

Congenital Cytomegalovirus Infection CMV 101 The Basics The Elephant in Our Living Room



**Texas Children's
Hospital®**

Baylor
College of
Medicine®



Gail J Demmler Harrison MD
Professor of Pediatrics, Section Infectious Diseases
Baylor College of Medicine
and
Texas Children's Hospital
Houston, Texas USA

Disclosures

- I will discuss off label use of ganciclovir, valganciclovir, valacyclovir, and CMV hyperimmune globulin, with findings supported by clinical trials, expert opinion, consensus panels, and guidance from AAP, ACOG, SOGC
- I have received research support from, and/or done consulting for, Merck, Moderna, and Microgen, and for other educational support from Elsevier, Wolters-Kluwer and WEBMED Medscape



Why ELEPHANTS and CMV?

CMV is a **BIG** problem that no one really talks about - CMV is the elephant in our living room.

Elephants are battling their own CMV-related virus, called Elephant Endotheliotropic Herpes Virus (EEHV), which threatens their elephant babies survival

Elephants never forget

CMV 101

Elephant Friends as Helpers

Baby Tupelo & Mother Tess



Baby Baylor & Mother Shanti

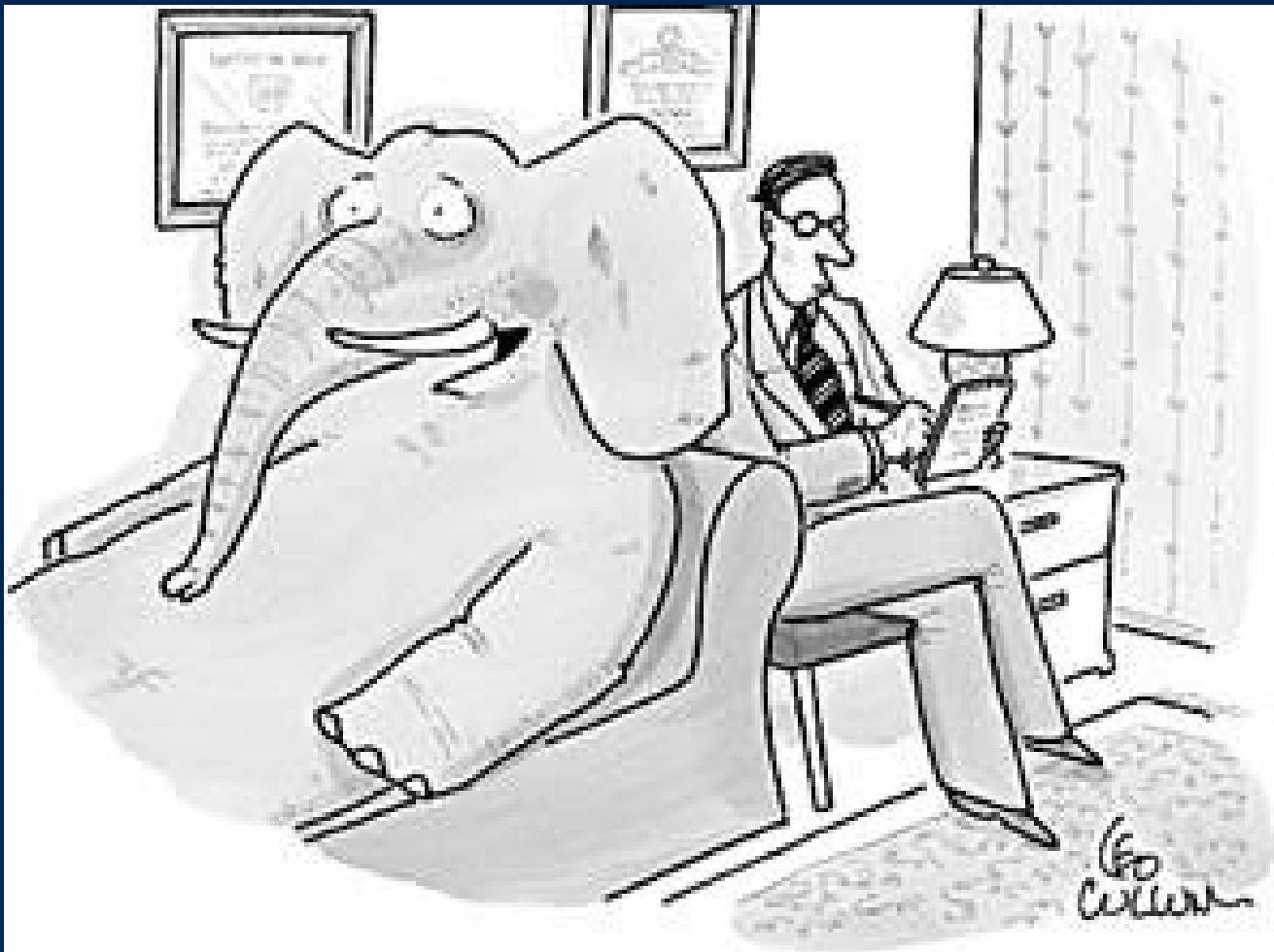


OBJECTIVES CCMV 101- COVER THE BASICS

- **BIOLOGY**
- **EPIDEMIOLOGY**
- **CLINICAL MANIFESTATIONS**
- **DIAGNOSIS**
- **TREATMENT**
- **PREVENTION**

WHO IS CMV?

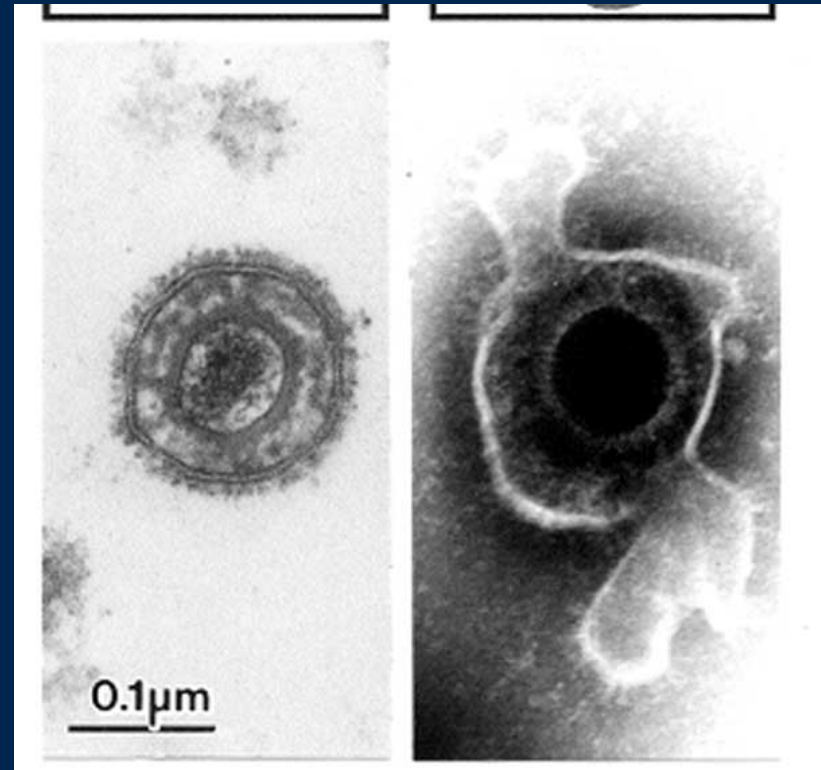
- CMV = CYTOMEGALOVIRUS
- AKA
 - Cyto= cell megal= big virus= L. poison
 - “A ubiquitous virus with protean manifestations”
 - An “opportunistic virus”
 - A “stealth virus”
 - “The most common virus most people have never heard of”
 - “The elephant in our living room”



"I'm right there in the room, and no one even acknowledges me."

FACIAL RECOGNITION of CMV

- Large ds DNA virus
 - 240 KB genome
 - 162 capsomeres
 - Icosahedral symmetry
 - Enveloped



Biological Characteristics of CMV

- Primary or first infections or second reinfections
- Latency/Persistence
 - A resting, dormant, but also expressive phase of infection
 - Virus expresses numerous viral proteins and mRNAs which mediate immune evasion
 - A variety of human cells in our body
- Reactivation
 - An active infection with viral gene expression and production of viral particles

Biological Characteristics of CMV

- Asymptomatic infections
 - Active viral infection that produces no obvious outward symptoms in the person
 - Most of CMV infections
- Symptomatic infections
 - Active viral infection that produces symptoms and signs
 - Many different signs and symptoms can occur
 - A minority of CMV infections

Biological Characteristics of CMV

- Primary infections
 - First infection with CMV
- Recurrent infections
 - Reactivation
 - A CMV endogenous in your body reactivates the infection
 - Most recurrent infections are probably reactivations
 - Reinfection
 - A new CMV infects your body

OBJECTIVES CCMV 101 – COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- TREATMENT
- PREVENTION

EPIDEMIOLOGY

- CMV INFECTION IS COMMON
 - **CONGENITAL**
 - Acquired from maternal transmission in utero
 - POSTNATAL
 - Breast milk, perinatal secretions, person-to-person
 - TODDLER
 - Day care, play groups, family, sharing
 - ADOLESCENCE
 - Intimacy, sharing food/drinks
 - ADULTHOOD
 - Intimacy, sharing, contact with young children

THE FETUS AND NEWBORN WITH CMV

Approximately 4 Million Births

Annually in the U.S.A.

0.5 to 1% with cCMV

20,000 to 40,000 Congenitally Infected Infants Each Year

```
graph TD; A[20,000 to 40,000 Congenitally Infected Infants Each Year] --> B[3-6,000 Symptomatic in utero or at birth; most neurologic or sensory sequelae common; fetal or neonatal death 8%]; A --> C[18-34,000 Asymptomatic or mildly symptomatic at birth; 25% hearing loss and 1-2% vision loss, may have developmental disabilities];
```

3-6,000 Symptomatic *in utero* or at birth; most neurologic or sensory sequelae common; fetal or neonatal death 8%

18-34,000 Asymptomatic or mildly symptomatic at birth; 25% hearing loss and 1-2% vision loss, may have developmental disabilities



Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative

0.1% to 1% recurrent CMV maternal infection

1% to 4% to 7% primary CMV maternal infection

CMV *in utero* fetus
congenital CMV newborn

40% CMV *in utero* fetus
congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn*

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

5% to 8% die
85% to 90% will have broad range disabilities

smaller size or GA
25% hearing loss
other disabilities?

OBJECTIVES CCMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- **CLINICAL MANIFESTATIONS**
- **DIAGNOSIS**
- **TREATMENT**
- **PREVENTION**



Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative

0.1% to 1% recurrent CMV maternal infection

1% to 4% to 7% primary CMV maternal infection

CMV *in utero* fetus
congenital CMV newborn

40% CMV *in utero* fetus
congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn*

85%-90% of babies have minimal or no signs or symptoms in — utero or at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

5% to 8% die
85% to 90% will have broad range disabilities

smaller size or GA
25% hearing loss
other disabilities?

CONGENITAL CMV (CCMV)

- SYMPTOMATIC CCMV
 - Symptoms at birth
- SYMPTOMATIC CCMV W/ CENTRAL NERVOUS SYSTEM OR BRAIN INVOLVEMENT
 - Clinical signs
 - Brain imaging
- PRIMARY NEUROPHENOTYPE SYMPTOMATIC CCMV
 - Only brain involved
 - May have sensory involvement too

SYMPTOMATIC CCMV



SYMPTOMATIC CCMV

- “Tip of the iceberg”
- Classic signs and symptoms – body somatic- ONE OR MORE OF THESE
 - Growth restriction or small for gestational age - IUGR or SGA
 - Jaundice w/ direct hyperbilirubinemia at birth
 - Skin rash - petechiae or purpura
 - Enlarged liver and spleen
 - Low platelets
 - Abnormal liver enzymes

SYMPTOMATIC CCMV W/ CNS INVOLVEMENT

- Microcephaly- at birth or later in infancy
- Neurologic signs
- Seizures
- Infantile spasms
- Hemiparesis
- Abnormal tone
 - Hypertonia
 - Hypotonia

SYMPTOMATIC CCMV W/ CNS INVOLVEMENT- BRAIN IMAGING

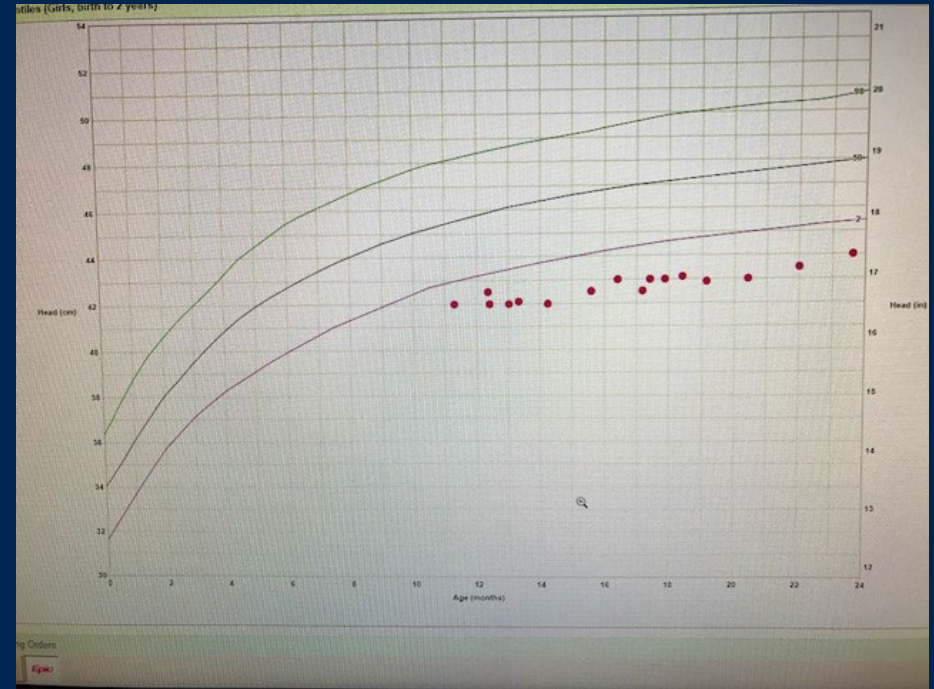
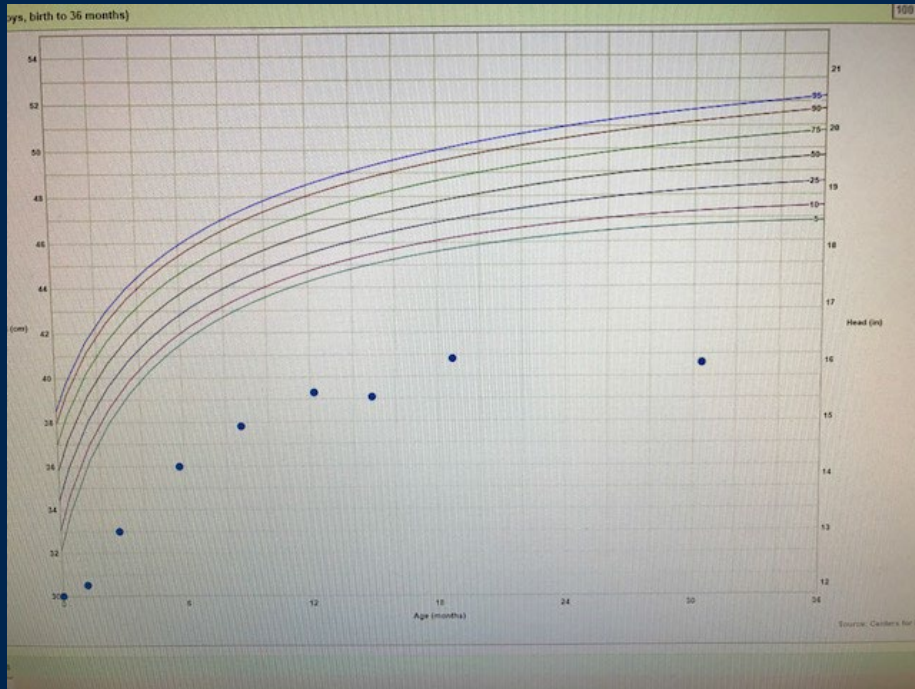
- Enlarged ventricles
- Calcifications of brain – usually periventricular
- Periventricular white matter lucencies
- Cerebral atrophy
- Cortical maldevelopment of brain
 - Polymicrogyria
 - Fetal brain disruption sequence
- Lenticulostriate vasculopathy
- Cysts

PRIMARY NEUROPHENOTYPE CCMV

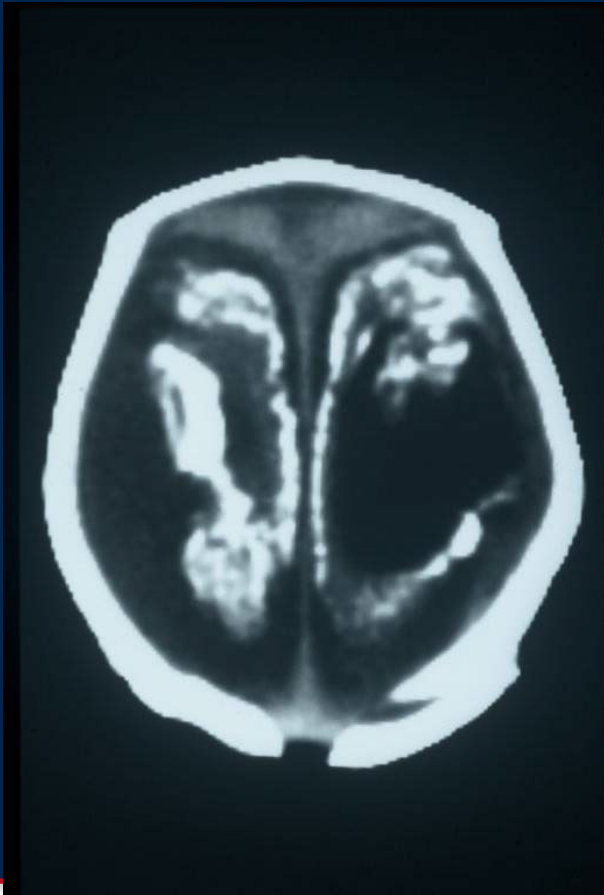
Emerging recognition that CCMV can present with only microcephaly or neurologic findings on exam, or neuro-imaging abnormalities

- Microcephaly
- Cortical maldevelopment
- Neuronal migration abnormalities
- Polymicrogyria – PMG - unilateral or bilateral
- Ca⁺ not as common ?
- Diagnosis often delayed
- Suspect if isolated microcephaly develops over first months of life

HEAD CIRCUMFERENCE PLOTS SHOWING MICROCEPHALY



SCCMV with CNS involvement- severe- fetal brain disruption sequence



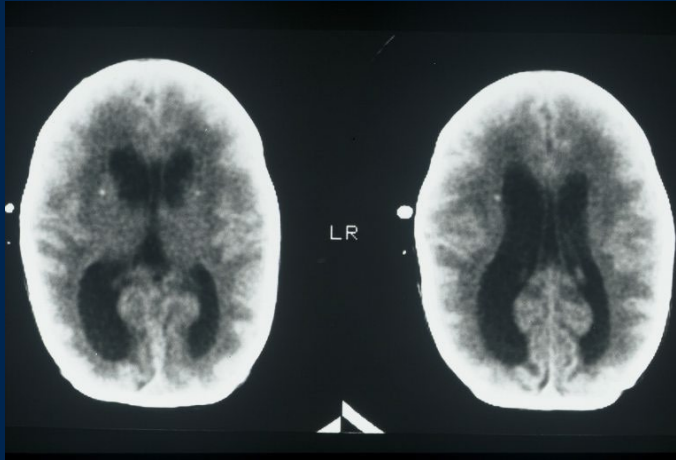
- Severe microcephaly with collapsed skull
- Severe brain malformation with periventricular Ca⁺

Classic congenital CMV with CNS involvement

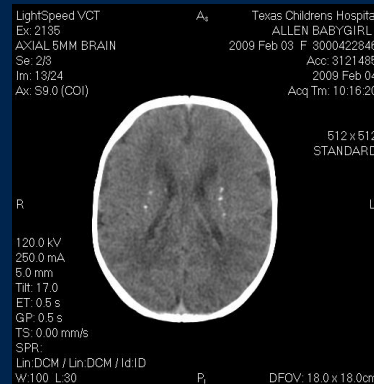


- Unenhanced CT scan of brain showed ventriculomegaly, linear periventricular Ca+, cerebral atrophy

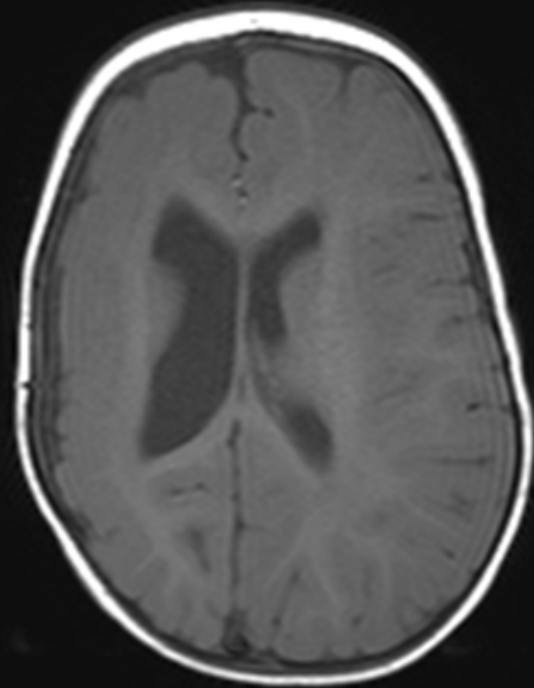
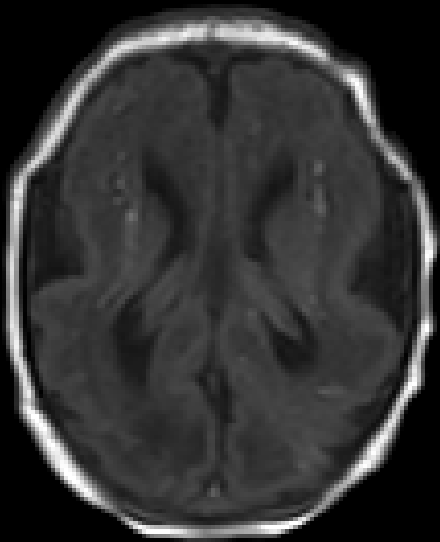
Mild to moderate ScCMV - Variations of CNS involvement



- Ventriculomegaly
- Punctate or beaded periventricular Ca⁺
- Periventricular leukomalacia

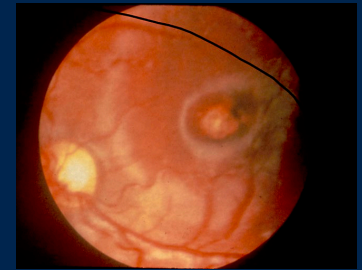


Cortical maldevelopment – unilateral or bilateral PMG



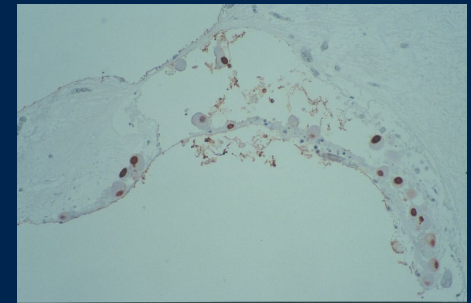
SYMPTOMATIC CCMV- VISION

- Active chorioretinitis
- Chorioretinal scars
- Optic nerve atrophy
- Cortical blindness with central vision impairment (CVI)
- Strabismus



SYMPTOMATIC CCMV- HEARING

- Hearing loss- most common sequelae
 - Conductive with middle ear effusion
 - Sensorineural
 - Progressive
 - Unilateral or bilateral
 - Congenital or later onset
 - Greatest risk first 5 years



SYMPTOMATIC CCMV-VESTIBULAR FUNCTION

– Vestibular Involvement

- Can occur in asymptomatic and symptomatic CCMV
- Can occur with or without hearing loss
- Monitor head lag, hypotonia, delayed sitting, imbalance when learning to walk
- Affects gross motor, coordination and QOL

– Shears et al. Arch Dis Child Fetal Neonatal Ed 2022;107:F630



Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative

0.1% to 1% recurrent CMV maternal infection

1% to 4% to 7% primary CMV maternal infection

CMV *in utero* fetus
congenital CMV newborn

40% CMV *in utero* fetus
congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn*

85%-90% of babies have minimal or no signs or symptoms in — utero or at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

5% to 8% die
85% to 90% will have broad range disabilities

smaller size or GA
25% hearing loss
other disabilities?

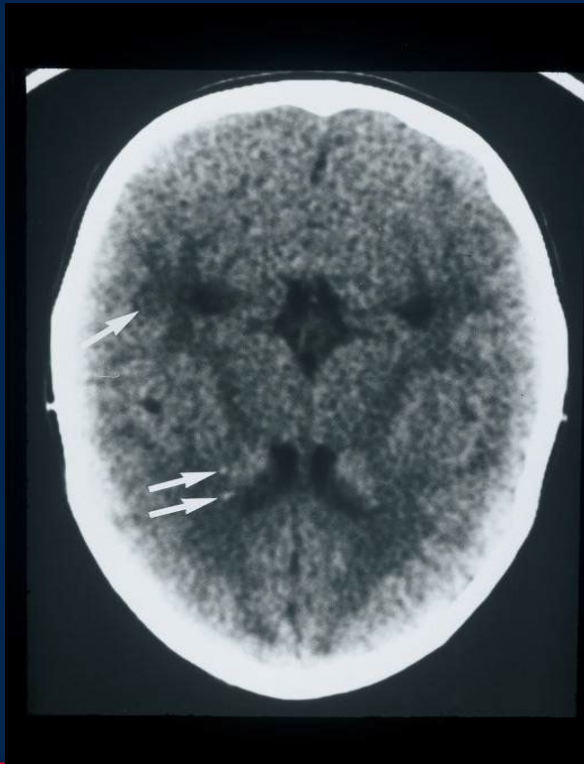
CONGENITAL CMV (CCMV)

- ASYMPTOMATIC CCMV
 - No apparent symptoms at birth
 - Normal hearing at birth
 - At risk later onset hearing loss
- ASYMPTOMATIC CCMV WITH ISOLATED HEARING LOSS
 - No apparent symptoms at birth
 - Fail/refer newborn hearing screen
 - Congenital hearing loss
 - Unilateral one side
 - Bilateral both sides
 - At risk for hearing loss progression

ASYMPTOMATIC CCMV

- MAY HAVE BRAIN IMAGING FINDINGS OF SUBTLE CNS BRAIN INVOLVEMENT
 - Ventriculomegaly, or asymmetrical ventricles
 - Periventricular cysts
 - White matter changes
 - Delayed myelination
 - Punctate tiny calcifications
 - Lenticulostriate vasculopathy

AcCMV Cranial CT images may have mild abnormalities 25%



- Periventricular leukomalacia
- Punctate periventricular calcifications
- Mild enlargement of ventricles

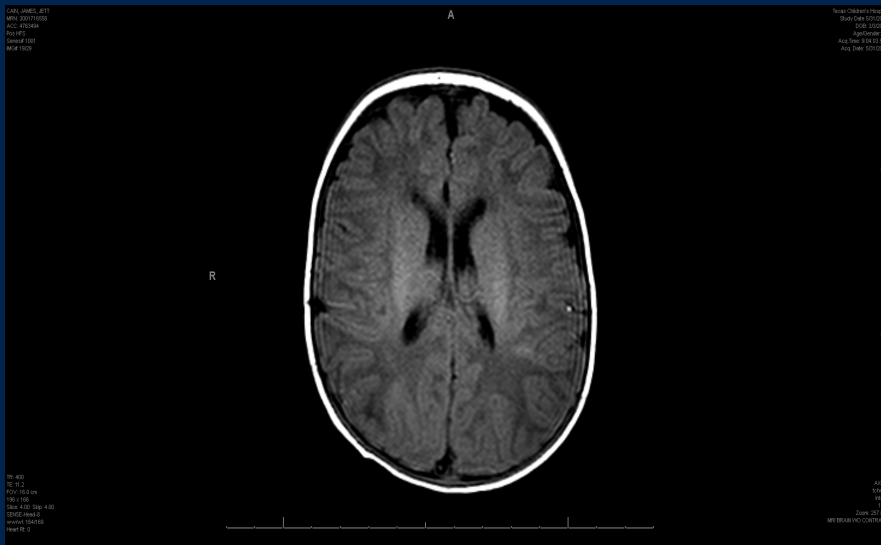
AcCMV Cranial head ultrasounds may show subtle nonspecific abnormalities of brain

- Asymmetrical ventricles, periventricular cysts



AcCMV Brain MRI may show subtle nonspecific abnormalities of brain

- Brain with delayed myelination, small germinolytic cysts, slightly enlarged ventricles



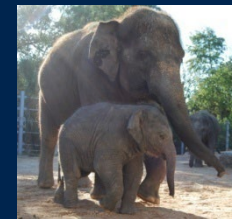
AcCMV long term outcomes

- Asymptomatic CCMV identified through newborn screening with normal hearing by age 2 years do not have significant IQ differences or academic achievement differences at 5 years and 18 years
- If hearing loss presents by age 2 years, full scale IQ and receptive vocabulary scores may be lower, and likely were due to the SNHL
- Can early detection and interventions minimize this impact ?

Lopez, et al Pediatrics 2017 Nov; 140(5).

OBJECTIVES CMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- **DIAGNOSIS**
- **TREATMENT**
- **PREVENTION**



Pregnant or Persons Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative

0.1% to 1% recurrent CMV maternal infection

1% to 4% to 7% primary CMV maternal infection

CMV *in utero* fetus
congenital CMV newborn

40% CMV *in utero* fetus
congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn*

85%-90% of babies have minimal or no signs or symptoms in — utero or at birth

symptoms at birth rare
hearing loss can occur
disabilities ?

5% to 8% die
85% to 90% will have broad range disabilities

smaller size or GA
25% hearing loss
other disabilities?

DIAGNOSIS OF CCMV

- **Timing**
 - First 21-28 days of life
- **Specimen**
 - Saliva
 - Urine
 - Blood/Plasma or Dried Blood Spot
 - Tissue
- **Method**
 - Culture/Shell vial
 - PCR or other NAAT/LAMP

DIAGNOSIS OF CCMV AFTER BIRTH- GOING BACK IN TIME

- **NEWBORN DRIED BLOOD SPOT CMV DNA DETECTION**
 - NB DBS can be retrieved from state newborn screening labs with parental permission
 - Reference lab can test NB DBS samples for CMV DNA by PCR methods
 - If positive, confirms CCMV
 - If negative, does not exclude CCMV, as false negatives occur
 - Time limitations of storage vary

NEWBORN CCMV DIAGNOSIS

- Diagnostic Testing- **NOW**
 - Newborns with signs or symptoms of CCMV tested
 - **Many are still missed**
- Targeted Newborn Screening-**EVOLVING**
 - Normal newborns with failed/referred NBHS tested
- Universal Newborn Screening-**EVOLVING !**
 - **ALL** newborns screened/tested for CCMV

Targeted Newborn Screening for CCMV for Failed NBHS- USA

- Connecticut, Florida, Iowa, Kentucky, Louisiana, New York, Texas, Utah, and Virginia perform state based targeted testing
- Many birthing hospitals in many other states
- If you are expecting a baby soon, ask your pediatrician if your birthing hospital performs targeted testing for CCMV in newborns who fail/refer on their NBHS
- For a list of hospitals see
 - <https://www.nationalcmv.org/overview/newborn->

Targeted Newborn Screening and Education for CCMV

- Illinois, Iowa, Kentucky, Maine, New York Pennsylvania, Texas, and Utah require state based CCMV education AND targeted newborn screening
- Many birthing hospitals in many other states
- If you are expecting a baby soon, ask your pediatrician if your birthing hospital performs targeted testing for CCMV in newborns who fail/refer on their NBHS
- For a list of hospitals see www.nationalcmv.org

Targeted Newborn Screening for CCMV and Failed NBHS-Canada

- British Columbia and Manitoba
 - Province wide
- Birthing hospitals in other Provinces
- If you are expecting a baby soon, ask your pediatrician if your birthing hospital performs targeted testing for CCMV in newborns who fail/refer on their NBHS
- For a list of hospitals <https://www.cmvcanda.com>

UNIVERSAL NEWBORN SCREENING FOR CCMV- USA

- RUSP application submitted March 27, 2019 by National CMV RUSP Multidisciplinary Nomination Team
- Under review by the Advisory Committee on Heritable Disorders In Newborns and Children - ACHDNC
- To support this effort go to www.nationalcmv.org website

Universal Newborn Screening Strategies for CMV

- **Detection of CMV in urine**
 - Viral Culture, DNA by PCR, CMV Ag
 - Rapid POCT in newborn nursery
- **Detection of CMV in saliva**
 - Viral Culture, DNA by PCR, CMV Ag
 - Rapid POCT in newborn nursery
 - Breast milk feeds may produce a low false positive result
 - Confirm all saliva positives with urine CMV test
- **Detection of CMV in newborn screen DBS by DNA PCR**



Universal Newborn Screening for CCMV- USA

- Minnesota
 - First state to adopt routine newborn screening for cCMV January 2023
 - Will use NB DBS
- Connecticut
 - Passed Universal CMV screening newborn law June 2023
 - Method under committee
- New York
 - Passed Universal screening newborn law Aug 2023
 - Urine CMV PCR test

Universal Newborn Screening for CCMV

- **Canada**
 - **Ontario**
 - **Saskatchewan**
 - **Manitoba- pending soon?**

National Case Definition for CCMV

- Council of State and Territorial Epidemiologists
 - Standardized Surveillance Case Definition for CCMV infection and Disease Position Statement
 - will go into effect Jan 2024
 - Lays groundwork for defining and reporting a case of CCMV at state level
 - CCMV may be made a reportable condition in some states
 - Will support other position statements
 - Allows baseline and trends of CCMV pre and post vaccine

OBJECTIVES CMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- **TREATMENT**
- **PREVENTION**

Pregnant or Persons of Childbearing Age



55% to 85% CMV seropositive

15% to 45% CMV seronegative

0.1% to 1% recurrent CMV maternal infection

1% to 4% primary CMV maternal infection

CMV *in utero* fetus congenital CMV newborn

40% CMV *in utero* fetus congenital CMV newborn

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

Hearing loss
Disabilities ?



10% to 15% have hearing loss
other disabilities ?

CCMV 101-ANTIVIRAL TREATMENT PROVIDES BENEFIT

- 1991-1999 Phase III randomized trial IV ganciclovir 6 mg/kg/dose every 12 hours for 6 week for CCMV w/ CNS involvement
- 2008-2011 Phase III randomized clinical trial oral valganciclovir 16 mg/kg/dose every 12 hours for 6 weeks vs 6 months

- Kimberlin et al J Ped 2003, Kimberlin et al J Clin Virol 2010

AAP Committee on Infectious Diseases and International Consensus Recommendations

- Neonates with symptomatic congenital CMV, with or without CNS involvement, should receive oral valganciclovir solution at 16 mg/kg /dose every 12 hours for 6 months or IV ganciclovir if they are unable to tolerate oral medications or feedings
- Start treatment within first month of life
- Monitor CBC diff plat, hepatic function, renal function
- Adjust valganciclovir dosing with weight gain
- Outpatient management feasible and affordable

Red Book 2021-2024 Report of COID 32st edition; Rawlinson W et al. Lancet Infect Dis 2017; 17(6): e177-188; Luck S, et al. Pediatr Infect Dis J 2017 Dec; 36(12): 1205-1213.

Symptomatic CCMV-Other interventions are also very helpful

- **Hearing aids, cochlear implants**
- **Speech language therapy**
- **Educational accommodations**
- **Physiotherapy, mobility aids, orthotics, orthopedics**
- **Seizure treatments**
- **Vision aids and therapies, strabismus surgery**
- **Nutritional interventions, diet and feeding therapies, G tube feedings, for growth disorders**

CCMV 101- Antiviral treatment – unanswered questions

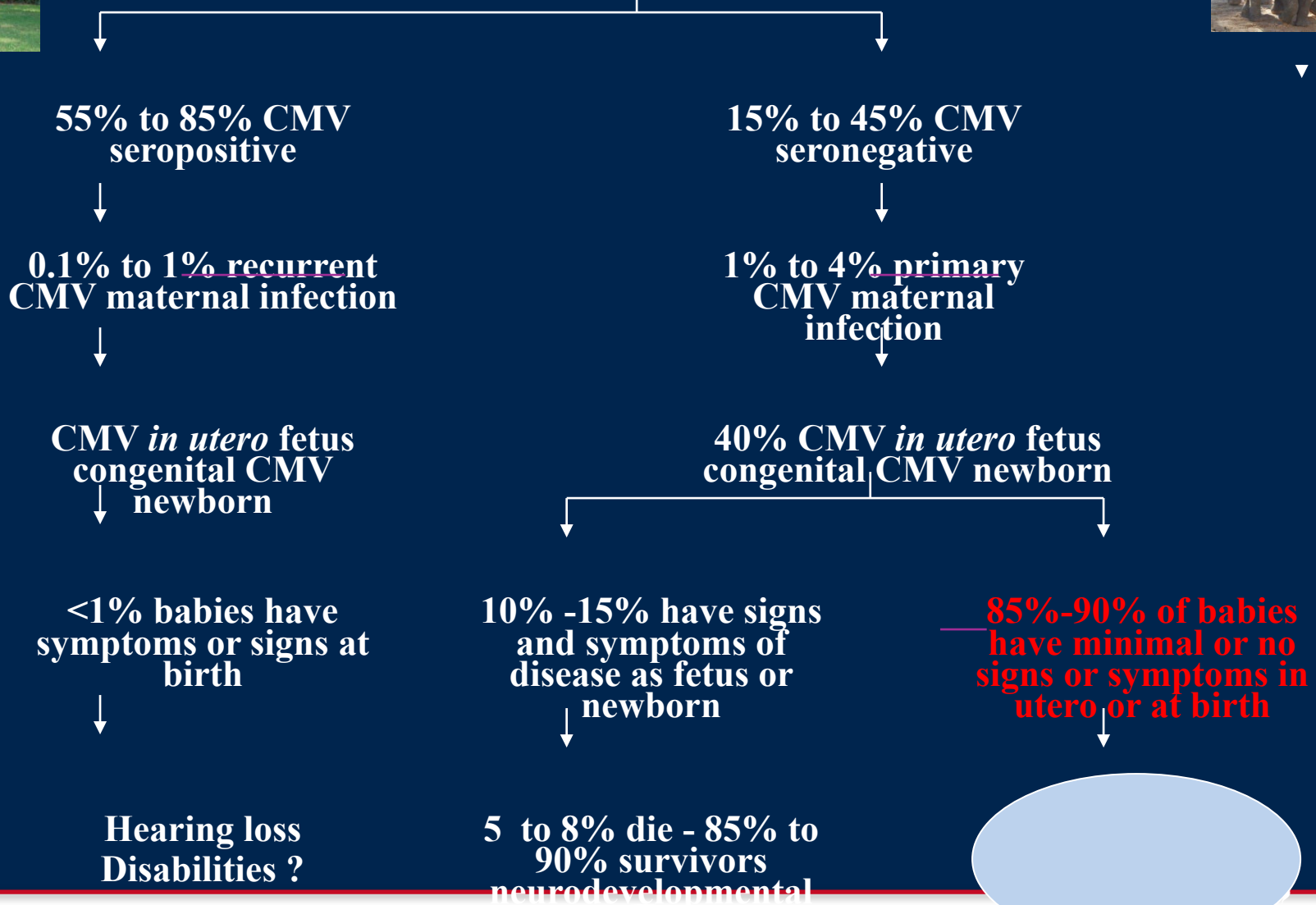
- Follow up in randomized clinical trials has been only for 6 months to 2 – 3 years
- Apparent short term benefits of antiviral therapy may not last long term
 - Hearing loss may start to progress and may continue to progress once antivirals are stopped
- Do we need to treat longer than 6 weeks to 6 months for long term benefits?
- Larger multicenter study underway to study longer outcomes
 - Lanzieri, et al. J Ped Infect Dis Soc, 2022

CCMV 101- Antiviral treatment – unanswered questions

- Will use of two antivirals be beneficial?
 - Expedite CMV viremia and symptoms resolution?
 - Improve outcomes?
- Letermovir + valganciclovir for CCMV Phase I study may begin soon
 - Both antivirals are orally administered
 - Safety data and PK data need to be collected first
 - www.clinicaltrials.gov



Pregnant or Person of Childbearing Age



CCMV Treatment – Unanswered questions

- Asymptomatic CCMV newborns with congenital hearing loss – will antiviral treatment prevent progressive hearing loss in both the affected and unaffected ear?
- Asymptomatic CCMV newborns with normal hearing – will antiviral treatment prevent later onset hearing loss?
- Biomarkers study underway to try and predict who is at greatest risk for progressive or later onset hearing loss

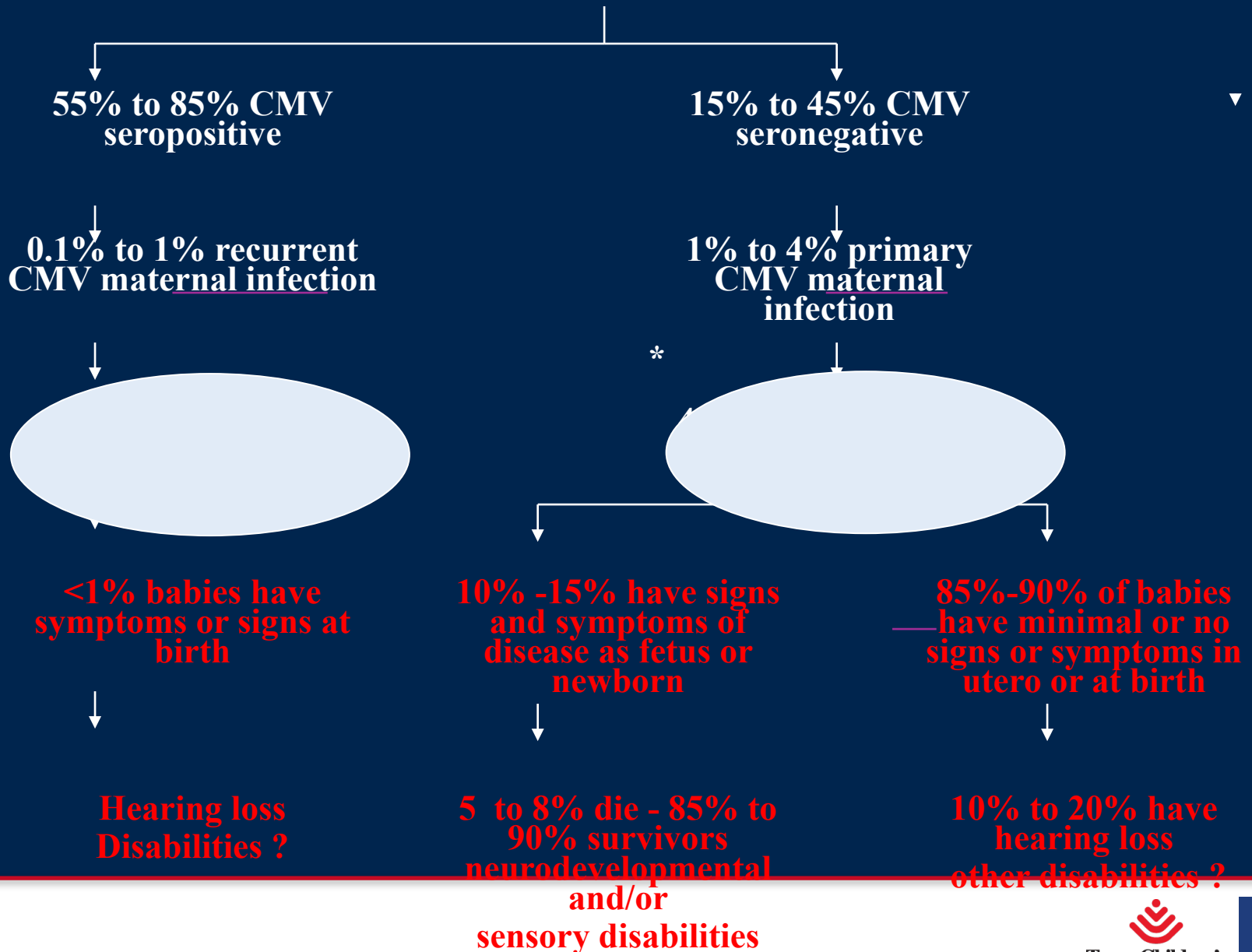
CCMV Treatment – Unanswered questions

- Currently, antiviral treatment is not routinely recommended for asymptomatic CCMV, by most experts, because the safety and efficacy has not been determined in clinical trials specifically designed for normal newborns.
- Some exceptions may be considered and warranted
 - Very high CMV viremia levels
 - Immune compromised at birth

Asymptomatic CCMV-Management

- Anticipatory guidance – at risk for progressive and later onset SNHL
- Regular hearing evaluations
 - Every 6 months for 3 years, then annually, or as needed if clinical change or suspicion of hearing loss progression
 - Hearing aids or cochlear implants, as indicated
- Speech/language therapy
- Educational accommodations if needed
- Sign language - education/awareness/inclusion

Pregnant or Person of Childbearing Age



Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

- Maternal Serology – NOT ROUTINE BUT IS AVAILABLE
- CMV IgG positive – CMV infection at some time
- Seroconversion (IgG negative to IgG positive)- primary infection
- CMV IgM positive
 - May mean recent primary infection, or recurrent infection, or false positive, or prolonged positive IgM serostatus
- CMV IgG avidity index
 - Low indicates recent infection < 4 months ago
 - High indicates CMV infection > 4 -6 months ago

Revello et al J Clin Virol 2011; Lazzarotto et al Clin Microbiol 2011; Yinon J Obstet Gynaecol Can 2010

Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

- ACOG- Not Recommended
- SOGC- In provinces where CMV IgG avidity testing is available, screening for CMV primary infection in the first trimester (using IgG and IgM antibodies followed by IgG avidity testing if the patient is IgM-positive) can be offered, especially in women at high risk (those who have a child under 3 years at home). CMV screening in pregnancy is not recommended in provinces where CMV IgG avidity testing is unavailable
- International CMV Consensus Reports- Not Recommended

Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

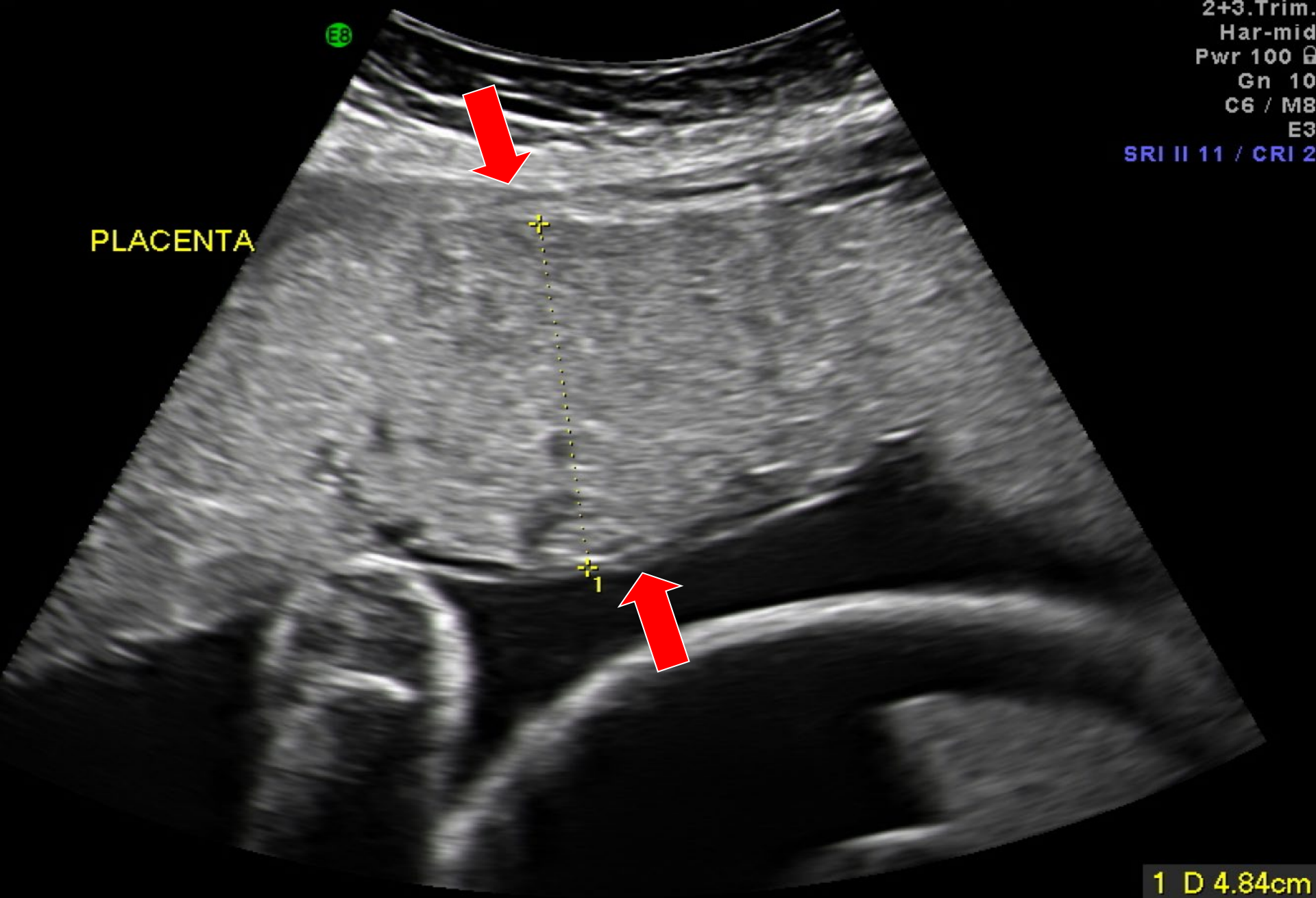
- **Second Trimester- Fetal Ultrasound- ROUTINE**
 - **Echogenic bowel, IUGR, hydrops, brain abnormalities may be first indication of CMV infection *in utero***
 - **Warrants CMV testing in mother and possibly fetus**

Goetzinger et al Obstet Gynecol 2011

Case

Cytomegalovirus Infection of a Fetus

- 24 y.o G2P1Ab0
- Ultrasound 20 weeks screening fetal anatomy scan and repeat 24 weeks gestation- thickened placenta, cerebral echogenic foci, fetal ascites, hepatosplenomegaly
- Maternal studies: CMV IgG +, CMV IgM +, CMV avidity high - Recent primary infection? Or not?
- Amniocentesis: + PCR/culture for CMV; viral load $> 1 \times 10^6$ copies/ml

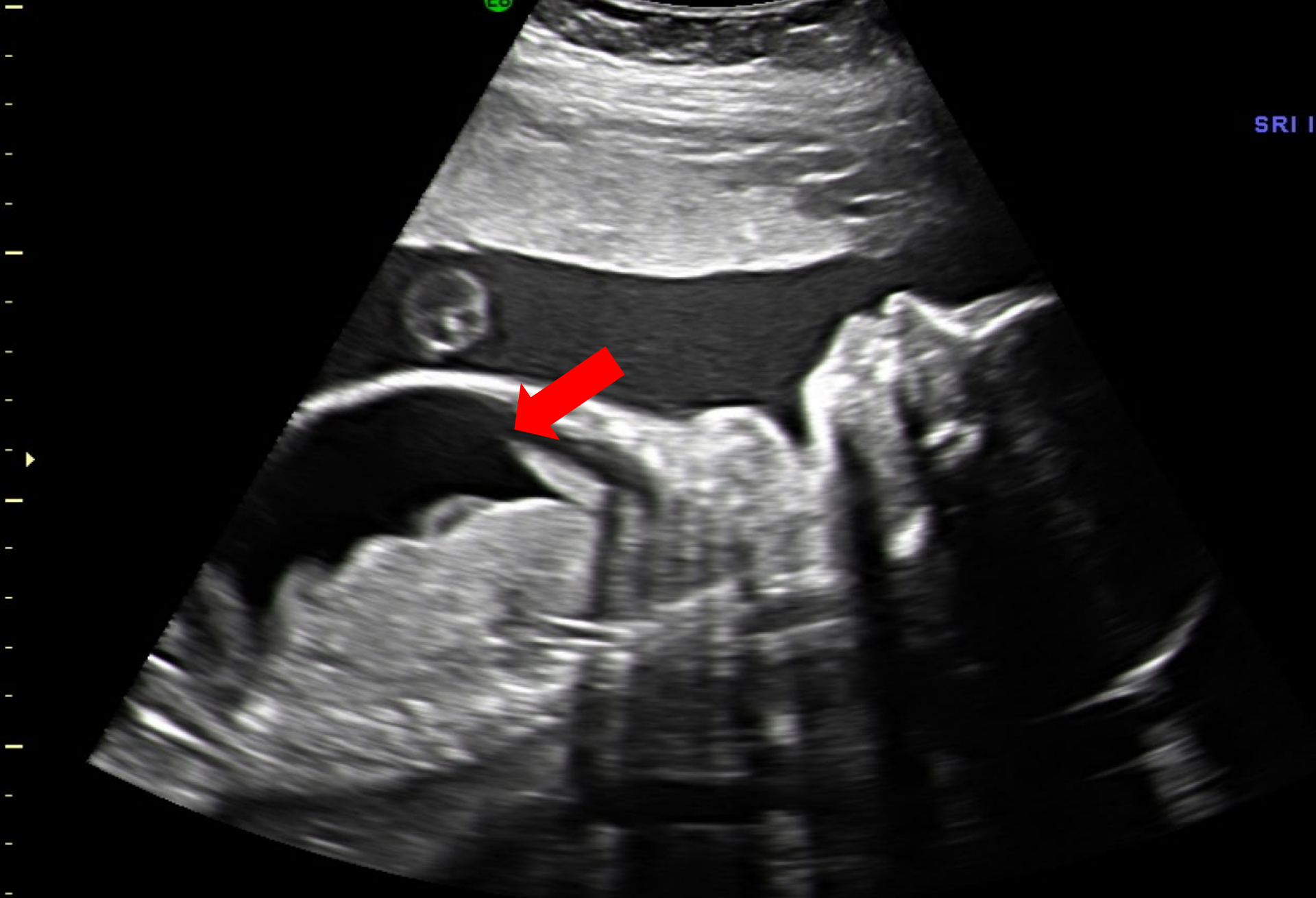


E8

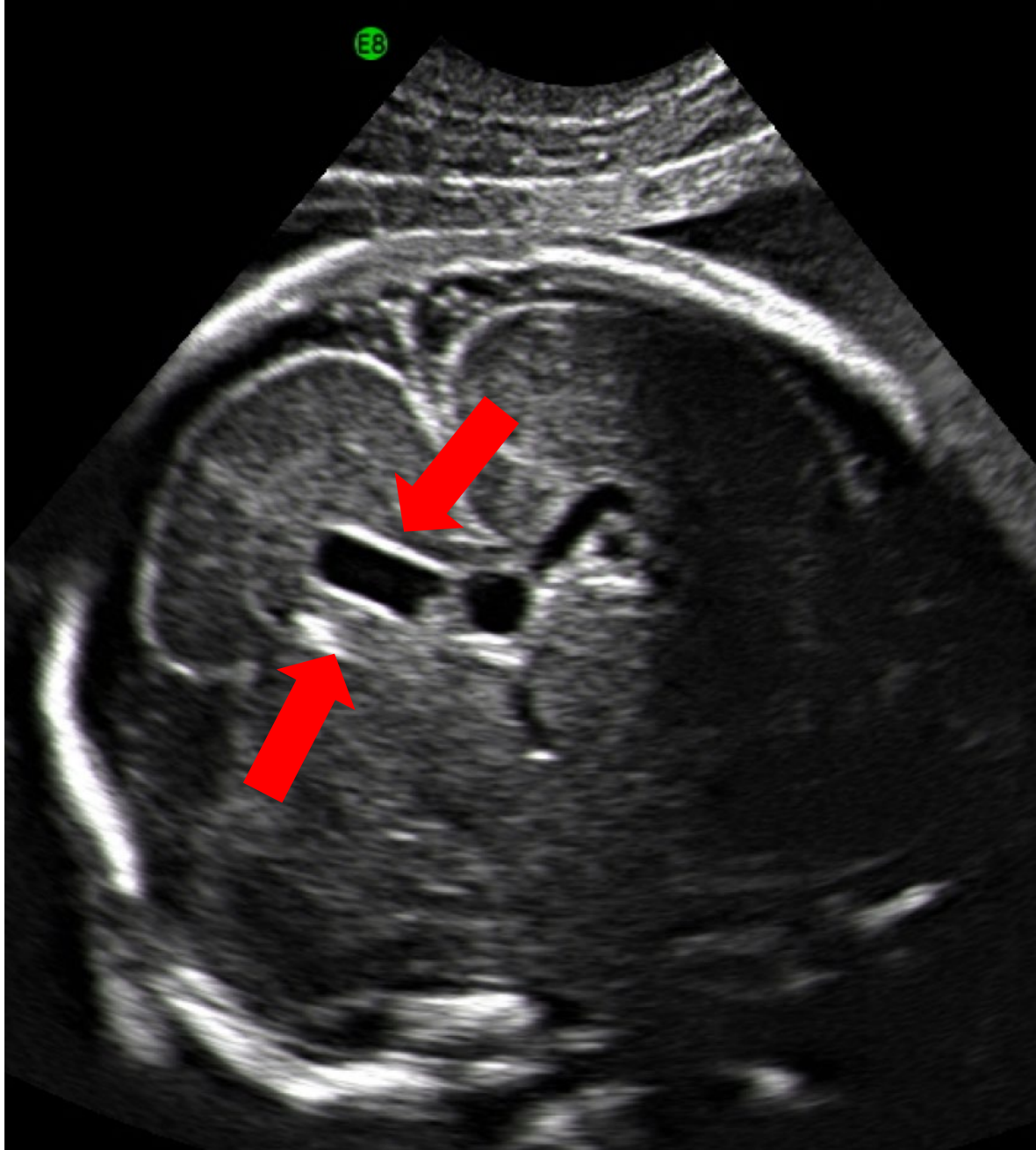
PLACENTA

2+3.Trim.
Har-mid
Pwr 100 B
Gn 10
C6 / M8
E3
SRI II 11 / CRI 2

1 D 4.84cm



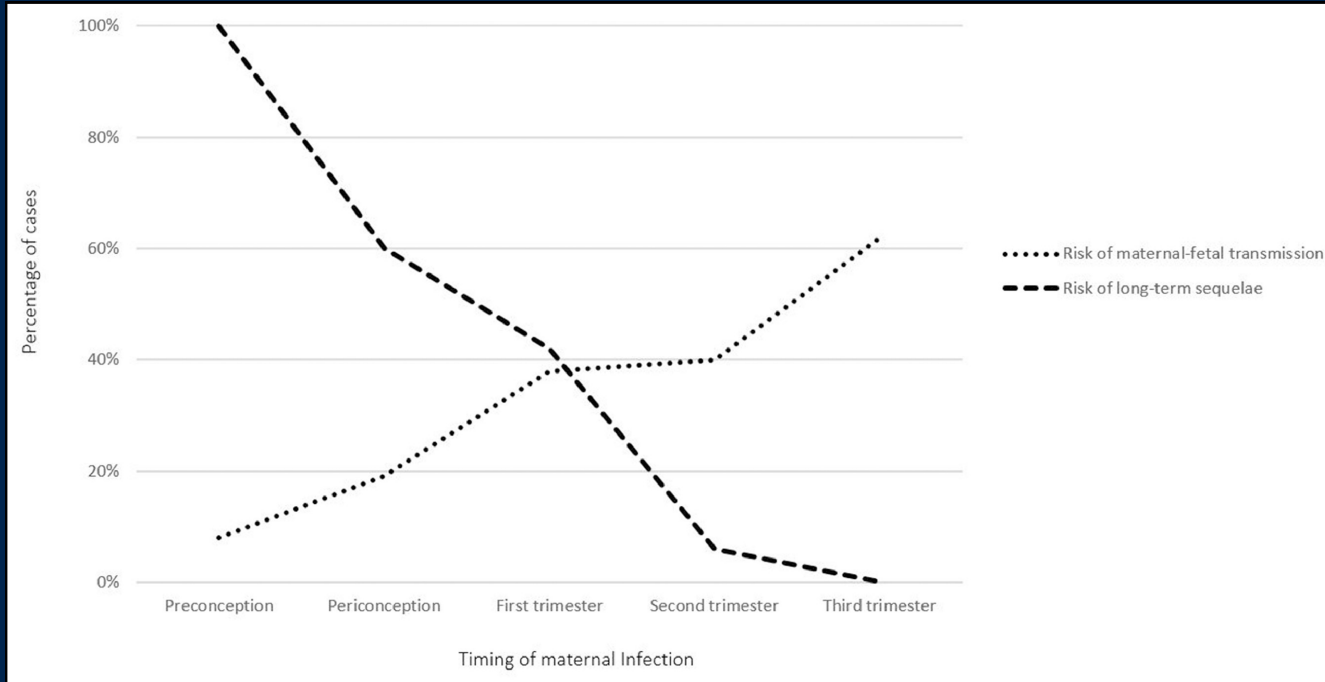
SRI I



Risk of fetal infection and risk of long term infant sequelae in relation to gestation age

SOGC Clinical Practice Guideline NO. 420 2021

Figure 2



Prenatal Treatment for In UTERO CCMV

- **CMV Hyperimmune Globulin Treatment**
 - Four prospective observational studies were promising and showed reduction in maternal fetal transmission and severity of CCMV disease in baby
 - RCTs did not demonstrate a significant benefit
 - Remains investigational and research
 - It is not standard treatment at this time
 - Not recommended by ACOG, SOGC, or International Consensus Guidelines at this time
 - Not being done anymore in most practices.

Prenatal Treatment for IN UTERO CCMV

- **Valacyclovir high dose treatment**
 - Randomized, double blind placebo controlled study of pregnant women with serologic evidence of primary CMV infection in early pregnancy
 - 8 grams daily valacyclovir vs placebo
 - Reduced rate of fetal CMV infection by 71%
 - 29.8% PLACEBO VS 11.1% VALACYCLOVIR
 - (P= 0.027; OR 0.29; 95% ci 0.09-0.9)

Shahar-Nissan et al Lancet, 2020.

Prenatal Treatment for IN UTERO CCMV

- **Valacyclovir high dose treatment**
 - Appears safe; used for HSV in pregnancy
 - Rare reports of acute, reversible renal failure
 - Considered research at this time
 - Not recommended routinely by ACOG, SOGC, International Consensus Guidelines at this time
 - Being used clinically in many centers/practices

Shahar-Nissan et al Lancet, 2020; Guideline 420 CMV in Pregnancy, JOGC 2021; Zammarchi, et al Clin Microbiol Infect 2020.

Prenatal Treatment for IN UTERO CCMV

- **Valacyclovir high dose treatment**
 - “In the case of documented primary CMV infection in the first trimester, early treatment with valacyclovir can be considered” SOGC
 - “For established congenital CMV infections during pregnancy, decisions concerning treatment options should be made in a shared process involving patients and experienced teams” SOGC

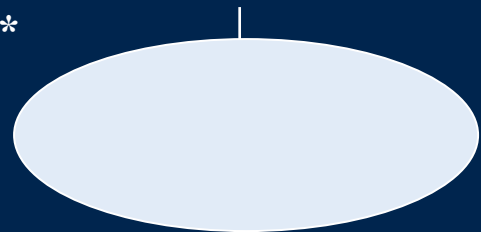
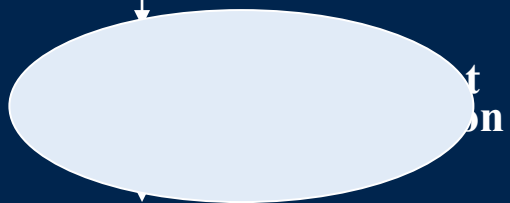
Shahar-Nissan et al Lancet, 2020; Guideline 420 CMV in Pregnancy, JOGC 2021; Zammarchi, et al Clin Microbiol Infect 2020; Leuruez-Ville, et al Am J Obstet Gynecol 2016; Faure-Bardon, et al Ultrasound Obstet Gynecol 2021.



Pregnant or Persons of Childbearing Age

55% to 85% CMV seropositive

15% to 45% CMV seronegative



**CMV in utero fetus
congenital CMV newborn**

**40% CMV in utero fetus
congenital CMV newborn**

<1% babies have symptoms or signs at birth

10% -15% have signs and symptoms of disease as fetus or newborn

85%-90% of babies have minimal or no signs or symptoms in utero or at birth

**Hearing loss
Disabilities ?**

5 to 8% die - 85% to 90% survivors neurodevelopmental

**10% to 15% have hearing loss
other disabilities ?**

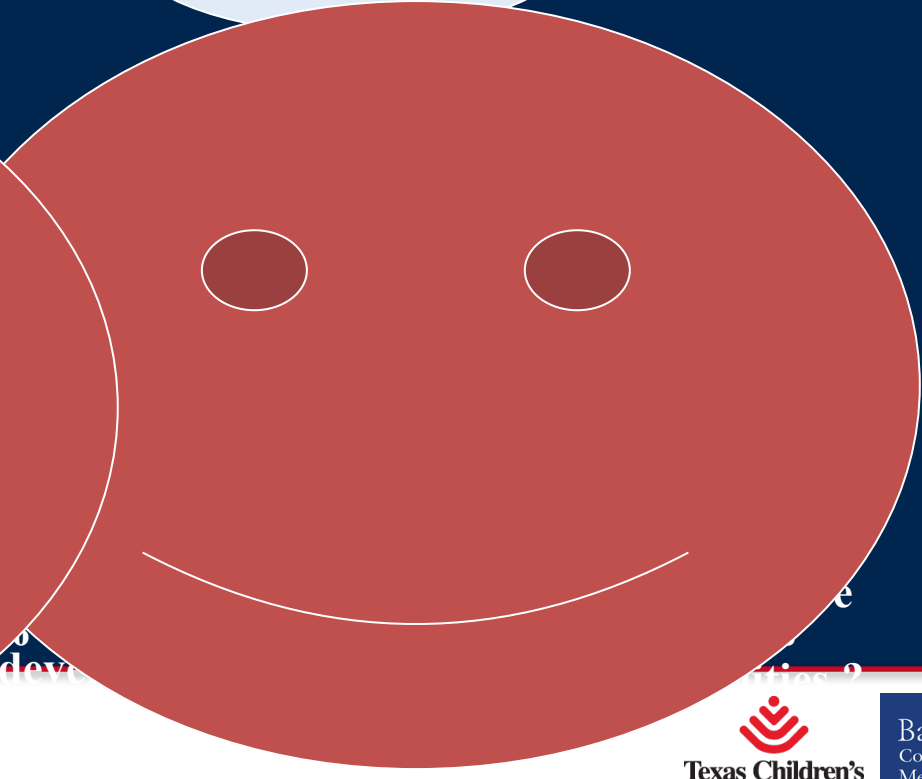
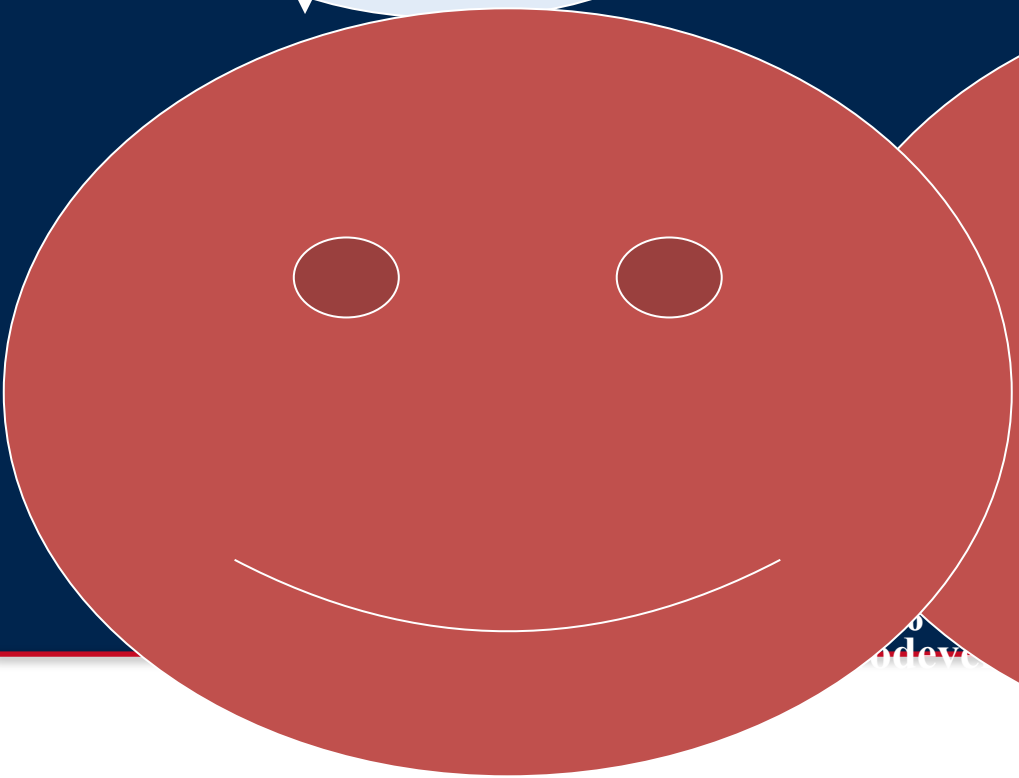
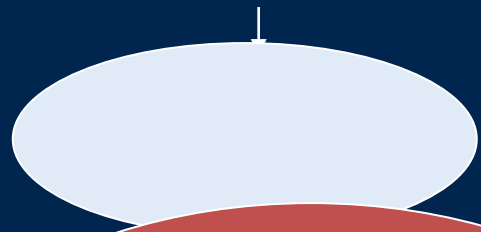
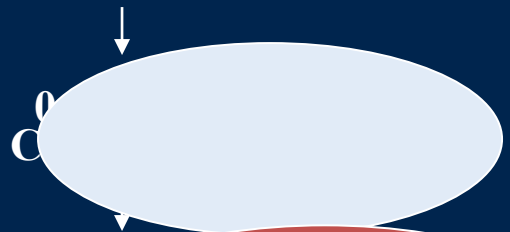


Pregnant or Persons of Childbearing Age



55% to 85% CMV seropositive

15% to 45% CMV seronegative



OBJECTIVES CMV 101- COVER THE BASICS

- BIOLOGY
- EPIDEMIOLOGY
- CLINICAL MANIFESTATIONS
- DIAGNOSIS
- TREATMENT
- **PREVENTION**

CCMV Prevention

- **CMV vaccine to prevent maternal CMV infection and CCMV in her baby**
 - CMV vaccine research ongoing since 1970s, many candidates are being evaluated, none so far successful
 - CMV Vaccine a priority for 21st Century in USA by Institute of Medicine*
 - Many CMV vaccine candidates under evaluation, active R&D pipeline, currently early clinical trials with results
 - Phase III clinical trial underway w/ mRNA platform**
 - **NO licensed CMV vaccine available yet**

* IOM Committee to Study Priorities for Vaccine Development for 21st Century Nat Academics Press 2000; ** www.clinicaltrials.gov, www.cmvictory.com

Can we prevent maternal CMV through other ways ?

- CMV is transmitted through close contact with others who have CMV infected body fluids
- Toddlers are “HOT ZONES” for CMV
- Annual seroconversion rates 15% day care workers and 50% in households with toddlers shedding CMV in saliva/urine
- Reduce risk by reducing contact with CMV infected secretions



“CMV Knowledge Vaccine” “Information Vaccination”

- An Ounce of CMV Awareness
- Three Simple Precautions –
 - Do not kiss young children on or near mouth
 - Do not share food or drink or pacifiers or toothbrushes with young children
 - Wash hands after all diaper changes and after wiping runny noses/drooling

Not recommended now routinely by obstetricians and by ACOG – “too burdensome” “unproven”-? reconsidering

Recommended by CMV experts, International Consensus Guidelines, AAP, SOGC, supported by clinical trials

Adler et al J Pediatr 2004; Cannon Br Med J 2005; Harvey et al 2008; Revello et al J Clin Virol 2011; Vauloup-Fellous et al J Clin Virol 2009, Rawlinson et al Lancet ID, 2017; SOGC Guideline 420 JOGC CMV Pregnancy, 2021; ACOG Practice Bulletin 151 CMV etc Pregnancy, 2015.



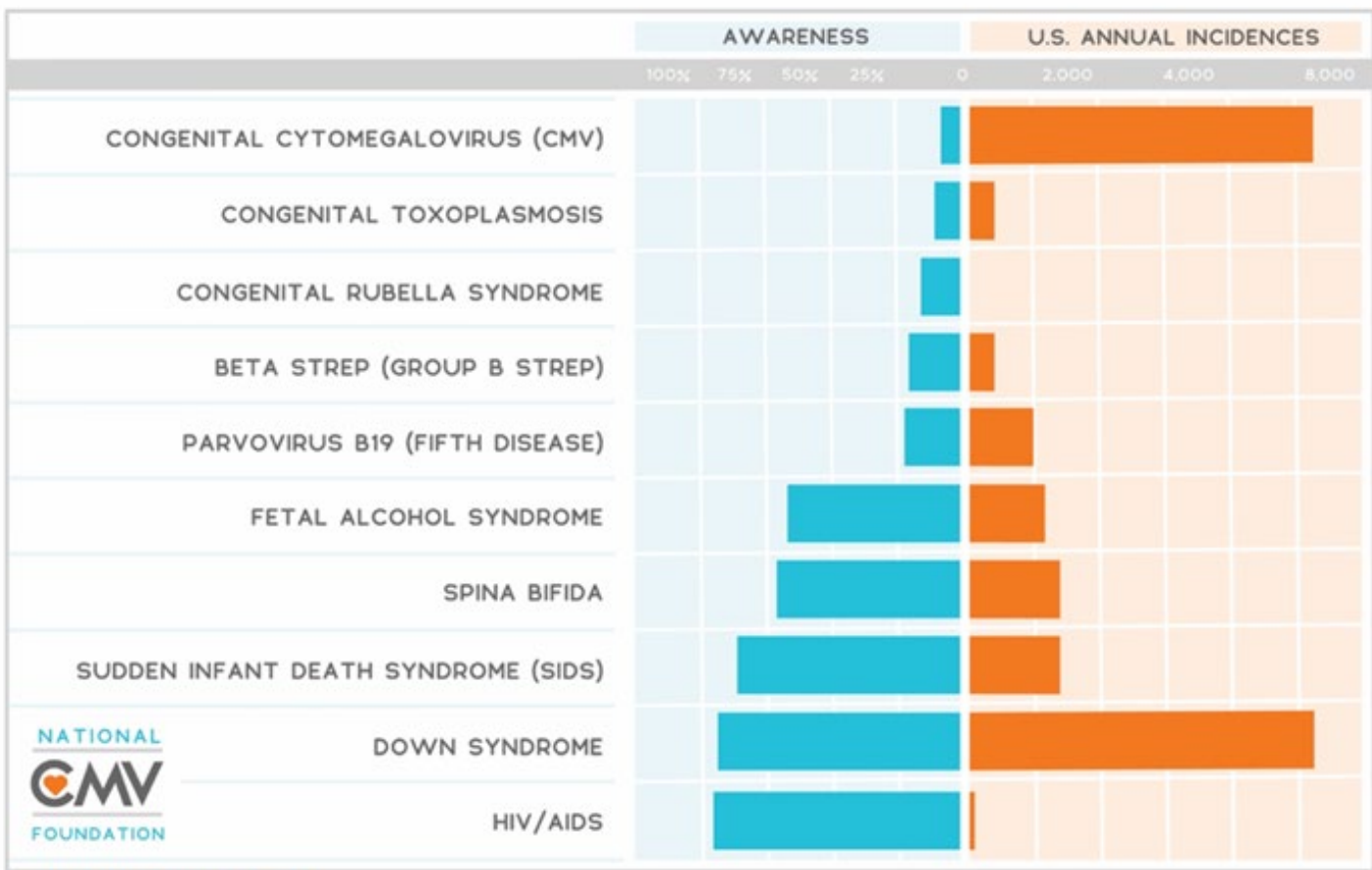
Who should know?

- Pregnant persons with contact with young children
 - Toddlers/ pre schoolers in household or extended family or babysitters or caretakers
 - Day care center workers
 - Should CMV information be required for licensure?
 - Pre school teachers
 - Speech/language therapists
 - Health care workers- routine universal precautions sufficient to prevent transmission in hospital- but there may be special circumstances



WE DO NOT PASS INSPECTION FOR CMV AWARENESS

WWW.NATIONALCMV.ORG



WWW.NATIONALCMV.ORG

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.*

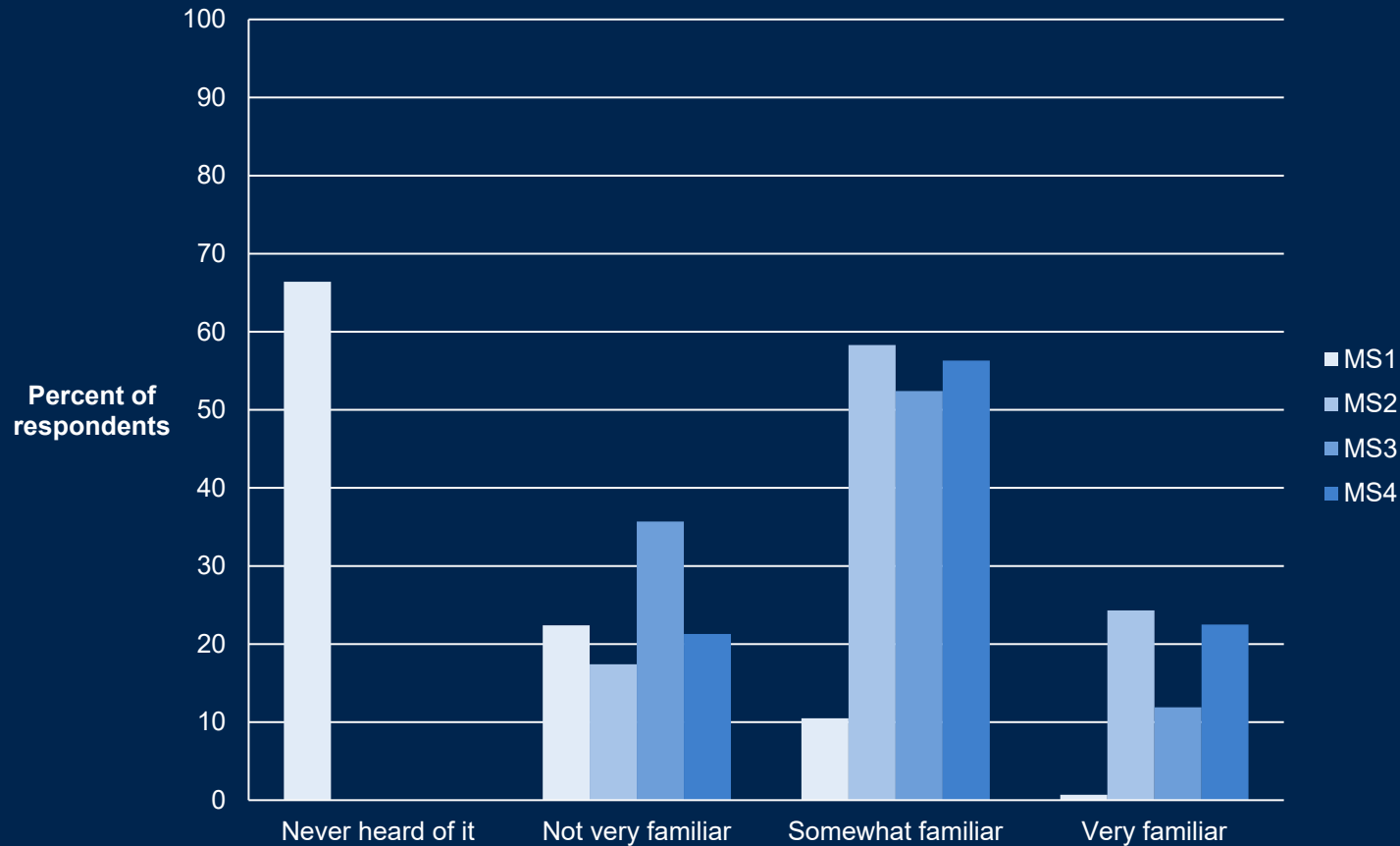
Survey of Congenital Cytomegalovirus (cCMV) Knowledge Among BCM Medical Student, Houston Texas

Most “young doctors to be” have never even heard of CMV !

More awareness amongst medical teams needed!

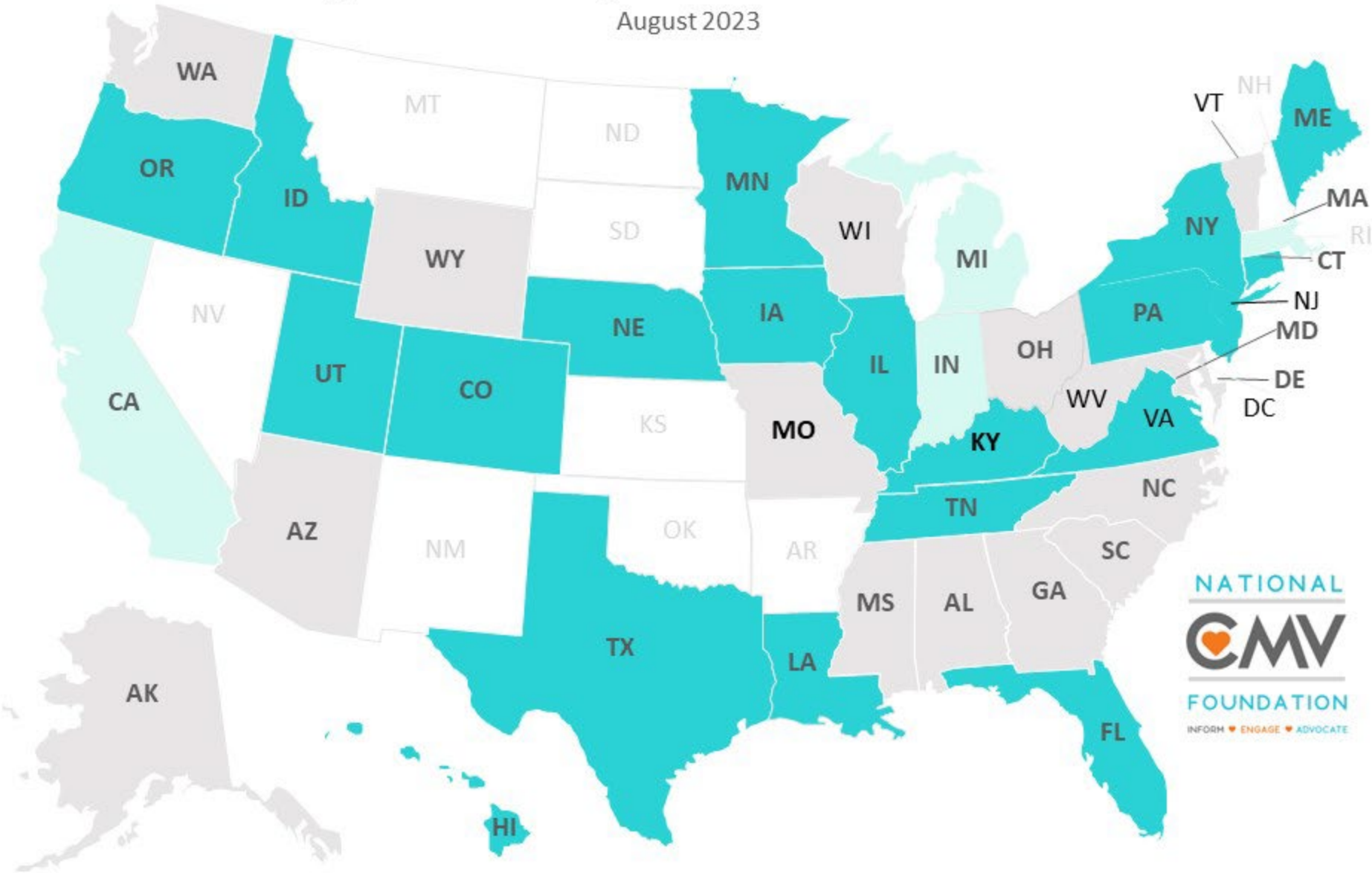
Baer HR, Corwin HE, Caviness AC, Demmler-Harrison GJ, J Clin Virol 2014

Self-Reported Familiarity With Congenital CMV



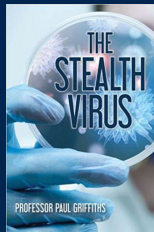
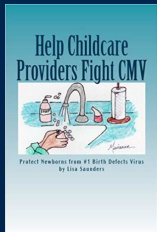
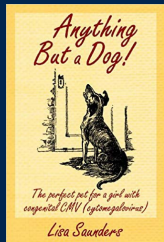
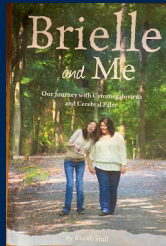
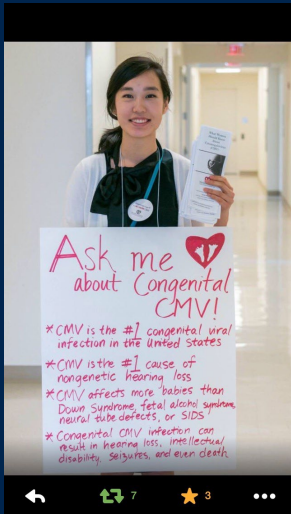
Congenital CMV Legislation in the United States

August 2023



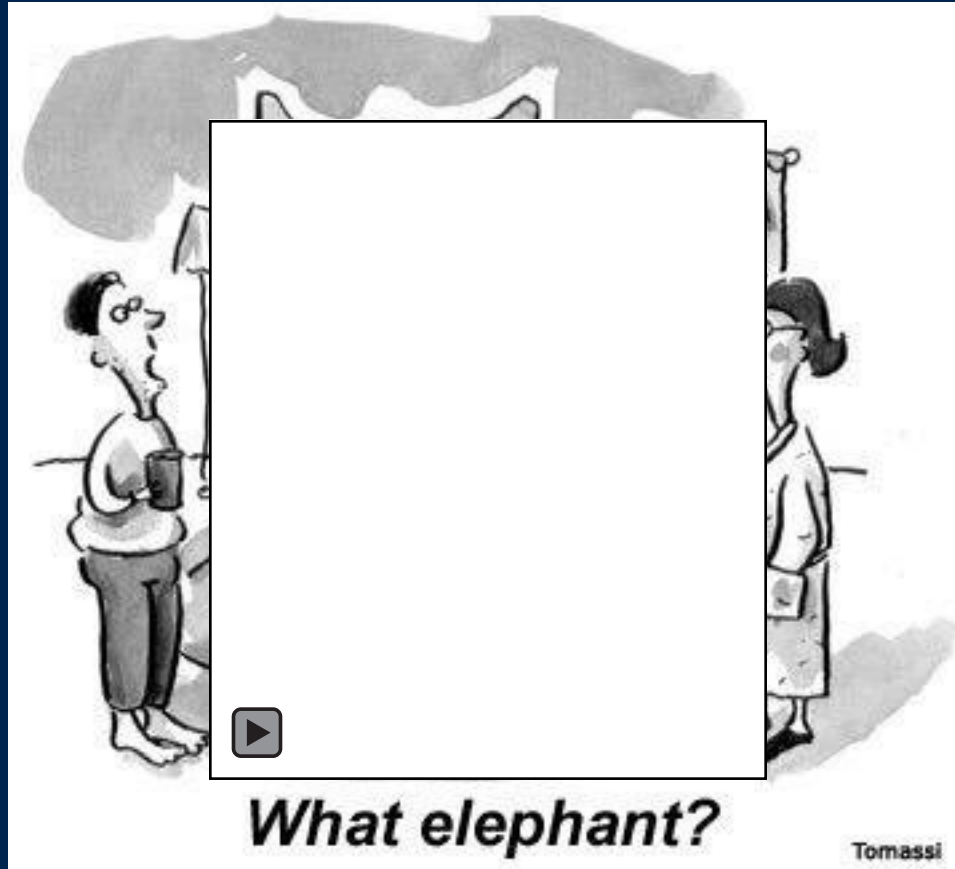
Other Law Enacted Screening or Education Law Enacted Law Proposed Stakeholder Interest in Legislation

CMV Advocacy



CMV ADVOCACY GROUPS

- Anti Cito (Italy)
- Chanter Marcher Vivre (France)
- Congenital CMV Association (Australia)
- CMV Action (UK)
- National CMV Foundation (USA)
- Idaho CMV Advocacy Project (USA)
- Utah CMV Council (USA)
- Congenital CMV News (USA)
- CMV Canada (Canada)
- Many Others!!



Congenital CMV challenge..... to take the next steps forward !



“If we stumble, it will not be because we lack for technology, vision or motivation.

It will be because we cannot set a direction and march collectively into the future.”

History of the Future 2004

Maternal CMV Screening in Pregnancy

CMV Knowledge Vaccine - Information Vaccination

Newborn cCMV Screening for Early Diagnosis

Antiviral Treatments for cCMV

CMV Vaccine



**“Good Bye”
It’s time to say “good-bye” to the
elephant in our living room !**

Thank you!





The End