



Congenital Cytomegalovirus: A Pilot Study

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Special Thanks

Centers for Disease Control and Prevention

This project is funded through the Emerging Infections Program Cooperative Agreement

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Objectives

- 1) Congenital cytomegalovirus (cCMV) basics
- 2) Minnesota CMV pilot study
- 3) CMV and newborn screening – the case for CMV
- 4) Questions



Cytomegalovirus (CMV) Basics

- It is the MOST common congenital viral infection in the USA
- Common cause of disability
- Infection rate is 0.6-0.7% of live births worldwide
- 15-20% of infected infants have permanent disability
- 6,000 children in the U.S. annually
- Low awareness – clinical impact mostly discussed with organ transplant recipients or HIV-infected individuals



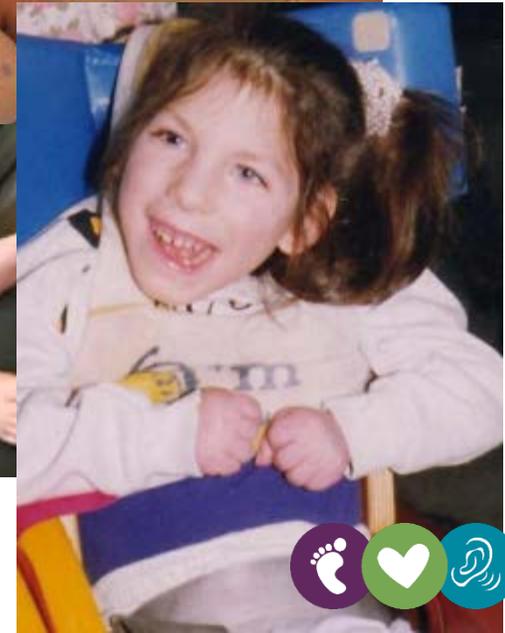
Congenital Cytomegalovirus (cCMV) Infections

- Most common cause of non-hereditary sensorineural hearing loss in children
- Three possible classifications for cCMV
 - Symptomatic – 10-15%
 - Asymptomatic with hearing loss (may or may not be present at birth) – 7-15%
 - Asymptomatic with no clinical concerns – 80%
- Can be treated with antiviral medication if identified early (ganciclovir and/or valganciclovir)
- Congenital vs acquired – distinguishable only within first 21 days of life



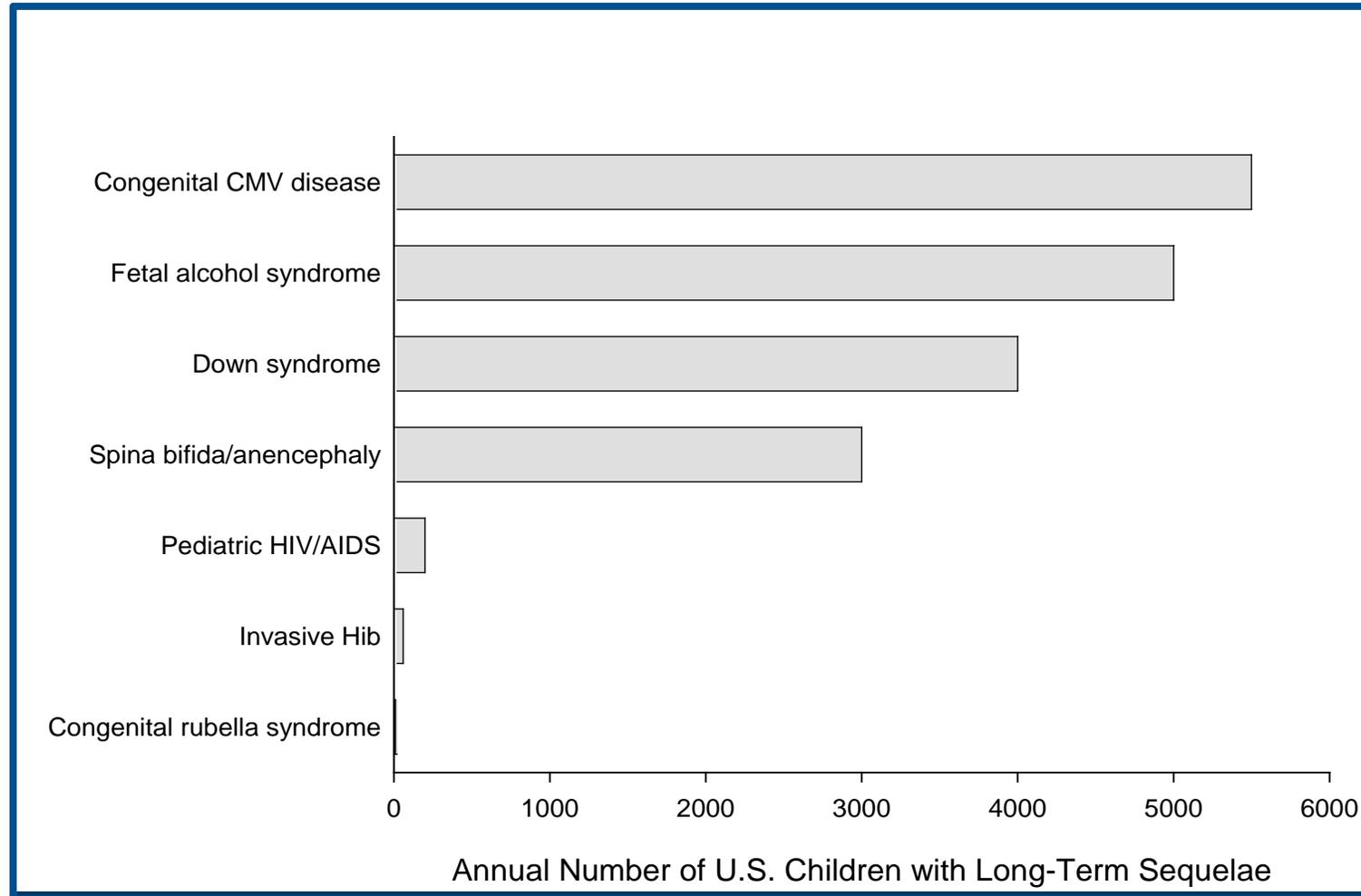
Impact of cCMV

- Prenatal findings can include: echogenic bowel, IUGR, ventriculomegaly, thick placenta
- Newborns can show: prematurity, liver disease, petechiae, thrombocytopenia
- Symptomatic children can present with:
 - Criteria – 2 or more features with CNS involvement
 - Cognitive impairment/mental disability – 55-66%
 - Vision loss – 22-58%
 - Hearing loss – 30-50%
 - Microcephaly
 - Cerebral palsy
 - Seizures
 - Death



* Advocates have dubbed CMV the “birth defects virus”

Childhood Conditions



By the Numbers

Minnesota – birth rate of ~70,000 per year

*assume an infection rate of 1/200

~350 newborns **each year** are born infected



Symptomatic

35 infants



Asymptomatic
with hearing loss

35 infants



Asymptomatic

280 infants



Minnesota Study

- Funded through CDC's Emerging Infection Program (EIP) Cooperative Agreement
- Partnerships with:
 - CDC – Sheila Dollard, PhD,
 - UMN – Mark R. Schleiss, MD
 - Hospitals: Fairview Health (UMMC, Ridges, Southdale) & Allina Health (Abbott Northwestern & United)

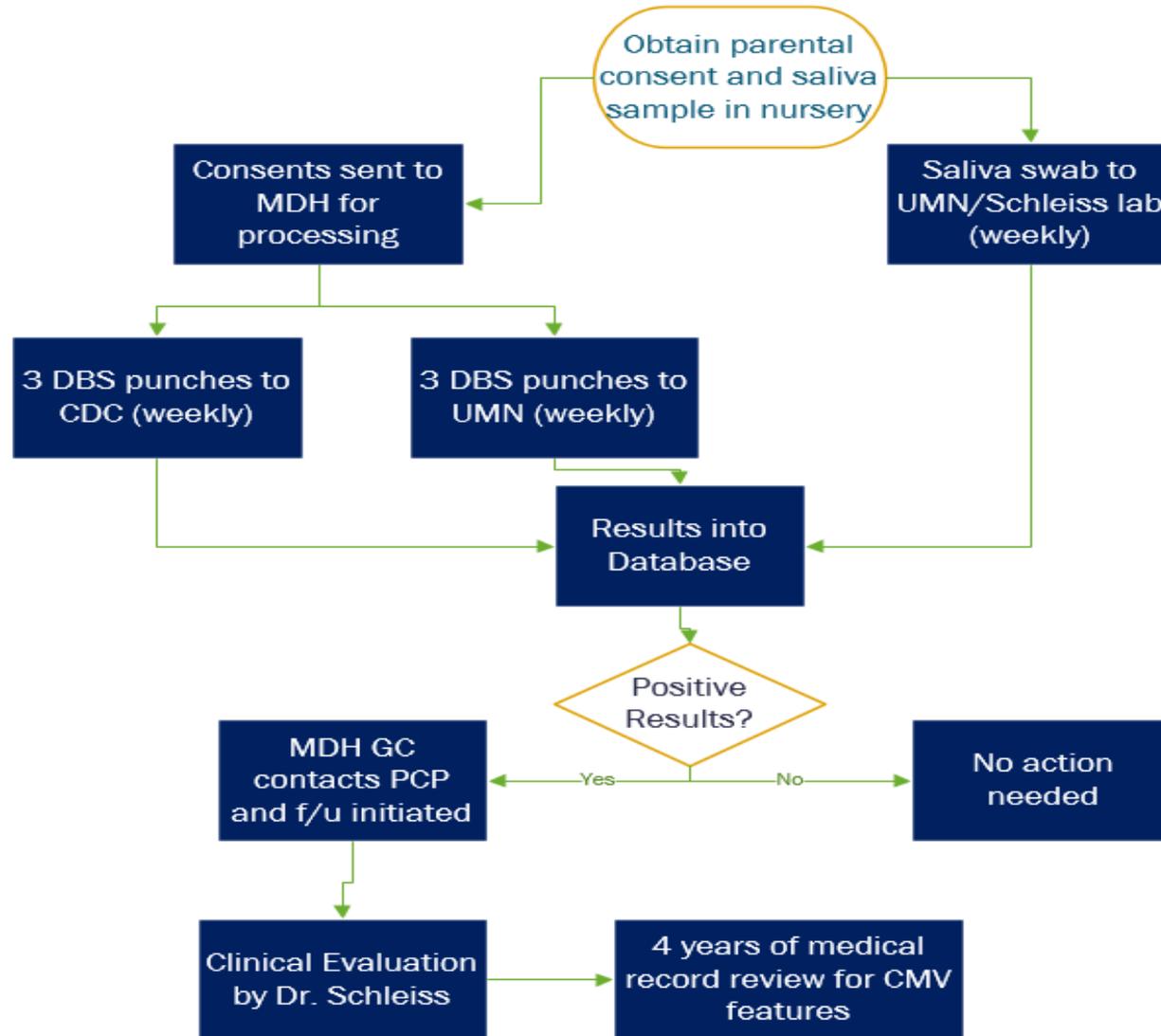


Study Aims

- Clinical sensitivity:
 - Compare two DBS PCR assays performed in independent laboratories (CDC/Dollard and UMN/Schleiss laboratory), using the newborn DBS as a source of CMV DNA
 - Compare DBS PCR results to PCR performed on saliva specimens obtained in the newborn nursery
 - Viral load is known to be higher in urine and saliva
- These results will help clarify which assay is more useful for universal newborn CMV screening
- Target enrollment: 30,000 infants



Study Design



Demographics collected:

GA at delivery
Living children (TPAL)
Birth weight
Head circumference
Race
Ethnicity



Clinical Evaluation

- Infant is evaluated by pediatric infectious disease provider familiar with CMV (to date all infants have seen Dr. Schleiss)
 - Hearing evaluation
 - History and physical exam
 - CNS imaging (selected)
- Positive infants upon clinical evaluation
 - Additional labs obtained for confirmation (Urine)
 - Parents are engaged in a discussion regarding treatment options
 - Hearing assessments at increased frequency – every 3 mo for first 3 years, and every 6 mo until age 4
 - Medical record review annually until age 4



Progress through Aug 14, 2017

First site began enrolling mid-February 2016

5 sites active with enrollment

Total of 3,395 infants enrolled

Enrollment rate: 55% overall, 72% when discussed

Number of positive infants: 10

Initial clinical evaluation of positive infants:

4 infants – symptomatic with hearing loss

6 infants – asymptomatic without hearing loss (at initial evaluation)

Delayed hearing loss:

1 ‘asymptomatic’ infant developed hearing loss (mild to moderate unilateral) identified on 6 month hearing assessment



Advocacy Efforts



The Case Against Universal Screening

- Lack of awareness of CMV
- So. Many. Babies.
 - This is a HUGE increase in follow-up burden (min. 350 infants per year)
- Asymptomatic infants/children – 80% of those identified
 - Persistent parental anxiety (fragile child syndrome)
 - Unnecessary medical attention



Case Against Cont.

- Treatment options
 - Ganciclovir and Valganciclovir are off-label for cCMV
 - Only treat some of the features – moderately favorable effect on long-term audiologic and neurodevelopmental outcomes in symptomatic children
 - Consensus papers recommend treating symptomatic children – not currently the recommendation for “asymptomatic with hearing loss” children but is occurring clinically
- A vaccine is a better option...
- Lack of validated laboratory method for dried blood spots (DBS)
 - CHIMES study found DBS detection of CMV was low (~ 30% sensitivity) however, their DBS method was proven to be low yield and out-of-date

The Case For Universal Screening

- Most CMV-associated disability not evident at birth and therefore not detected
 - Symptomatic infants missed
- Early intervention improves outcomes for these infants
 - Increased monitoring
 - Non-pharmaceutical therapies become an option
- Good evidence for benefit with antiviral tx for symptomatic infants
- CMV screening would avoid diagnostic odyssey for newborns with symptoms



Case For Cont.

- Targeted approaches fall short
 - Utah example: Misses delayed onset hearing loss therefore misses opportunity for treatment
- EHDI programs are unequipped to deal with a laboratory testing platform
- 10 years since CHIMES
 - Technology has changed and improved
- Advocates are organized
 - Universal saliva collection would be EXPENSIVE
 - DBS may be 'good enough'

The screenshot shows the Utah Department of Health website. The header includes the Utah.gov logo, navigation links for Services and Agencies, and a search bar. The main title is "Children With Special Health Care Needs" with contact information: Phone (801) 584-8284 and Toll Free (800) 829-8200. A navigation menu includes Home, About Us, Programs (highlighted), Families, Resources, Data, Forms, and Contact Us. Below the menu is a large image of a newborn baby. The main content area is titled "Cytomegalovirus (CMV) Public Health Initiative" and features a photo of a young child. To the right of the photo is text about H.B. 81 (2013 General Session) UCA 26-10-10, which directs the Utah Department of Health to create a public education program. A sidebar on the right contains contact information for the CMV Office: (801) 584-8215, Monday thru Friday - 8 am to 5 pm, and email cmv@utah.gov. It also includes social media icons for Facebook and Twitter. A "Did You Know?" section at the bottom right states: "Congenital CMV is the leading non-genetic cause of childhood hearing loss."

This law also directs medical practitioners to test infants who fail newborn hearing screening for congenital

Does it Meet Criteria?

- Medically serious condition with well described case definition
 - Yes
 - However, with 80% unaffected cCMV is unlike any other disorder on the NBS panel
- Accurate, high throughput diagnostic test available
 - No, not currently – working on it
- Effective treatment available
 - Yes - early intervention and promising antiviral treatments for symptomatic newborns

Acknowledgements

CDC

Sheila Dollard
Tatiana Lanzieri
Marcus Gaffney

Allina

Abbey Sidebottom
Whitney Duncanson
Dhimpho Orionzi*
Anna Shelley

UMN

Mark Schleiss
Nelmary Hernandez-Alvarado
Amanda Galster
Claudia Fernandez
Anne Hopper

MDH

Mark McCann
Ruth Lynfield
Kirsten Coverstone
Jill Simonetti
Carrie Wolf
Trenna Lapacinski
Alisha Wruck

Fairview

Consenters:

Mary Pat Osborne
Amy Ash
Amy Hanson*
Jenna Wassenaar
Kristin Chu
Loralie Peterson
Michelle Roesler*

Champions:

Jordan Marmet
Anne Skemp

Additional funding

Minnesota Vikings Children's Fund
"If you don't pass, Screen"

* Individual has rolled-off the study

A special **thank you** to all our families for participating in the study!

