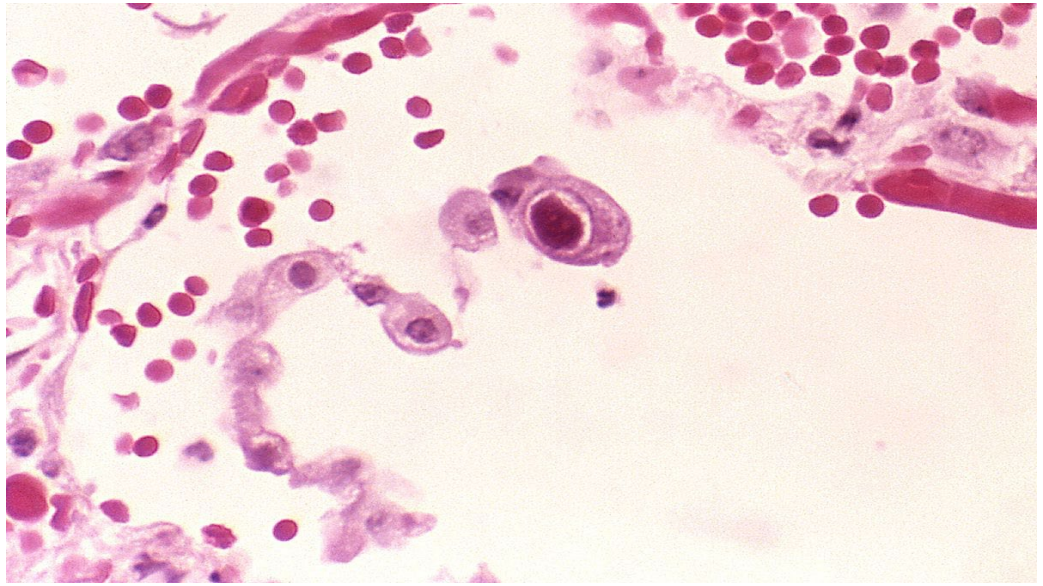
DEPARTMENT OF HEALTH

Congenital Cytomegalovirus (cCMV)

Sondra Rosendahl | Licensed Genetic Counselor

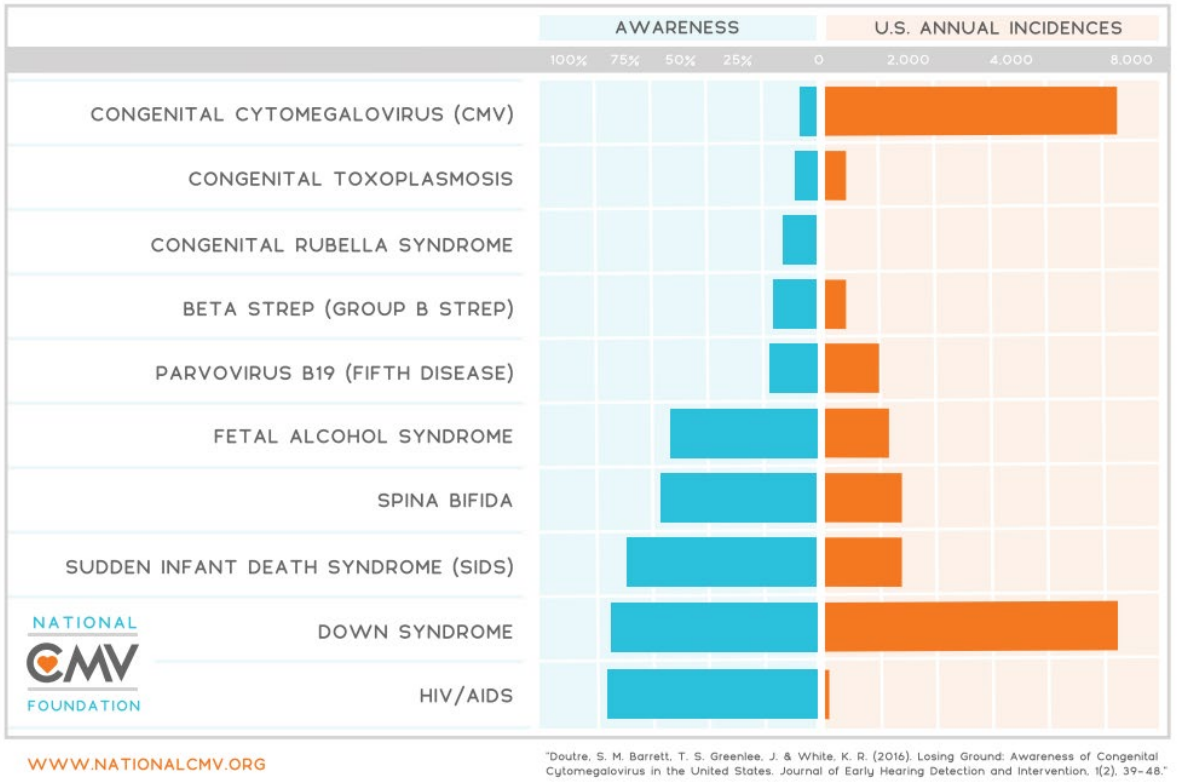
What is cytomegalovirus (CMV)?

- Member of the herpes simplex virus family
- Able to establish lifelong latency after initial infection
- Transmitted by body fluids (urine, saliva, blood, tears, semen, and breastmilk)



Acquired vs congenital cytomegalovirus (cCMV)

- Acquired CMV:
  - Occurs at any age
  - Most people have mild to no symptoms; sometimes causes mononucleosis-like symptoms
  - VERY common (1 in 3 infected by age 5; over half of adults by age 40)
  - Newborns can acquire it from mother's breastmilk
  - Older children (toddlers) often acquire CMV infection in group daycare or from exposure to other children
- Congenital CMV:
  - Occurs when the CMV infection is passed from a pregnant woman to her fetus
  - Could be a primary infection vs reinfection vs reactivation
  - About 1 in 200 infants born with cCMV, but not many people know about it



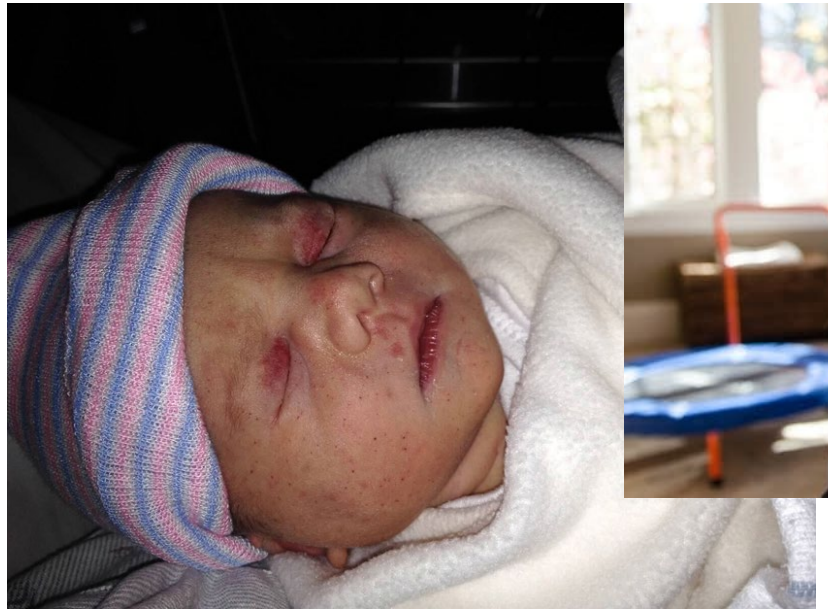
cCMV Testing Complications

- Testing mother during pregnancy is unreliable
  - Not always transmitted to fetus, no one good time to test, could be exposed anytime, etc
- Clinicians often mistakenly order TORCH titers, which cannot unequivocally make the diagnosis – only indirect evidence of infection

Bottom line: congenital CMV can't be accurately diagnosed in a newborn beyond 14-21 days of age

The Many Faces of cCMV

- Symptomatic (~10%) – 2 or more features with central nervous system involvement
  - Signs at birth can include:
    - Microcephaly
    - Petechiae (purpura)
    - Jaundice
    - Hepatosplenomegaly
    - Hearing loss
  - Long-term health problems:
    - Hearing loss (30-50%)
    - Vision loss (22-58%)
    - Intellectual disabilities (55-66%)
    - Cerebral palsy
    - Seizures
    - Death
- Asymptomatic with hearing loss (~10%)
  - Majority of children do not have hearing loss at birth
- Asymptomatic (~80%)



Why is it of interest to newborn screening?

- VERY common
- Many children are asymptomatic at birth but at risk for long-term health problems
- Early detection is key – only a 21-day window to determine if congenital infection has occurred
- Early detection leads to early intervention of hearing loss and the option of antivirals for those who may benefit

Minnesota's Universal Screening Study

- Funded through CDC's Emerging Infection Program (EIP) Cooperative Agreement

- Partnership between:
  - CDC – Sheila Dollard, PhD
  - UMN – Mark R. Schleiss, MD
  - MDH

- 6 hospitals, including
  - 3 with NICUs
  - 3 different health systems (Fairview, Allina, and CentraCare)

University of Minnesota

CDC Centers for Disease Control and Prevention

Fairview

CentraCare

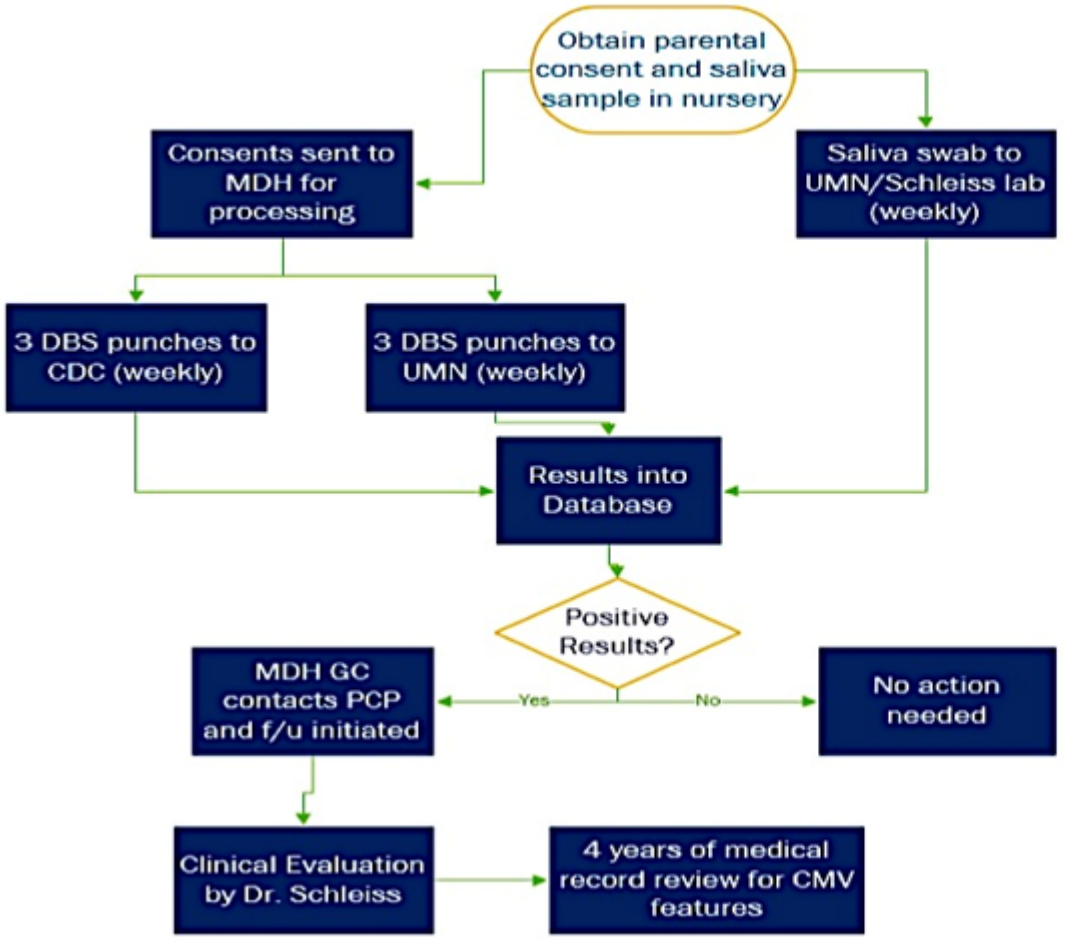
Allina Health

Department of Health

Study Overview

- Research question:
  - What is the sensitivity of cCMV detection using newborn dried bloodspots compared to saliva?

The Process…



Demographics collected:

GA at delivery

Living children (TPAL)

Birth weight

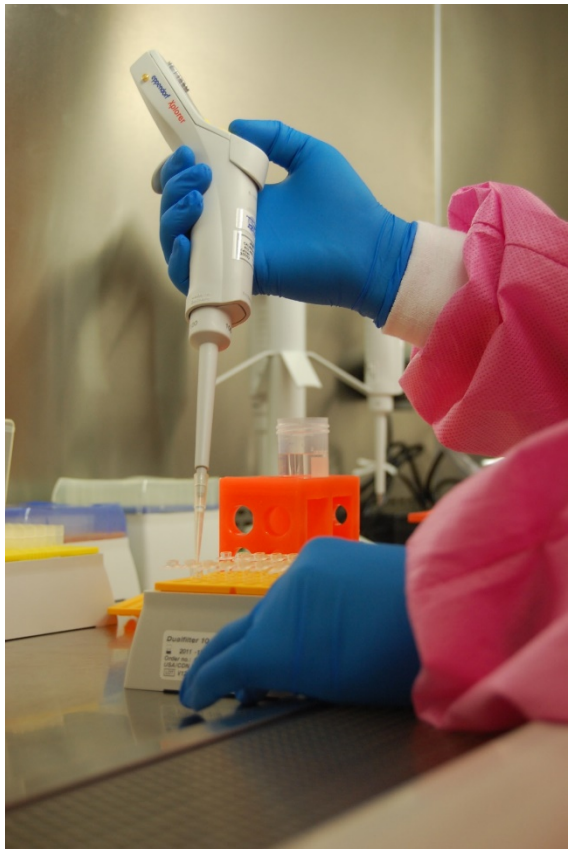
Head circumference

Race

Ethnicity

Laboratory Testing

- CMV PCR testing used on both saliva and dried blood spots
  - Saliva – UMN lab
  - DBS – UMN and CDC labs (different testing methods used)



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

Sheila C. Dollard, PhD[1]; Maggie Dreon, MS[2]; Nelmary Hernandez-Alvarado, MS[3]; Minal M. Amin, MPH[1]; Phili Wong, MS[1]; Tatiana M. Lanzieri, MD, MPH[1]; Erin A. Osterholm, MD[4]; Abbey Sidebottom, PhD[5]; Sondra Rosendahl, MS[2]; Mark T. McCann, BA[2]; Mark R. Schleiss, MD[3]

» Author Affiliations | Article Information

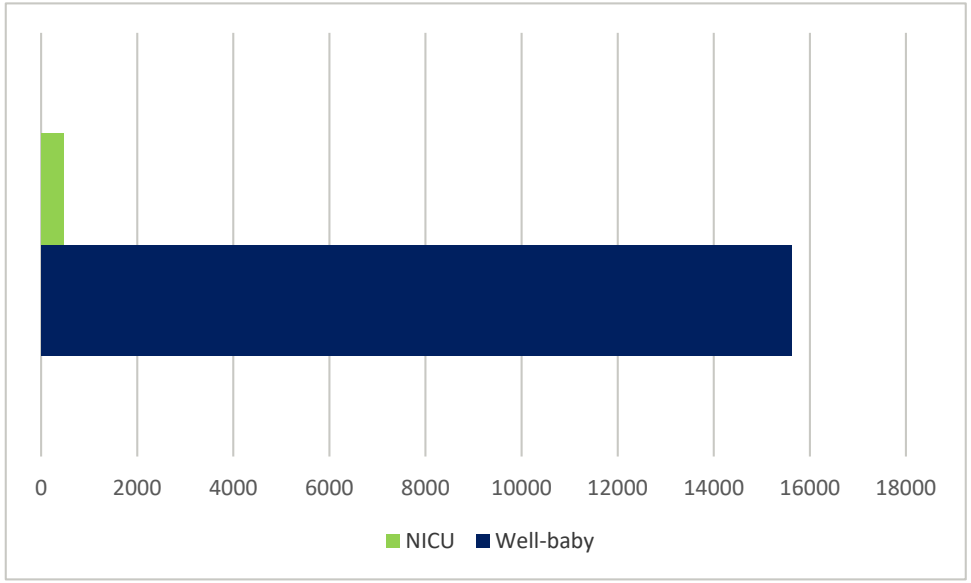
JAMA Pediatr. Published online February 1, 2021. doi:10.1001/jamapediatrics.2020.5441

Clinical Follow-up

- 98% received clinical follow-up by Dr. Mark Schleiss, infectious disease expert at UMN
- Typical follow-up:
  - Physical exam
  - Urine CMV PCR confirmation
  - Hearing evaluation
  - Head ultrasound
  - Eye exam

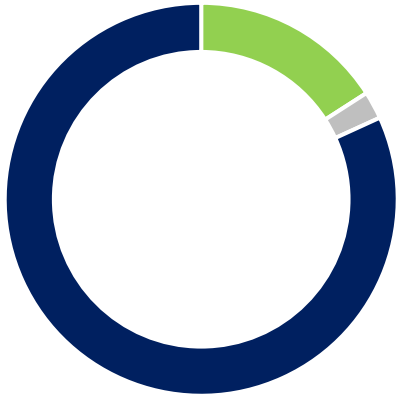
Study Numbers

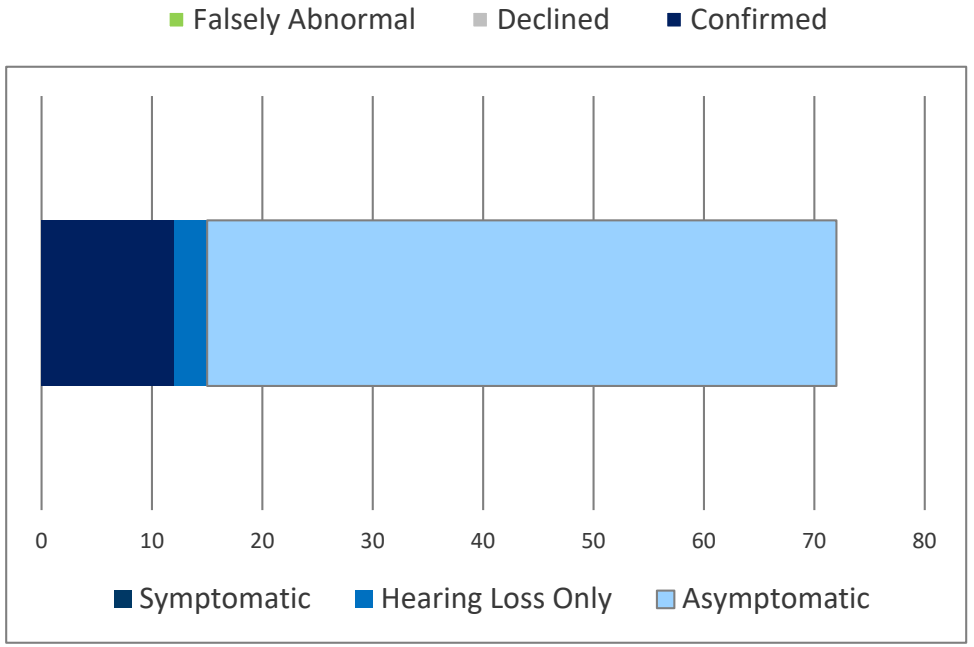
- 16,096 consented (2/8/2016 – 11/30/2020)
- ~70% enrolled when approached with option
- 16,092 newborns screened (excludes QNS, withdrawals, etc):
  - 15,619 (97.1%) from well-baby nursery
  - 473 (2.9%) from NICU



Diagnostic Outcomes

- 88 newborns with actionable result
  - 72 confirmed (prevalence of 0.45% or 4.5 per 1000; same rate reported in literature)
  - 14 falsely abnormal
  - 2 declined follow-up
- Of the 72 confirmed:
  - 12 (17%) symptomatic – mild to severe
  - 3 (4%) hearing loss only – one was a delayed onset
  - 57 (79%) asymptomatic to date





So, how does DBS compare to saliva?

SALIVA

	cCMV (72)	No cCMV (16,020)		Percent
Positive Screen	67	13	**Sensitivity**	93.1
Negative Screen	5	16,007	**Specificity**	99.9

DBS-L1

	cCMV (72)	No cCMV (16,020)		Percent
Positive Screen	52	0	**Sensitivity**	72.2
Negative Screen	20	16,020	**Specificity**	100.0

DBS-L2

	cCMV (72)	No cCMV (16,020)		Percent
Positive Screen	54	1	**Sensitivity**	75.0
Negative Screen	18	16,019	**Specificity**	100.0

Combined DBS Sensitivity:
60/72 = 83.3%

CMV and Donor Milk

- Consenters try to wait at least 30 minutes after a feeding to collect a sample to minimize the risk of a false positive result from CMV DNA in mother's colostrum/milk
- Observations:
  - Several false positive saliva results happened in clusters – why?
  - Many of the false positives had low signal on PCR testing
- Of the 13 false positive saliva results, 9 used donor milk (69%)
  - Pooled, pasteurized milk – would inactivate the virus preventing infection but this may be causing these false positive saliva results

Food for Thought

- Targeted screening for those who don't pass hearing screening WILL result in missing children with cCMV
- Sensitivity of detecting cCMV via DBS has vastly improved
  - What is the threshold/good enough?
- ~80% of children identified are "asymptomatic" – concern for vulnerable child syndrome
  - Many babies – increase in follow-up burden
  - Are they actually asymptomatic or have we just not associated health problems with an underlying cCMV infection?
- Screening card real estate (three 3mm punches; more blood required than any other test)
- Without universal screening, many kids will continue to go through diagnostic odyssey without answers

Next Steps

- Continue enrollment
- Parental assessment survey in process
  - Main question: What is the **emotional impact** on the family when a child's CMV status is known?
  - Decisional regret, risk perception, vulnerable child syndrome, etc

Conclusions

- Parents and providers seem to be accepting of this testing
  - ~70% of parents approached consented
  - ~98% of families with abnormal results worked with their provider to pursue follow-up
- Our results shows that the sensitivity of DBS testing for CMV is higher than previously reported (72-80% vs 34%)
  - Perhaps with improved methodologies we could reach 90-95% in the next few years
- Our study shows the potential of DBS in newborn screening without changing sample type

Acknowledgements

CDC
Sheila Dollard
Tatiana Lanzieri
Phili Wong
Minal Amin

UMN
Mark R. Schleiss
Nelmary Hernandez-Alvarado
Mark Blackstad
Amanda Galster
Claudia Fernández-Alarcón
Liz Ramey

Fairview
Emily Graupmann
Sagal Jama
Elizabeth Tepozteco
Martha DeMeules
*All past consenters who have rolled off the study

Allina
Abbey Sidebottom
Whitney Wunderlich
Jessica Taghon
Anna Schulte
*All past consenters who have rolled off the study

MDH
Mark McCann
Ruth Lynfield
Kirsten Coverstone
Jill Simonetti

Carrie Wolf
Trenna Lapacinski
Garen Frogner
*All past staff who have rolled off the study

Additional funding supporting work
Minnesota Vikings Children's Fund
"If you don't pass, Screen"

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

DEPARTMENT OF HEALTH

Thank you!

Sondra Rosendahl

Sondra.Rosendahl@state.mn.us

651-201-5922