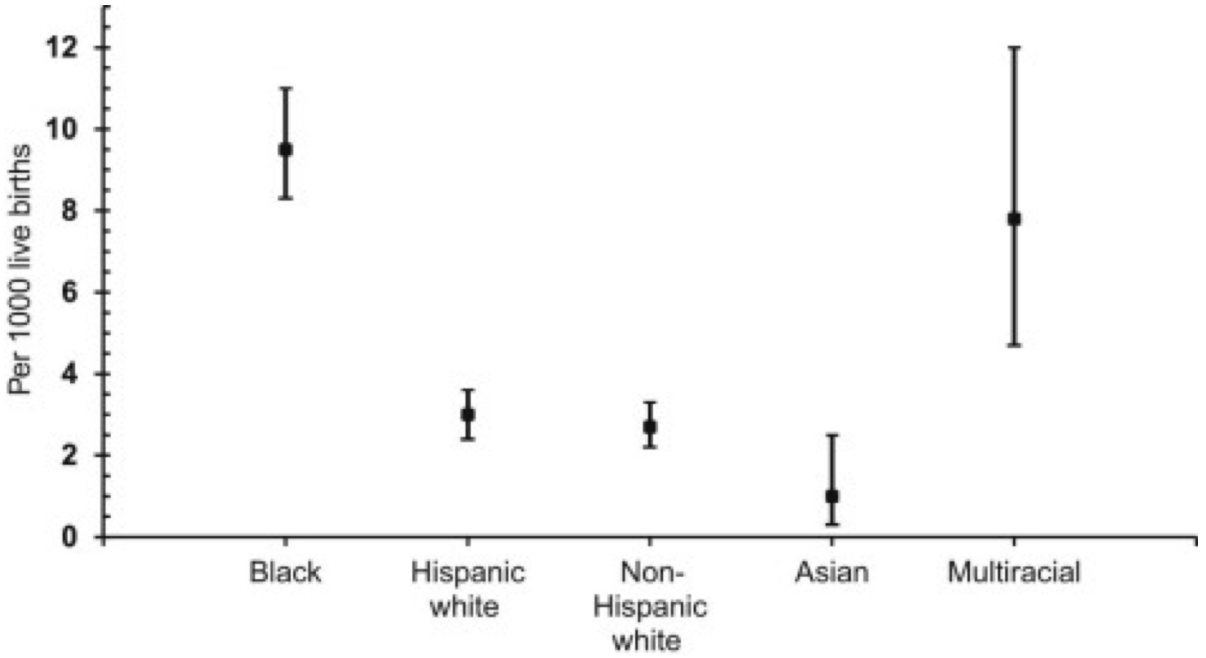
Congenital CMV Epidemiology

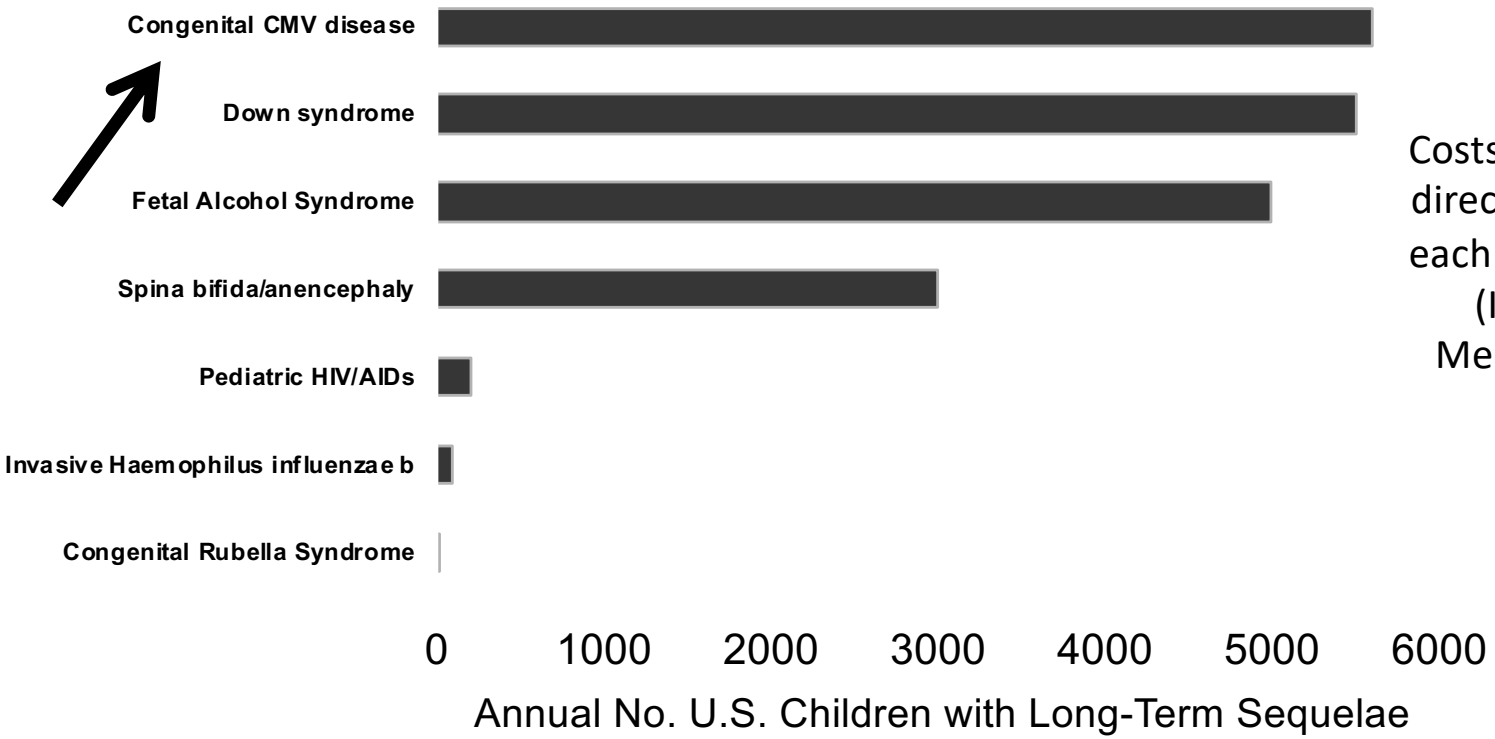
Prevalence of congenital CMV infection
4.5 per 1000 live births (95% CI, 4.1-4.9)



Fowler et al, J Pediatr. 2018 May 18.

The CHIMES Study

Disease burden of congenital CMV infection

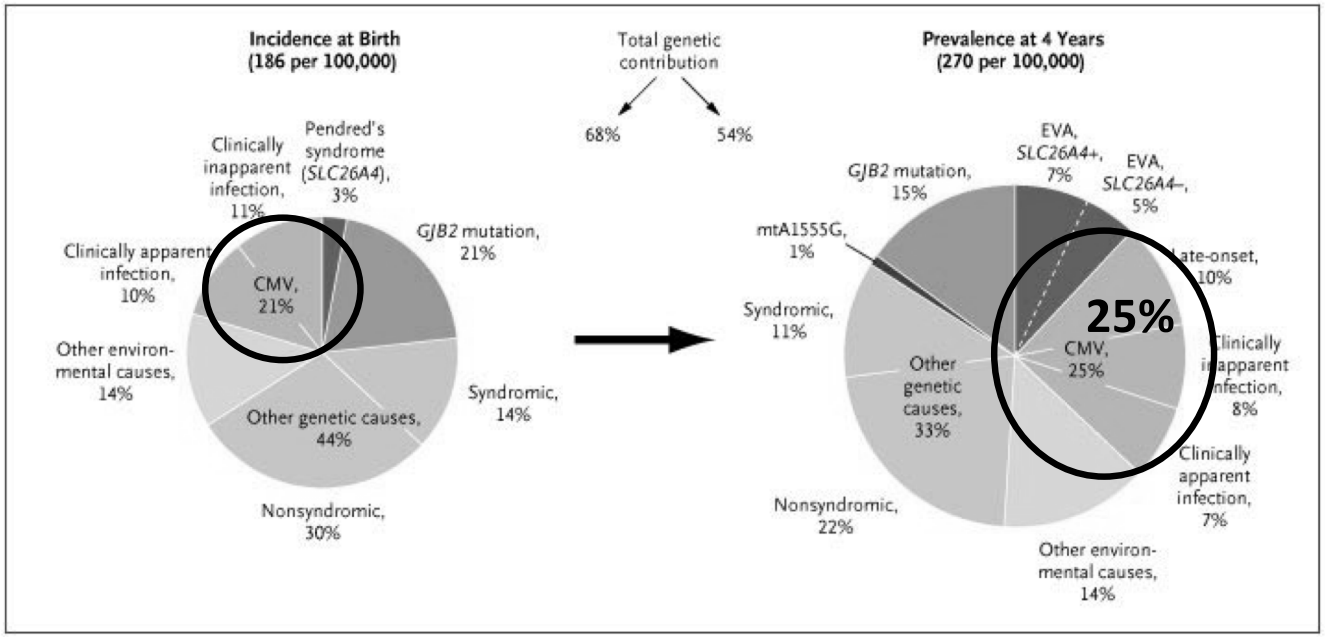


Costs > $1 billion in direct medical care each year in the US (Institute of Medicine, 2000)

Cannon J Clin Virol 2009

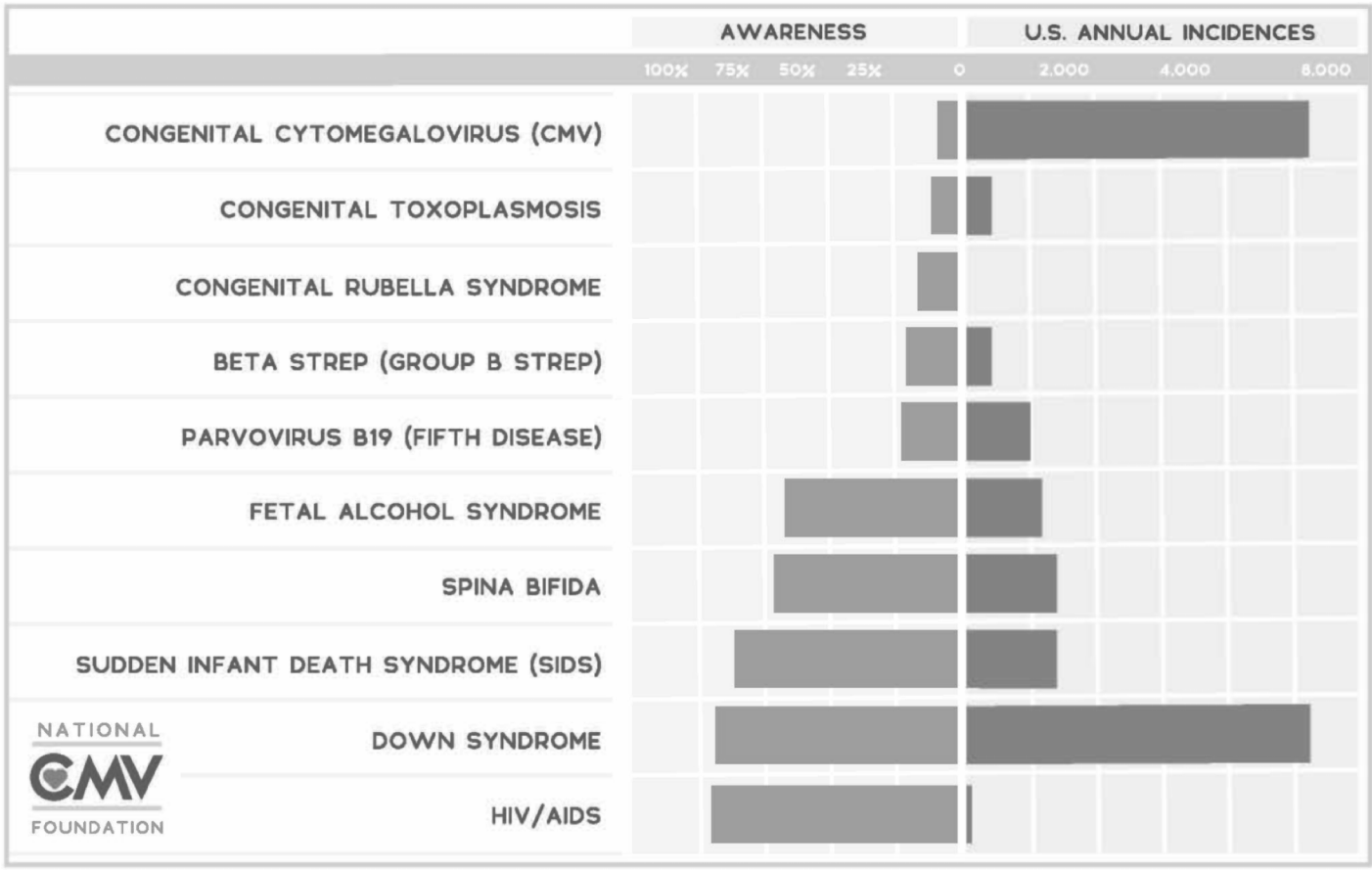
Disease burden of congenital CMV infection

Hearing Loss in Infants & Children



Morton & Nance NEJM 2006

Awareness of CMV and Incidence



"Doutre, S. M. Barrett, T. S. Greenlee, J. & White, K. R. (2016). Losing Ground: Awareness of Congenital Cytomegalovirus in the United States. Journal of Early Hearing Detection and Intervention, 1(2), 39-48."

Symptomatic Congenital CMV

Clinical Finding	Screened (n=78)	Referred (n=100)
Petechial rash	55 %	74%
Purpuric rash	3%	17%
Hepatosplenomegaly	17%	57%
Jaundice	40%	59%
Microcephaly	35%	53%
Seizures	1%	7%
Chorioretinitis	9%	18%
Laboratory and Imaging		
Elevated AST	55 %	75%
Thrombocytopenia	38%	72%
Neuroimaging abnormalities	71%	74%
Calcifications	48%	58%

Dreher et al, J Pediatr. 2014 Apr;164(4):855-9

Systematic Review of Hearing loss Outcomes
Overall rate of Sensorineural Hearing Loss (SNHL) 12.6%

	Asymptomatic	Symptomatic
	% (95% CI)	
Hearing Loss	9.9%	32.8%
Characteristics of Loss		
Unilateral	56.9 (41.1-71.8)	28.8 (22.2-35.9)
Bilateral	43.1 28.2–58.6	71.2 (64.2-77.8)
Bilateral Severe to Profound Loss	42.6 (20.2-66.7)	65.1 (54.2-75.2)
Delayed Onset Loss	9 (0.8-24.5)	18.1 (5.9-36.2)
Fluctuating	24 (2.1-59.6)	21.5 (9.3-37)
Progressive Loss	20.3 (5.3-41.8)	17.7 (3.2-39.4)

Goderis et al., Pediatrics. 2014 Nov;134(5):972-82

Hearing loss in cCMV

	Asymptomatic	Symptomatic
Total Number of Children	651	209
	%	
Hearing Loss	7.4	41
Characteristics of Loss		
Unilateral	52	33
Bilateral	48	67
Delayed Onset Loss	38	27
Median Age	44mo (24-182)	33mo (6-197)
Progressive Loss	54	54

Dahle AJ., J Am Acad Audiol. 11: 283-290, 2000

Degree of Hearing Loss

Degree of Loss	Asymptomatic	Symptomatic
Mild (21 – 45 dB HL)	17%	12%
Moderate (46 – 70 dB HL)	15%	13%
Severe (71 – 90 dB HL)	17%	31%
Profound (>90 dB HL)	51%	44%

Fluctuating hearing loss- Improvement in threshold levels in 48% of asymptomatics and 21% of symptomatics

Dahle AJ., J Am Acad Audiol. 11: 283-290, 2000

DBS PCR for Newborn CMV Screening

Total positive: 92 (saliva, DBS or both)

Saliva Rapid Culture	DBS PCR		Total
	P	N	
P	28	64	91
N	0	20356	20357
Total	28	20420	20448

Sensitivity <40%

Boppana, et al. JAMA 2010;303:1375-1382

The CHIMES Study

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)	

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

Comparison of dried blood spots and dried saliva specimens with wet saliva specimens in screening for congenital cytomegalovirus infection in 2 counties of Shandong Province, China, 2011 to 2013

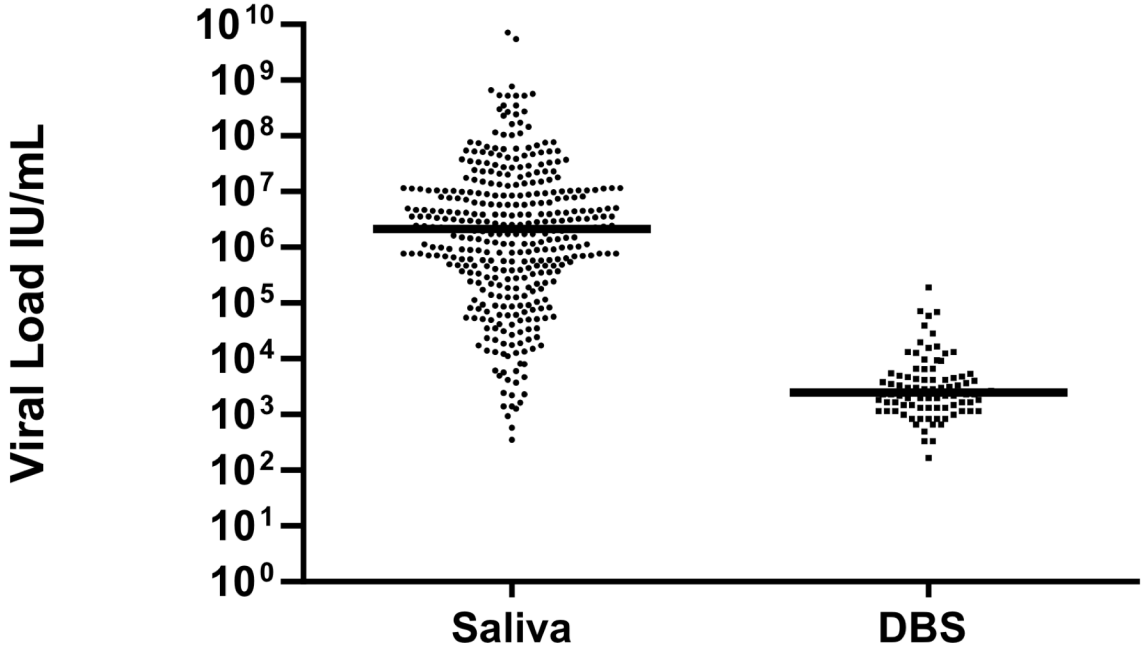
	Dried blood spots (N = 3953)		Dried saliva (N = 7720)	
Wet saliva	**Positive**	**Negative**	**Positive**	**Negative**
Positive	11	17	46	3
Negative	3	3922	6	7665
Sensitivity (95% CI)	39.3% (22.1%–59.3%)		93.9% (82.1%–98.4%)	
Specificity (95% CI)	99.9% (99.8%–100.0%)		99.9% (99.8%–100.0%)	
Positive predictive value (95% CI)	78.6% (48.8%–94.3%)		88.5% (75.9%–95.2%)	
Negative predictive value (95% CI)	99.6% (99.4%–99.8%)		100.0% (99.9%–100.0%)	

CI = confidence interval.

MEDICINE

Medicine96(5):e6007, February 2017.
doi: 10.1097/MD.0000000000006007

Newborn Viral Load



The CHIMES Study

Data from the NIDCD-funded CHIMES Study
Ross et al. in preparation and J Pediatr. 2017 May;184:57-61

Contribution of Breastfeeding to Screening Saliva False Positives

23/74788 infants screened were false positive (0.03%; 95% CI 0.02%-0.05%)

	N	# False Pos.	CMV Seroprevalence	No. Infants at risk	Adjusted False Pos %
Black	23,857	6	76.6%	7,781	0.08% (0.03%-0.17%)
White, Hispanic	32,189	5	80.0%	16,683	0.03% (0.01%-0.07%)
White, Non-Hispanic	36,962	10	35.7%	7,387	0.14% (0.06%-0.25%)
Asian	4,150	1	83.8%	1,999	0.05% (.001%-0.28%)
Multiracial	2,408	1	79.0%	1,513	0.07% (.001%-0.37%)

- Seroprevalence and BF rates from NHANES and NIS
- Assumed 100% shedding of CMV in colostrum

Ross et al. JID 2018;217

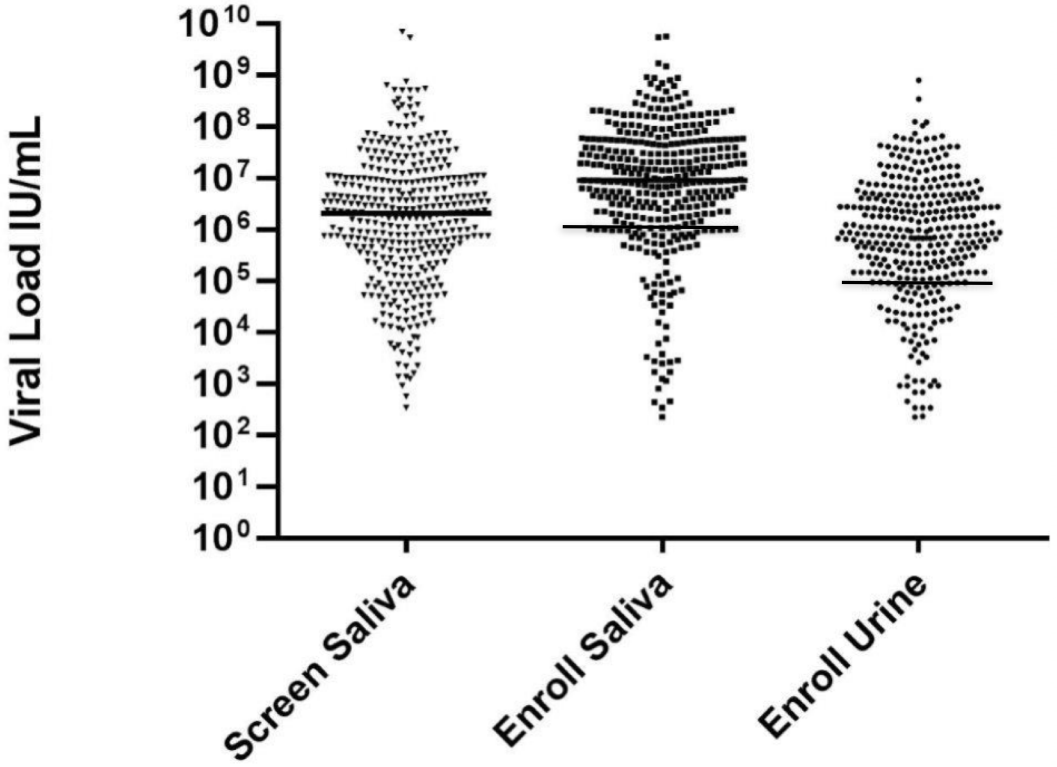
Urine and Saliva PCR for Diagnosis of CMV in the Newborn

	Urine PCR			Saliva PCR			
Culture	P	N	Total	**Culture**	P	N	Total
P	76	0	76	**P**	78	0	78
N	3	1	4	**N**	2	0	2
Total	79	1	80	**Total**	80	0	80

Ross SA, et al. J Infect Dis 2014

The CHIMES Study

Saliva VL is higher than urine



Data from the NIDCD-funded CHIMES Study
Ross et al. in preparation

A Sound Tomorrow Starts Today
The 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

Pediatrics. 2017 Feb;139(2). pii: e20162128

Possible Targeted Approach to CMV Screening

Congenital CMV Infection & SNHL at Birth

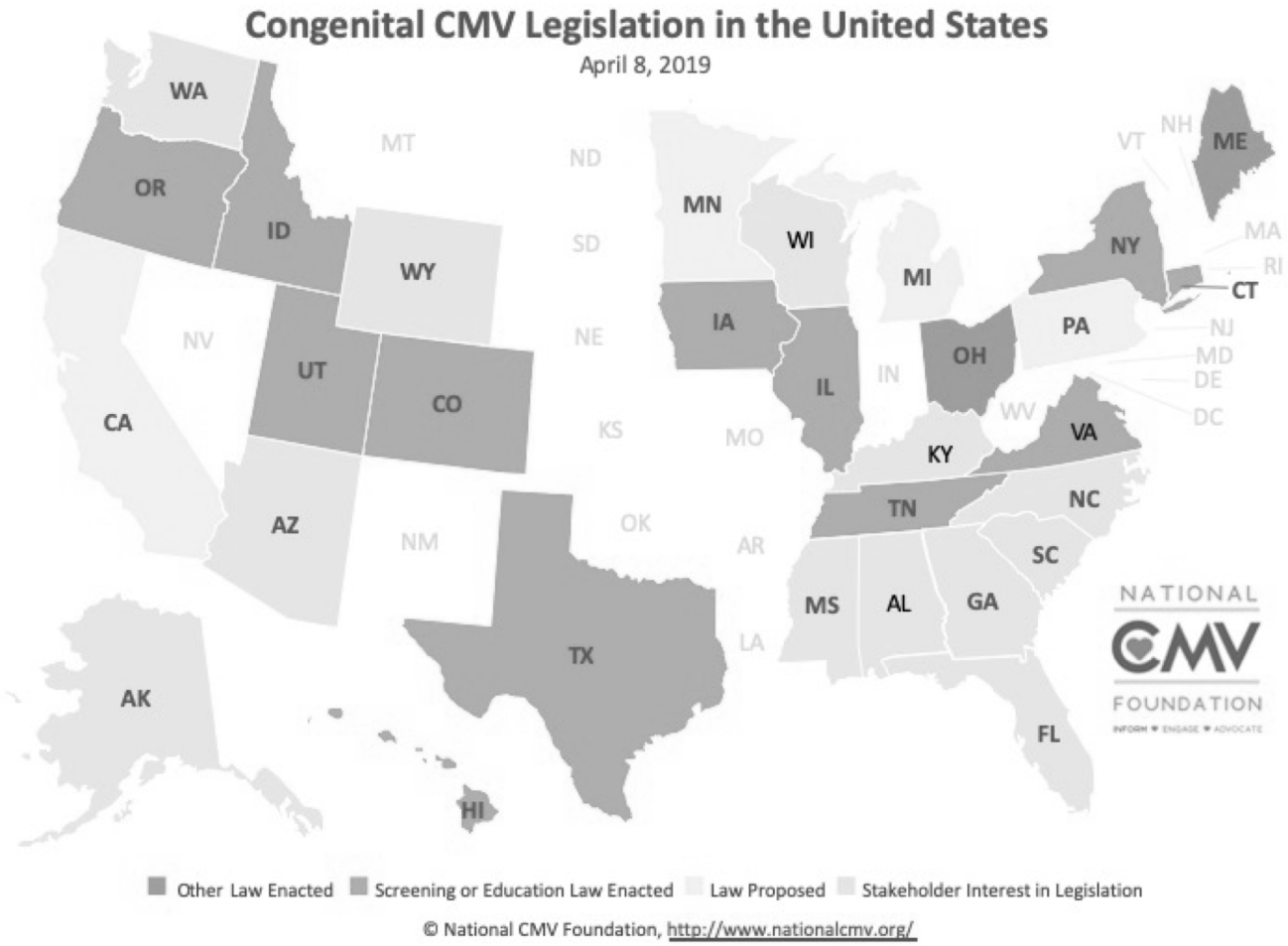
	Newborn Hearing Screen	
	Refer	Pass
SNHL	20 (65%)	15 (3.6%)
NO SNHL	11	397

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

Pediatrics. 2017 Feb;139(2). pii: e20162128

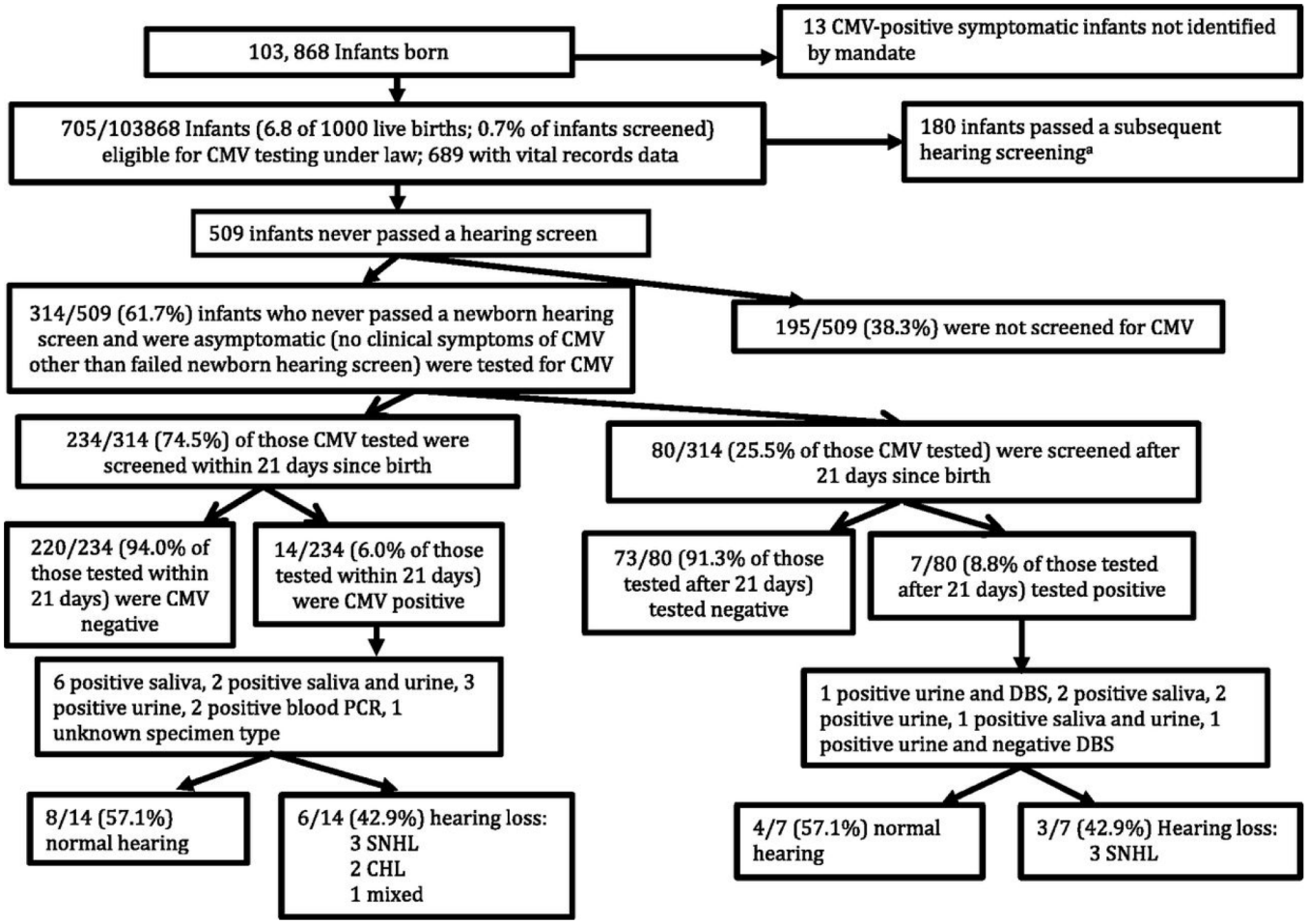
Legislation Components

CMV Education/ Awareness & Newborn CMV Screening



Feasibility of Targeted Approach to CMV Screening

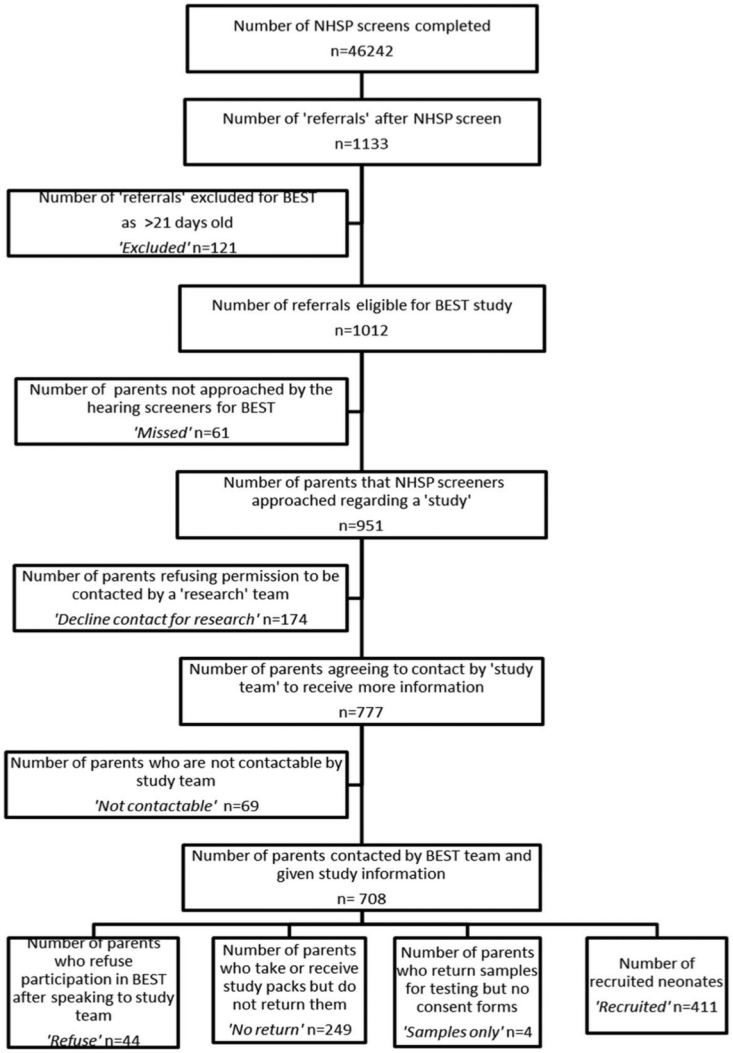
- Utah first state to enact CMV public health initiative on CMV education and targeted screening
- 14 infants identified as CMV-positive within 21 days after birth
  - 6 with hearing loss
- Infants born after this legislation more likely to undergo diagnostic hearing evaluation by 3 months of age



Pediatrics. 2017 Feb;139(2). pii: e20162128

Feasibility and Acceptability of Targeted Approach to CMV Screening

- UK 2010-2012
- Urine and saliva samples collected at home by parents
  - 99% of participants returned a saliva sample while 50% returned urine
- Using saliva 97.6% were successfully screened for CMV within 21 days
- 6/404, 1.5% CMV positive by saliva PCR
  - Results provided by median of 9 days of age
- Maternal anxiety was not increased in mothers of infants screened



Williams EJ, Kadambari S, Berrington JE*, et al Arch Dis Fetal Neonatal Ed* 2014;**99:**F230-F236.

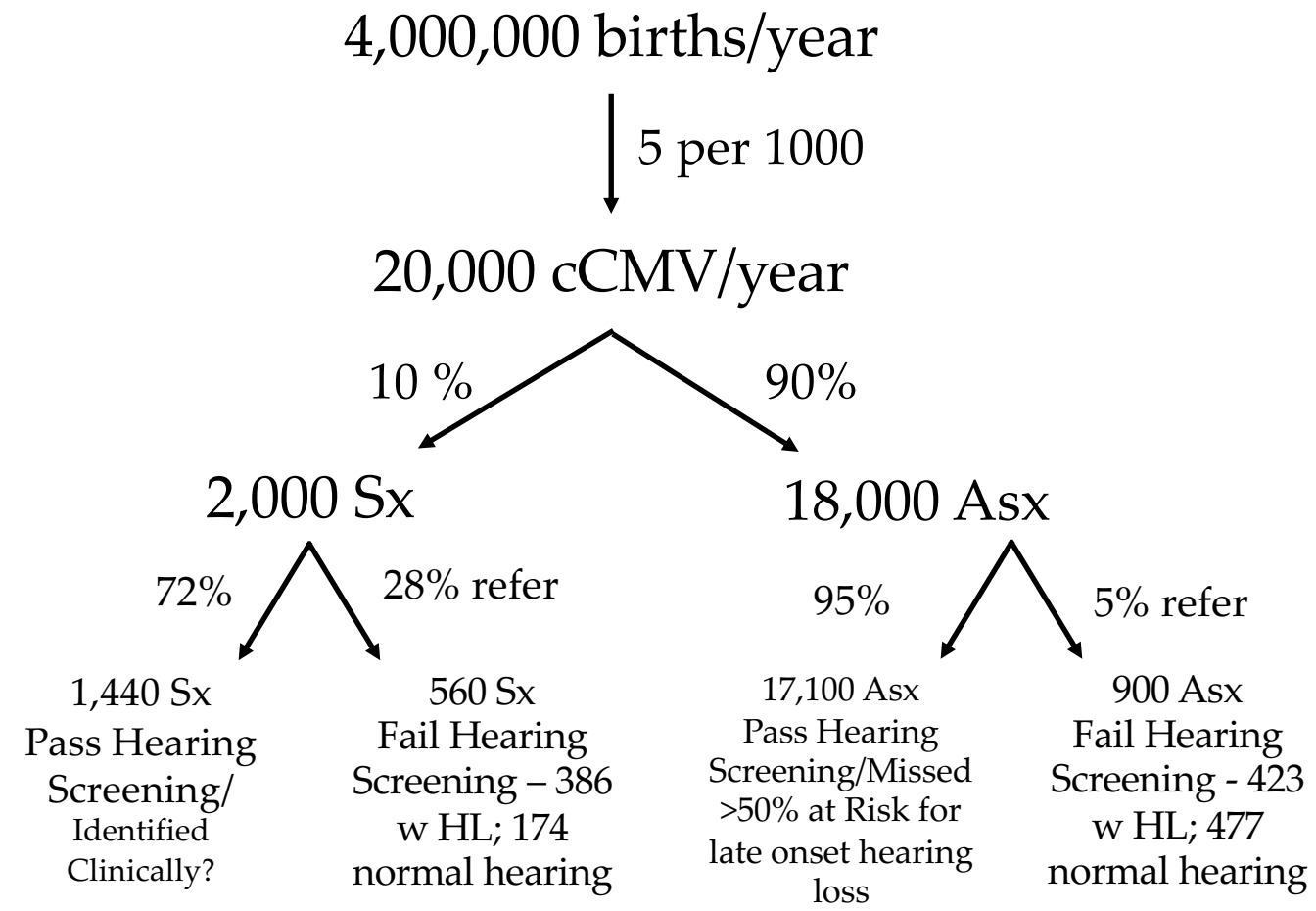
Acceptability of CMV Screening

Attitudes towards prenatal and newborn cytomegalovirus screening by pregnancy history.

Question	Response	All (n = 726) n (%)	Recently Pregnant (n = 204) n (%)	Never Pregnant (n = 522) n (%)	Chi-Square p-value
Prenatal Screening for CMV					
Think it should be offered	Strongly agree	368 (50.7)	81 (39.7)	287 (55.0)	<0.0001
	Somewhat agree	147 (20.2)	48 (23.5)	99 (19.0)	
	Agree	185 (25.5)	59 (28.9)	126 (24.1)	
	Somewhat disagree	20 (2.8)	12 (5.9)	8 (1.5)	
	Strongly disagree	6 (0.8)	4 (2.0)	2 (0.4)	
Would choose to be screened	Yes	556 (76.6)	132 (64.7)	424 (81.2)	<0.0001
	No	56 (7.7)	29 (14.2)	27 (5.2)	
	I don't know	114 (15.7)	43 (21.1)	71 (13.6)	
Newborn Screening for CMV					
Think it should be offered	Strongly agree	404 (55.6)	93 (45.6)	311 (59.6)	0.0062
	Somewhat agree	125 (17.2)	47 (23.0)	78 (14.9)	
	Agree	169 (23.3)	52 (25.5)	117 (22.4)	
	Somewhat disagree	21 (2.9)	9 (4.4)	12 (2.3)	
	Strongly disagree	7 (1.0)	3 (1.5)	4 (0.8)	
Would choose for baby to be screened	Yes	596 (82.1)	149 (73.0)	447 (85.6)	0.0005
	No	38 (5.2)	17 (8.3)	21 (4.0)	
	I don't know	91 (12.5)	37 (18.1)	54 (10.3)	
	Missing	1 (0.1)	1 (0.5)	0	

Tastad, *et al PLOS ONE* 2019;14(8): e0221725..

Targeted vs Universal Congenital Cytomegalovirus Screening



Fowler, et al unpublished

Cost Effectiveness of Congenital Cytomegalovirus Screening

Table 5. Estimated Mean Savings of Newborn cCMV Screening Strategies[a]

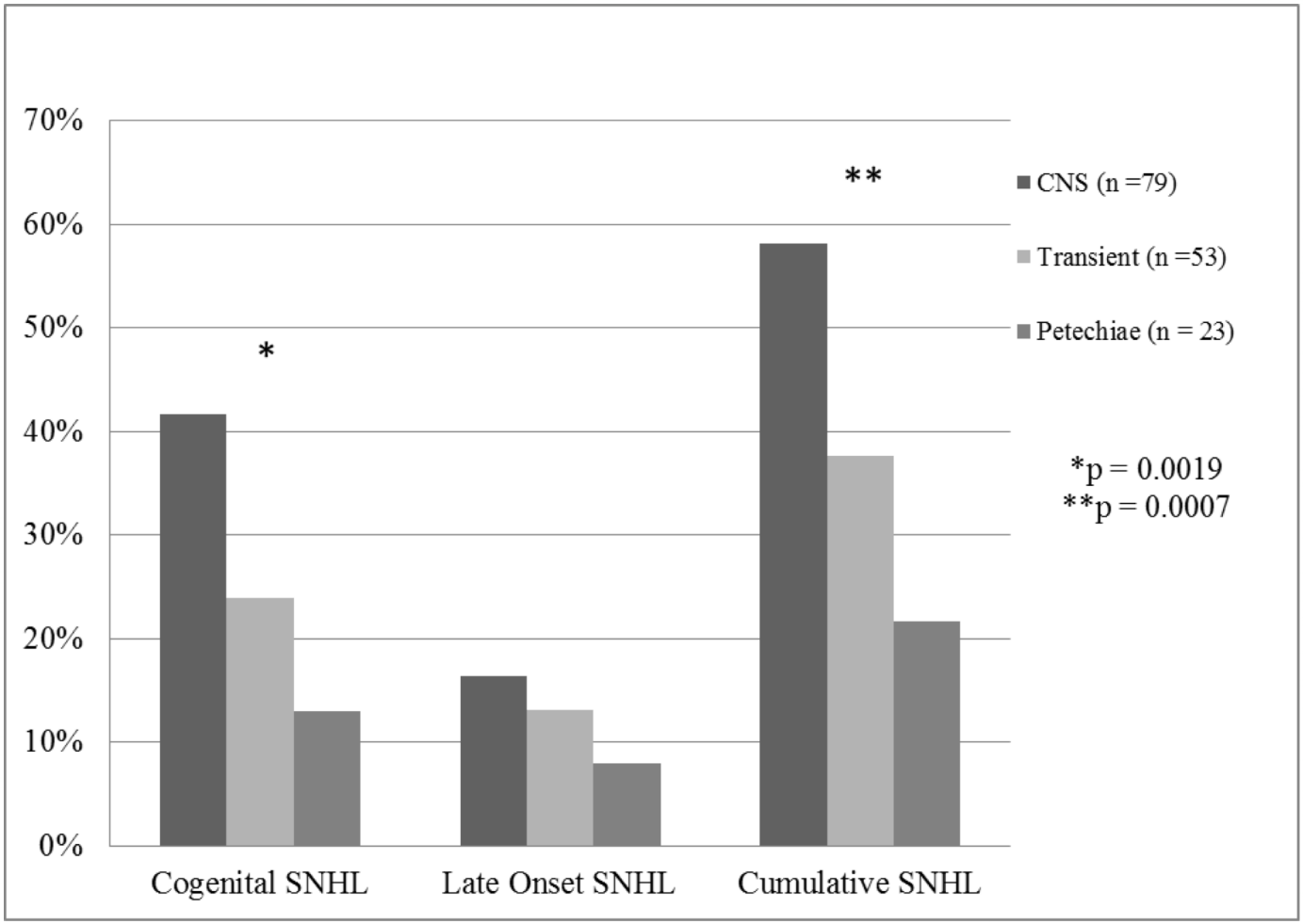
Outcome	Screening Strategy[b]					
	Universal			Targeted		
	Treat cCMV-Infected Symptomatic Newborns Only	Treat cCMV-Infected Symptomatic Plus Asymptomatic Newborns With Hearing Loss at Birth	No Treatment	Treat cCMV-Infected Symptomatic Newborns Only	Treat cCMV-Infected Symptomatic Plus Asymptomatic Newborns With Hearing Loss at Birth	No Treatment
Reduction in severe to profound cases enabled by screening, %	7.5 (2.5 to 12.6)	13 (5.3 to 21)	NA	4.2 (1.4 to 7)	9.7 (4.1 to 15.2)	NA
Costs/savings per newborn excluding loss-of-productivity costs, $	−10.86 (−14.73 to −6.97)	−6.83 (−12.98 to −0.68)	−14.16	0.90 (−0.82 to 3.51)	4.95 (0.50 to 9.15)	−2.01
Net costs/savings per newborn including loss-of-productivity costs, $	21.34 (6.54 to 36.17)	37.97 (14.60 to 61.34)	1.67	10.66 (2.57 to 19.67)	27.31 (10.21 to 43.59)	−1.80

Abbreviations: cCMV, congenital cytomegalovirus; NA, not applicable.

[a] Assumes a screening test cost of $10 per newborn. All costs/savings are in 2016 US dollars.

[b] Treatment consists of valganciclovir hydrochloride. Values shown are derived using the estimated benefit of valganciclovir on hearing loss as described in the Methods section, with a sensitivity analysis shown in parentheses in which the estimated benefit is 50% lower or higher.

Clinical Predictors of Hearing loss in symptomatic congenital CMV



Pinninti et al, 2015, Pediatr Infect Dis J. 2016 Aug;35(8):924-6.

Neuroimaging to Predict Neurological outcome

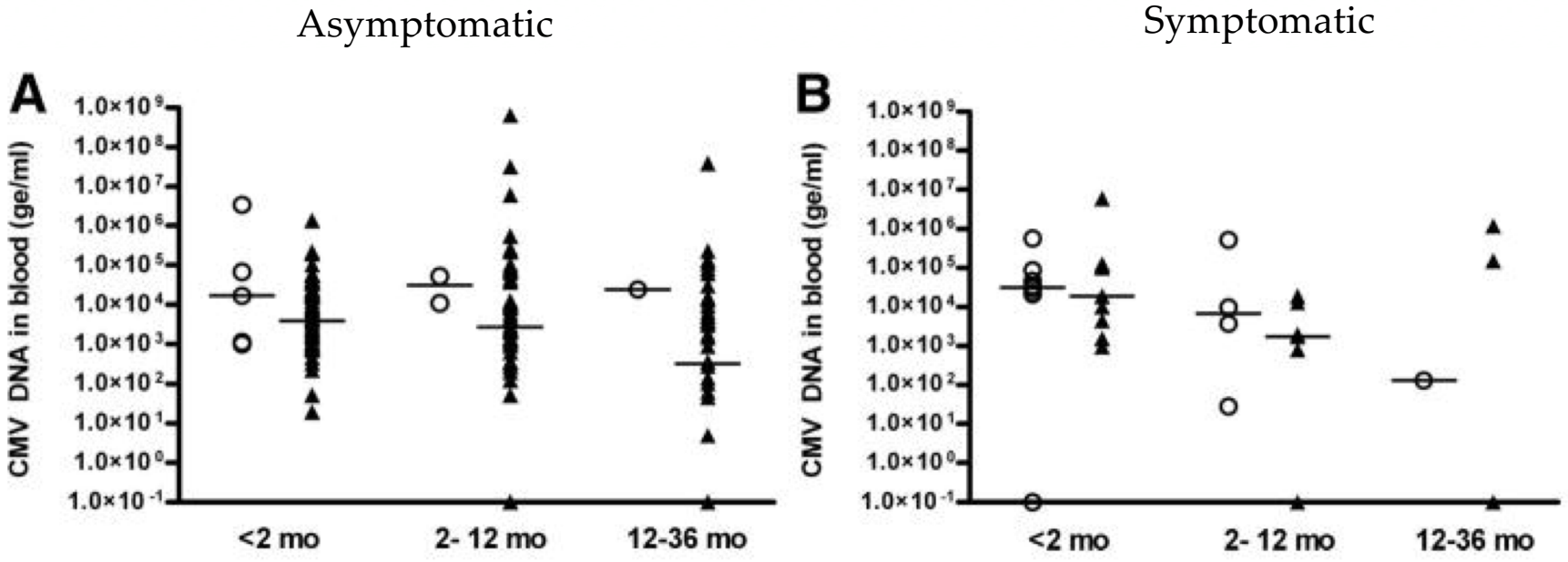
Table 2. MRI score, only white matter and lateral ventricles appearance is considered in this *new score* system.

	Normal	Cortical simplification	Micropoligyria/dysplasia	Lissencephaly pachygyria
Cortex	0	1	2	3
White matter (WM)	Normal	Myelination delay	Periventricular WM disease/ germinolytic cysts	Parietal/anterior temporal WM disease/ periventricular temporal cysts
	0	1	2	3
Cerebellum	Normal	Mild hypoplastic	Moderate hypoplastic	Hypoplastic
	0	1	2	3
Lateral ventricles	Normal	Ventriculomegaly		
	0	1		
Calcifications	Normal	Punctate periventricular	Extensive periventricular/WM	WM and deep gray matter
	0	1	2	3

- 9 children with normal MRI (score 0): 7 were asymptomatic at birth and 2/7 had sequelae
- 35 children with MRI score >0: 10 asymptomatic at birth and 8/10 developed sequelae
- 25 symptomatic with MRI score >0: 20 developed adverse neurological outcome

Pediatr Infect Dis J. 2018 Oct;31(10):1028-33

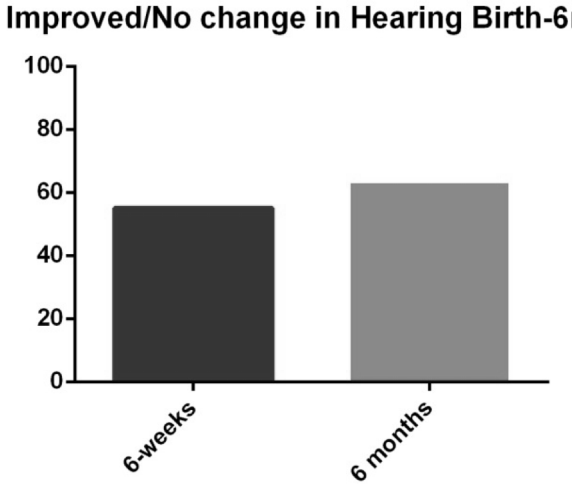
Blood viral load as a predictor of hearing loss



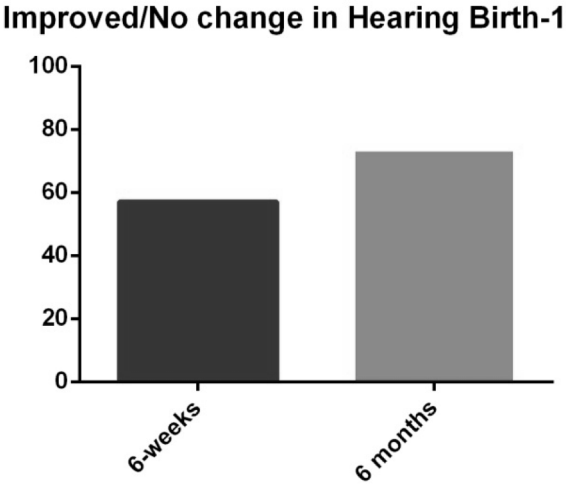
hearing loss (○) and normal hearing (▲)

Pediatr Infect Dis J. 2009 Jul; 28(7): 588–592

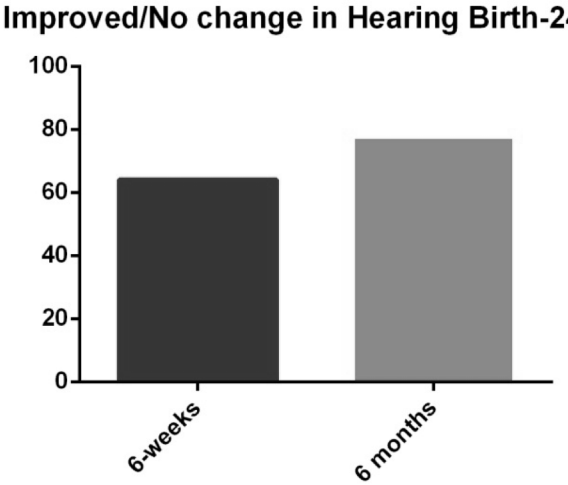
Valganciclovir Treatment Study
6 weeks vs. 6 months in symptomatic congenital CMV



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

“Treatment” of Asymptomatic Congenital CMV

HEAR Center

The HEAR Center at Children's of Alabama aims to provide comprehensive diagnostic and treatment services for families and professionals working on behalf of children with hearing loss, while emphasizing the development of auditory skills and spoken language in a variety of communication formats. The multidisciplinary team includes an otolaryngologist, pediatric audiologists specializing in hearing aids and cochlear implants, and speech-language pathologists certified in Auditory-Verbal Therapy.

Services

- Auditory-verbal therapy services with certified listening and spoken language specialists (LSLS Cert. AVT)
- Aural rehabilitation therapy services according to chosen communication modality
- Cochlear implant candidacy evaluations, programming, and management
- Fitting and verification of hearing aids using research-based protocols
- Speech/Language/Auditory evaluation, individual therapy, and group therapy for children with hearing loss
- Parent mentoring

https://www.childrensal.org/hear-center

Alabama's Early Intervention System

The early years are critical to the success of any child, but are especially vital for a child who has a developmental delay or disability.

Created as Part C of the Individuals with Disabilities Education Act (IDEA), Alabama's Early Intervention System (AEIS) is the beginning of Pre-K services for children with disabilities and developmental delays; school readiness is its sole function.

http://www.rehab.alabama.gov/individuals-and-families/early-intervention