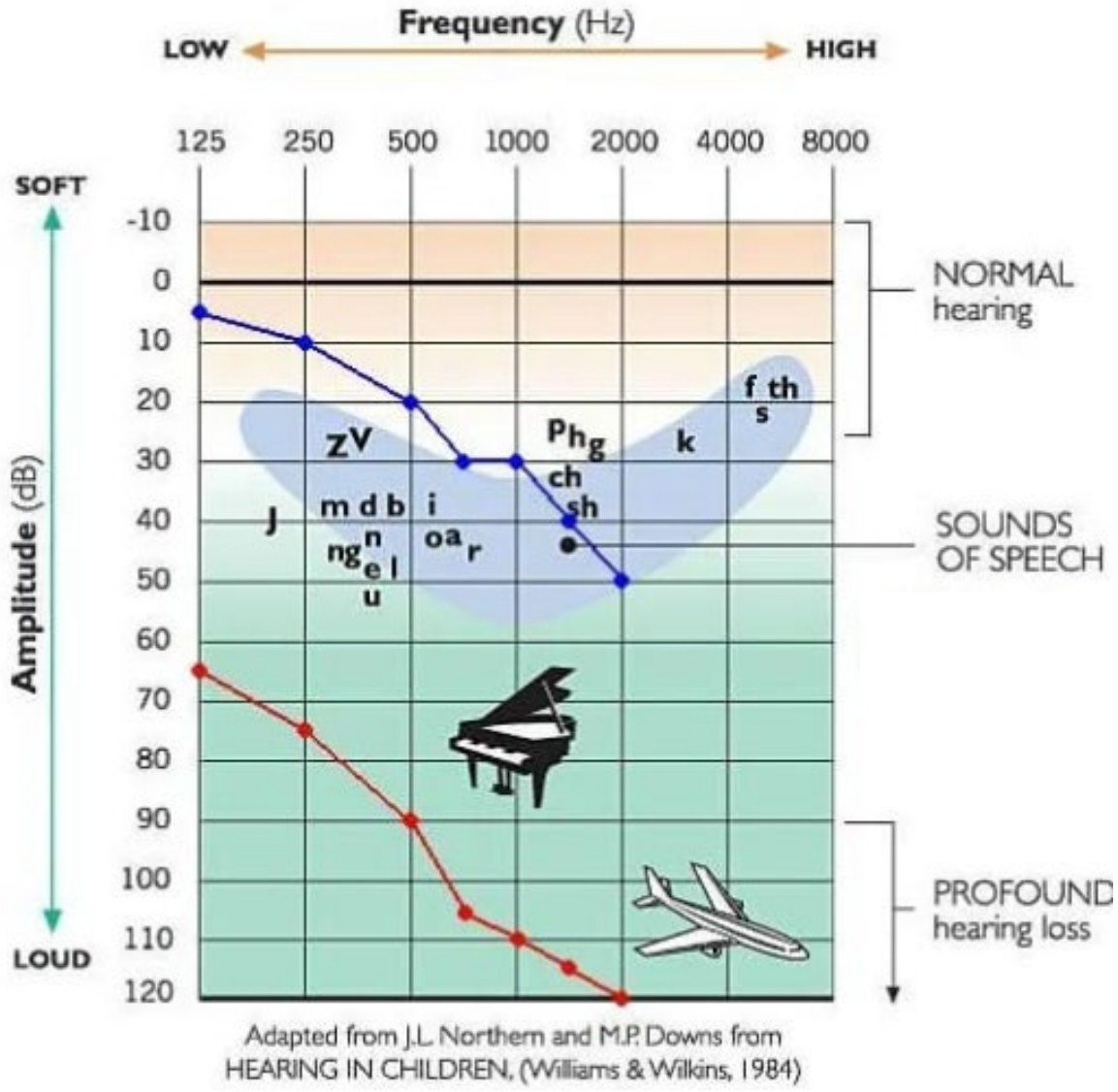
- Sensorineural:
  - Hearing loss due to a pathology of the cochlea, auditory nerve, or central nervous system
  - Often permanent in nature
- Conductive:
  - Abnormal mechanical transmission of sound from the external or middle ear to the inner ear
  - Often treated with medication and/or surgery
- Mixed:
  - A combination between abnormal mechanical conduction of sound and pathology of the cochlea
  - May be partially treatable

Hearing Loss: The Basics

Degree of hearing loss	Hearing loss range (dB HL)
Normal	-10 to 15
Slight	16 to 25
Mild	26 to 40
Moderate	41 to 55
Moderately severe	56 to 70
Severe	71 to 90
Profound	91+

Source: Clark, J. G. (1981). Uses and abuses of hearing loss classification. Asha, 23, 493-500.

Hearing Loss: The Audiogram



Adapted from J.L. Northern and M.P. Downs from HEARING IN CHILDREN. (Williams & Wilkins, 1984)

- Other Assessment Tools
  - Otoscopy
  - Tympanometry
  - Acoustic reflexes
  - Otoacoustic emissions
- Other Hearing Loss Characteristics
  - Unilateral and bilateral
  - Fluctuating
  - Progressive

Characteristics of Hearing Loss and cCMV

- cCMV is responsible for hearing loss in 20% of children (no other risk factors)
- The characteristics of cCMV-related hearing loss are highly variable:
  - Sensorineural in nature and can occur in symptomatic or asymptomatic cases
    - Hearing loss is more severe in symptomatic cases
    - Typically, bilateral HL symptomatic cases, and unilateral in asymptomatic cases
    - Poorer ear often worsens earlier and faster than better hearing ear
  - Often fluctuates irrespective of middle ear conditions
  - Hearing loss can be progressive over years (risk reduces after age 5)
  - Can be late-onset in 10-20% of cases

Aide et al., 2023 Review

Characteristics of Hearing Loss and cCMV

- Of 68 children, 59 had symptomatic CMV and 9 had symptomatic CMV

- Of the asymptomatic children:
  - 16 had SNHL at their first visit and 11 had SNHL at their last visit
  - 3 had bilateral hearing loss
  - 16 had unstable thresholds

- Of the symptomatic children:
  - 6 had SNHL at their first visit and 5 had a SNHL at their last visit
  - 4 had bilateral hearing loss
  - 4 had unstable thresholds

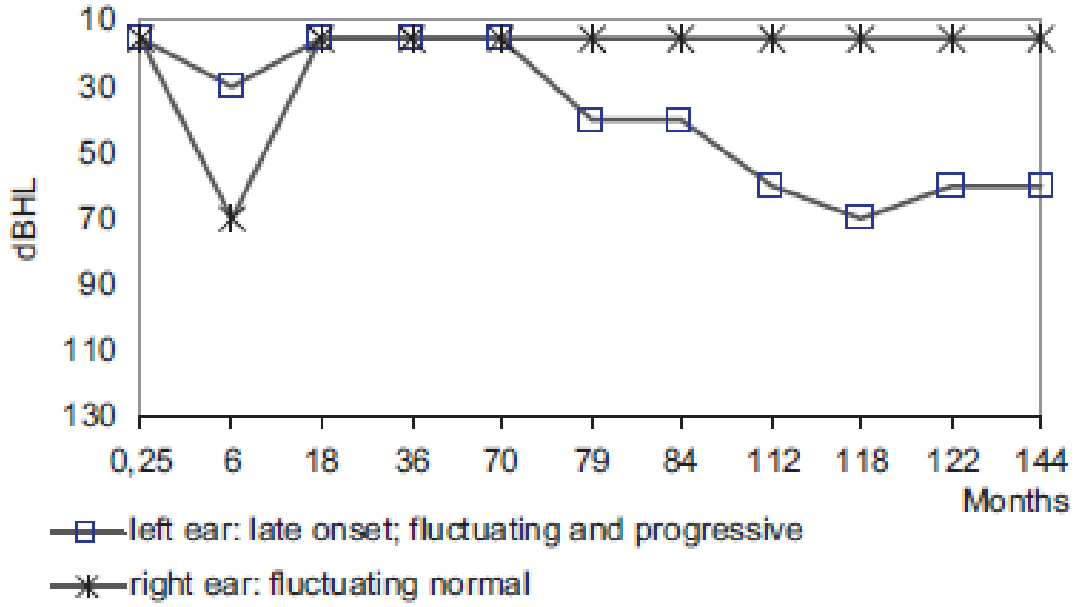
- Of the 16 children with SNHL at their last visit:
  - 10 had unstable hearing (primarily fluctuating and improvement)
  - 7 children had instability exceeding 30 dB

- Overall, 32.4% initially had SNHL, and 29.4% of children had unstable thresholds

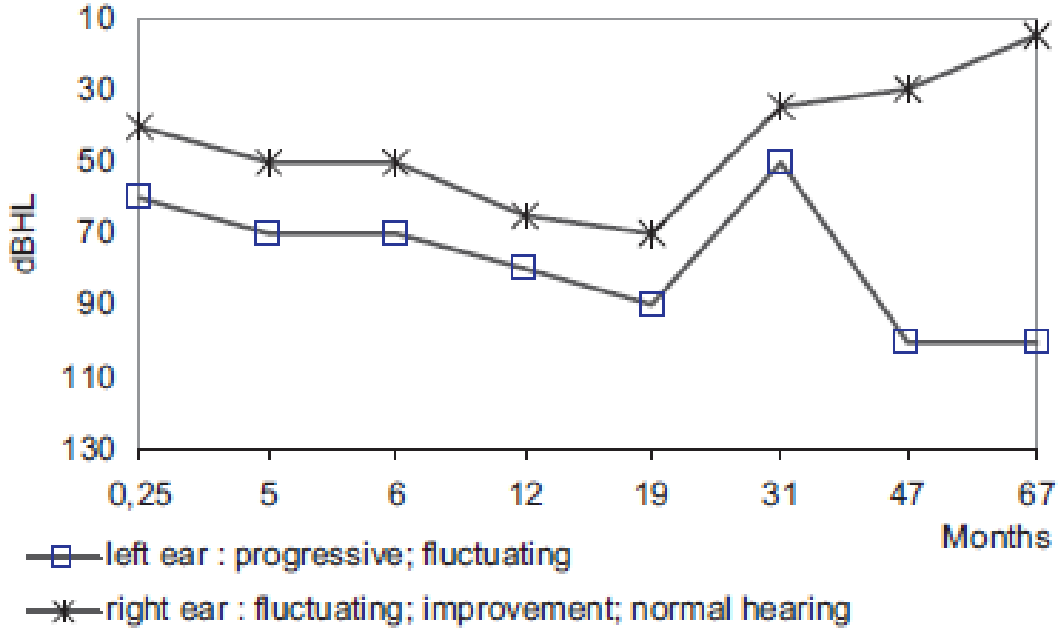
Foulon et al., 2012

Congenital CMV: The Audiogram Over Time

child 1



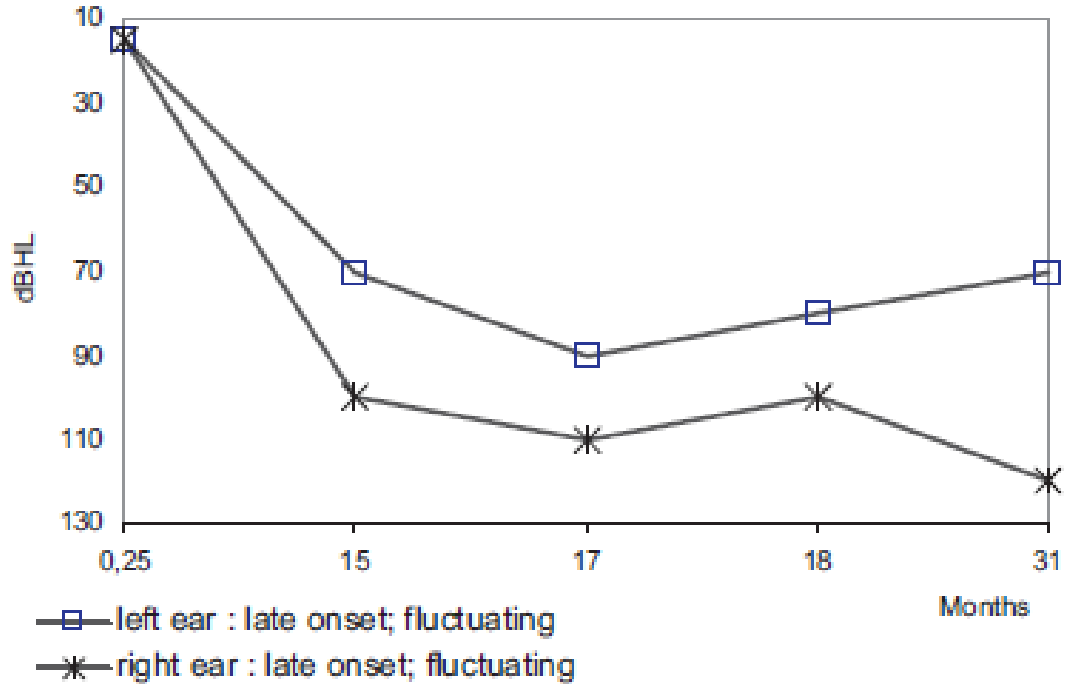
child 4



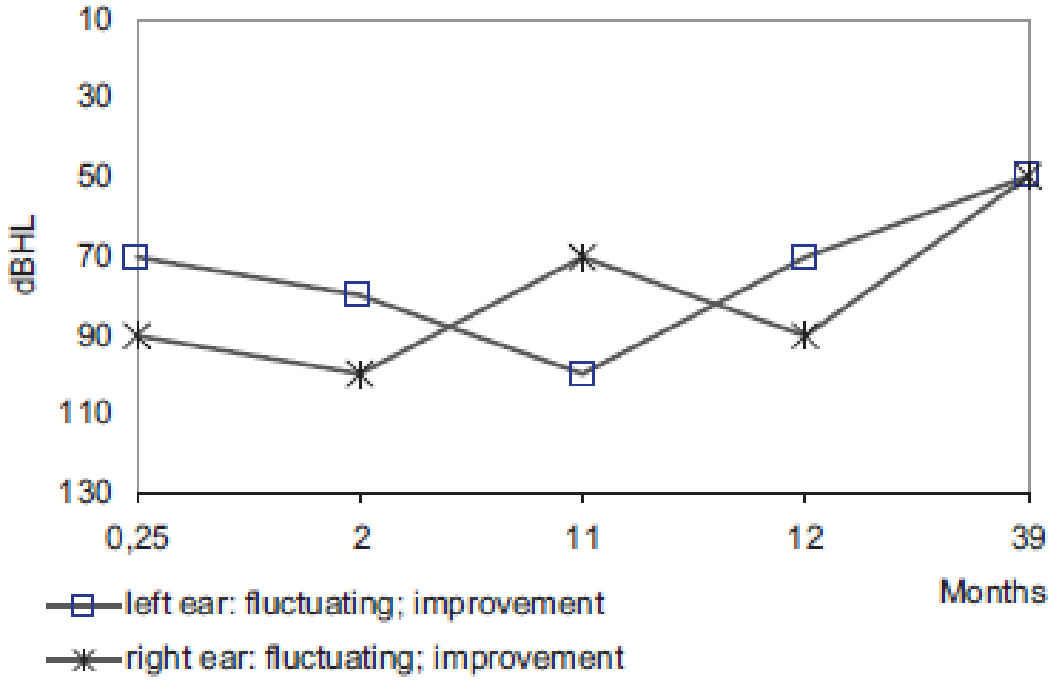
Foulon et al., 2012

Congenital CMV: The Audiogram Over Time

child 2



child 5



Foulon et al., 2012

U.S. FOOD & DRUG ADMINISTRATION

Hearing Assessment in the Pediatric Population

Objective Hearing Assessment in Children

- Otoacoustic Emissions (OAE)
  - OAEs are sounds recorded from the inner ear. An abnormal OAE may indicate a hearing loss and/or fluid in the ear.
  - Typically, representative of outer hair cell function

- Auditory Brainstem Response (ABR)
  - ABRs record the auditory nerve response to sound and can provide an estimate of the child's hearing loss.
  - Can be screening or diagnostic

American Academy of Audiology

Behavioral Hearing Assessment in Children

- Visual Reinforcement Audiometry (VRA)
  - Typically used for children ranging from 6 months to 2 years of age.
  - The child is trained to turn toward a reward (puppet, video) when he or she hears a sound. Performed with speakers in the sound field (no ear-specific information)

- Conditioned/Play Audiometry
  - Used for children between 2 and 5 years of age.
  - The child is taught to play a listening game such as putting a block in a bucket when he or she hears a sound. May be able to get ear-specific information.

- Conventional Audiometry
  - Used for children 5 and older. The child is asked to raise his or her hand, push a button, or say “I hear it” when he or she hears a sound.

American Academy of Audiology

Example of Hearing Assessment Protocol in cCMV

- All children diagnosed with cCMV infection undergo:
  - Otomicroscopy
  - Tympanometry
  - Reflex threshold measurements
  - Behavioral audiometry
  - Click-evoked ABRs
  - Tone burst-evoked ABRs
- Every 3 months up to 1 year of age
- Every 6 months from 1 to 3 years of age
- Every year from 3 to 6 years of age

Aide et al., 2023 Review

U.S. FOOD & DRUG ADMINISTRATION

Considerations for Study Endpoints in the Pediatric cCMV Population

Audiological Endpoints: General Considerations

- Consider your treatment and/or study goals
  - Prevent/stop progression of hearing loss?
  - Improve existing hearing loss?
  - Stabilize thresholds (i.e., reduce fluctuations?)

- Consider your comparator group(s)
  - A comparator group may impact how you structure your endpoints
  - Consider comparing intervention to standard of care
    - May be available audiometric information for comparison

Audiological Endpoints: General Considerations

- Demographics of targeted population
  - Age at both CMV and hearing loss diagnosis may be variable
  - Age at hearing loss assessment will impact testing approach and data you can generate
  - Some children may use amplification (hearing aids, cochlear implants) in one or both ears

- Test conditions to use for your primary endpoint(s)
  - Test conditions should reflect your study goal(s)
  - May focus on the worse ear to measure maximal benefit from treatment
  - May focus on better ear or both ears if your goal is hearing loss prevention or improvement

- Demonstrating benefit through measuring functional outcomes
  - Measure audiometric improvement in the “best-aided” test condition
  - Measure speech discrimination in unaided and/or aided conditions
  - Parental questionnaires for younger children (e.g., IT-MAIS)

Audiological Endpoints: Timepoint Considerations

- Short-term assessment of hearing status post-intervention
  - The frequency of hearing evaluation and study timepoints may vary depending on treatment
  - Children may be younger for these evaluations, which impacts the data you can collect

- Long-term assessment of hearing (and language) post-intervention
  - May want to stability of hearing status over time, which can pose difficulties due to the nature of cCMV-related hearing loss
  - Language development in relation to hearing status may provide additional functional outcome information in older children

- Consider pre- to post-market balance when developing timepoints
  - May propose a timepoint for the premarket application endpoint up to a certain age post-intervention and continue follow-up in a post-approval study
  - Whether this approach is viable depends on the study design, proposed indications for use, intended population, and desired marketing claims

Summary of Study Endpoint Considerations

- Clearly define the treatment and/or study goal(s) and both the intervention and comparator group(s)
- Carefully consider the intended treatment population, which will impact the test metrics and conditions used in the study
- When developing endpoints, consider both short- and long-term hearing assessment goals to demonstrate the effectiveness of treatment and longer-term stability of hearing status
- Depending on the study design and intervention, shorter-term timepoints may be acceptable in the premarket space, with longer-term timepoints in the post-market space.

Conclusions

- Hearing loss in children with cCMV is often a moving target
- Hearing assessment in children changes with age, which changes the type of obtainable audiometric information
- These factors will directly impact how treatment evaluation of cCMV-related hearing loss develop study endpoints
- Use the pre-IND process to discuss your proposed protocol with FDA, which will help guide you further

Alternative Route of Drug Administration for Hearing Loss: Transtympanic Injection

May 8, 2024

Ryan Kau, MD
Division of Health Technology 1B/ENT Device Team
Office of Health Technology 1
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Outline

- Background
- Transtympanic injection procedure
- Anatomy of the cochlea
  - Structures to be affected by drug administration
- Potential complications and advantages of transtympanic injection
- Considerations related to the congenital CMV hearing loss population

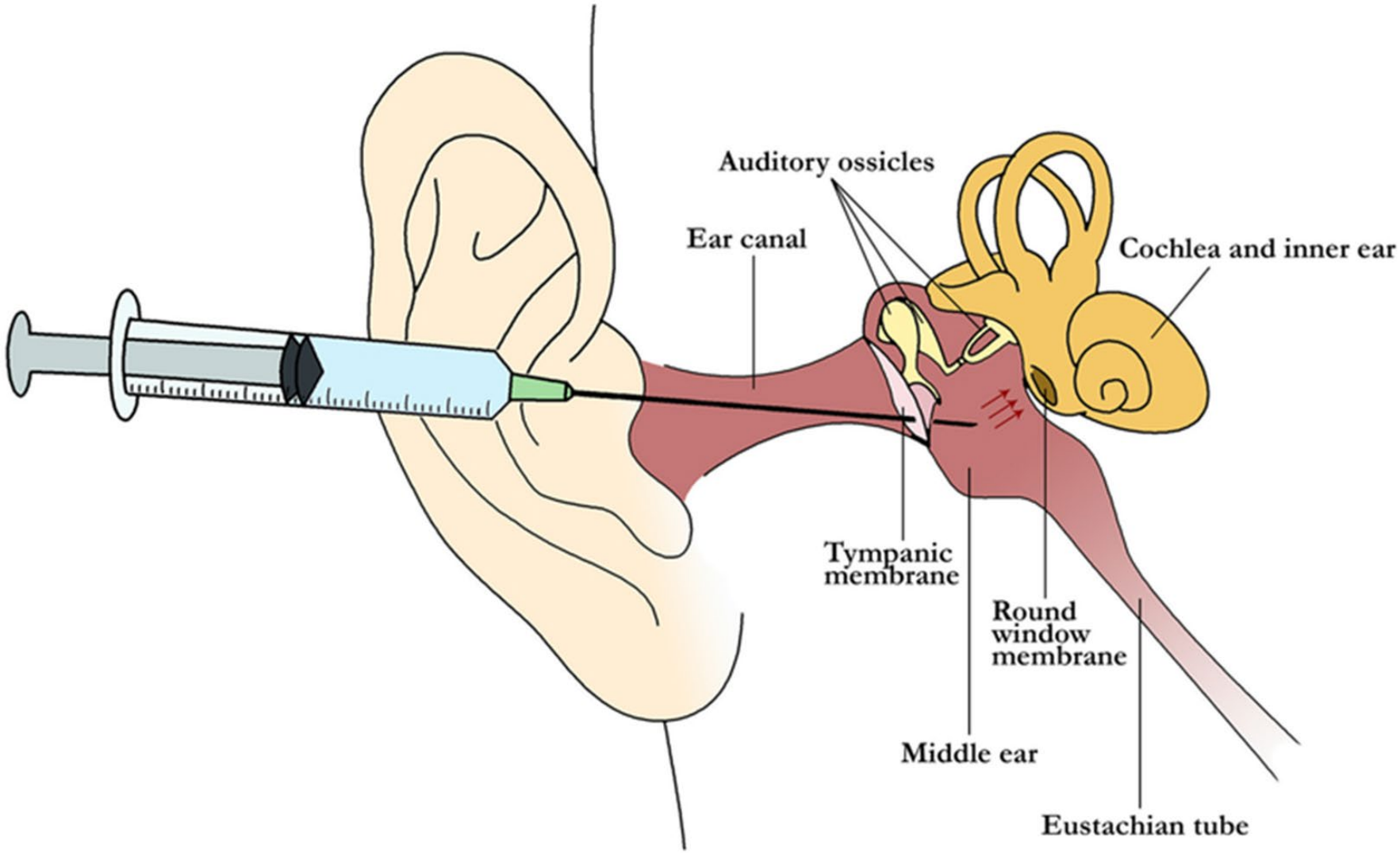
Background

- Transtympanic route first used in the 1950's
  - Aminoglycosides for treatment of vertigo

- Current off-label uses
  - Corticosteroid
    - Sudden sensorineural hearing loss, Ménière's disease, autoimmune inner ear disease
  - Aminoglycosides
    - Vertigo (Ménière's disease)

Injection Procedure

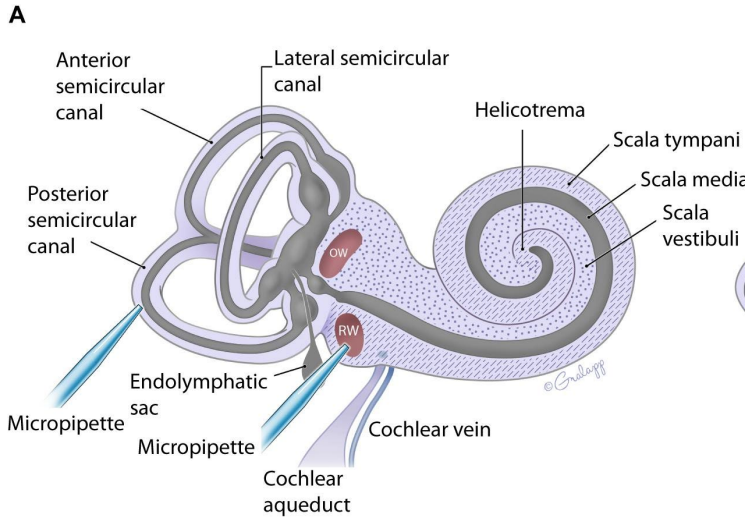
- Typically accomplished in the office with otomicroscopy
- Patient in supine position
- Anesthetize the tympanic membrane site of injection
- Delivery through the tympanic membrane
  - Transtympanic needle perforation
    - Option of placement of second hole to allow for pressure relief
  - Myringotomy with tympanostomy tube
    - Recurring treatments
- Patient will remain in supine position with treated ear turned away from the ground

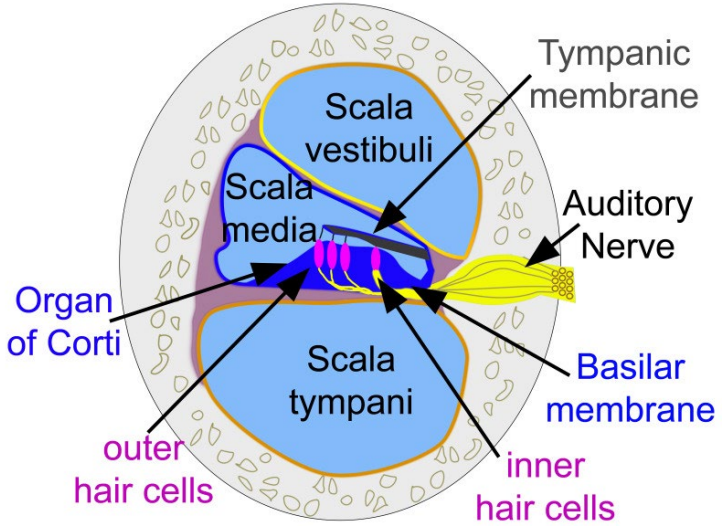


Santimetaneedol, et al., 2019

Anatomy of Cochlea

- Perilymph
  - Scala tympani
  - Scala vestibuli
  - Communicate at apex
- Endolymph
  - Scala media
- Blood labyrinthine barrier
  - Barrier between the vasculature and inner ear fluids





Talaei, et al., 2019; Krogmann, et al., 2023

Potential Complications

- Pain
- Ear fullness
- Dizziness
- Headache
- Hearing loss
- Tinnitus
- Infection
- Syncopal episode
- Persistent tympanic membrane perforation
- Tongue numbness

Potential Advantages

- Local delivery of drug to the affected location
  - Higher local concentration
  - Lower dose
- Avoidance of systemic side effects
- Avoidance of first-pass effect
- Bypass blood labyrinthine barrier

Considerations for Use in cCMV Hearing Loss

- Tolerability
  - Age considerations
    - Anesthesia vs in-office
    - Myringotomy tube placement
- Dose frequency
- Dosing duration

Summary

- Transtympanic injection has potential advantages for drug delivery to the cochlea
- Consideration of the young age of the targeted cCMV population when weighing the advantages and disadvantages


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Neurodevelopmental outcomes in Congenital CMV: A wide spectrum

Megan H. Pesch, MD, MS

Clinical Assistant Professor

Developmental and Behavioral Pediatrics

University of Michigan

DISCLOSURES

Past President of the National CMV Foundation
Consultant for Moderna and MedScape/WebMD
Research funding –NICHD

Overview

1. Why can CMV cause developmental differences?
2. Who is at risk of delays and disabilities?
3. Specific areas of disability, delay and differences
4. Treatment, management and support

Congenital CMV in a Nutshell

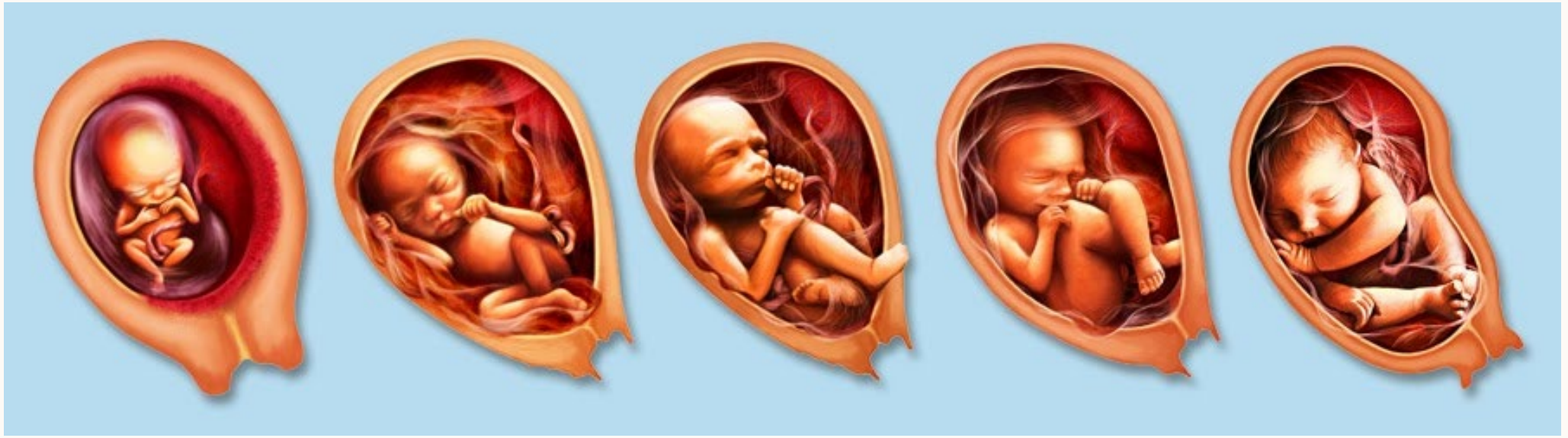
Leading non-genetic cause of neonatal/childhood hearing loss

Risk of neurodevelopmental delays

Pesch MH, Schleiss MR. Pediatrics. 2022;150:e2021055896.

Pathophysiology of CMV Infection During Pregnancy

Severity

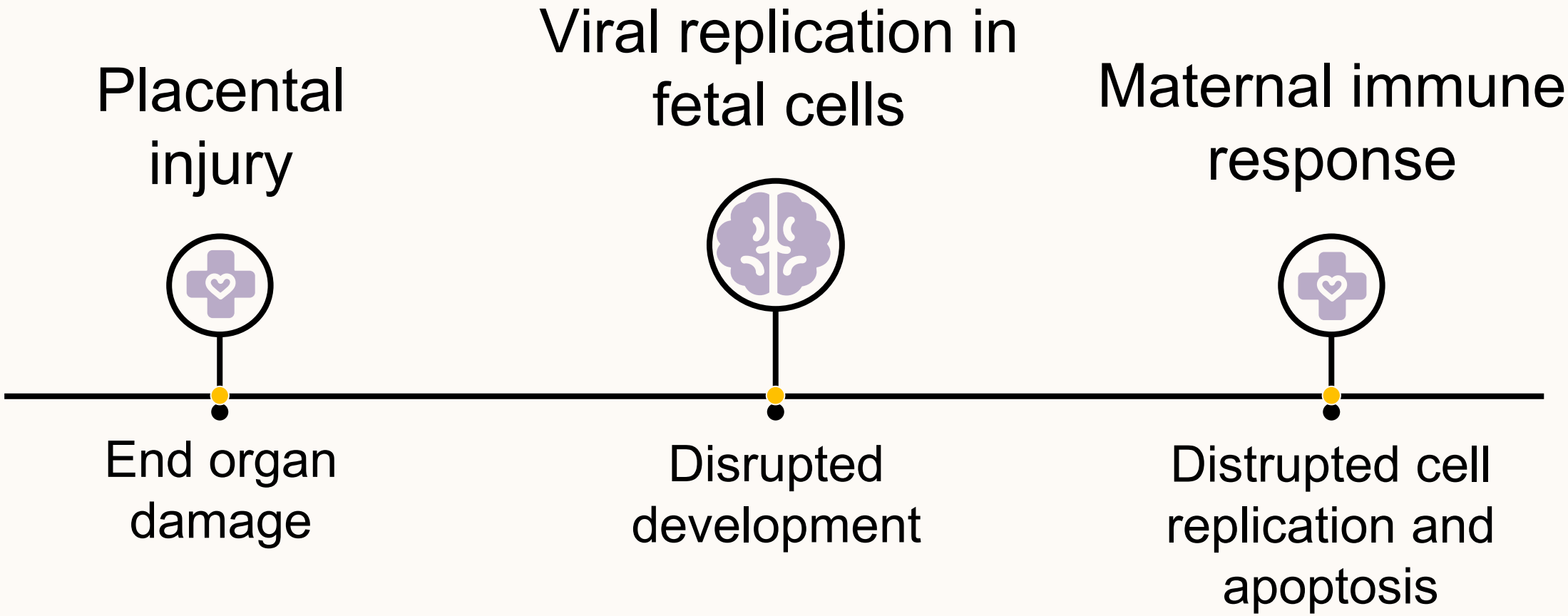


Transmission

CMV, cytomegalovirus.

Chatzakis C, et al. Am J Obstet Gynecol. 2020;223:870-883.

Mechanisms of fetal injury



Krstanović F, Britt WJ, Jonjić S, Brizić I. Cytomegalovirus Infection and Inflammation in Developing Brain. Viruses. 2021 Jun;13(6):1078.

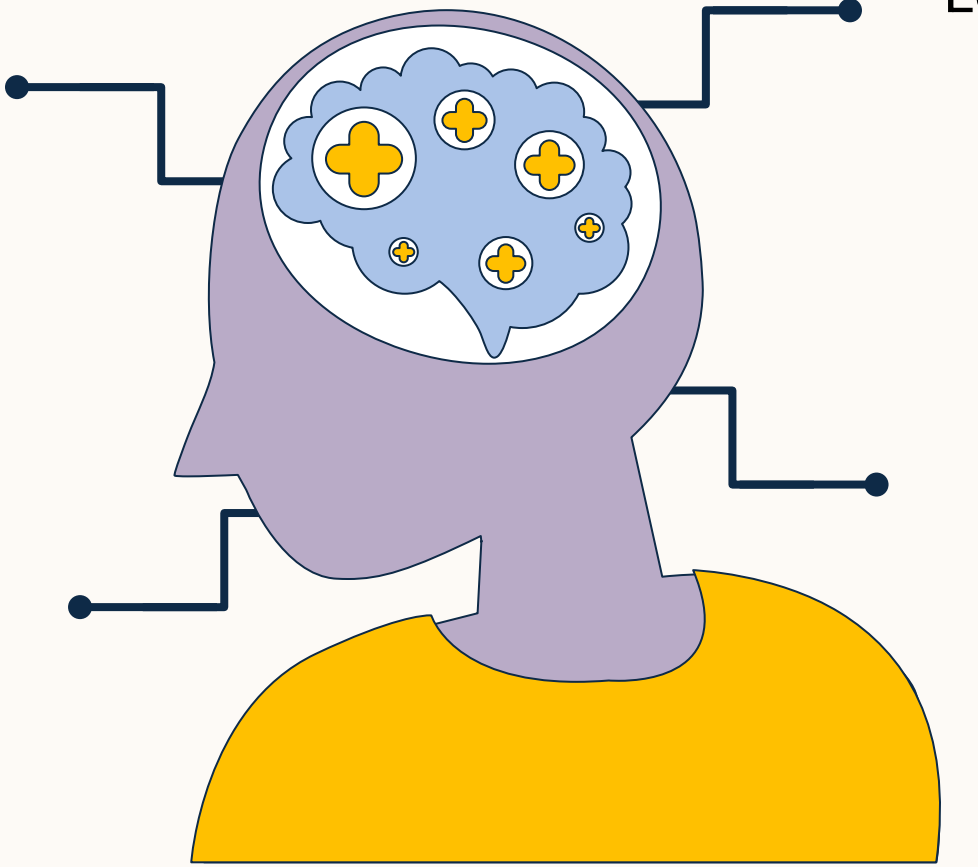
Neuro-developmental outcomes

Intellectual disability

Learning disabilities

Cerebral palsy

Motor planning disorders



Epilepsy

Autism*

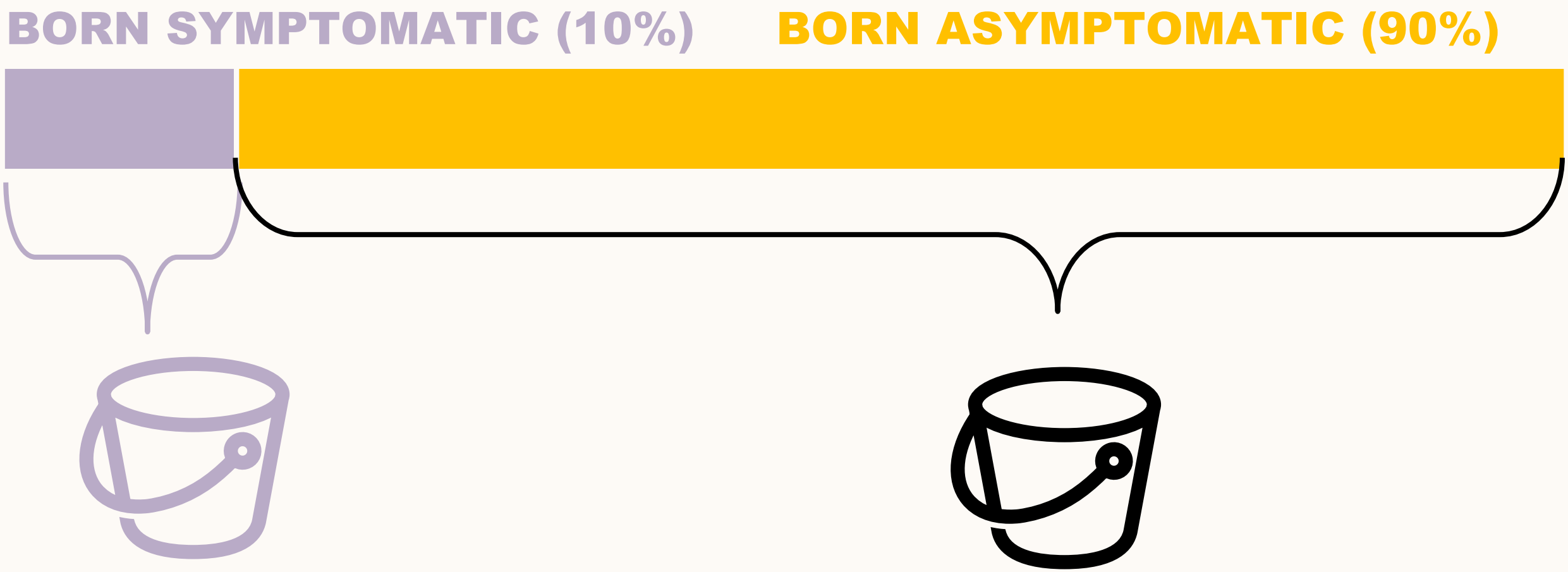
Hearing loss

Vestibular disorders

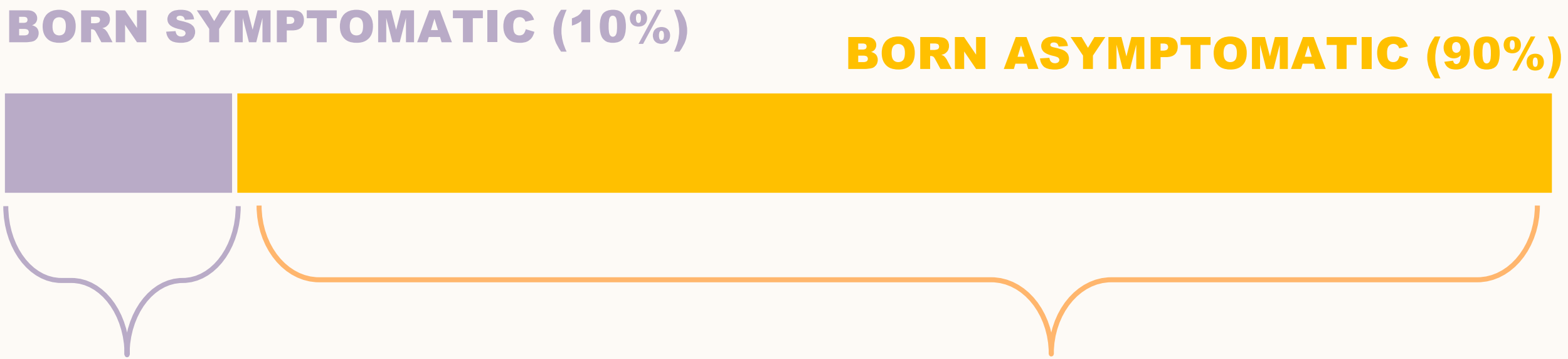
Visual loss/impairment

Giannattasio et al. Neuroimaging profiles and neurodevelopmental outcome in infants with congenital cytomegalovirus infection. *The Pediatric Infectious Disease Journal*, *37*(10), pp.1028-1033.

Classic Categories of cCMV Severity



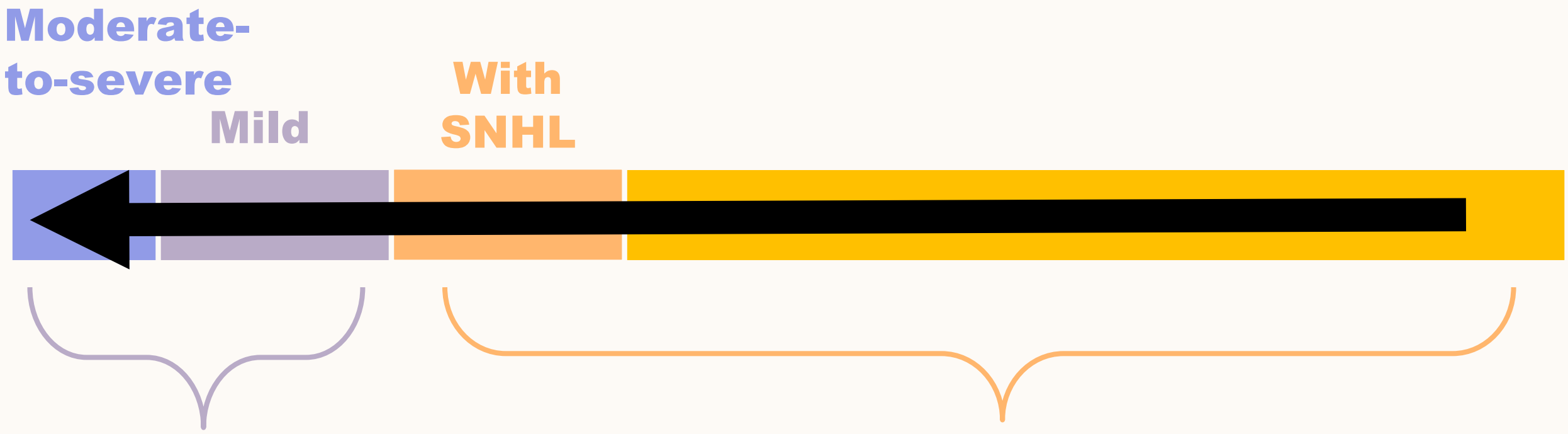
Classic Categories of cCMV Severity



- **Signs at birth**
- **May have SNHL**
- **Most go on to have “atypical” development**

- **Clinically inapparent**
- **May have SNHL**
- **Most go on to have “typical” development**

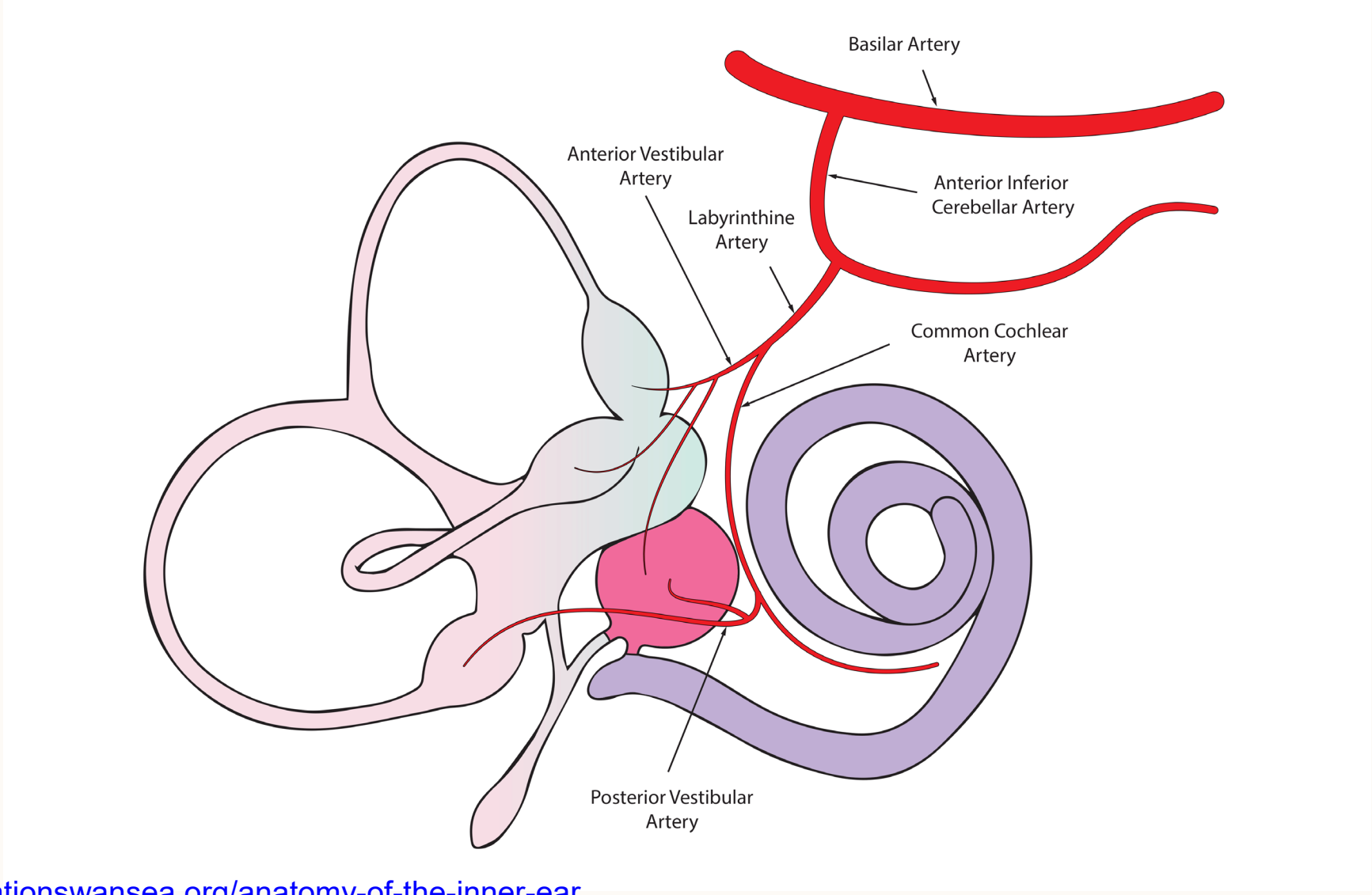
Risk of neurodevelopmental sequelae



Other factors that impact long term developmental outcomes

- Maternal education
- Access to therapies
- Access to health care
- Gestational age
- Singleton vs. multiple pregnancy
- Socioeconomic status
- Social determinants of health

CMV Injures the Inner Ear Blood Vessels



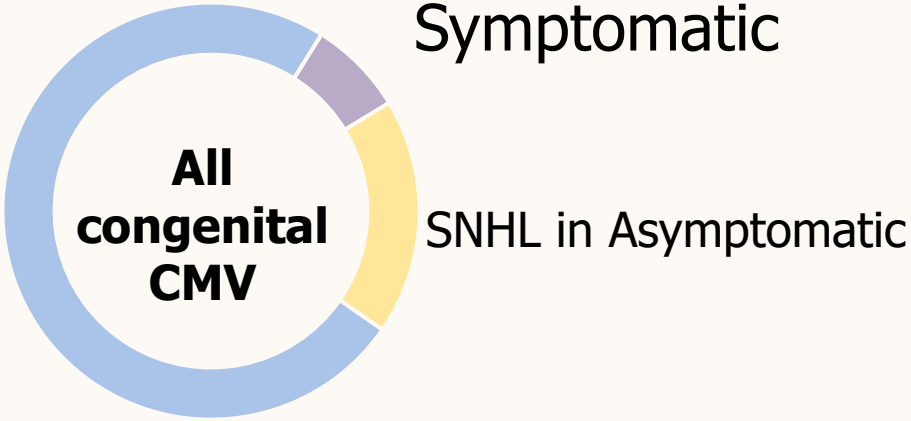
https://www.enteducationswansea.org/anatomy-of-the-inner-ear

Sensorineural Hearing Loss and cCMV

~20% of all children with cCMV

Of all cCMV associated hearing loss

- 50% – Present at birth
- 50% – Progressive
- 50% – Fluctuating
- 33–50% – Late onset



Clin Infect Dis. 2013 Dec 15; 57(Suppl 4): S182–S184. doi: 10.1093/cid/cit609.

Long-term Outcomes in Asymptomatic Congenital CMV

~20%

Hearing loss by 18 years

~45%

Vestibular & gaze stability dysfunctions

30%

Balance difficulties

Goderis et al. Pediatrics. 2014;134:972-82; Pinninti et al. Pediatrics 147.2 (2021).

Sensorineural Hearing Loss and cCMV

- Close audiologic follow-up through teen years
- Unilateral cochlear implantation
- CI outcomes depend on other sequelae
- Multimodal communication important

Clin Infect Dis. 2013 Dec 15; 57(Suppl 4): S182–S184. doi: 10.1093/cid/cit609.

Motor delays and disabilities

- Low tone
- Slow attainment of motor milestones
- Poor coordination
- Cerebral palsy

De Kegel A, Maes L, Dhooge I, van Hoecke H, De Leenheer E, Van Waelvelde H. Early motor development of children with a congenital cytomegalovirus infection. Res Dev Disabil. 2016 Jan;48:253-61. doi: 10.1016/j.ridd.2015.11.014. Epub 2015 Dec 7. PMID: 26630616.

Feeding disorders

- Under studied
- Textures
- Coordination of chewing/swallowing – association with hearing loss
- Swallow-study, feeding therapy, occupational therapy

Communication disorders

- Associated with hearing loss
- Coordination of muscles challenging
- Layered with autism/ social communication differences
- Multimodal communication (ASL, spoken language, AAC)

Walsh H, Zuwala J, Hunter J, Oh Y. Congenital Cytomegalovirus and Human Immunodeficiency Virus: Effects on Hearing, Speech and Language Development, and Clinical Outcomes in Children. Front Pediatr. 2021 Dec 16;9:771192. doi: 10.3389/fped.2021.771192. PMID: 34976894; PMCID: PMC8716614.

Autism

- Increased risk in children with cCMV
- Different approaches to therapies and communication may be needed
- Early intervention with supports (not cures)
- Overlap between the Autistic and Deaf communities

https://cmv.usu.edu/schedule/grid-details.cfm?pg=none&aid=16059&ts=3333&ty=grid&des=reg

Behavioral disorders and challenges

- Externalizing behaviors
- Internalizing behaviors
- Impulsivity
- Compounded by communication and movement difficulties

Rodríguez-Molino, Paula MD*,†,‡; Alarcón, Ana MD, PhD§,¶,‖; Martínez-Biarge, Miriam MD, PhD**; Cabrera-Lafuente, Marta MD, PhD††; Aldecoa, Victoria MD, PhD‡‡; Fernández-Sánchez, Aránzazu LCP§§; Fernández-Jiménez, Eduardo LCP, PhD§§,‡,¶¶; Baquero-Artigao, Fernando MD, PhD*,†; García-Alix, Alfredo MD, PhD‖‰,***. Behavioral Problems and Family Impact in Congenital Cytomegalovirus Infection. The Pediatric Infectious Disease Journal ():10.1097/INF.0000000000004280, February 15, 2024. | DOI: 10.1097/INF.0000000000004280

Spectrum of Congenital CMV Sequelae

BORN SYMPTOMATIC (10%) **BORN ASYMPTOMATIC (90%)**

Death	Medically fragile	Multiple Disabilities	Developmental Delays	Hearing Loss	None
- Miscarriage - Stillbirth - Infant or child loss	-Cerebral palsy - Seizures - Failure to thrive - Hearing loss - Vision loss	- Cerebral palsy - Vision loss - Hearing loss - Autism	- Cognitive delays - Learning issues - Feeding and sleeping issues - Vision loss - Hearing loss	- Hearing aids - Cochlear implants - Communication and learning issues	No visible delays or sequelae

Thank you

pesch@umich.edu

@DrCMVMom

@MeganPeschMD

Megan H Pesch, MD, MS

@Megan.PeschMDMS

cCMV Drug Development: Where do we go from here? Experience of the Pediatric Trials Network

May 8, 2024

Rachel G. Greenberg, MD MB MHS
Associate Professor of Pediatrics, Division of Neonatology
Duke University School of Medicine
Duke Clinical Research Institute

PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

Outline

- What is the Pediatric Trials Network?
- Why is PTN interested in congenital CMV treatment?
- Barriers to studies of congenital CMV treatment
- Where do we go from here?

PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

What is the Pediatric Trials Network?

"Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health."

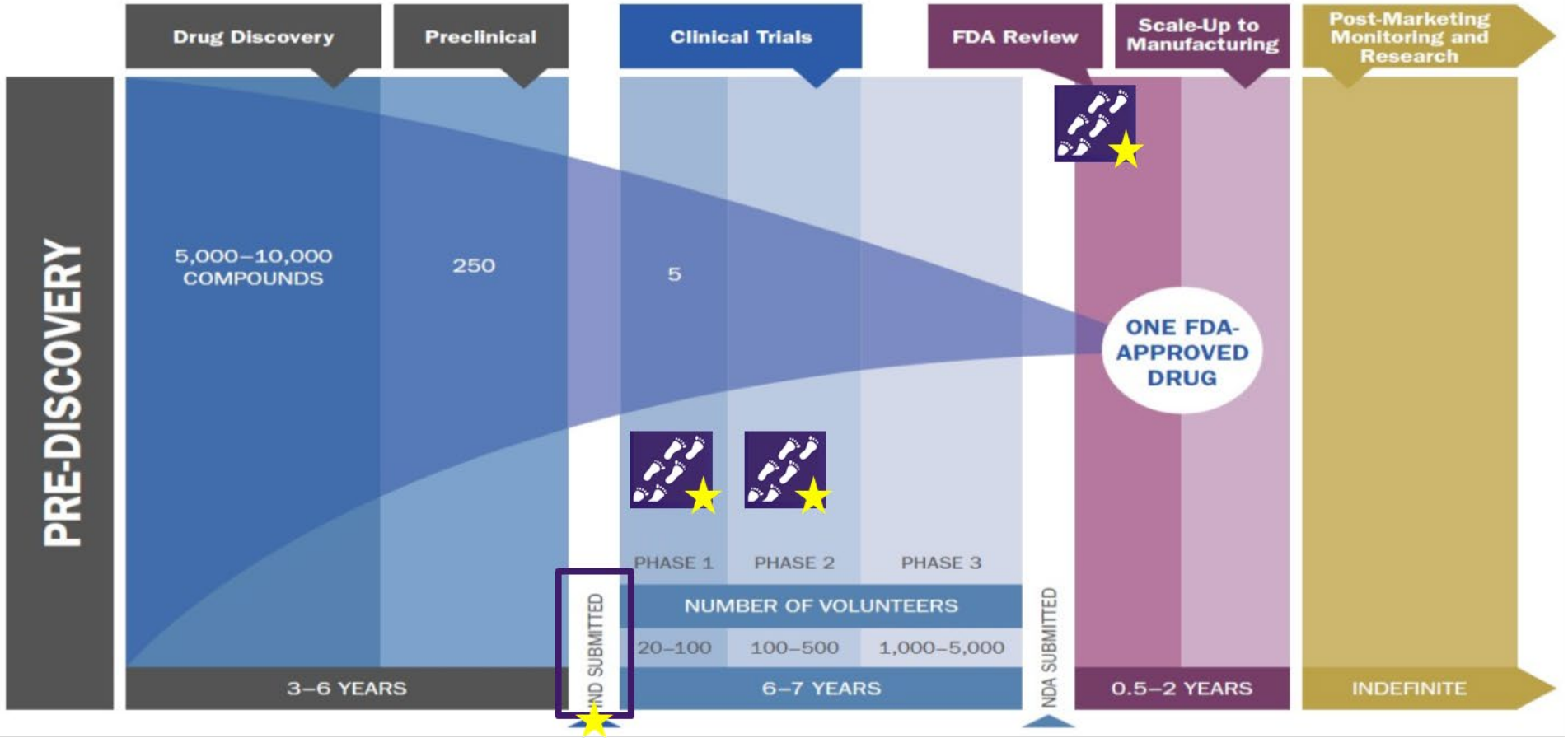
- Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- Success defined by improving dosing, safety information, labeling, and ultimately child health
- Focus on off-patent therapeutics

PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

Types of studies that PTN performs



PEDIATRIC TRIALS NETWORK

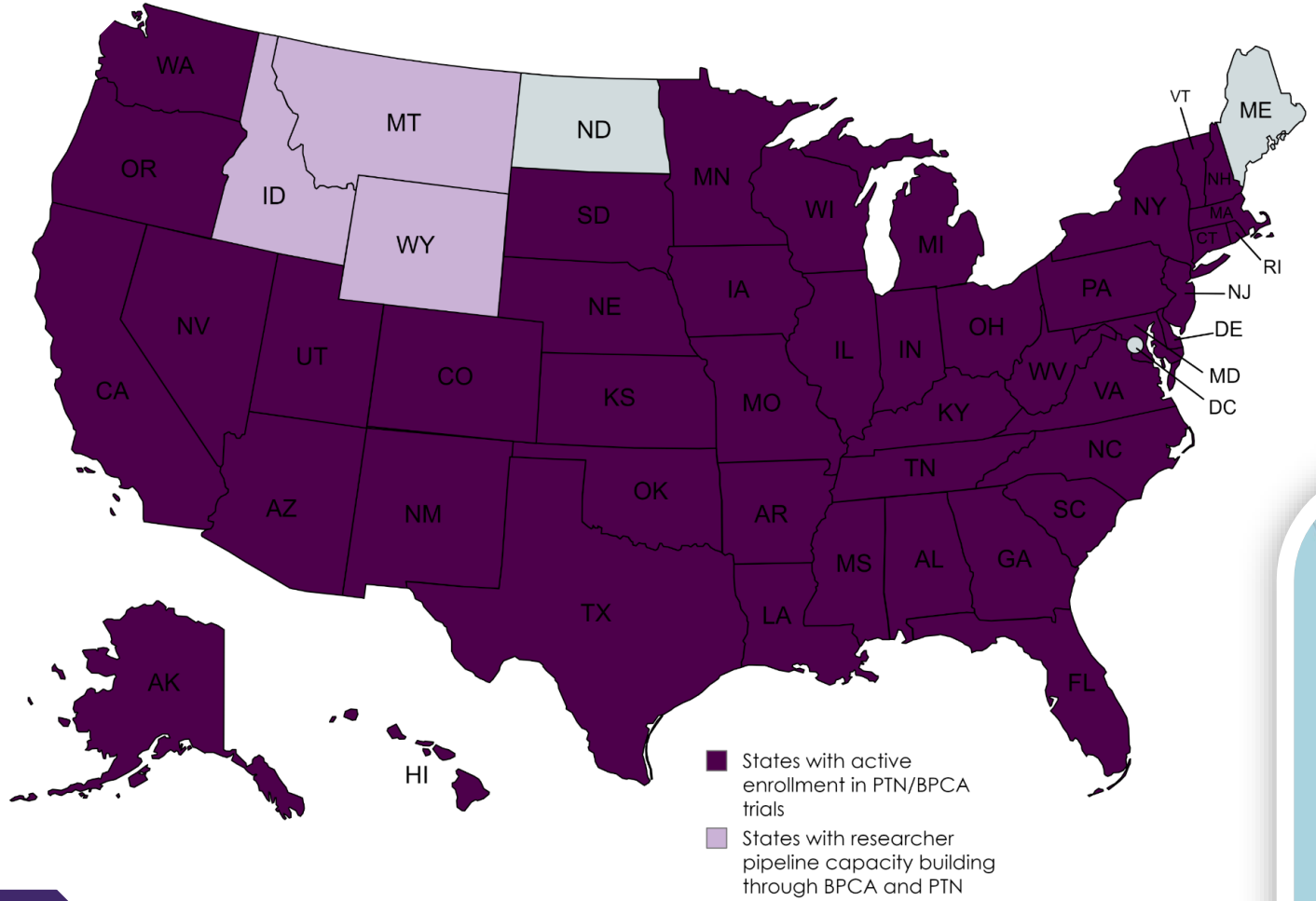
NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

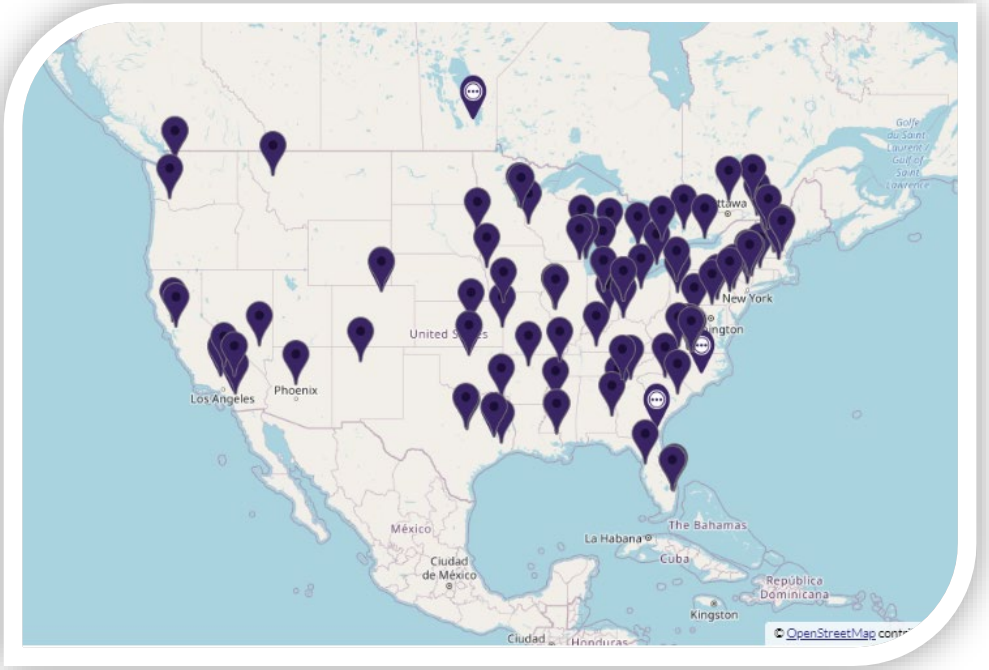
A project of the Best Pharmaceuticals for Children Act

PTN's Pathway to Labeling

1. Section 409I of Public Health Service Act mandates NIH to:
   - Collaborate with FDA, develop and publish NICHD's BPCA priority list of therapeutic areas in critical need of pediatric research
   - Sponsor pediatric trials
2. NICHD awarded contracts to a clinical coordinating center (Duke) and a data coordinating center (Emmes) to conduct trials in pediatric patients in areas identified on the priority list
3. PTN conducts necessary studies
4. Study data are submitted to FDA for review and consideration for label change negotiation

PTN Sites





PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

PTN Successes

>12,500
participants enrolled

27
products submitted to the FDA

301
sites in

45
states and

5
countries outside the U.S.

21
therapeutic areas studied

54
studies

20
label changes

>100
publications

>200
methods developed

PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

20 PTN Label Changes

- Ampicillin
- Trimethoprim-sulfamethoxazole
- Lithium
- Lorazepam
- Lisinopril
- Meropenem
- Doxycycline
- Acyclovir
- Caffeine Citrate
- Clindamycin Obesity
- Mercy Tape
- Mercy Baby Tape
- Sodium Nitroprusside
- Propylthiouracil
- Pralidoxime
- Diazepam
- Clindamycin
- Rifampin
- Levetiracetam
- Fluconazole

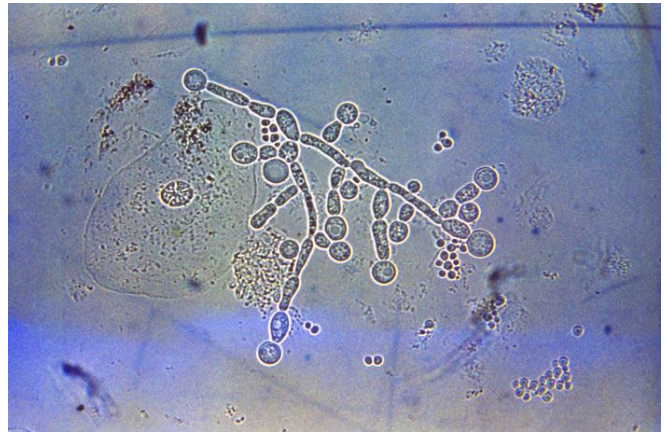
PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

Fluconazole Label Change

- The old label contained almost no information related to how to use this drug in infants, even though it is commonly used to treat *Candida* (yeast) infections, which are often fatal in infants and cause long-lasting health problems for those that survive
- The update to the label is extensive and involves data from multiple studies and analyses supported by PTN
- The new label contains information on pharmacokinetics and dosing suggestions (including the use of a “loading” or initial higher dose), as well as safety and efficacy of fluconazole for both treatment and prophylaxis of *Candida* infections in full-term and premature infants
- Importantly, information on dosing for pediatric patients on ECMO is also newly included



PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

PTN's interest in infants

- Infants, particularly hospitalized infants, are frequently prescribed medications off-label
- Of the top 50 medications used in infants with extremely low birth weight, only 20 (40%) are FDA-labeled for use in infants
- Goal → to create a "master protocol" for hospitalized infants that could be used to study multiple diseases and medications under a single study

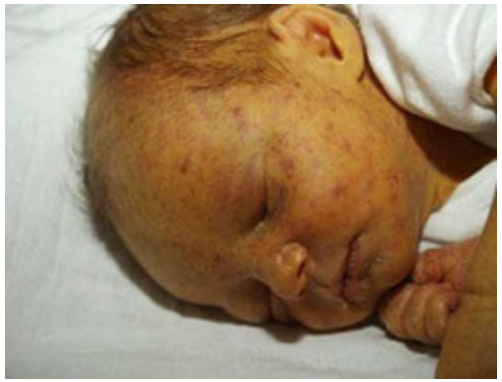
PEDIATRIC TRIALS NETWORK

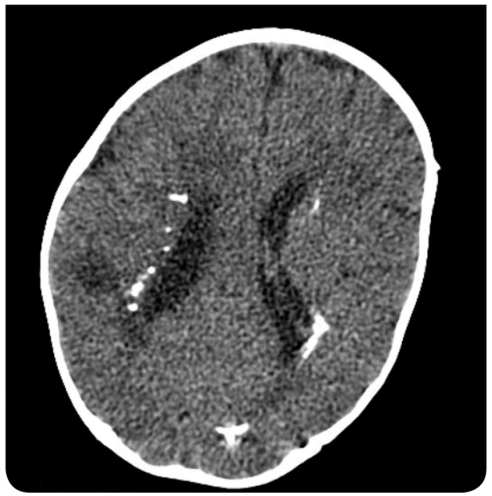
NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

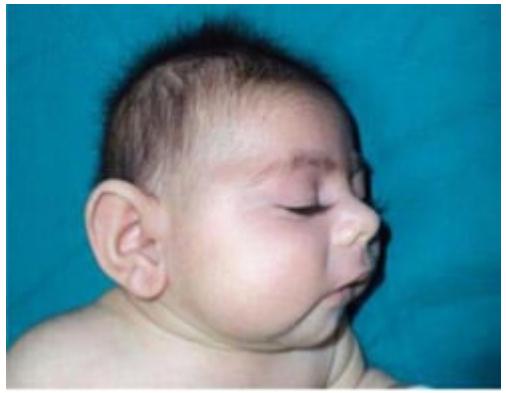
A project of the Best Pharmaceuticals for Children Act

PTN's interest in congenital CMV

- Most clinicians use ganciclovir/valganciclovir to prevent cCMV related outcomes – hearing loss and neurodevelopmental impairment
  - Based on existing data and consensus guidelines







Am Fam Physician. 2018 Jun 1;97(11):753-754.

https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/quick-reference-handbook/congenital-cytomegalovirus.html

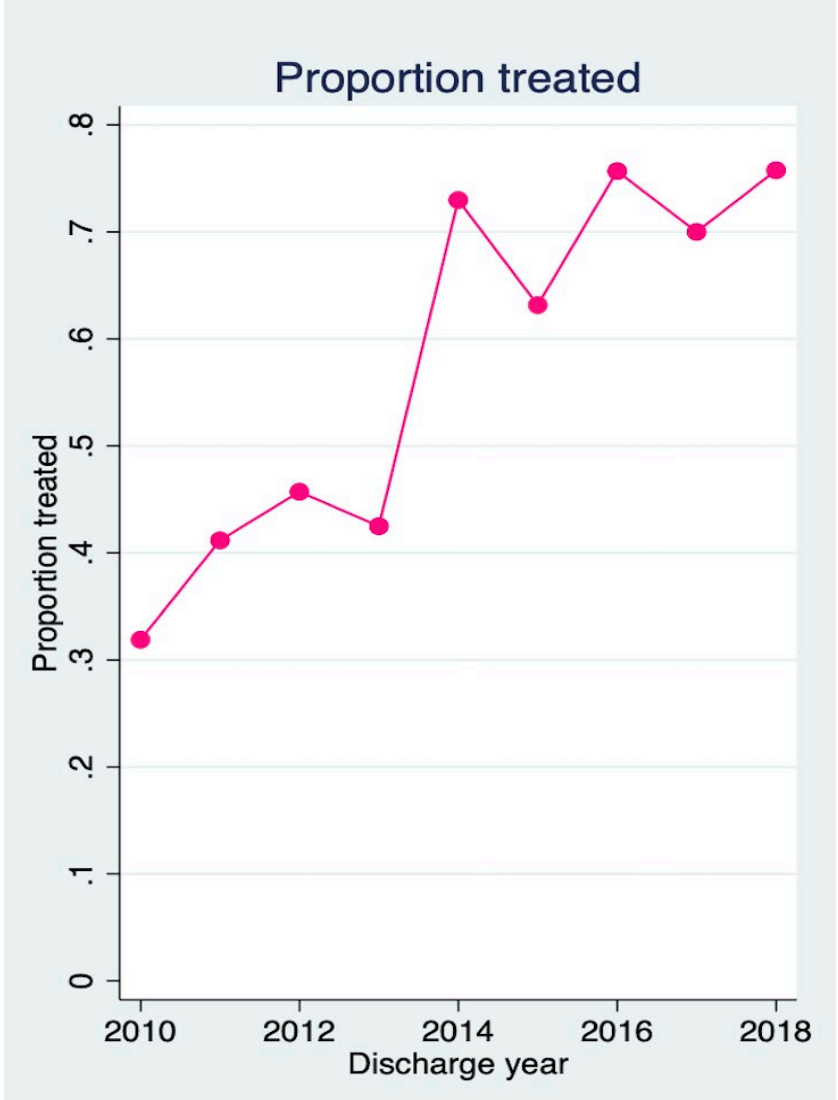
PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

cCMV is a priority for study

- The BPCA Priority List includes “Infections in Neonates” as an area of therapeutic need ✓
- Ganciclovir/valganciclovir are included within that therapeutic area as a drug for which label updates are needed ✓
- Clinicians are using these medications without FDA guidance ✓



PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

What is evidence base for treatment?

- Kimberlin (2003): n=100 symptomatic, 6 weeks ganciclovir vs. placebo: prevention of hearing deterioration at 6 months of age
- Kimberlin (2015): n=96 symptomatic, 6 months valganciclovir vs. 6 weeks valganciclovir: longer treatment had no benefit at 6 months, but improved hearing at 12 and 24 months, and improved neurodevelopmental scores

PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

What is evidence base for treatment?

- Kimberlin (2003): n=100 symptomatic, 6 weeks ganciclovir vs. placebo: prevention of hearing deterioration at 6 months of age
- Kimberlin (2015): n=96 symptomatic, 6 months valganciclovir vs. 6 weeks valganciclovir: longer treatment had no benefit at 6 months, but improved hearing at 12 and 24 months, and improved neurodevelopmental scores

Issue: only 42% follow-up of primary outcome

Issue: study did not show efficacy in primary outcome

Where do we go from here?

Could PTN help to perform a well-controlled trial to establish efficacy?

The problem: equipoise

Lack of definitive data

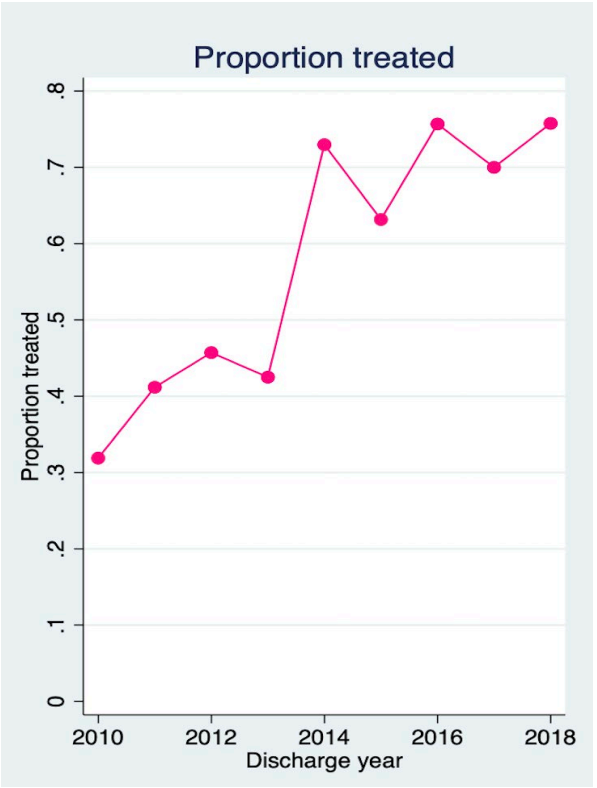
PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

The problem: equipoise

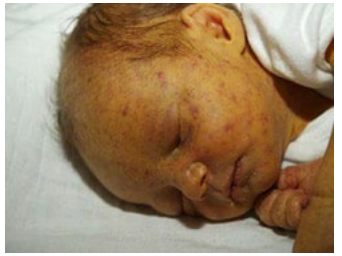
Lack of definitive data

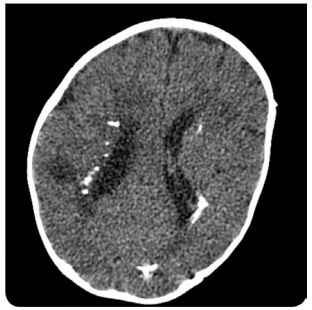


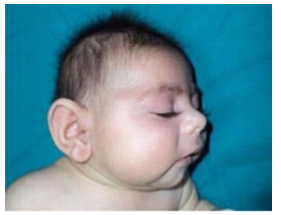
PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act







And yet we are stuck with…

- Ganciclovir package insert

1 INDICATIONS AND USAGE

1.1 Treatment of CMV Retinitis

GANCICLOVIR INJECTION is indicated for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS) *[see Clinical Studies (14)]*.

1.2 Prevention of CMV Disease in Transplant Recipients

GANCICLOVIR INJECTION is indicated for the prevention of CMV disease in adult transplant recipients at risk for CMV disease *[see Clinical Studies (14)]*.

And…

- Valganciclovir package insert

1 INDICATIONS AND USAGE

1.1 Adult Patients

Treatment of Cytomegalovirus (CMV) Retinitis: VALCYTE is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) *[see Clinical Studies (14.1)]*.

Prevention of CMV Disease: VALCYTE is indicated for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]) *[see Clinical Studies (14.1)]*.

1.2 Pediatric Patients

Prevention of CMV Disease: VALCYTE is indicated for the prevention of CMV disease in kidney transplant patients (4 months to 16 years of age) and heart transplant patients (1 month to 16 years of age) at high risk *[see Clinical Studies (14.2)]*.

Where do we go from *here*?

- Could use of real-world data provide compelling evidence?
- Should we try to study something else, which has more equipoise?

Pivot to postnatal CMV?

- Acquired after birth, causes symptomatic sepsis-like illness in premature infants
- Observational studies suggest it is associated with adverse long-term outcomes (bronchopulmonary dysplasia, hearing loss)
- Many clinicians use ganciclovir/valganciclovir to treat postnatal CMV, but they are not approved by FDA for this indication
- Further studies are needed to determine natural history of postnatal CMV and develop potential trial endpoints

THANK YOU

rachel.greenberg@duke.edu

PEDIATRIC TRIALS NETWORK

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

U.S. FOOD & DRUG ADMINISTRATION

Clarifying Questions and Answers

U.S. FOOD & DRUG ADMINISTRATION

Lunch Break

U.S. FOOD & DRUG ADMINISTRATION

Panel Discussion on Drug Development Considerations for Products to Treat cCMV Infection

Session 3:
Congenital CMV Infection
Trial Design Challenges Panel

- Tien Bo, PharmD; Takeda Pharmaceuticals
- Paul Griffiths, MD, DSc, FRCPath; University College London
- David Kimberlin, MD; University of Alabama at Birmingham

- John Concato, MD, MS, MPH; FDA
- Lindsay DeVries, AuD, PhD; FDA
- Ryan Kau, MD; FDA
- An Massaro, MD; FDA
- Lily (Yeruk) Mulugeta, PharmD; FDA
- Kunyi Wu, PharmD; FDA

- Roberta DeBiasi, MD, MS; Children's National Hospital and Research Institute
- Rachel Greenberg, MD, MB, MHS; Duke University Medical Center and Duke Clinical Research Institute
- Tatiana Lanzieri, MD; CDC
- Emma Mohr, MD, PhD; University of Wisconsin - Madison
- Megan Pesch, MD, MS; University of Michigan/Michigan Medicine
- Betsy Pilon; Hope for HIE
- Mark Schleiss, MD; University of Minnesota Medical School

Panel Discussion on Drug Development Considerations for Products to Treat cCMV Infection

1. Please discuss the key challenges in antiviral drug development for the treatment of cCMV infection
   - Comment on what additional nonclinical or basic science work may be needed to help drive therapeutic development for treatment of cCMV infection
2. Please discuss potential strategies that could be considered to improve collaboration between industry, academia, and parents/caregivers to facilitate antiviral therapeutic development for the treatment of cCMV infection

U.S. FOOD & DRUG ADMINISTRATION

Panel Discussion on Clinical Trial Designs to Evaluate Treatment of cCMV Infection

1. Please discuss the ideal study population(s) for clinical trial enrollment (e.g., symptomatic, hearing loss only, asymptomatic)
2. Considering the different populations, please discuss the appropriate efficacy endpoints
    - Hearing loss (total ear vs worst ear vs best ear; at what time point?)
    - Neurodevelopmental outcomes

1. Please discuss the most appropriate comparator treatment group
    - Please comment on the potential role of real-world data and real-world evidence

U.S. FOOD & DRUG ADMINISTRATION

Closing Remarks


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Real World Evidence

- **Real-world data** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

- Center for Biologics Evaluation and Research & Center for Drug Evaluation and Research Real-World Evidence | FDA

- Guidance Documents
- Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products (2024)
- Framework for FDA's Real-World Evidence Program (2018)
- Use of Electronic Health Records in Clinical Investigations (2018)
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics (2022)
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (2023)
- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023)
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (2023)
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (2023)
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (2023)