2017 Alabama Newborn Screening Conference

Marriott Hotel and Conference Center
Prattville, Alabama
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Congenital Cytomegalovirus Screening: The Past, Present and Future

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The PAST
UAB – Congenital CMV infection

In the 1960's cytomegalic inclusion disease begin to be described in living newborns

Dr. Charlie Alford returned to UAB after working with Dr. Thomas Weller, nobel prize recipient in Boston

Cytomegalovirus (CMV) may be transmitted from mother to fetus anytime during gestation and may or may not cause any apparent damage to the fetus

(Congenital CMV Infection)

Congenital CMV infection in the Newborn

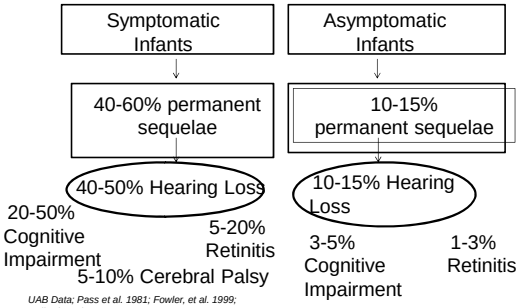
No Clinical Manifestations	~ 90%
Disseminated Disease Generalized petechial rash Purpuric rash Hyperbilirubinemia (jaundice) Hepatosplenomegaly (enlarged spleen or liver) Thrombocytopenia	~10%
CNS Abnormalities Seizures Intracranial calcifications Microcephaly (< 5%tile) Other focal or generalized neurologic deficits Retinitis	

Sequelae of Congenital CMV Infection

Sensorineural hearing loss	19%
Mental retardation (IQ ≤ 70)	19%
Retinitis	6%
Cerebral Palsy	4%
Neurologic problems/Seizures	6%

Based on UAB data

Outcome following Congenital CMV infection



UAB Data; Pass et al. 1981; Fowler, et al. 1999; Dollard, et al. 2007

Diagnosis of Congenital CMV Infection (Past Methods)

- Urine or Saliva
- Within the first 2-3 weeks of life
- Virus isolation (culture) – Urine
- 1990s - identification (immunofluorescence test-DEAFF) of virus in saliva

Primary vs NonPrimary Maternal CMV Infections

- Seronegative women who acquired CMV for the first time during pregnancy are at the greatest risk of transferring CMV to their fetus – (30%)
- Seropositive women were thought to have a reactivation of CMV – in the past there was uncertainty of whether congenital CMV could be the result of a reinfection with another CMV virus(es). – (1%)

Sequelae by Type of Maternal Infection

	Primary N=132	Sero + N=65	
SN Hearing Loss	15%	5%	0.05
Bilateral HL	8%	0%	0.02
Speech Threshold ≥ 60dB	8%	0%	0.03
IQ ≤ 70	13%	0%	0.03
Retinitis	6%	2%	0.20

Fowler et al. NEJM 1992

Sequelae by Type of Maternal Infection, con't.

	Primary N=132	Sero + N=65	
Other neurologic sequelae including microcephaly, seizures, paresis or paralysis	6%	2%	0.13
Death	2%	0%	0.29
Any Sequela	25%	8%	0.003

Fowler et al. NEJM 1992

Interval Between Births

Congenital CMV infection rate and 95% CIs according to interval between births

Mos Betw Births	Seroconverters (n=142)		Sero+ Mothers (n=2,857)	
	#	% (95% CI)	#	% (95% CI)
< 24 Mos	11/44	25 (13.2 –40.3)	12/711	1.7 (0.9 – 2.9)
25-48 Mos	5/50	10 (3.3 – 21.8)	9/954	0.9 (0.4 – 1.8)
> 48 Mos	2/48	4.2 (0.5 – 14.3)	7/1,192	0.6 (0.2 – 1.2)

Fowler et al. CID 2004

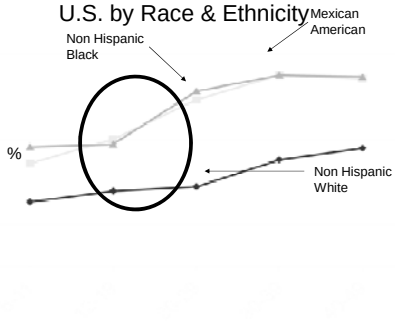
Epidemiology of CMV Infections

- CMV is a herpesvirus, and is a common virus
- CMV is transmitted through direct or indirect person-to-person contact through infected secretions– saliva, urine, tears, breast milk, cervical & vaginal secretions, semen, & blood

Epidemiology of CMV Infections

- CMV is <u>not very contagious</u> and the spread of virus requires <u>close or intimate contact</u> with infected secretions
- CMV infection is usually asymptomatic in the immunocompetent host

NHANES -CMV Seroprevalence in Females in the U.S. by Race & Ethnicity

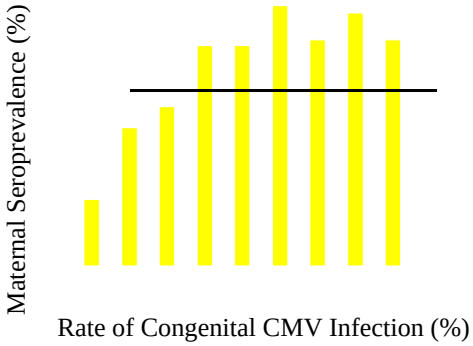


Bate et al. 2010

Adjusted for sex, household income level, education, marital status, insurance, area of residence, census region, family size, country of birth

CMV seroprevalence rates in US, Canada, Australia, England, and Western Europe range from 30 - 60% in women of childbearing age – resulting in women who are susceptible for acquiring CMV for the first time during their pregnancies.

However, in parts of Asia, Africa, Central and South America, CMV seroprevalence rates in women of childbearing age are >70% and in some populations 95-100% - resulting in women who are not acquiring CMV for their first time during pregnancy but possibly acquiring another CMV strain during their pregnancies.



CMV Infections

- So how do women and potential mothers-to-be acquire virus and pass the virus onto their infant?
- One source of virus:
- Young Children – either in the household or friend's & family's children

CMV Infections

- CMV is prevalent in day cares and other places that young children gather and play

CMV Infections

- Studies in day care centers have shown that young children shed virus in saliva & urine creating exposure opportunities for virus transmission to other children, to their parents and day care or nursery workers.

CMV Infections

- Children may acquire virus and infect a previously CMV negative mother or caregiver.

CMV Infections

- Sanitizing toys and surfaces to prevent the spread of flu also clean the surfaces of CMV!
- However, since CMV is fairly ubiquitous it is unlikely that a day care or any place where children interact handling "saliva" laded toys and items will be completely free of the virus.

CMV Infections

- The other source of CMV infection for women is
- Sexual Activity
- CMV may be transmitted through semen or vaginal secretions, although not considered a sexually transmitted infection – CMV is sexually transmissible.

Factors associated with acquisition of CMV in newborns

Factors Independently Associated with Congenital CMV Infection

	aOR (95% CI)
Direct care of children < 5 years	2.9 (1.8 – 4.7)
Sexually transmitted infections during pregnancy	1.6 (1.1 – 2.5)
Sexual activity < 2 years	2.5 (1.4 – 4.5)
Combined- recent onset sexual activity & care of young children	7.2 (3.2 – 16.1)

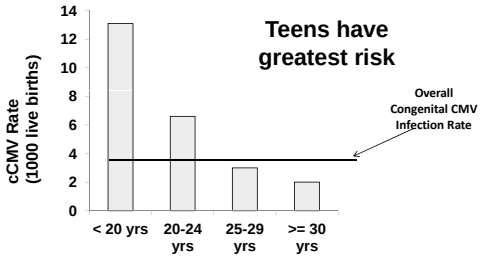
Model includes age, race, parity, number in household, & history of STIs

Fowler, et al. 2006

Factors associated with acquisition of CMV in newborns

Population & Date	N	Risk Factors
Hamilton, Canada, 1980	15,212	Young maternal age No previous pregnancies < 12 years education Unmarried
London, England, 1986	8,026	Young maternal age Black race Unmarried
Birmingham, AL, 1993	27,045	Young maternal age Black race Lower SES
Iowa City, IA, 1994	7,229	Young maternal age Unmarried
San Luis Potosi, Mexico, 2003	599	Young maternal age No previous pregnancies Residence in rural area

CHIMES Study CMV Prevalence Maternal Age



Fowler et al. unpublished.

Significant racial/ethnic disparities exist in the prevalence of congenital CMV infection

Congenital CMV Infection Rates by Maternal Race & Ethnicity

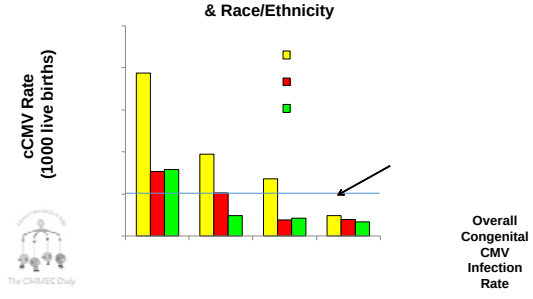
	aOR (95% CI)*
Infant Race & Ethnicity	
Black, Non Hispanic	1.9 (1.4 – 2.4)
White, Hispanic	0.7 (0.5 – 0.9)
Asian	0.8 (0.3 – 1.6)
Multiracial	1.8 (1.1 – 2.9)
White, Non Hispanic	1.0

*Model included race & insurance status, maternal age

Fowler et al. submitted.

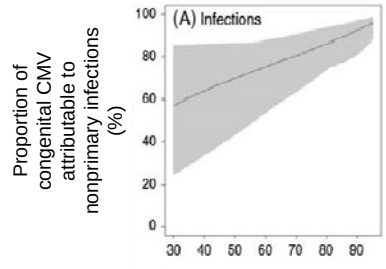
Young maternal age increases the risk of congenital CMV infection with non-Hispanic black infants of teen mothers having the greatest risk of congenital CMV infection

Congenital CMV Infection Rates by Maternal Age & Race/Ethnicity



Congenital CMV & the Present

Proportion of congenital CMV infections attributable to **Non-Primary Maternal Infections**



deVries et al. Rev Med Virol 2013

The CMV & Hearing Multicenter Screening Study

Funded by the NIDCD, 2005 – 2015

UAB Lead Institution

CHIMES Study Population

Site	N
UAB Hospital, Alabama	12,346
MS Med Center, Mississippi	6,436
St Peter's Hospital, New Jersey	10,727
Carolinas Med Ctr, North Carolina	15,094
Good Samaritan, Ohio	14,152
Magee-Women's, Pennsylvania	19,204
Parkland Hospital, Texas	22,648
Total	100,607

DBS PCR for Newborn CMV Screening

Table 2. Use of the 2 DBS Real-time PCR Assays to Identify Infants With Confirmed Congenital CMV Infection

	Single-Primer DBS PCR			2-Primer DBS PCR		
Congenital CMV Infection	Positive	Negative	Total	Positive	Negative	Total
Positive	17	43	60	11	21	32
Negative	4	11 343	11 347	1	8385	8386
Total	21	11 386	11 407	12	8406	8418
Other analyses, % (95% confidence interval)						
Sensitivity	29.3 (17.4-41.4)			34.4 (18.6-53.2)		
Specificity	99.9 (99.9-100)			99.9 (99.9-100)		
Positive likelihood ratio	806.7 (278.1-2317.9)			3089.9 (410.8-23 226.7)		
Negative likelihood ratio	0.7 (0.6-0.8)			0.7 (0.5-0.8)		
Positive predictive value	80.9 (58.1-94.5)			91.7 (61.5-99.8)		
Negative predictive value	99.6 (99.5-99.7)			99.8 (99.6-99.9)		

Abbreviations: CMV, cytomegalovirus; DBS, dried blood spots; PCR, polymerase chain reaction.

DBS PCR –Not Sensitive for a Screening Diagnostic Test

Boppana SB et al. JAMA 2010;303(10):1375-82

Saliva PCR for Newborn CMV Screening

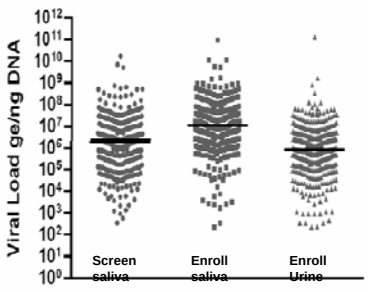
Table 2. Real-Time Polymerase-Chain-Reaction (PCR) Assays of Liquid- and Dried-Saliva Specimens, vs. Rapid Culture, Used to Screen for Congenital Cytomegalovirus Infection.

Rapid Culture	Liquid-Saliva PCR Assay			Dried-Saliva PCR Assay		
	Positive	Negative	Total	Positive	Negative	Total
Positive	85	0	85	74	2	76
Negative	8	17,569	17,577	8	17,243	17,251
Total	93	17,569	17,662	82	17,245	17,327
Sensitivity (95% CI) — %	100 (95.8–100)			97.4 (90.8–99.7)		
Specificity (95% CI) — %	99.9 (99.9–100)			99.9 (99.9–100)		
Positive likelihood ratio (95% CI)	2197 (1099–4393)			2100 (1049–4202)		
Negative likelihood ratio (95% CI)	0 (0.0–0.1)			0.03 (0.0–0.1)		
Positive predictive value (95% CI) — %	91.4 (83.8–96.2)			90.2 (81.7–95.7)		
Negative predictive value (95% CI) — %	100 (99.9–100)			99.9 (99.9–100)		

Saliva PCR –Rapid, Relatively Inexpensive Diagnostic Test

Boppana SB et al. N Engl J Med 2011;364:2111

PCR for Diagnosis of CMV in the newborn



Infants shed ⇧ quantities of CMV in saliva & urine

CHIMES Study CMV Prevalence

Overall prevalence of congenital CMV infection =
4.5 per 1000 live births (95% CI, 4.1 – 4.9/1000)

1 in 200 live births

Fowler et al. submitted.

CHIMES Study CMV Prevalence

Race & Ethnicity

Infant Race & Ethnicity	/1000 live births (95% CI)
Black, Non Hispanic	9.5 (8.3 – 11/1000)
White, Non Hispanic	2.7 (2.2 – 3.3/1000)
White, Hispanic	3.0 (2.4 – 3.6/1000)
Multiracial	7.8 (4.7 – 12/1000)
Asian	1.0 (0.3 – 2.5/1000)

Fowler et al. submitted

CHIMES Study SNHL at Birth

SNHL at birth was defined as the presence of hearing loss at the first full diagnostic audiology evaluation at enrollment into follow-up (3-6 weeks of life) – not based on hearing screening refer/fail

Sensorineural hearing loss (SNHL) at birth = 7.9% (95% CI, 5.6% – 10.8%)

Fowler et al. submitted.

CHIMES Study SNHL at Birth

Asymptomatic vs. Symptomatic Infections & SNHL at Birth

	% (95% CI)
Asymptomatic	4.7% (2.9 – 7.3%)
Symptomatic	38.1% (23.6 – 54.4%)

CHIMES Study SNHL at Birth

Bilateral vs Unilateral SNHL Present at Birth

	Bilateral	Unilateral
Asymptomatic	37%	63%
Symptomatic	56%	44%

CHIMES Study SNHL at Birth

Progression & Fluctuation of SNHL SNHL Present at Birth*

	Progression % (95% CI)	Fluctuation % (95% CI)
Asymptomatic	67 (38 – 88) (range, 7 – 48 mo)	20 (4 – 48)
Symptomatic	50 (19 – 81) (range, 7 – 36 mo)	0 (0 – 31)

**Non treated*

CHIMES Study SNHL at Birth

Progression & Fluctuation of SNHL
SNHL Present at Birth/Treated

	Progression	Fluctuation	Stable
Asymptomatic (n=4)	2 (1 @ 30 mo, 1 @ 42, 48 mo)	1	1
Symptomatic (n=5)	3 (1 @ 7 mo, 1 @ 12, 24, 30 mo, 1 @ 30, 48 mo)	1	3*

**1 received Cochlear Implant at 7 mo*

CHIMES Study Late Onset SNHL

Late Onset SNHL

	Late onset Loss
Asymptomatic (n=13)	41.9% (range, 7 – 48 mo)
Symptomatic (n=2)	12.5% (range, 24 – 36 mo)*

**Unilateral to Bilateral Loss*

Degree of SNHL reported at last audiologic evaluation

Degree of Loss	Asymptomatic	Symptomatic
Mild (26 – 40 dB HL)	33.3%	10.7%
Moderate (41 – 55 dB HL)	19.0%	13.3%
Moderate-Severe (56 – 70 dB HL)	4.8%	0%
Severe (71 – 90 dB HL)	23.8%	42.9%
Profound (>90 dB HL)	19.0%	32.1%

Summary: CMV Auditory Characteristics

- **Hearing may be normal**
- **Hearing loss**
  - **May be present at birth**
  - **May be delayed in onset early in life or after several years**

Summary: CMV Auditory Characteristics

- **May be stable, progressive, and/or fluctuating**
- **May be unilateral or bilateral**
- **Can be of varying degrees**
- **There is no consistent audiometric configuration!**

CHIMES Study

Possible Targeted Approach to CMV Screening

Hearing Screening Refers by CMV Status

CMV Screen	Hearing Refer* % (95% CI)
CMV Positive (n=443)	7.0% (4.8 – 9.8%)
CMV Negative (n=99,500)	0.9% (0.9 – 1.0%)

P < 0.0001

Fowler et al. Pediatrics 2017

CHIMES Study

Possible Targeted Approach

Congenital CMV Infection & SNHL at Birth

	Newborn Hearing Screen	
	Refer	Pass
SNHL	20 (65%)	15 (3.6%)
NO SNHL	11	397

Newborn hearing screening identified 57% (95% CI, 39% - 74%) of CMV-Related SNHL in the newborn period.

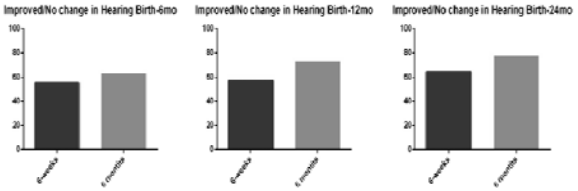
Fowler et al. Pediatrics 2017

Treatment of Congenital CMV Infection

- Controlled trials of antiviral therapy only performed in infants with SYMPTOMATIC infection with primary outcome of improvement in hearing function
  - Ganciclovir or oral equivalent valganciclovir
- Collaborative Antiviral Study Group (CASG)

Valganciclovir Treatment Study

6 weeks vs. 6 months in symptomatic congenital CMV



aOR (95% CI): 1.70 (0.77,3.79)

aOR (95% CI): 3.34 (1.31,8.53)

aOR (95% CI): 2.66 (1.02,6.91)

Kimberlin et al., NEJM 2015;372:933-43

Consensus Recommendations for Treatment of Congenital CMV

- Symptomatic congenital CMV disease (Moderate to severe disease)
  - Only group recommended because it is the only population in which there is randomized, controlled data proving benefit
- 6 month of oral valganciclovir 16mg/kg/DOSE bid
- Treatment should be initiated within the first month of life

Consensus Recommendations for Treatment of Congenital CMV

- Monitor neutrophil counts and transaminases regularly
- Viral load monitoring not indicated (no correlation with treatment effect or clinical outcome)
- Treatment duration of 6 months

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

Rawlinson, Boppana, Fowler, Kimberlin et al., Lancet Infect Dis 2017; 17(6):e177-e188

Consensus Recommendations for Treatment of Congenital CMV

- Antiviral therapy NOT routinely recommended for mildly symptomatic congenital CMV disease
- Antiviral therapy NOT routinely recommended for asymptomatic congenital CMV with isolated SNHL

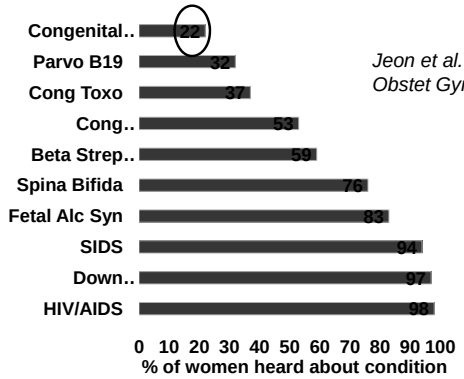
Consensus Recommendations for Treatment of Congenital CMV

- Antiviral therapy NOT recommended for babies with asymptomatic congenital CMV
- Antiviral therapy NOT routinely recommended in infants <32 weeks gestational age

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

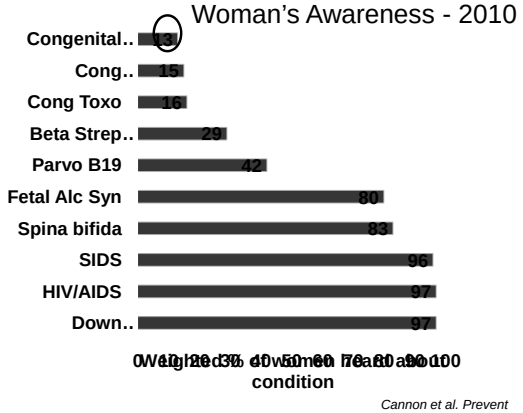
Rawlinson, Boppana, Fowler, Kimberlin et al., Lancet Infect Dis 2017; 17(6):e177-e188

Woman's Awareness - 2005



Jeon et al. Infect Dis Obstet Gynecol 2006

Woman's Awareness - 2010



Cannon et al. Prevent Med 2012

Women's Awareness about CMV

2005 annual HealthStyles™ survey, a mail survey of the U.S. population aged >18 years found that only 14% of women had heard of CMV

(D. Ross et al. J Women Health, 2008).

Women's Awareness about CMV

Current UAB cognitive-behavioral intervention study (n=215) just completed in pregnant women aged 16-29 years found 14% of women had heard of CMV

(Fowler, Davies, Kempf, Boppana, Cannon, Tita, Edwards, unpublished).

- **Cognitive-Behavioral Intervention:**
- **(help individuals to identify helpful and unhelpful behaviors, establish goals, and develop skills to solve problems and implement new behaviors)**
- **215 women were randomized:**

Fowler, et al. in preparation

- **108 “CMV Prevention in Pregnancy” intervention group (PREVENT) – CMV education and prevention intervention**
- **107 “Taking Care of Me” intervention group (CONTROL) educational stress reduction intervention.**

Fowler, et al. in preparation

- **Cognitive-Behavioral Intervention, con’t:**
- **For both groups, each woman had**
- **a 15-20 min individual behavioral skills session with study personnel,**
- **watched a short video,**

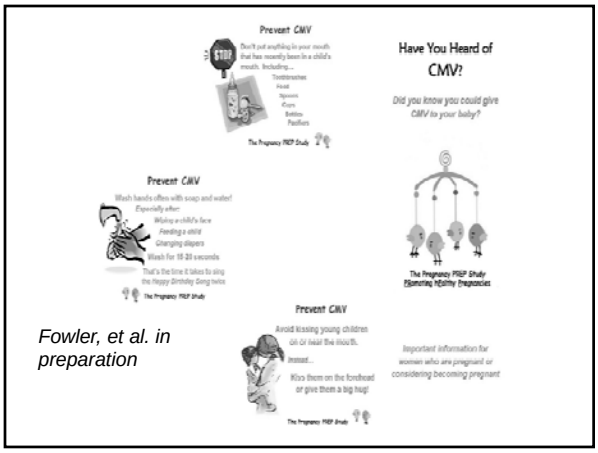
Fowler, et al. in preparation

- **received a take home packet,**
- **received weekly text messages for 12 weeks to deliver the PREVENT or CONTROL interventions.**

Fowler, et al. in preparation

- **Cognitive-Behavioral Intervention, con’t:**
- **In addition, each woman attended 6 and 12 week follow-up visits for an intervention boost for the PREVENT group and where post-intervention CMV knowledge and risk behaviors were assessed via questionnaires in both groups.**

Fowler, et al. in preparation



Fowler, et al. in preparation

Fowler, et al. in Preparation

Fowler, et al. in preparation

Fowler, et al. in preparation

CMV Risk Behaviors

	PREVENT N=97	CONTROL N=99	P value
	PRE Intervention at Enrollment		
Kiss young children on the mouth	40.2% (30.4 – 50.6%)	40.4% (30.7 – 50.7%)	0.9
	POST Intervention		
Kiss young children on the mouth	10.3% (5.1 – 18.1%)	27.3% (18.8 – 37.1%)	0.002

Fowler, et al. in preparation

CMV Risk Behaviors

	PREVENT N=97	CONTROL N=99	P value
	PRE Intervention at Enrollment		
Share food, drinks, eating utensils, etc. with young children	47.4% (37.2 – 57.8%)	50.5% (40.3 – 60.7%)	0.7
	POST Intervention		
Share food, drinks, eating utensils, etc. with young children	15.5% (8.9 – 24.2%)	30.3% (21.5 – 40.3%)	0.01

Fowler, et al. in preparation

CMV Risk Behaviors

	PREVENT N=97	CONTROL N=99	P value
	PRE Intervention at Enrollment		
Not always wash hands after feeding, wiping face & hands, etc.	58.8% (48.3 – 68.7%)	54.5% (44.2 – 64.6%)	0.6
	POST Intervention		
Not always wash hands after feeding, wiping face & hands, etc.	43.3% (33.3 – 53.7%)	42.4% (32.5 – 52.8%)	0.9

Fowler, et al. in preparation

CMV Risk Behaviors

	PREVENT N=97	CONTROL N=99	P value
	PRE Intervention at Enrollment		
Not always wash hands after changing diapers	29.9% (21.0 – 40.0%)	36.4% (26.9 – 46.6%)	0.3
	POST Intervention		
Not always wash hands after changing diapers	20.6% (13.1 – 30.0%)	28.3% (19.7 – 38.2%)	0.2

Fowler, et al. in preparation

CMV Risk Behaviors

	PREVENT N=97	CONTROL N=99	P value
	PRE Intervention at Enrollment		
CMV risk behavior score (0-44, 44 highest risk score)	5.2 ± 5.9 (range, 0 - 23)	5.7 ± 6.1 (range, 0 - 32)	0.5
	POST Intervention		
CMV risk behavior score (0-44, 44 highest risk score)	1.7 ± 2.6 (range, 0 - 12)	3.4 ± 4.6 (range, 0 - 26)	0.002

Fowler, et al. in preparation

Parent Advocacy

Founded in 2014, the National CMV Foundation joined forces with 3 regional NPOs in Dec 2015 in an effort to combine resources and increase reach in 1) educating women about CMV and 2) influencing research priorities regarding CMV prevention, treatment, and intervention

https://www.nationalcmv.org/

Parent Advocacy

VISION: Eliminate cCMV in the United States for the next generation.

MISSION: To educate women of childbearing age about congenital CMV.

https://www.nationalcmv.org/

Parent Advocacy

Strategic pillars

• **INFORM:** To raise awareness and educate women and families about the risks and prevention of congenital CMV

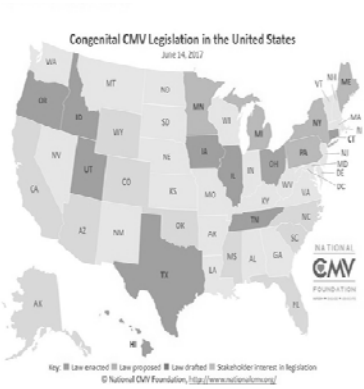
• **ENGAGE:** To conduct targeted outreach with medical professionals to further CMV education, and to form human connections with those affected by cCMV by linking users with the appropriate resources

https://www.nationalcmv.org/

Parent Advocacy

• **ADVOCATE:** To increase local, regional, and national community involvement through various means – fundraising, legislation, strategic partnerships and corporate development – that calls for improved cCMV information and education, which will drive behavioral change.

https://www.nationalcmv.org/



Congenital CMV & the Future

- Targeted CMV Screening for congenital CMV for any newborn who refers (fails) on newborn hearing screen (unilateral or bilateral) when the etiology of possible hearing loss is uncertain or unknown (& for CMV positive babies refer to ID) – Saliva PCR

Congenital CMV & the Future

- Ontario is implementing universal CMV screening – Maine is considering through their legislation
- Parents advocating for universal CMV screening

Congenital CMV & the Future

- Further Studies of antivirals
  - Clinical trial of asymptomatic CMV infection without SNHL underway – valganciclovir by 30 days give 4 mos
  - Clinical trial of CMV infection with SNHL identified by targeted screening underway – placebo vs. valganciclovir

Congenital CMV & the Future

- Further Studies of asymptomatic infants – do they need further testing (besides hearing assessments) or specific clinical management?

Congenital CMV & the Future

- Understanding the role of non-primary CMV infections including immunology and genomic studies
- Vaccine development underway – several companies
- Development & implementation of behavioral interventions –with CMV awareness and CMV risk reduction behaviors

Congenital CMV & the Future

- Parent Advocacy
  - CMV awareness campaigns
  - Promoting universal CMV screening
  - Promoting/Drafting CMV legislation and policy
  - Developing messaging (videos, etc.) to reach all young women with CMV information

Video

Evaluation and follow-up of infants with symptomatic congenital CMV

At Birth

- Thorough physical exam to assess for growth parameters, HSM, petechiae, purpura
- CBC, LFTs
- Neuroimaging- sonography or MRI
- Ophthalmologic examination

Evaluation and follow-up of infants with symptomatic congenital CMV

- Full diagnostic auditory evaluation- NOT hearing screen

Follow-up

- Age-appropriate hearing testing every 6 months until age 3, then annually until age 5-6 (?adolescence)
- Developmental assessments in some children

Evaluation and follow-up of infants with asymptomatic congenital CMV (with or without SNHL)

At Birth

- Thorough physical exam to assess for symptoms
- Ophthalmologic examination (could be later – 0/77 Asx w retinitis)
- Full diagnostic auditory evaluation-NOT hearing screen

Evaluation and follow-up of infants with asymptomatic congenital CMV (with or without SNHL)

Follow-up

- Age-appropriate hearing testing every 6 months until age 3, then annually until age 5-6 (?adolescence)
- Careful developmental screening assessments

Symptomatic Congenital CMV

9.8% Symptomatic (44/449)

Symptoms	% (#)
Generalized Petechial rash	27.2 % (12/44)
Purpuric rash	4.5% (2/44)
Hepatomegaly	20.5% (9/44)
Splenomegaly	20.5% (9/44)
Jaundice with Direct Bilirubin >3	15.9% (7/44)
CNS Abnormalities	
Microcephaly	38.6% (17/44)
Seizures	6.8% (3/44)
Focal/generalized neurologic deficits	6.8% (3/44)
Chorioretinitis	4.5% (2/44)

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