What you need to know before starting a Universal CMV screening program? Some Key Considerations!

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CMV-PHP webinar

November 9, 2021

- What is step 1 in beginning a universal CMV screening program?

Awareness is key!

- Advocacy Groups
- Philanthropic Groups
- AAP, SPR, APA
- Audiology Groups
- Lions Clubs

The New York Times

CMV Is a Greater Threat to Infants Than Zika, but Far Less Often Discussed

Three-year-old Evelyn Steadman of Crete, Ill., was born with the CMV virus and has microcephaly and deafness.
WHITTEN SABBATINI FOR THE NEW YORK TIMES

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

A-Z Index

Search

Cytomegalovirus (CMV) and Congenital CMV Infection

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- CMV Awareness Month
- For Healthcare Providers +
- CMV Resource Center –
  - For Pregnant Women and Parents –

CMV Fact Sheet for Pregnant Women and Parents

English (US)

Most people have been infected with cytomegalovirus (CMV), but do not have symptoms. If a pregnant woman is infected with CMV, she can pass it to her developing baby. This is called congenital CMV, and it can cause birth defects and other health problems.

- What stakeholders should be at the table from the beginning?

ENT
Neonatology
Hospitalists
OB/GYN
Audiology
State Health Department
State Legislatures
EHDI

Consider Funding Sources for Moving the Work Forward!

- Should screening be targeted or universal? Why?

Universal…but…

Contribution of CMV Infection in the Setting of Established Hearing Loss in Minnesota Children

- The majority of children who have CMV-related hearing loss do not have it at birth
- Many ‘failed’ newborn hearing screenings are found in children with normal hearing
- Diagnostic evaluations for nonsyndromic SNHL are often unsuccessful in older children
- Congenital CMV infection cannot be reliably diagnosed beyond the first 2–3 weeks of life

Contribution of CMV Infection in the Setting of Established Hearing Loss in Minnesota Children

- To examine archived newborn blood spots for the presence of CMV DNA by real-time PCR in children 6 months – ten years of age in a referral clinic population
- Collaboration with Minnesota Department of Health Newborn Screening Program
- Archived, stored blood spots are available from State Health Department dating back to 2001
- 'Lions Clinic' in Otolaryngology at University of Minnesota: a multidisciplinary clinic for evaluation and therapy of hearing loss in children

Results from Lion's Clinic Cohort

- 70 families were approached
- 68 (97%) gave consent
- CMV DNA was found on 19 of these newborn blood spots (28%)
- An additional 5 children (7%) had post-natal explanation for acquired hearing loss
- 23 children (34%) were identified as having a genetic or anatomic etiology for hearing loss
  - Connexin (GJB2) mutations (n=4)
  - Mondini malformation (n=3)
  - Other anatomic or presumed genetic causes – see table
- Etiology remained unclear in 21 children (31%)

Subject	DOB	NBHS	Current/last documented Status	Cochlear Implant
1. MA-F	2/05	Passed	Severe-to-profound L>R	L (8/08); R (7/06)
2. JB-J	1/08	Failed	Mild-to-mod bilateral (?)	
3. JB-M	7/01	Passed	L: Normal; R: profound	
4. DC-M	11/06	Passed	Severe -to-profound - Bilat	B (12/08)
5. TF-M	9/06	Failed	R: Profound; L: Moderate	
6. MF-F	9/06	Failed	Profound - Bilat	R (11/08)
7. NF-F	10/06	Failed	L: Severe-to-profound; R: Profound	R (7/09)
8. IG-F	10/08	Failed	Profound - Bilat	B (12/09)
9. CH-F	2/08	Failed	N/A	
10. JJ-M	8/07	Passed	L: Mod-to-severe; R: profound	
11. SK-F	10/04	Passed	Profound - Bilat	L (7/06)
12. JL-M	2/07	Failed	Profound - Bilat	B (5/09)
13. MM-F	12/99	N/A	R: Mod; L: Normal	
14. AO-M	11/01	Failed	L: Profound; R: Normal	
15. AR-M	11/08	Failed	R: Severe-to-profound; L: Mod to profound	
16. AS-M	6/08	Passed	R: Mod-to-severe; L: Mild	
17. ET-M	4/08	Failed	Profound - Bilat	L (5/09)
18. GT-F	12/06	Failed	L: Mod-to-severe; R: Profound	R (2/09)
19. TW-M	9/05	Passed	Profound - B, neuropathy	L (9/07)

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journal homepage: www.elsevier.com/locate/amjoto

Analysis of archived newborn dried blood spots (DBS) identifies congenital cytomegalovirus as a major cause of unexplained pediatric sensorineural hearing loss

Lucy Meyer [a], Bazak Sharon [a], Tina C. Huang [b], Abby C. Meyer [c], Kristin E. Gravel [b], Elizabeth C. Swanson [a], Hannah E. Herd [e], Nelmary Hernandez-Alvarado [a], Kirste[illegible], Mark McCann [f], Mark R. Schleiss [a,*]

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Targeted Screening is Now Standard-of-Care in the Fairview System!

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 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

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)

Rationale for Minnesota Study

- Sensitivity of DBS for CMV varies widely across studies:
- Most important variable is DNA extraction

Highest sensitivity: **80%** Johansson 1997; **70%** Soetens 2008 (unsuitable methods)

Lowest sensitivity: **28%** CHIMES (M48 high throughput robot)

CDC NBS Branch determined low sensitivity in CHIMES due to **M48 robot** used:

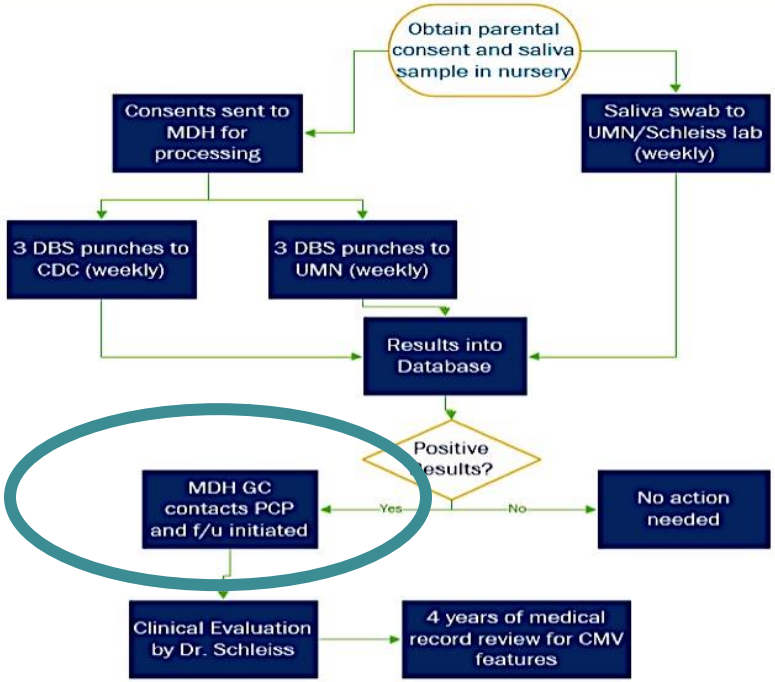
Koontz et al., *Evaluation of DNA extraction methods for CMV. JVM. 2015*

- Public Health emphasizes best use of limited health care dollars, using existing infrastructures when possible (NBS program)

Hypothesis: Improved DBS analytical sensitivity may identify all children with symptoms and sequelae (100% clinical sensitivity)

Are only the DNAemic children at risk? Or greater risk?

Study Design



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

Study Design

Babies born at Minnesota area hospitals offered enrollment

- 30,000 infants over 5 years (by 2021)
- Exclude parents who refuse newborn screening
- Exclude critically ill or extremely premature infants

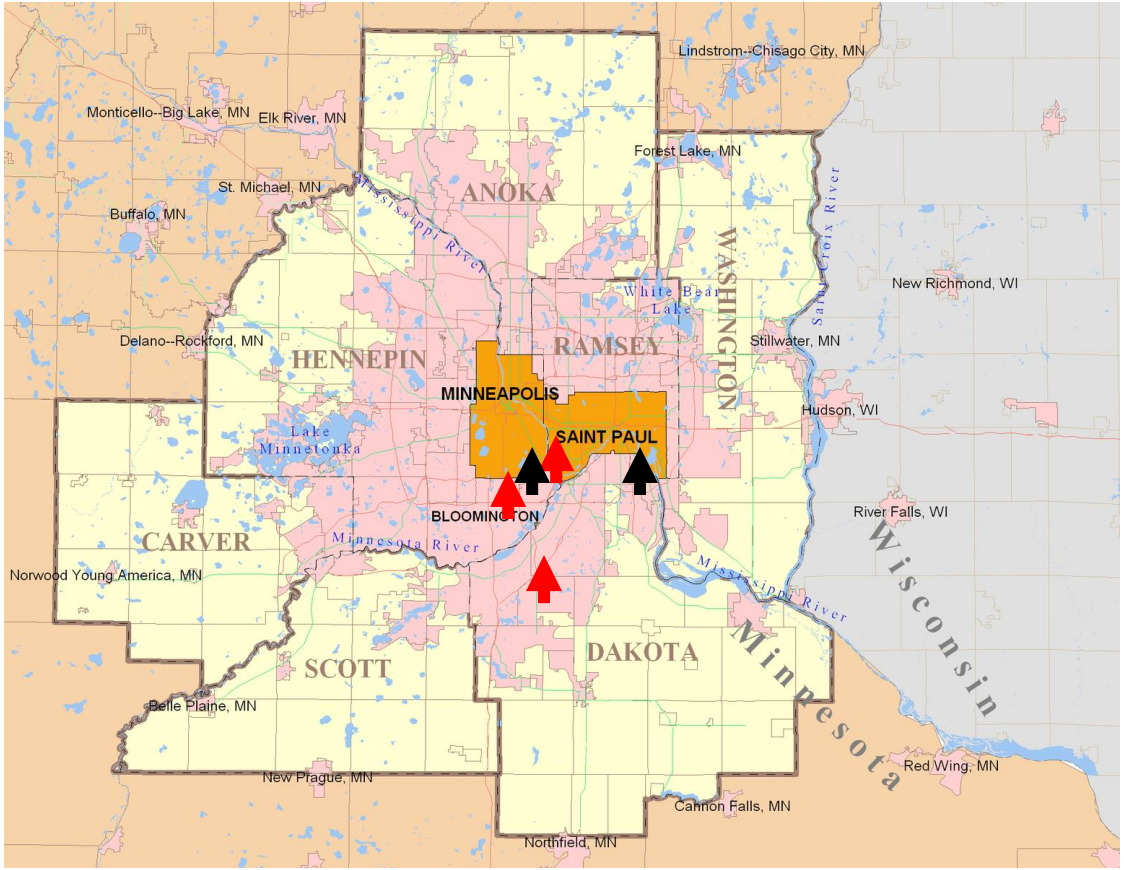
Specimens and testing

- Saliva swab collected for study tested by UMN only
- DBS already collected for NBS tested by CDC and UMN
- Infants CMV + on any test (out of 3) receive urine confirmation testing

Clinical follow-up

- CMV+ children reported to parents and PCP, examined at birth for symptoms
- Annual review of medical records and follow-up by primary care physician until age 4 years

Meyer et al., Am J Otolaryngol. 2017 Sep - Oct;38(5):565-570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St. Michael, MN
ANOKA
Buffalo, MN
Mississippi River
WASHINGTON
St. Croix River
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Northfield, MN

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

IMPORTANCE The sensitivity of dried blood spots (DBS) to identify newborns with congenital cytomegalovirus (cCMV) infection has not been evaluated in screening studies using the current, higher-sensitivity methods for DBS processing.

OBJECTIVE To assess the sensitivity of DBS polymerase chain reaction (PCR) for newborn screening for cCMV infection using saliva as the reference standard for screening, followed by collection of a urine sample for confirmation of congenital infection.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study took place at 5 newborn nurseries and 3 neonatal intensive care units in the Minneapolis/Saint Paul area in Minnesota from April 2016 to June 2019. Newborns enrolled with parental consent were screened for cCMV using DBS obtained for routine newborn screening and saliva collected 1 to 2 days after birth. Dried blood spots were tested for CMV DNA by PCR at both the University of Minnesota (UMN) and the US Centers for Disease Control and Prevention (CDC). Saliva swabs were tested by CMV DNA PCR at the UMN laboratory only. Newborns who screened positive by saliva or DBS had a diagnostic urine sample obtained by primary care professionals, tested by PCR within 3 weeks of birth. Analysis began July 2019.

EXPOSURES Detection of CMV from a saliva swab using a PCR assay.

MAIN OUTCOMES AND MEASURES Number of children with urine-confirmed cCMV and the proportion of them who were CMV positive through DBS screening.

RESULTS Of 12 554 individuals enrolled through June 2019 (of 25 000 projected enrollment), 56 newborns were confirmed to have cCMV (4.5 per 1000 [95% CI, 3.3-5.7]). Combined DBS results from either UMN or CDC had a sensitivity of 85.7% (48 of 56; 95% CI, 74.3%-92.6%), specificity of 100.0% (95% CI, 100.0%-100.0%), positive predictive value (PPV) of 98.0% (95% CI, 89.3%-99.6%), and negative predictive value (NPV) of 99.9% (95% CI, 99.9%-100.0%). Dried blood spot results from UMN had a sensitivity of 73.2% (95% CI, 60.4%-83.0%), specificity of 100.0% (100.0%-100.0%), PPV of 100.0% (95% CI, 91.4%-100.0%), and NPV of 99.9% (95% CI, 99.8%-99.9%). Dried blood spot results from CDC had a sensitivity of 76.8% (95% CI, 64.2%-85.9%), specificity of 100.0% (95% CI, 100.0%-100.0%), PPV of 97.7% (95% CI, 88.2%-99.6%), and NPV of 99.9% (95% CI, 99.8%-99.9%). Saliva swab results had a sensitivity of 92.9% (52 of 56; 95% CI, 83.0%-97.2%), specificity of 99.9% (95% CI, 99.9%-100.0%), PPV of 86.7% (95% CI, 75.8%-93.1%), and NPV of 100.0% (95% CI, 99.9%-100.0%).

CONCLUSIONS AND RELEVANCE This study demonstrates relatively high analytical sensitivity for DBS compared with previous studies that performed population-based screening. As more sensitive DNA extraction and PCR methods continue to emerge, DBS-based testing should remain under investigation as a potential low-cost, high-throughput option for cCMV screening.

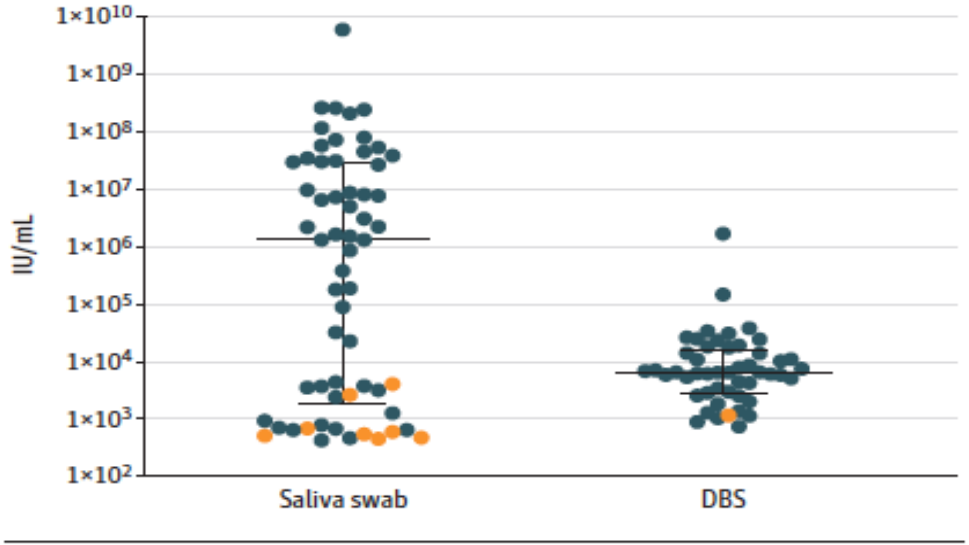
Editorial

Author Affiliations: US Centers for Disease Control and Prevention, Atlanta, Georgia (Dollard, Amin, Wong, Lanzieri); Public Health Laboratory, Newborn Screening, Minnesota Department of Health, Saint Paul (Dreon, Rosendahl, McCann); Division of Pediatric Infectious Diseases and Immunology, University of Minnesota Medical School, Minneapolis (Hernandez-Alvarado, Schleiss); Division of Neonatology, University of Minnesota Medical School, Minneapolis (Osterholm); Allina Health, Care Delivery Research, Minneapolis, Minnesota (Sidebottom).

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)		[illegible]		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)	

Figure. Distribution of Cytomegalovirus Viral Load for All Screen Positive Results for Saliva (n = 60) and for Dried Blood Spots (DBS) (n = 49)



- How should monitoring and follow-up of newborns with congenital CMV identified through screening be carried out?

Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

William D Rawlinson, Suresh B Boppana, Karen B Fowler, David W Kimberlin, Tiziana Lazzarotto, Sophie Alain, Kate Daly, Sara Doutré, Laura Gibson, Michelle L Giles, Janelle Greenlee, Stuart T Hamilton, Gail J Harrison, Lisa Hui, Cheryl A Jones, Pamela Palasanthiran, Mark R Schleiss, Antonia W Shand, Wendy J van Zuylen

Lancet Infect Dis 2017;
17: e177–88

Published Online
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http://dx.doi.org/10.1016/S1473-3099(17)30143-3

- Multidisciplinary Group
- Primary Care Provider: Key Role

Panel 2: Definitions of congenital cytomegalovirus infection and disease

Moderately to severely symptomatic congenital cytomegalovirus disease

- Multiple manifestations attributable to congenital cytomegalovirus infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of cytomegalovirus DNA in cerebrospinal fluid

Mildly symptomatic congenital cytomegalovirus disease

- Might occur with one or two isolated manifestations of congenital cytomegalovirus infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation

Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss

- No apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss (≥21 decibels)

Asymptomatic congenital cytomegalovirus infection

- No apparent abnormalities to suggest congenital cytomegalovirus disease, and normal hearing

Definitions as published by Kimberlin and colleagues,[6] with minor emendation from discussions of the International Congenital Cytomegalovirus Recommendations Group

Summary as of 7/12/2021

- 18,708 babies screened
- 76 babies positive for cCMV (0.41%)

Single Table Analysis

		Disease (+)	Disease (-)	
Exposure	(+)	70	15627	15697
	(-)	6	2993	2999
		76	18620	18696

Results

- 60 infants classified as **asymptomatic**
- 3 infants classified as **asymptomatic with isolated SNHL**
- 8 infants classified as **mildly symptomatic**
- 5 infants classified as **moderately-to-severely symptomatic**

17% of cCMV infants symptomatic

16 infants treated with valganciclovir

Results

- 9 babies have had hearing loss
  - Some **isolated hearing loss with no other signs or symptoms** (2)
  - Some (4) with hearing loss as a **delayed manifestation** of asymptomatic cCMV
  - Some (3) with hearing loss as part of **symptomatic** cCMV

Research

JAMA Pediatrics | Original Investigation

Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection

Soren Gantt, MD, PhD, MPH; Francois Dionne, PhD; Fred K. Kozak, MD; Oran Goshen, MD; David M. Goldfarb, MD; Albert H. Park, MD; Suresh B. Boppana, MD; Karen Fowler, DrPH

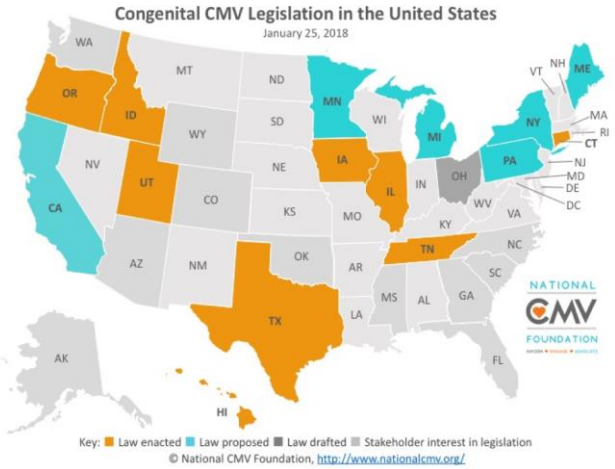
JAMA Pediatr. 2016;170(12):1173-1180. doi:10.1001/jamapediatrics.2016.2016
Published online October 10, 2016. Corrected on October 31, 2016.

MAIN OUTCOMES AND MEASURES The incremental costs of identifying 1 cCMV infection, identifying 1 case of cCMV-related hearing loss, and preventing 1 cochlear implant; the incremental reduction in cases of severe to profound hearing loss; and the differences in costs per infant screened by universal or targeted strategies under different assumptions about the effectiveness of antiviral treatment.

RESULTS Among all infants born in the United States, identification of 1 case of cCMV infection by universal screening was estimated to cost $2000 to $10 000; by targeted screening, $566 to $2832. The cost of identifying 1 case of hearing loss due to cCMV was as little as $27 460 by universal screening or $975 by targeted screening. Assuming a modest benefit of antiviral treatment, screening programs were estimated to reduce severe to profound hearing loss by 4.2% to 13% and result in direct costs of $10.86 per newborn screened. However, savings of up to $37.97 per newborn screened were estimated when costs related to functionality were included.

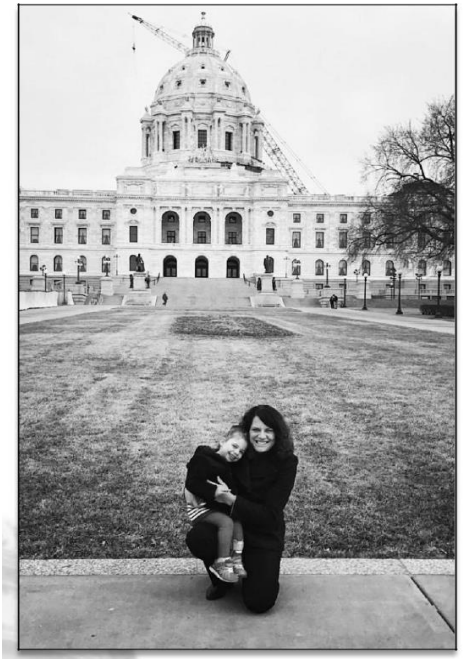
CONCLUSIONS AND RELEVANCE Newborn screening for cCMV infection appears to be cost-effective under a wide range of assumptions. Universal screening offers larger net savings and the greatest opportunity to provide directed care. Targeted screening also appears to be cost-effective and requires testing for fewer newborns. These findings suggest that implementation of newborn cCMV screening programs is warranted.

- What role did parents of children with CMV play in implementation of a screening program?



What is Congenital CMV?

- Congenital Cytomegalovirus (CMV) is the most common cause of birth defects and childhood disabilities in the US
- CMV causes symptoms similar to the common cold – but when a pregnant mother develops an active infection, she can pass the virus to her unborn baby
- This infection **can be prevented** during pregnancy through hygienic precautions and education of women and their care providers – but knowledge and awareness is lacking!



'Vivian's Bill' hopes to educate doctors, parents on cytomegalovirus

Published March 16, 2018 | News | FOX 9 Minneapolis-St. Paul

ST. PAUL, Minn. (KMSP) - Cytomegalovirus is perhaps the most common virus you've never heard of--though an effort by Minnesota lawmakers hopes to change that.

Advocacy for Increased Awareness!

https://www.youtube.com/watch?v=qEc0jncqBQQ

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

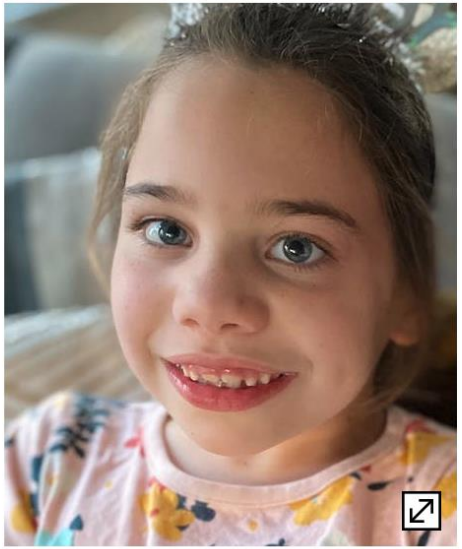
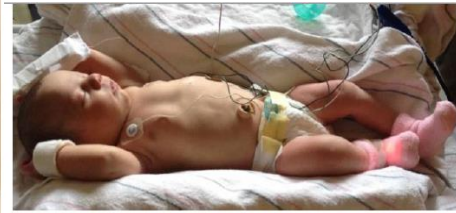


PHOTO COURTESY OF LEAH HENRIKSON

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."



SF1698 VIVIAN ♥ ACT

- What is one piece of advice you would give to someone attempting to implement a screening program?

Dr. Robert Guthrie:
The Father of Newborn Screening

- Family Members with PKU (Phenylketonuria)
- Devised Screening Test
- Resistance from AMA

Int J Neonatal Screen. 2021; 7, 5. doi: 10.3390/ijns7010005

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Ethical and Public Health Implications of Targeted Screening for Congenital Cytomegalovirus

Ladawna L. Gievers, Alison Volpe Holmes, Jaspreet Loyal, Ilse A. Larson, Carlos R. Oliveira, Erik H. Waldman and Sheevaun Khaki

Pediatrics 2020;146;
DOI: 10.1542/peds.2020-0617 originally published online June 26, 2020;

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