Congenital Cytomegalovirus: A Pilot Study

Maggie Dreon

Mark Schleiss, Sheila Dollard, Tatiana Lanzieri, Nelmary Hernandez-Alvarado, Carrie Wolf, Kirsten Coverstone, Ruth Lynfield, Mark McCann

Special Thanks

Centers for Disease Control and Prevention

This project is funded through the Emerging Infections Program Cooperative Agreement

Sheila Dollard, PhD, Lab director in Infectious Disease – CDC PI

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

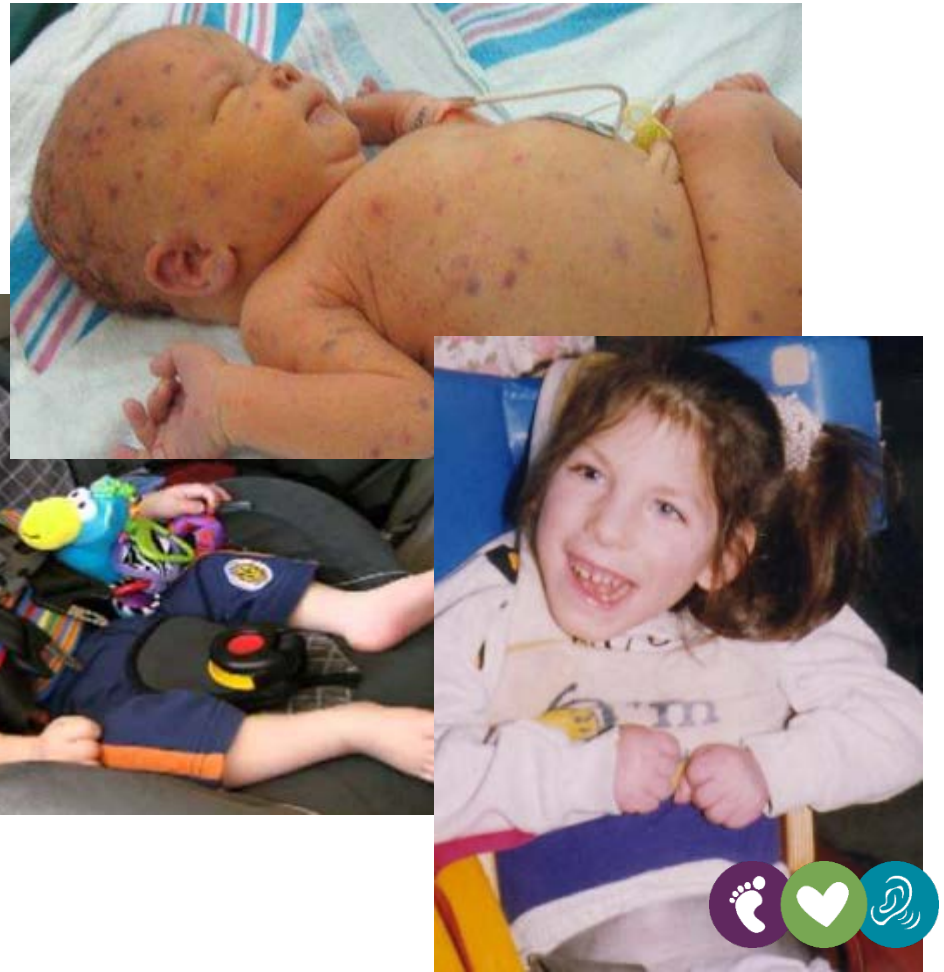
- It is the MOST common congenital viral infection in the USA
- Common cause of disability
- Infection rate is 0.6-0.7% of live births worldwide
- 15-20% of infected infants have permanent disability
- 6,000 children in the U.S. annually
- Low awareness – clinical impact mostly discussed with organ transplant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

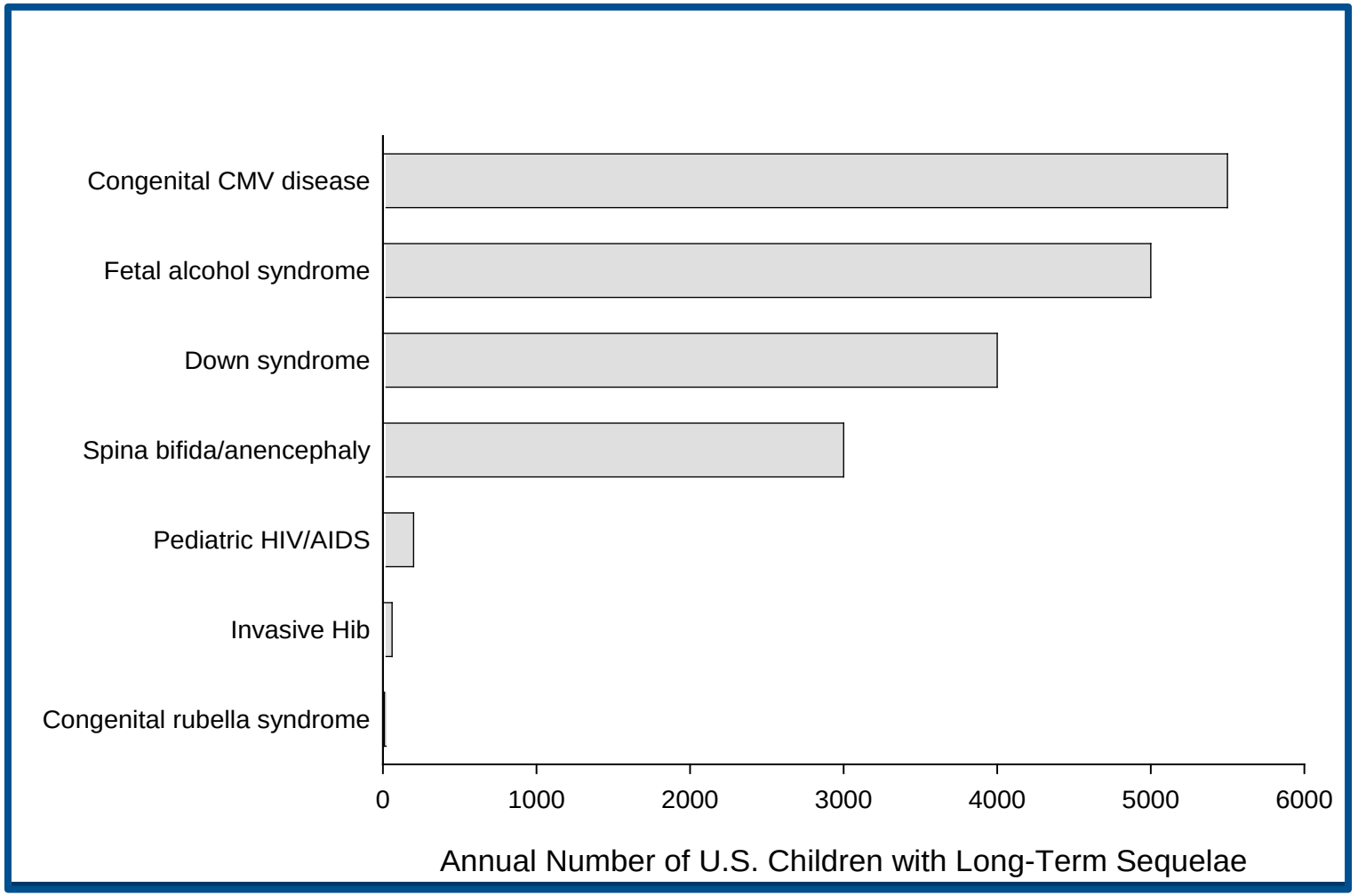
- Prenatal findings can include: echogenic bowel, IUGR, ventriculomegaly, thick placenta
- Newborns can show: prematurity, liver disease, petechiae, thrombocytopenia
- Symptomatic children can present with:
  - Criteria – 2 or more features with CNS involvement
    - Cognitive impairment/mental disability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



* Advocates have dubbed CMV the “birth defects virus”

Burden of CMV

Childhood Conditions



Cannon et al., 2004

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

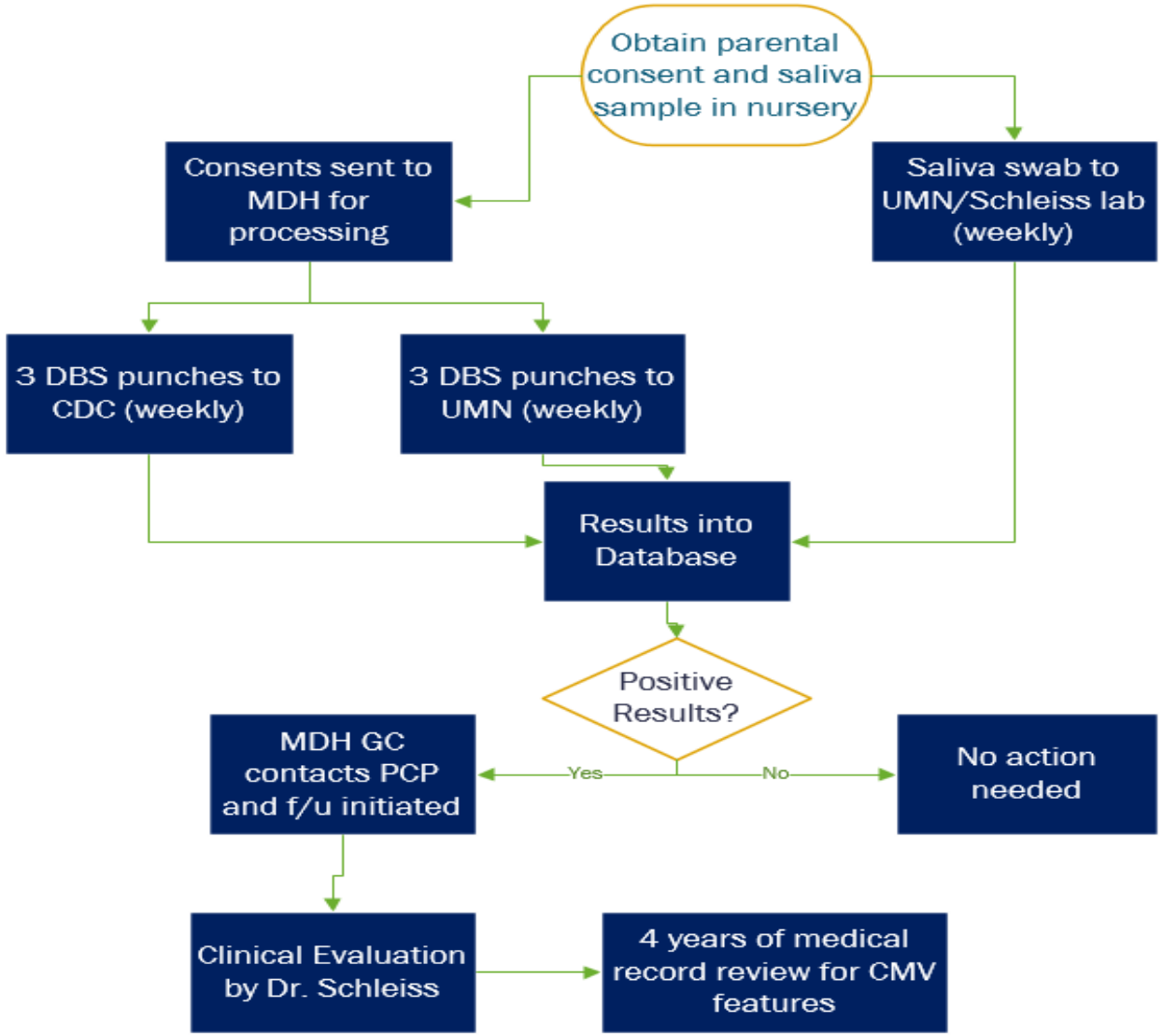
Minnesota Study

- 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



<u>Demographics collected</u>:

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’

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

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

Fairview
Consenters:
Mary Pat Osborne
Amy Ash
Amy Hanson*
Jenna Wassenaar
Kristin Chu
Loralie Peterson
Michelle Roesler*
Champions:
Jordan Marmet
Anne Skemp

Allina
Abbey Sidebottom
Whitney Duncanson
Dhimpho Orionzi*
Anna Shelley

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

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!