Advancing Care: Latest Insights on Screening and Managing Congenital Cytomegalovirus in Newborns

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Disclosures

- I have no disclosures

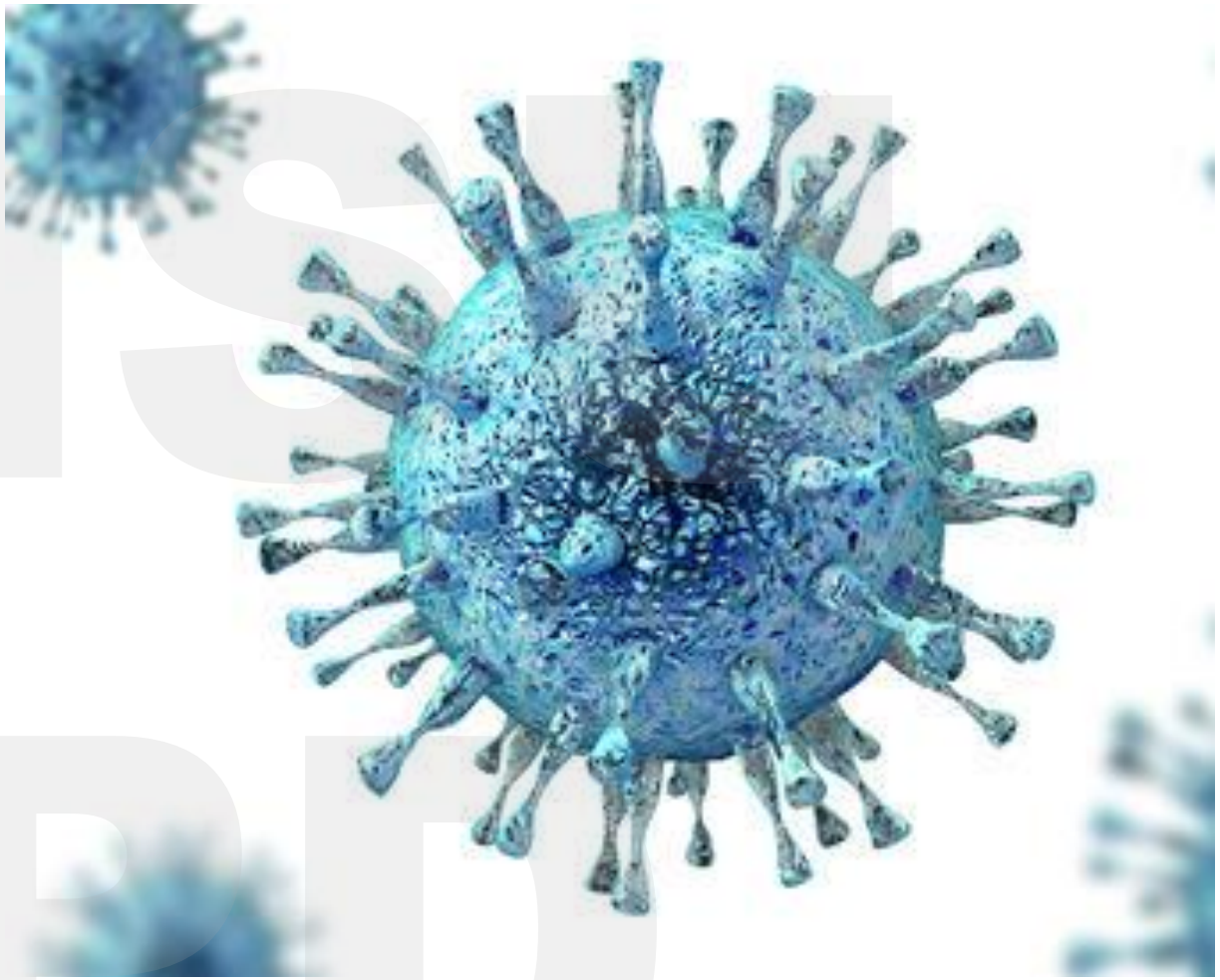
Objectives

- **Understand cCMV Basics**
- **Identify & Evaluate Screening Methods**
- **Recognize Diagnostic Techniques**
- **Discuss Management Strategies**
- **Emphasize Long-term Follow-Up**
- **Explore Future Directions**
- **Encourage Advocacy and Awareness**

cCMV as a Public Health Issue

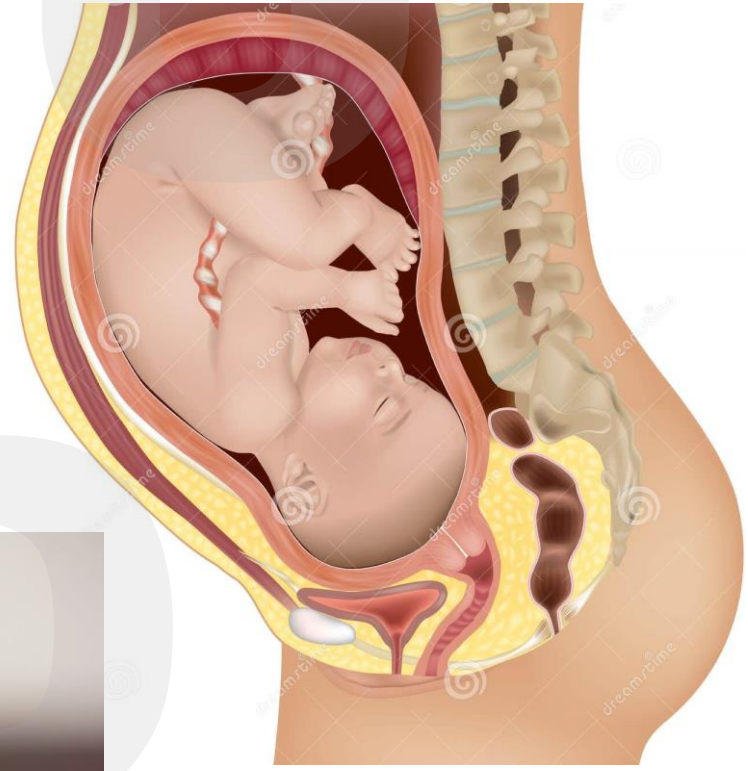
What is cytomegalovirus (CMV)?

- Member of the *Herpesviridae* family
- Often acquired in childhood
- Remains latent in multiple organs
- Symptoms include:
  - Sore throat
  - Fever
  - Fatigue



How is CMV transmitted?

- Transmitted:
  - Bodily Fluids
  - Transplacental
- Highest Transmission:
  - 1st infection
- Highest Severity:
  - 1st trimester



Epidemiology

- Leading cause of congenital infections
- cCMV rate in US: 4.5/1000 LB
- Approx 20,000-40,000 infants/yr

  affected in US
- Racial and ethnic differences exist

CHIMES Study	N	cCMV Infection (/1000)
Black Infants	24,100	9.5/1000
Non-Hispanic White Infants	37,219	2.7/1000
Hispanic White Infants	32,310	3.0/1000
Asian Infants	4,166	1.0/1000
Multiracial Infants	2,436	7.8/1000

NICHD-funded CHIMES Study, *Infection J Pediatr 2018*

Epidemiology

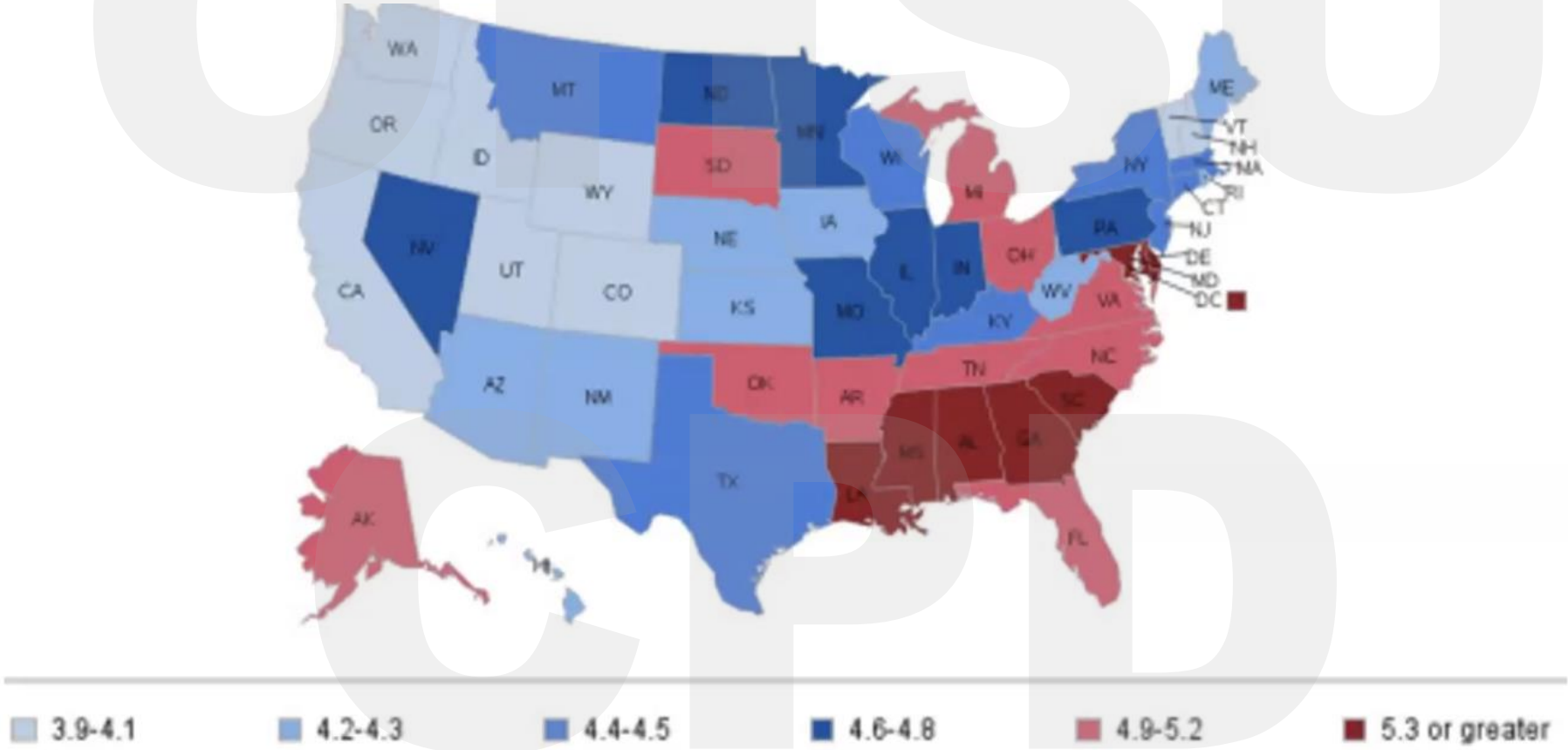
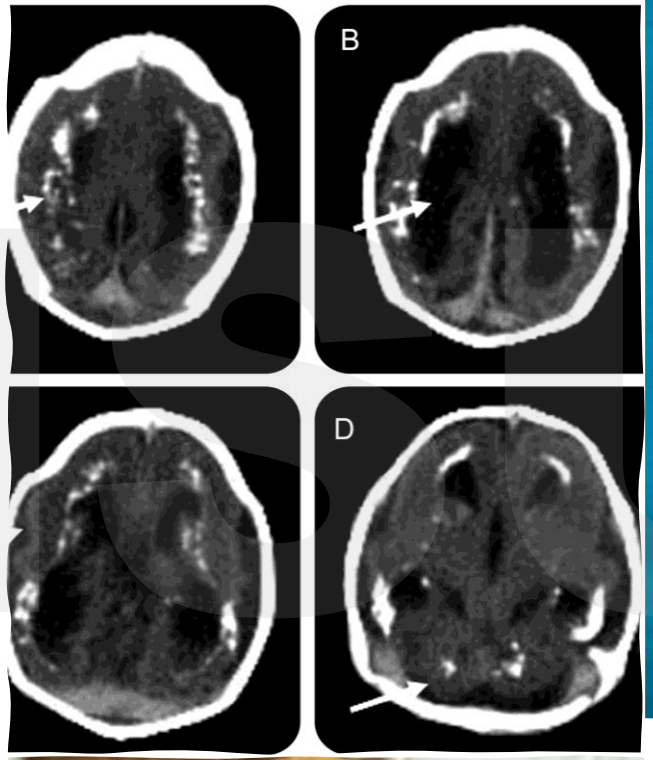


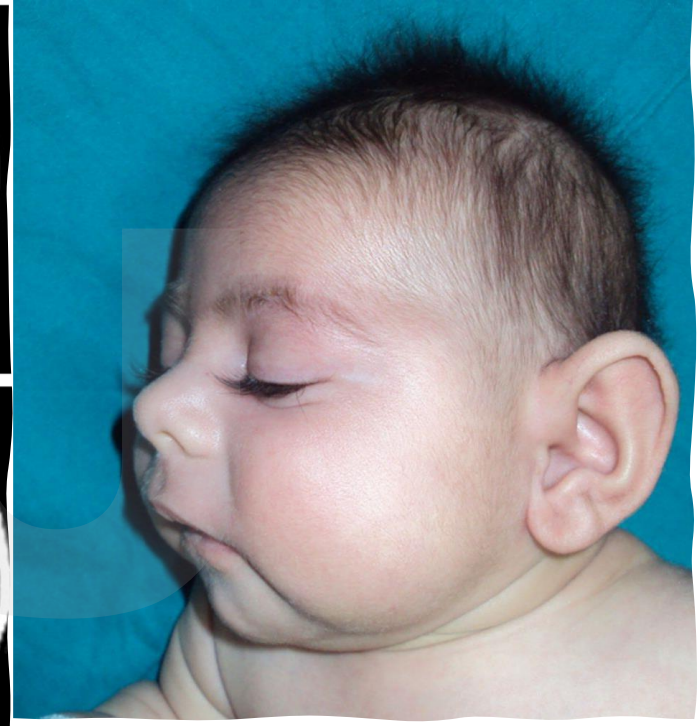
Figure 1. Maternal Race & Ethnicity-Adjusted cCMV Infection Prevalence per 1000 Live Births, Panel E. 2022

• DOI: 10.1097/PHH.0000000000002043

Clinical features

- 10-15% of infants with cCMV are symptomatic
- 85-90% of infants with cCMV are asymptomatic
  - 15% can go on to develop sequelae, sensorineural hearing loss (SNHL)



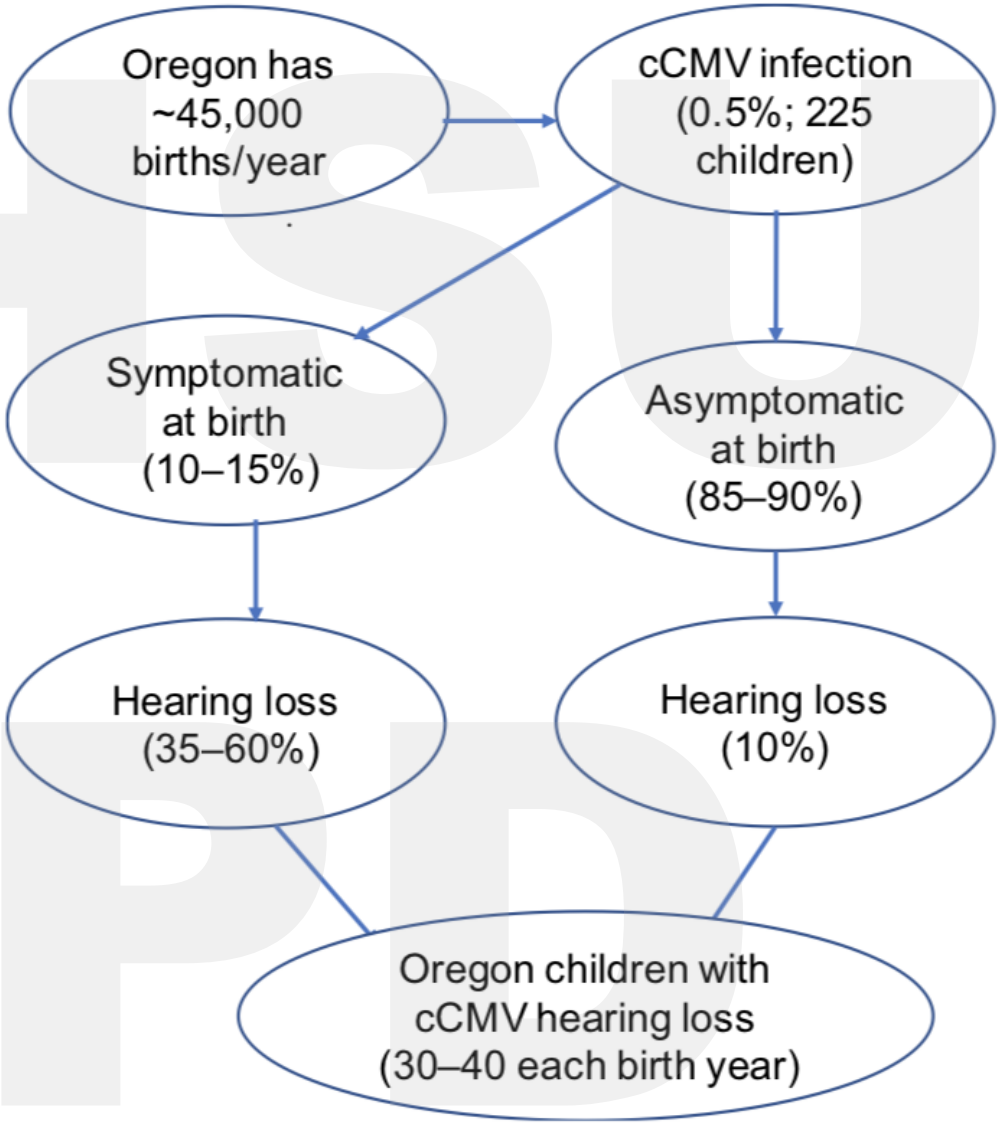


cCMV-related Hearing Loss

- Leading cause of non-genetic SNHL
- cCMV-related hearing loss leads to significant morbidity
  - 76% severe-profound hearing loss
- Early identification and intervention are key
  - Critical period for brain development

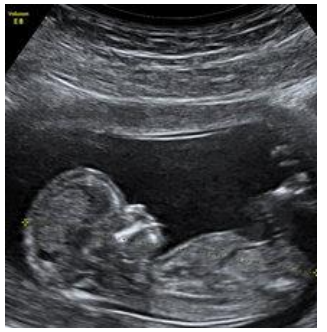
https://www.cdc.gov/ncbddd/childdevelopment/early-brain-development.html

What about in Oregon?



- https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDIS ARYNEWSLETTER/Documents/2018/ohd6709.pdf

Diagnosis



- Non-specific findings on prenatal US
- CMV DNA PCR within first 21 days of life

PCR Sensitivity & Specificity for cCMV Screening

	Urine PCR	Saliva PCR	DBS (CDC lab)
Sensitivity	>90%	>90%	77%
Specificity	>90%	>90%	>90%

Which Babies should be Screened?

- Universal vs Targeted

Principles of a screening test

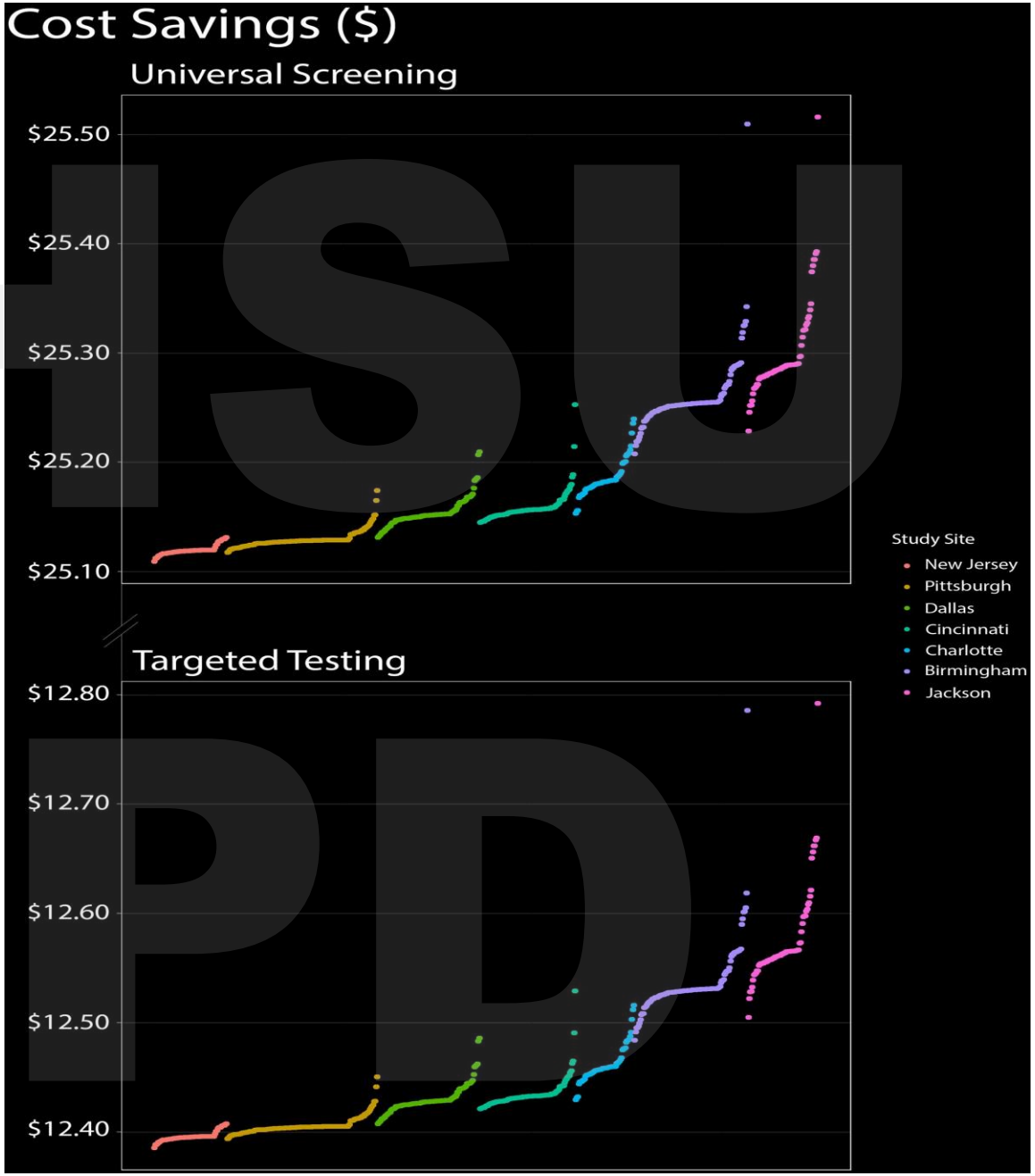
- WHO
  - Screen for diseases with serious consequences
  - Test must be reliable
  - Effective treatment when detected early

Newborn screening programs

Universal Screening

- Testing all newborns for CMV allows for closer monitoring of CMV+ babies
- Leads to further work up: CBC, LFTs, neuroimaging, ophthalmology, audiology
- Must decide whom to offer treatment

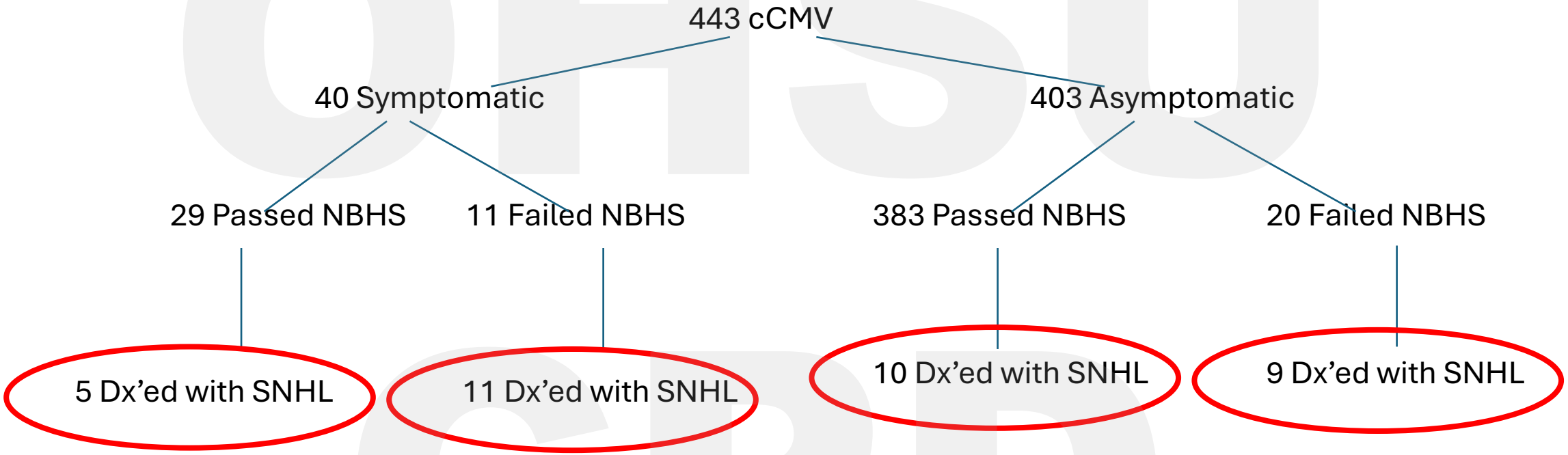
Universal Screening



https://doi.org/10.1093/ofid/ofae311

Targeted Screening

- Test neonates who refer on their NBHS
  - *Fowler et al 2017:* ~100,00 infants tested for CMV & received NBHS as part of CHIMES study
    - All CMV + infants received diagnostic audio eval @ 3-8wk
    - Prospective, 5 year study across 7 US medical centers


443 cCMV
40 Symptomatic
403 Asymptomatic
29 Passed NBHS
11 Failed NBHS
383 Passed NBHS
20 Failed NBHS
5 Dx'ed with SNHL
11 Dx'ed with SNHL
10 Dx'ed with SNHL
9 Dx'ed with SNHL

Expanded Targeted Screening

If any of the following present:

1) Mother positive for CMV infection during pregnancy
2) Abnormal head size (OFC <10th %ile OR ~~>90th %ile at birth~~)
3) Intrauterine growth restriction (weight <10th %ile for gestational age)
4) Unexplained hydrops
5) Intracranial OR intraabdominal calcifications on first imaging exam
6) Unexplained hepatomegaly OR splenomegaly (>1 cm below the right or left costal margin)
7) AST or ALT >100 U/L OR unexplained direct bilirubin >1.0 mg/dL
8) Petechial rash or blueberry muffin rash at any time
9) Leukomalacia, polymicrogyria, lissencephaly, pachygyria, schizencephaly
10) Unexplained persistent thrombocytopenia (platelets < 100k/mm3)
11) Failed hearing screen

Send urine CMV PCR
(obtain by 21 days of life when possible)

Suarez et al. 2023

Screening at OHSU

Concern for Symptomatic cCMV?

- Maternal CMV during pregnancy
- Consider if symmetric SGA (2 or more SD below mean)[1]
- Microcephaly (2 or more SD below mean for gestational age)
- Fetal hydrops, ascites, abdominal calcifications, or thickened bowel on prenatal US
- Exam: Hepatomegaly, splenomegaly, petechial "blueberry muffin" rash, chorioretinitis, jaundice
- Seizures with no other explanation
- AST or ALT >100 U/L, Dbili >1.0 mg/dL, Plts <100k/mm3
- Abnormal brain imaging concerning for cCMV[2]

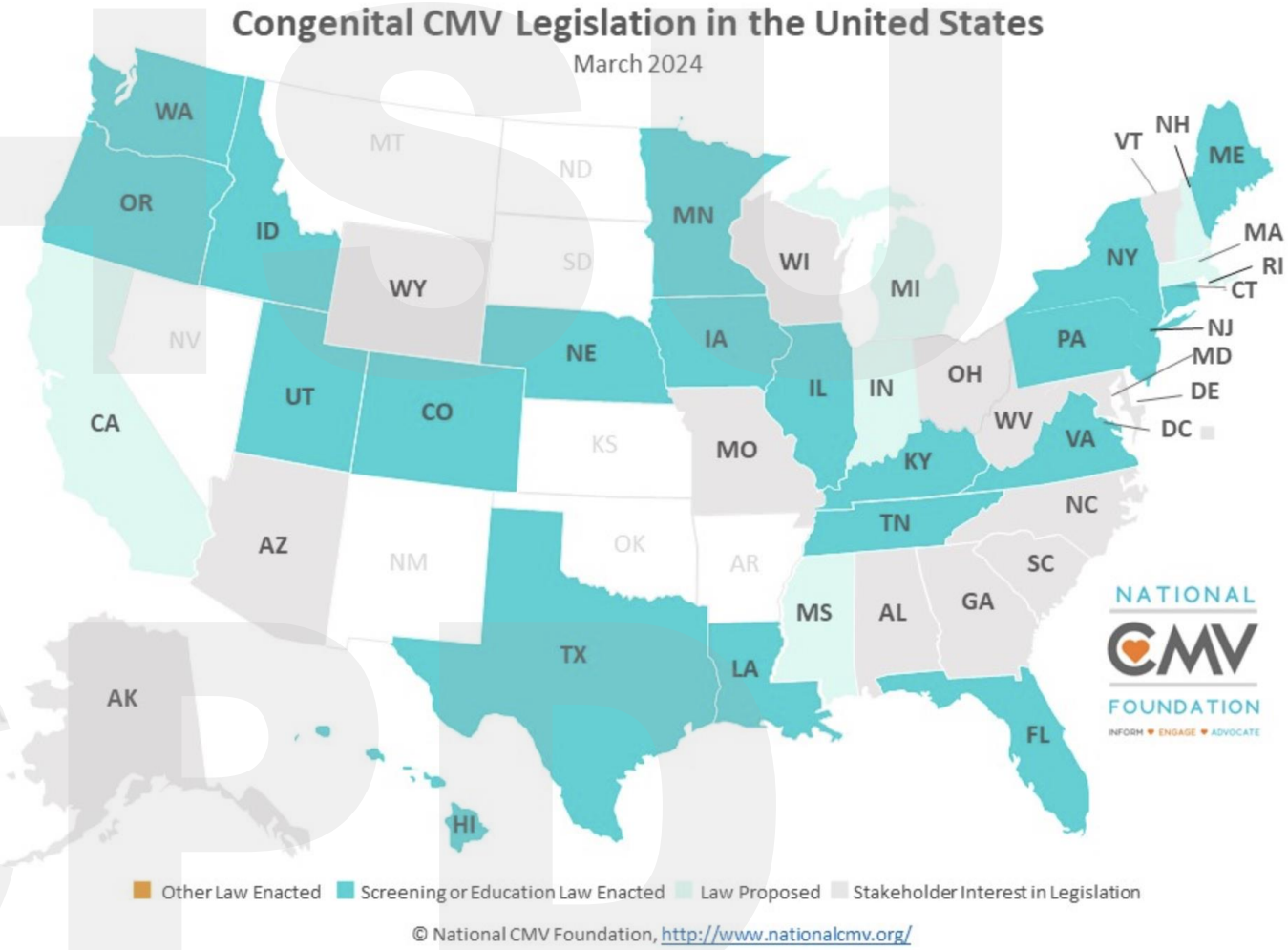
Concern for Asymptomatic cCMV?

- Referred hearing screen x 2 (unilateral or bilateral) in MBU
- Normal exam and prenatal imaging

Work Up at OHSU for cCMV

- Referrals to:
  - Pediatric Infectious Disease
  - Pediatric Audiology
  - Pediatric Ophthalmology
  - Developmental Evaluation Clinic (formerly NICU f/u clinic)
- Blood work: CBC+diff, CMP, quantitative serum CMV PCR
- Head US

Screening & Law



Oregon Legislation

Provide education information

Hospitals that perform NBHSs provide information about cCMV to parents

Audiologists must provide information about cCMV when hearing loss is diagnosed

Recommended schedule for hearing screening

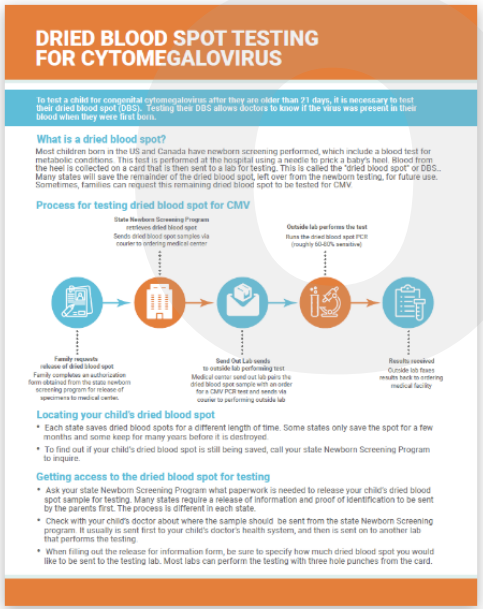
Treatment of congenital CMV

- Primary Care Provider
- Audiologist
- Speech therapists
- Early intervention programs
- Family education & support resources

Treatment of congenital CMV

CMV Disease Severity	Signs and Symptoms	Treatment
Moderately to severely symptomatic	One or more of the following: • Single severe or multiorgan disease or life-threatening organ dysfunction • Multiple persistent (eg, ≥2 weeks) manifestations attributable to congenital CMV infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, hepatitis • Central nervous system involvement such as microcephaly, radiographic abnormalities • Greater than 2 mild disease manifestations	Valganciclovir given orally for 6 **months**; treatment should be started within the first 13 weeks following birth
Asymptomatic with isolated sensorineural hearing loss	No clinically apparent signs to suggest congenital CMV disease, but sensorineural hearing loss	Valganciclovir may be offered and given orally for 6 **weeks**; treatment should be started within the first 13 weeks following birth
Mildly symptomatic	Two or fewer transient (eg, <2 weeks) or clinically insignificant findings	There are insufficient data to recommend routine treatment, but it may be considered on a case by case basis
Asymptomatic	No apparent signs to suggest congenital CMV disease, and normal hearing	Therapy not recommended outside of a research study

CMV Blood Spot Testing



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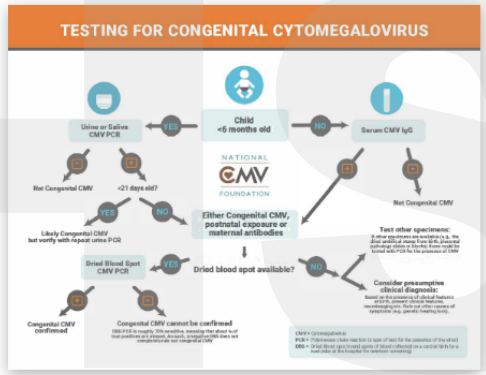
CMV Testing After Birth



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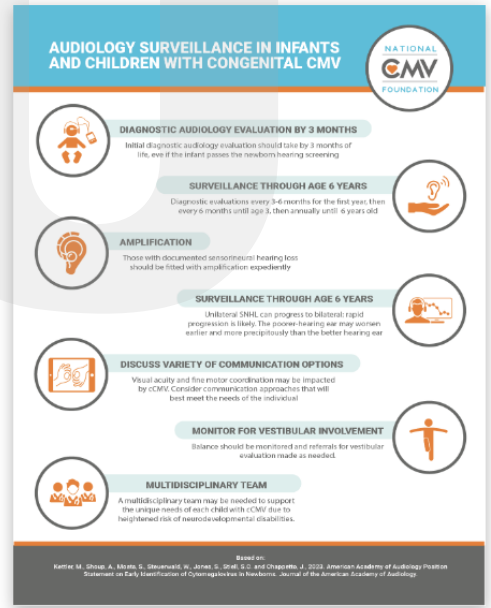
Congenital CMV Audiology Surveillance



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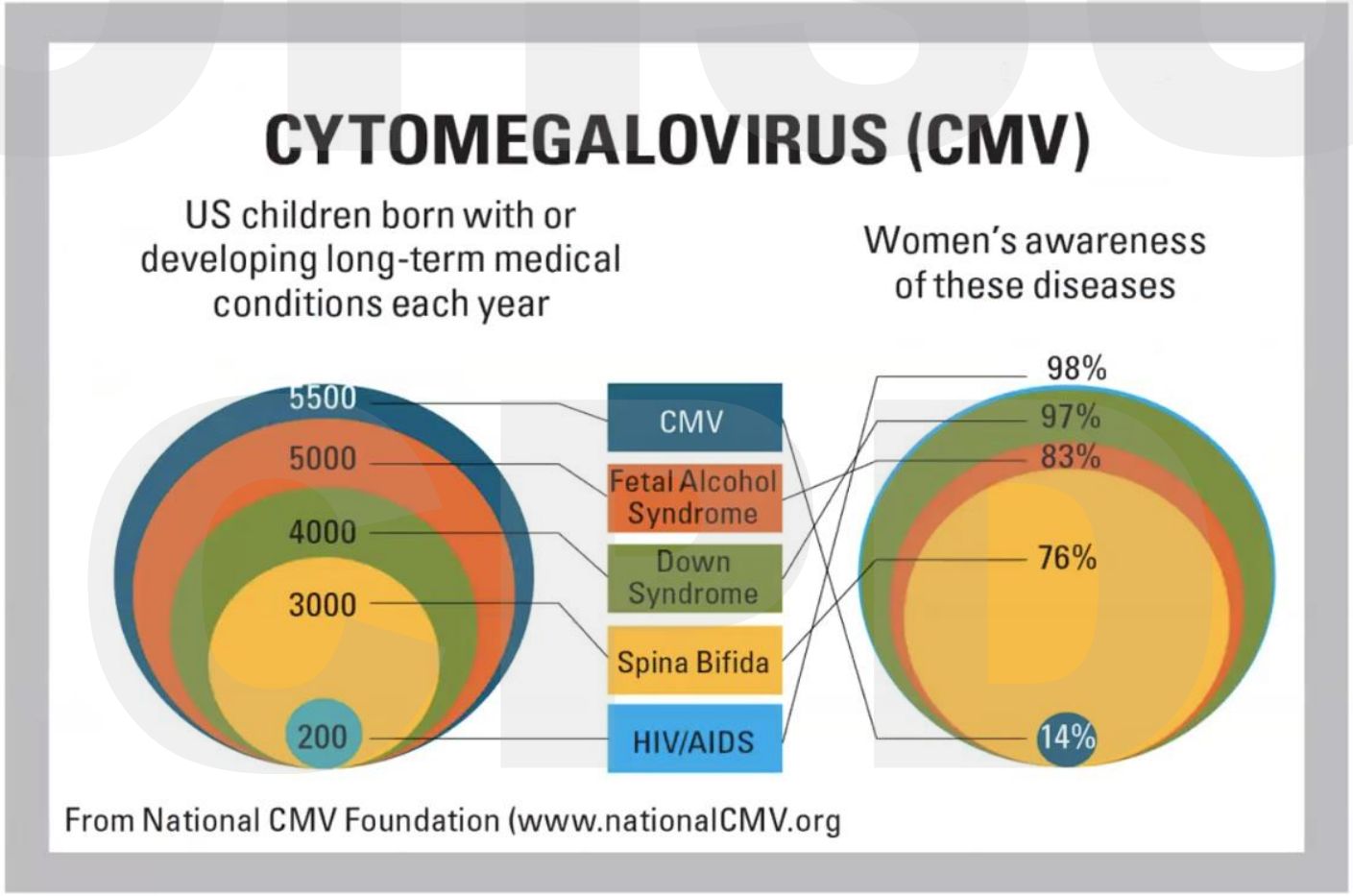
https://www.nationalcmv.org/resources/educational-downloads

Future Directions

- Awareness and Prevention
- Pre-conception/-natal Testing
- Optimal Screening Approach
- Vaccination?

Prenatal considerations

Prenatal considerations



Prenatal considerations

PREVENTION OF CHILD-TO-MOTHER TRANSMISSION OF CYTOMEGALOVIRUS AMONG PREGNANT WOMEN

STUART P. ADLER, MD, JACK W. FINNEY, PHD, ANNE MARIE MANGANELLO, RN, AND AL M. BEST, PHD

Objective To determine if protective behavior prevents child-to-mother transmission of cytomegalovirus (CMV) during pregnancy.

Study design We studied 166 seronegative mothers (94% white women; mean age, 33 years) with a child <36 months of age attending a day care facility. Mothers, either pregnant or attempting pregnancy, were randomly assigned by day care center to either a control or intervention group. Mothers in the intervention group received instructions for hand washing, glove use, and for avoiding types of intimate contact with their child. The control group received no instructions or information about their serologic status or whether their child was shedding CMV.

Results In the intervention group, 7.8% of women (9 of 115) seroconverted, as did 7.8% of women (4 of 51) in the control group. Two independent predictors of maternal infection were (1) a child shedding and (2) a mother attempting pregnancy at enrollment. For 41 women attempting pregnancy at enrollment with a child shedding CMV, 10 of 24 became infected compared with only 1 of 17 women who were already pregnant at enrollment ($P = .008$).

Conclusions For seronegative women who already know they are pregnant, intervention may be highly effective for preventing CMV acquisition. *(J Pediatr 2004;145:485-91)*

Approximately 50% of infants born to mothers who acquire a primary cytomegalovirus (CMV) infection during pregnancy will be infected in utero and born with a congenital CMV infection.[1] Congenital CMV infection can result in mental retardation, deafness, and other neurologic handicaps.[2] Seronegative mothers with infected children acquire CMV infections at rates 20 to 25 times higher than other women, and at least half of seronegative mothers will become infected within 1 year after their child becomes infected.[3-6] Children younger than 3 years of age who acquire CMV after birth excrete CMV in urine and saliva for 6 to 42 months (mean, 18 months).[7] In the United States, approximately 60% of mothers of children in day care are seronegative and at least half of all young children are in group child care. Between 15% and 70% of all children in group day care acquire CMV infection.[8] Prevention of maternal infection during pregnancy is important for reducing the frequency of congenital infection.

See editorial, p 435.

Because vaccines against CMV are unavailable, it is important to determine whether modifying certain maternal behavior reduces the rate at which CMV-seronegative pregnant women acquire CMV from their children. We previously developed an intervention protocol that was feasible and acceptable to mothers and that could potentially change behavior for mothers of young children in day care.[9,10] In a trial with a small sample size, we found that the protocol was effective for pregnant women but ineffective for nonpregnant women using contraception. We sought to evaluate the

From the Departments of Pediatrics and Biostatistics, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, and the Department of Psychology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia.

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

Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital

Christelle Vauloup-Fellous[a,b,*,1], Olivier Picone[c,d,1], Anne-Gaëlle Cordier[c], Isabelle Parent-du-Châtelet[e], Marie-Victoire Senat[c,f], René Frydman[c,d], Liliane Grangeot-Keros[a,b]

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ABSTRACT

Background: Cytomegalovirus (CMV) is the most frequent cause of congenital viral infection in developed countries.
Objectives: The objective of this study was to evaluate the impact of our prenatal CMV infection screening and counseling policy.
Study design: Since 2005, all pregnant women in our obstetric center have been informed about CMV infection, and if they agree, given a serological test at around 12 weeks of gestation (WG). If this first test is negative, the women and their partners are given hygiene counseling on how to prevent CMV infection, and a second test is performed at around 36 WG.
Results: Among the 5312 women who had an unknown immune status, or were known to be seronegative when they had their first visit to our center for their current pregnancy, 97.4% agreed to CMV screening. Primary infection was detected in 11 women between 0 and 12 WG (0.42%), and seroconversion was diagnosed in five women between 12 and 36 WG (0.19%).
Conclusions: These results suggest that if clear information is given on CMV infection during pregnancy, the rate of seroconversion is lower following counseling than before counseling.

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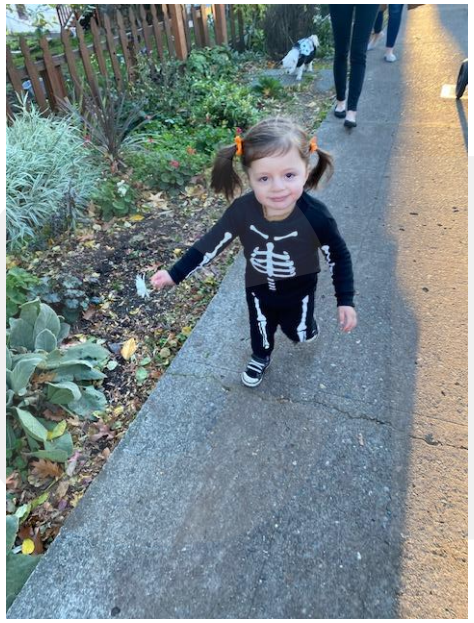

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