



CCMV 101

Congenital Cytomegalovirus Infection

The Basics



**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

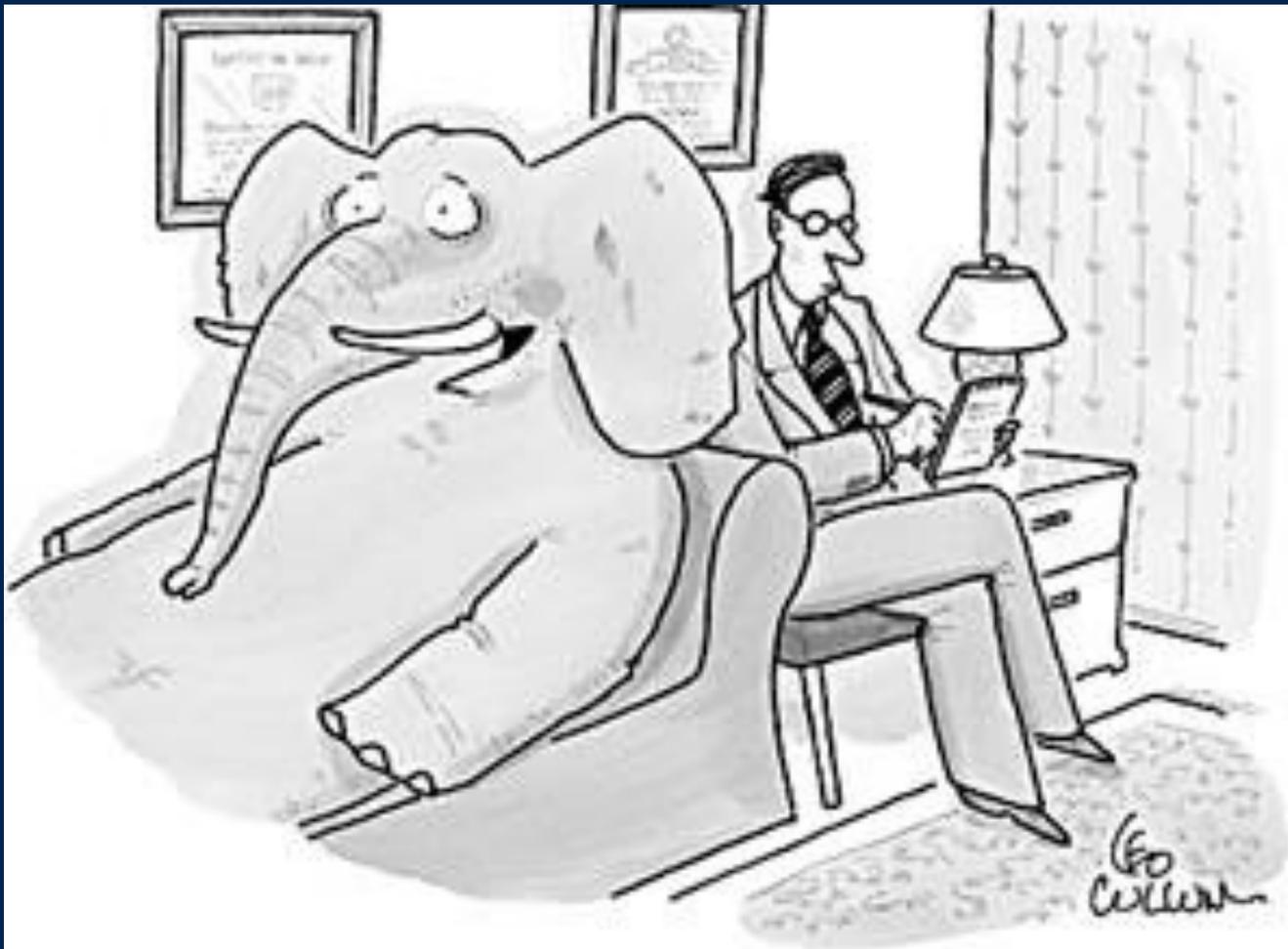
- I will discuss off label use of ganciclovir, valganciclovir, valacyclovir, and CMV hyperimmune globulin, with findings supported by clinical trials, expert opinion, consensus panels, and guidance from AAP
- I have received research support from NIH, CDC, Merck & Co, and other private donation sources, and data from this support will be discussed

OBJECTIVES CCMV 101- COVER THE BASICS

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

WHO IS CMV?

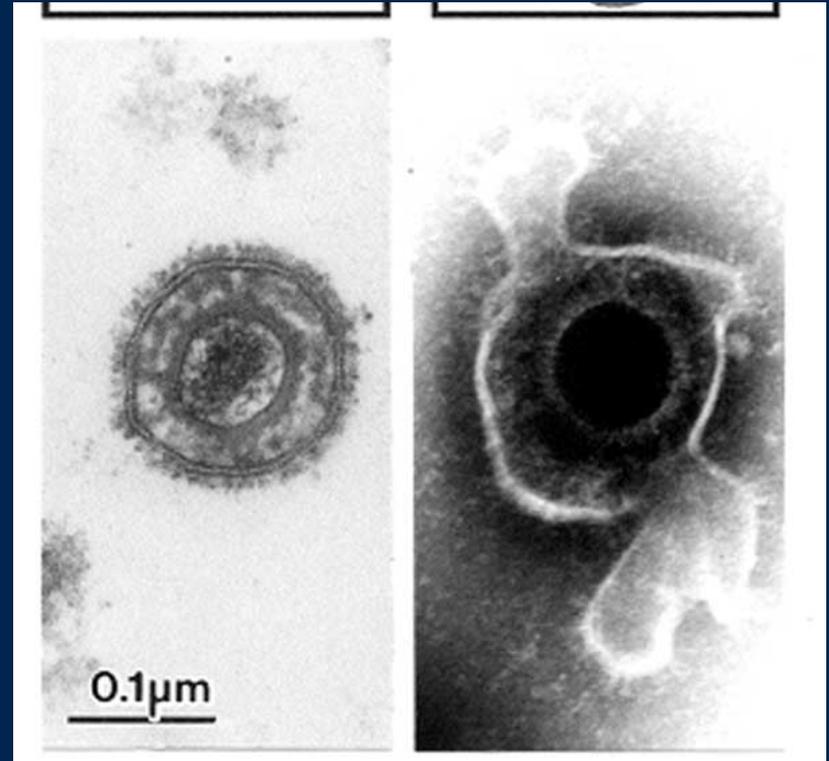
- CMV = CYTOMEGALOVIRUS
- AKA
 - Cyto= cell megal= big virus= L. poison
 - “A ubiquitous virus with protean manifestations”
 - An “opportunistic virus”
 - A “stealth virus”
 - “The most common virus most people have never heard of”
 - “The elephant in our living room”



"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

- 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
 - A variety of human cells in our body

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
 - IN UTERO / CONGENITAL
 - POSTNATAL
 - TODDLER
 - ADOLESCENCE
 - ADULTHOOD

THE FETUS AND NEWBORN WITH CMV

Approximately 4 Million Births

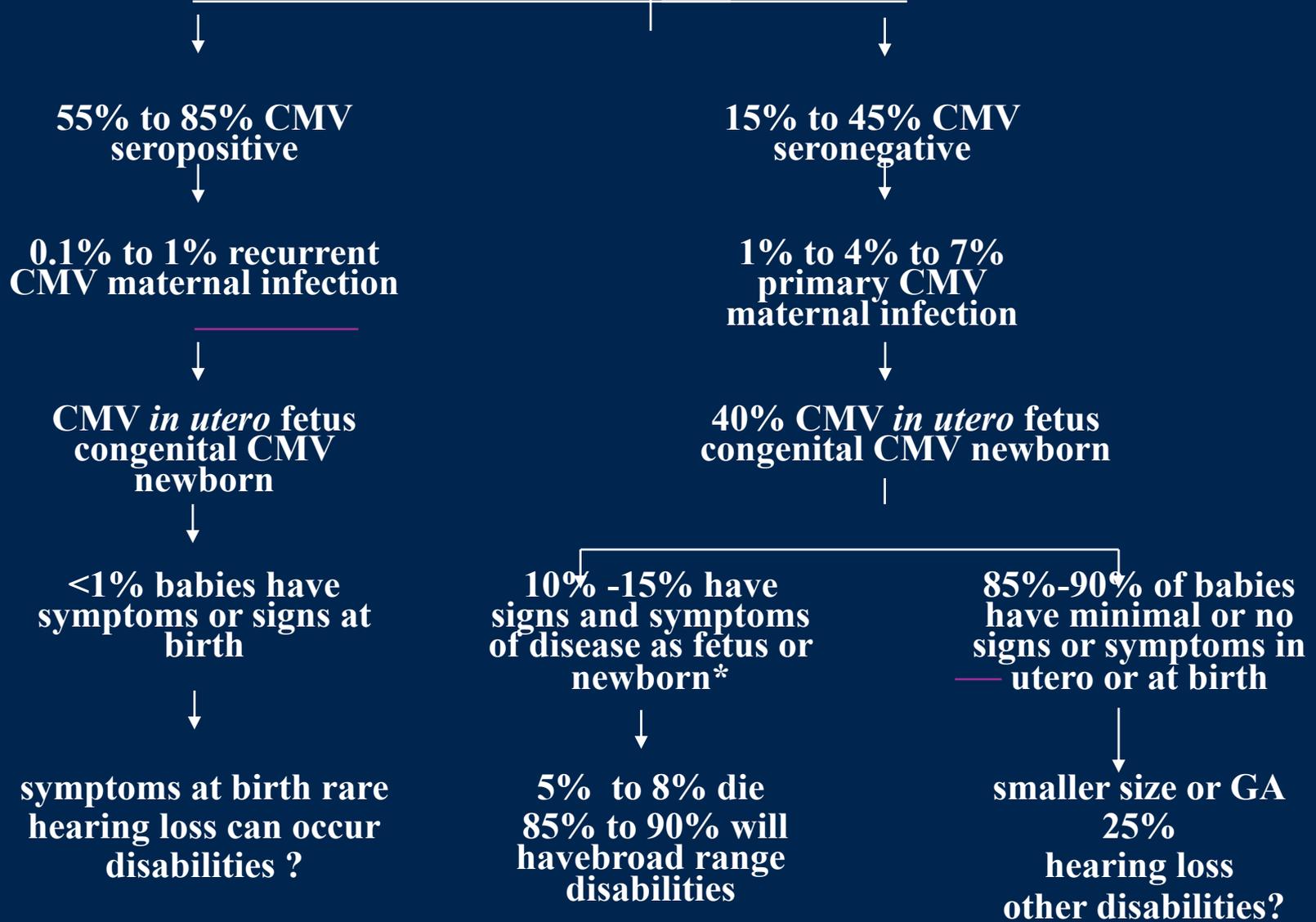
Annually in the U.S.A.

40,000 Congenitally Infected Infants Each Year

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

34,000 Asymptomatic or mildly symptomatic at birth; 25% hearing loss and 1-2% vision loss

Pregnant Women In the United States



OBJECTIVES CCMV 101- COVER THE BASICS

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

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
- Neurologic signs
- Seizures
- Infantile spasms
- Hemiparesis
- Abnormal tone
 - Hypertonia
 - Hypotonia

SYMPTOMATIC CCMV W/ CNS INVOLVEMENT- BRAIN IMAGING

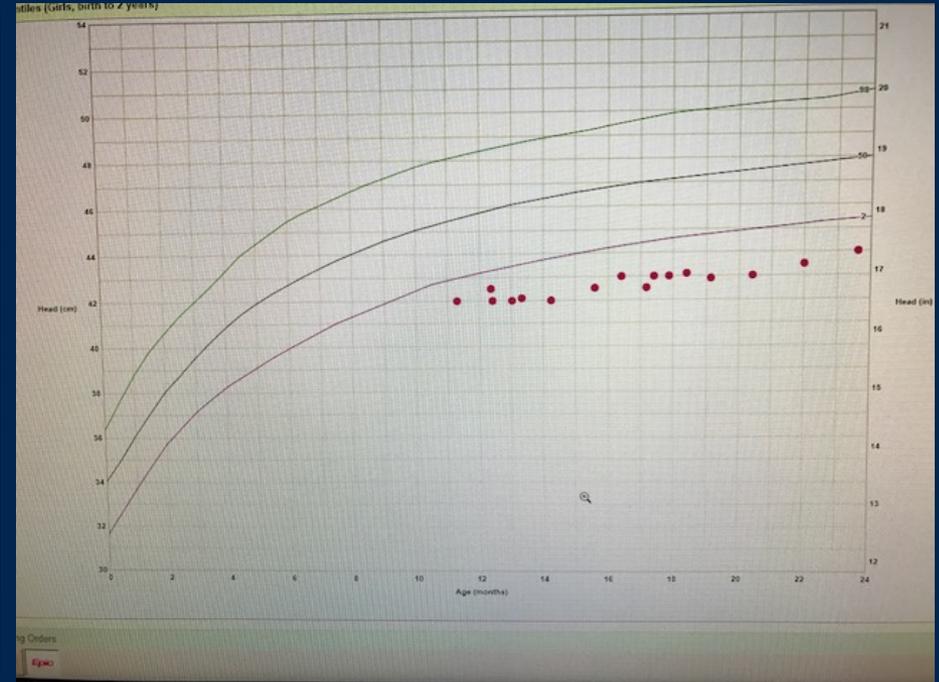
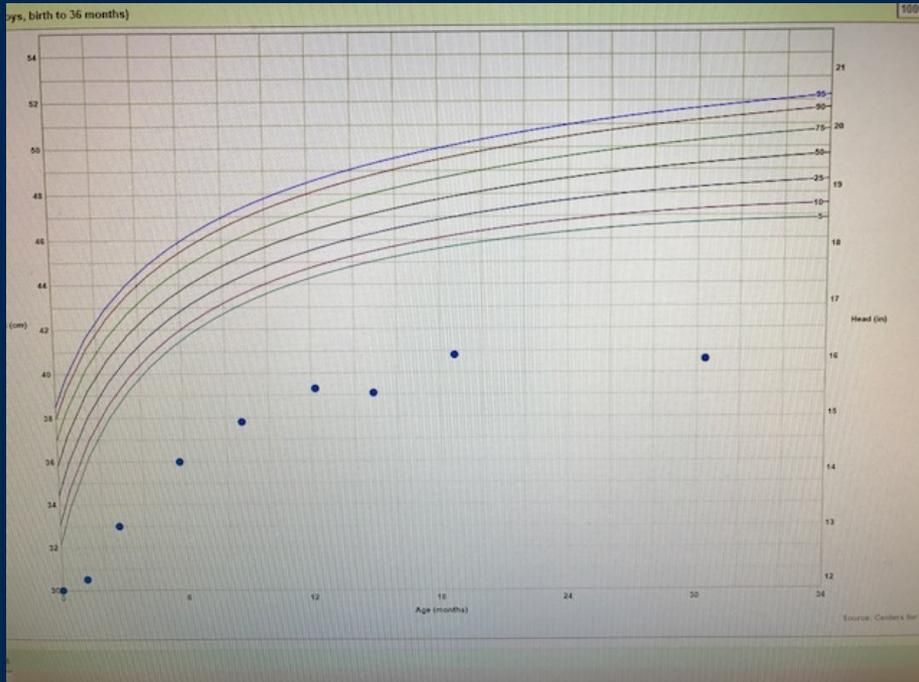
- Enlarged ventricles
- Calcifications of brain – usually periventricular
- Periventricular white matter lucencies
- Cortical maldevelopment of brain
 - Polymicrogyria
 - Fetal brain disruption sequence
- Lenticulostriate vasculopathy
- Cysts

PRIMARY NEUROPHENOTYPE CCMV

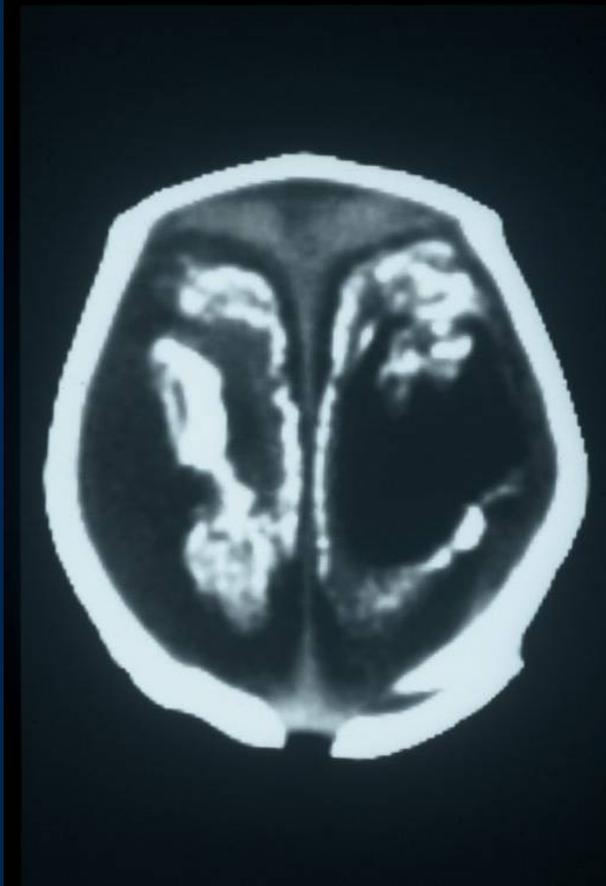
Emerging recognition that CCMV can present with only microcephaly or neurologic findings on exam, or neuro-imaging abnormalities

- 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

HEAD CIRCUMFERENCE PLOTS SHOWING MICROCEPHALY



SCCMV with CNS involvement- severe- fetal brain disruption sequence



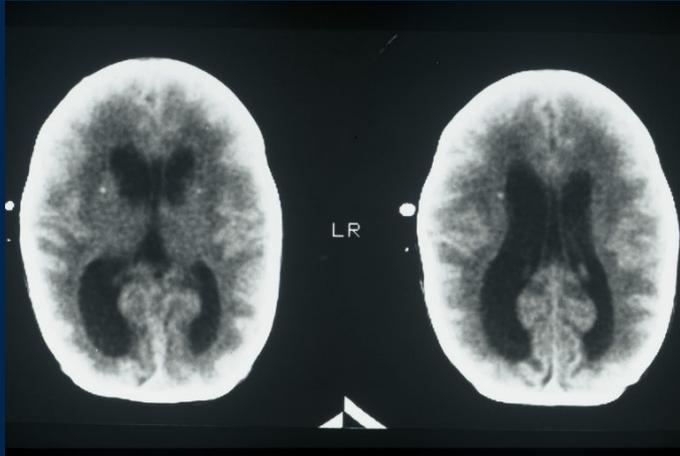
- Severe microcephaly with collapsed skull
- Severe brain malformation with periventricular Ca⁺

Classic congenital CMV with CNS involvement

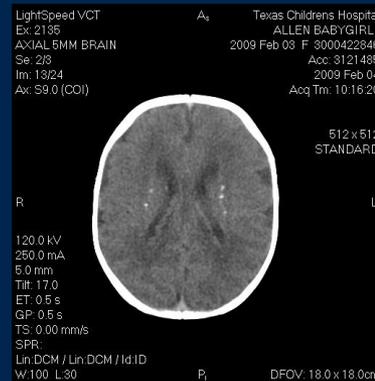


- Unenhanced CT scan of brain showed ventriculomegaly, linear periventricular Ca+, cerebral atrophy

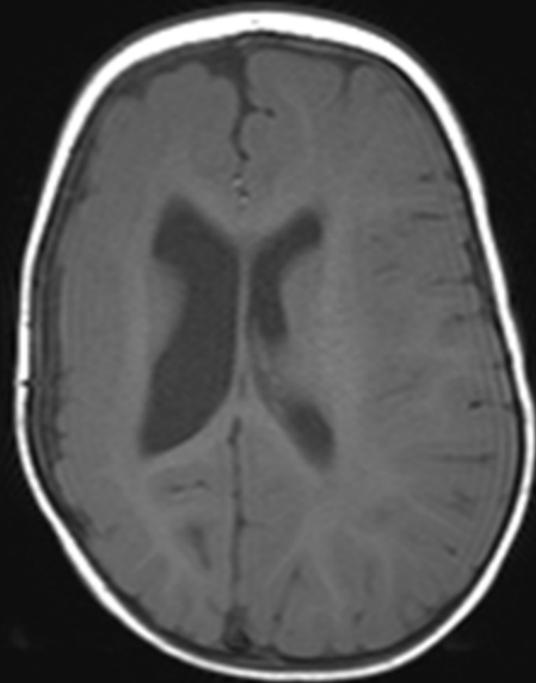
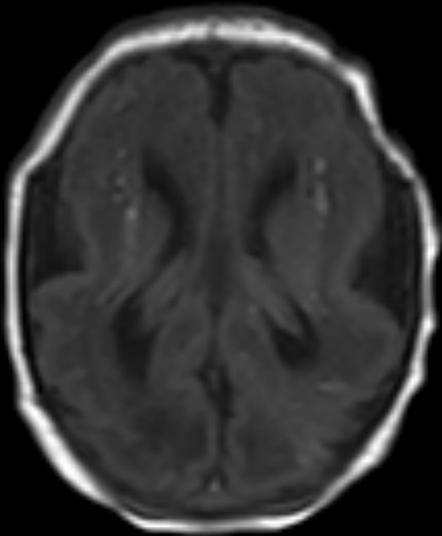
Mild to moderate ScCMV - Variations of CNS involvement



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

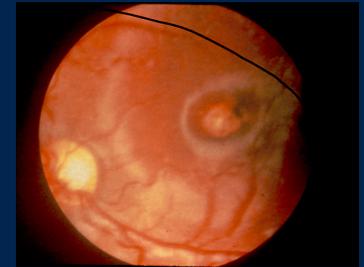


Cortical maldevelopment – unilateral or bilateral PMG



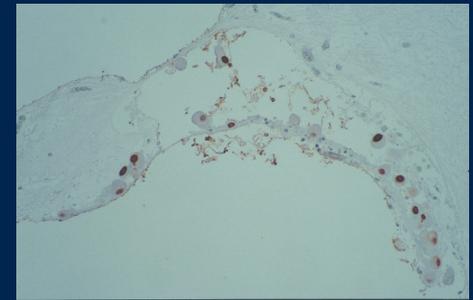
SYMPTOMATIC CCMV- VISION

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



SYMPTOMATIC CCMV- HEARING

- Hearing loss
 - Conductive with middle ear effusion
 - Sensorineural
 - Progressive
 - Unilateral or bilateral
 - Congenital or later onset



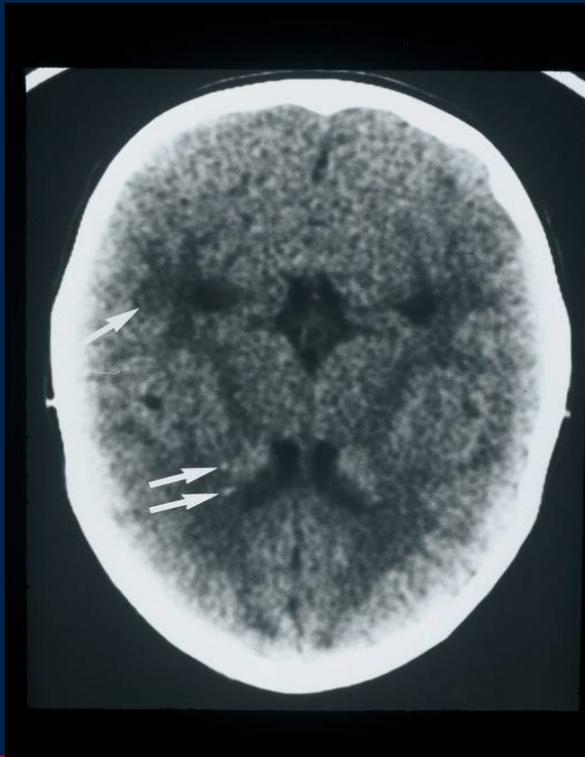
CONGENITAL CMV (CCMV)

- ASYMPTOMATIC CCMV
 - No apparent symptoms at birth
 - Normal hearing at birth
- 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

ASYMPTOMATIC CCMV

- NORMAL NEWBORN W/ OR WITHOUT HEARING LOSS
- MAY HAVE BRAIN IMAGING FINDINGS OF SUBTLE CNS INVOLVEMENT
- AT SIGNIFICANT RISK 10-25% OF HEARING LOSS
 - CONGENITAL
 - LATER ONSET
 - PROGRESSIVE

CCMV 101- AcCMV Cranial CT images may have mild abnormalities 25%



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

Asymptomatic CCMV neonatal HUS findings can include

- Ventriculomegaly
- Cysts/pseudocysts
- Lenticulostriate vasculopathy
- Germinolytic cysts
- Punctate periventricular calcifications

CCMV 101-

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 were 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**

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

NEWBORN CCMV DIAGNOSIS

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

Targeted Newborn Screening for CCMV and Failed NBHS

- Connecticut, Iowa, Illinois, New York, Utah and Virginia perform 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-screening>

UNIVERSAL NEWBORN SCREENING FOR CCMV-

- 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, sign the Change.org petition <http://chnng.it/bjYvSmWCsQ> or go to the www.nationalcmv.org website

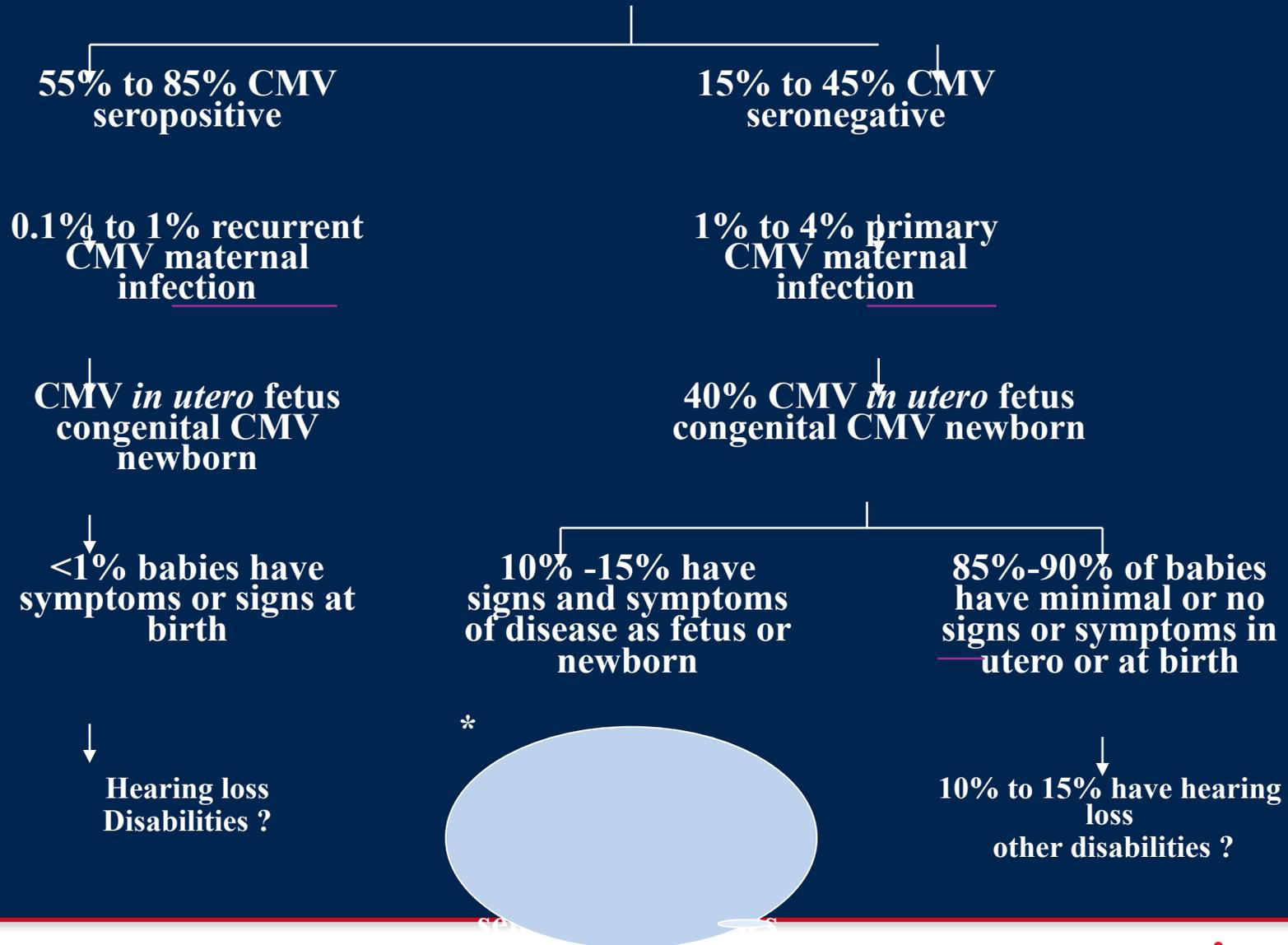
DIAGNOSIS OF CCMV AFTER BIRTH- GOING BACK IN TIME

- **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

OBJECTIVES CMV 101- COVER THE BASICS

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

Pregnant Women In the United States



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 JCV 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
- Makes outpatient management feasible and affordable

Red Book 2018-2021 Report of COID 31st 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

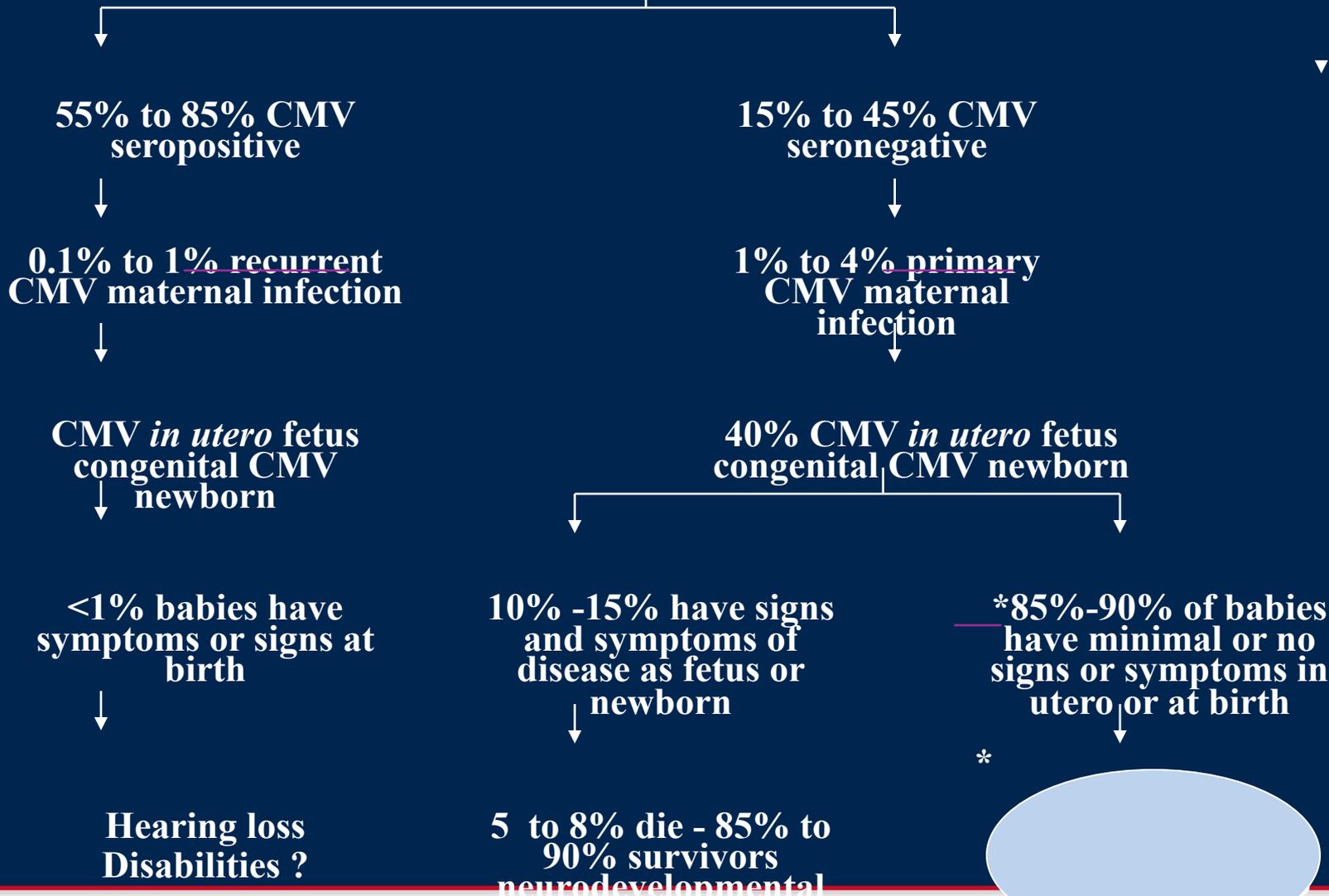
- **Speech language therapy**
Hearing aids, cochlear implants
- **Educational accommodations**
- **Physiotherapy, mobility aids, orthotics, orthopedics**
- **Seizure treatments**
- **Vision aids and therapies, strabismus surgery**
- **Nutritional interventions for growth disorders**

CCMV 101- Antiviral treatment – unanswered questions??????????

- Follow up in clinical trials has been only for 6 months to 2 – 3 years
- It is not known how long the apparent benefits of antiviral therapy will last
- Is antiviral therapy helpful for the “worse ear” or the “good ear” or both or neither?
- Do we need to treat longer than 6 months for long term benefits?

– Park et al Abstract CMV Public Health and Policy Meeting, Burlington, VT, 2018

Pregnant Women In the United States



CCMV Treatment – Unanswered questions ??????????????????????

- Asymptomatic CCMV newborns with congenital hearing loss to prevent progressive hearing loss in both the affected and unaffected ear
- Asymptomatic CCMV newborns with normal hearing to prevent later onset hearing loss
- Currently, not recommended by most experts, to routinely receive antiviral treatment because the safety and efficacy has not been determined in clinical trials specifically designed for normal newborns.

CCMV ANTIVIRAL TREATMENT CLINICAL TRIALS

- VALGANCICLOVIR FOR CMV INFECTED HEARING IMPAIRED INFANTS (VALEAR)-NIH-NIDCD- DR ALBERT PARK PI
 - Randomized, placebo controlled, clinical trial, MULTICENTER, to evaluate valganciclovir to reduce hearing loss progression
 - 2018-2024
 - Asymptomatic newborns with hearing loss
 - Positive CMV detection test at birth or by NB DBS

www.clinicaltrials.gov

CCMV ANTIVIRAL TREATMENT CLINICAL TRIALS

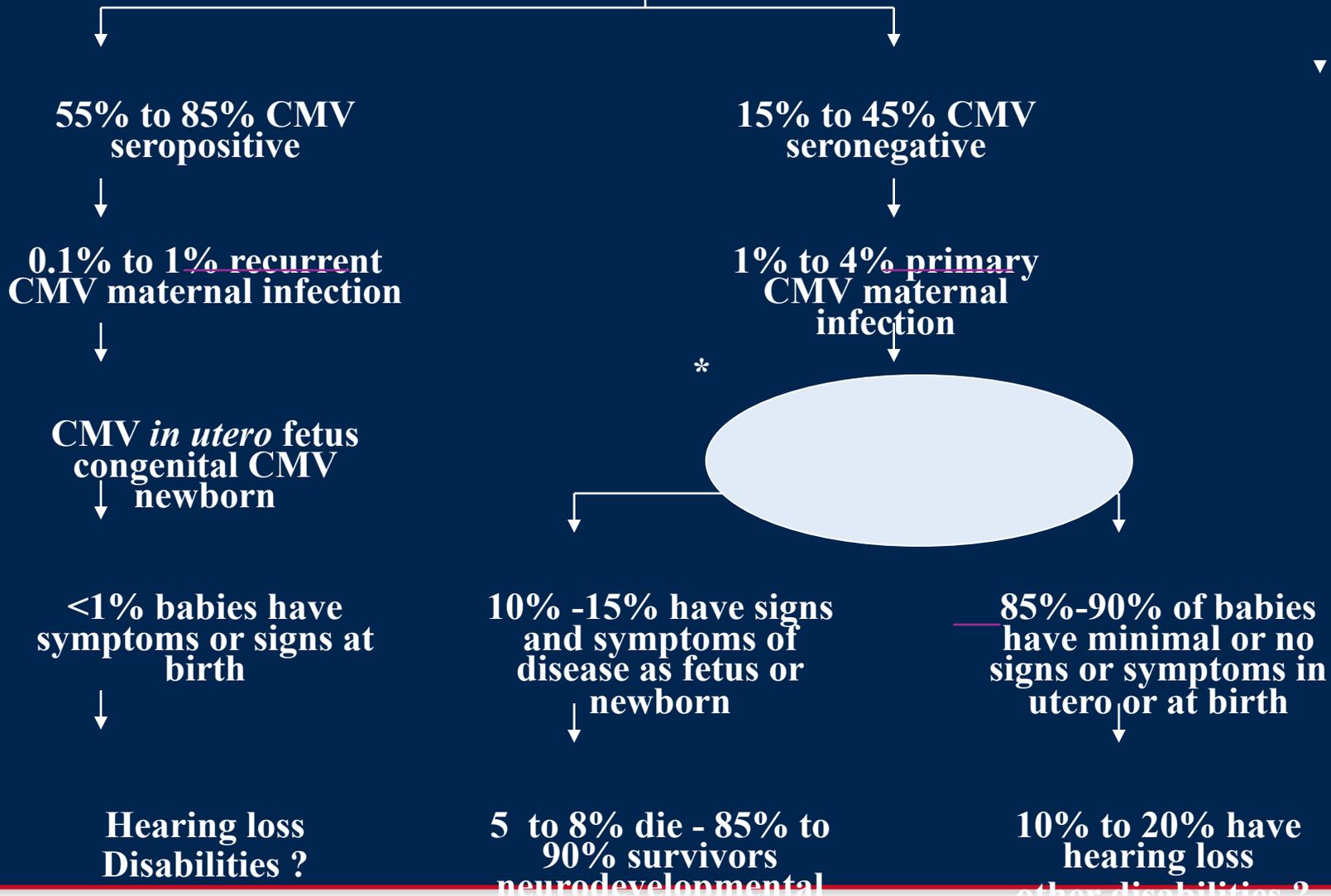
- ASYMPTOMATIC CONGENITAL CMV TREATMENT- NIH-NIAID-CASG-Dr David Kimberlin PI
 - Phase II, MULTICENTER, open-label trial to evaluate valganciclovir as treatment to prevent later onset SNHL in infants with A CCMV.
 - 2019-2024
 - Asymptomatic newborns with normal hearing
 - Positive CCMV test at birth through newborn screening

www.clinicaltrials.gov

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

Pregnant Women In the United States



CCMV 101-

Prenatal Testing or Screening to Diagnose Maternal CMV Infection during Pregnancy

- Maternal Serology – NOT ROUTINE
- CMV IgG positive or seroconversion (IgG negative to IgG positive)
 - CMV IgM positive
 - CMV 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

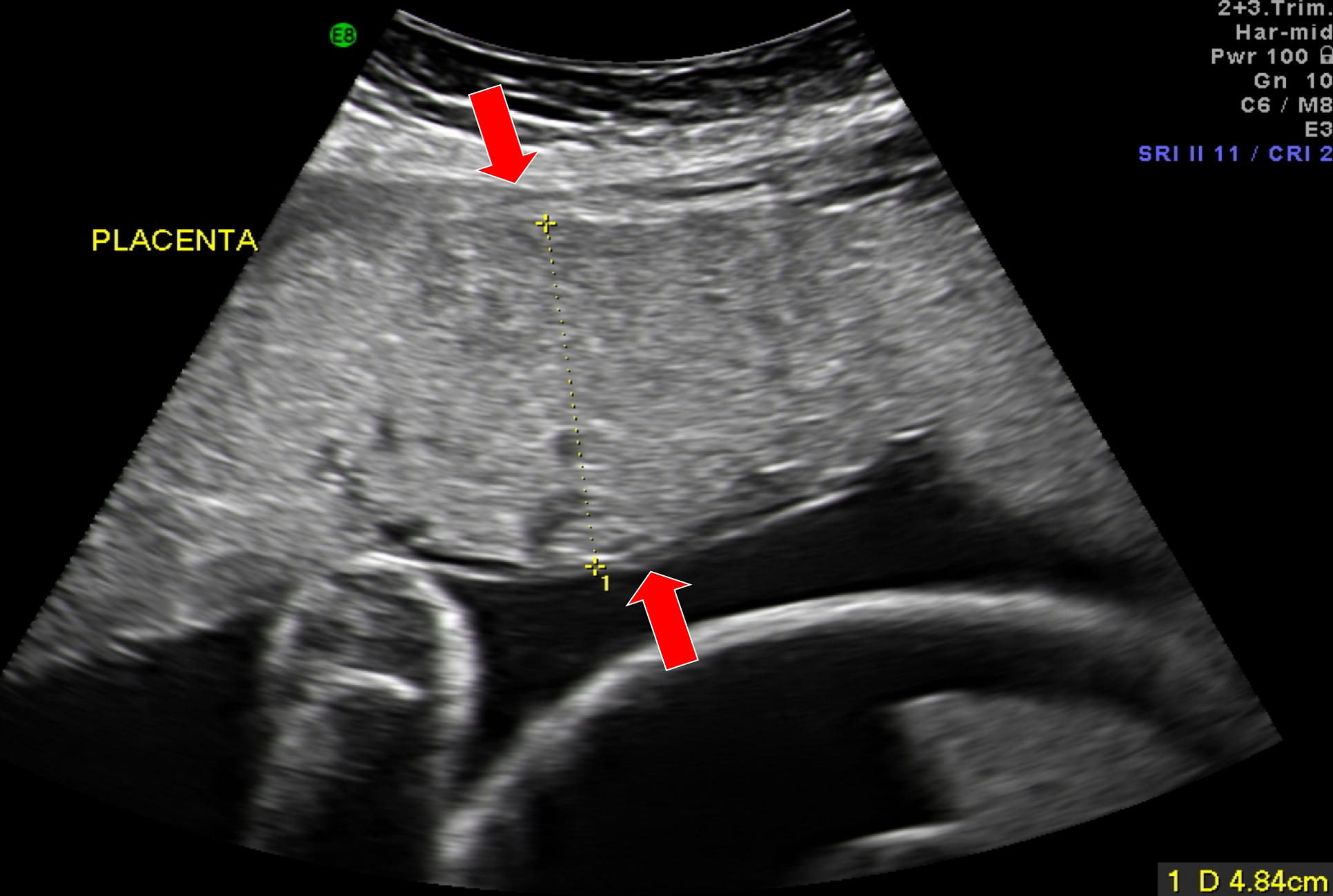
- Second Trimester- Fetal Ultrasound- ROUTINE
 - Echogenic bowel, IUGR, hydrops, brain abnormalities may be first indication of CMV infection *in utero*

Goetzinger et al Obstet Gynecol 2011

CCMV 101- Case

Cytomegalovirus Infection of a Fetus

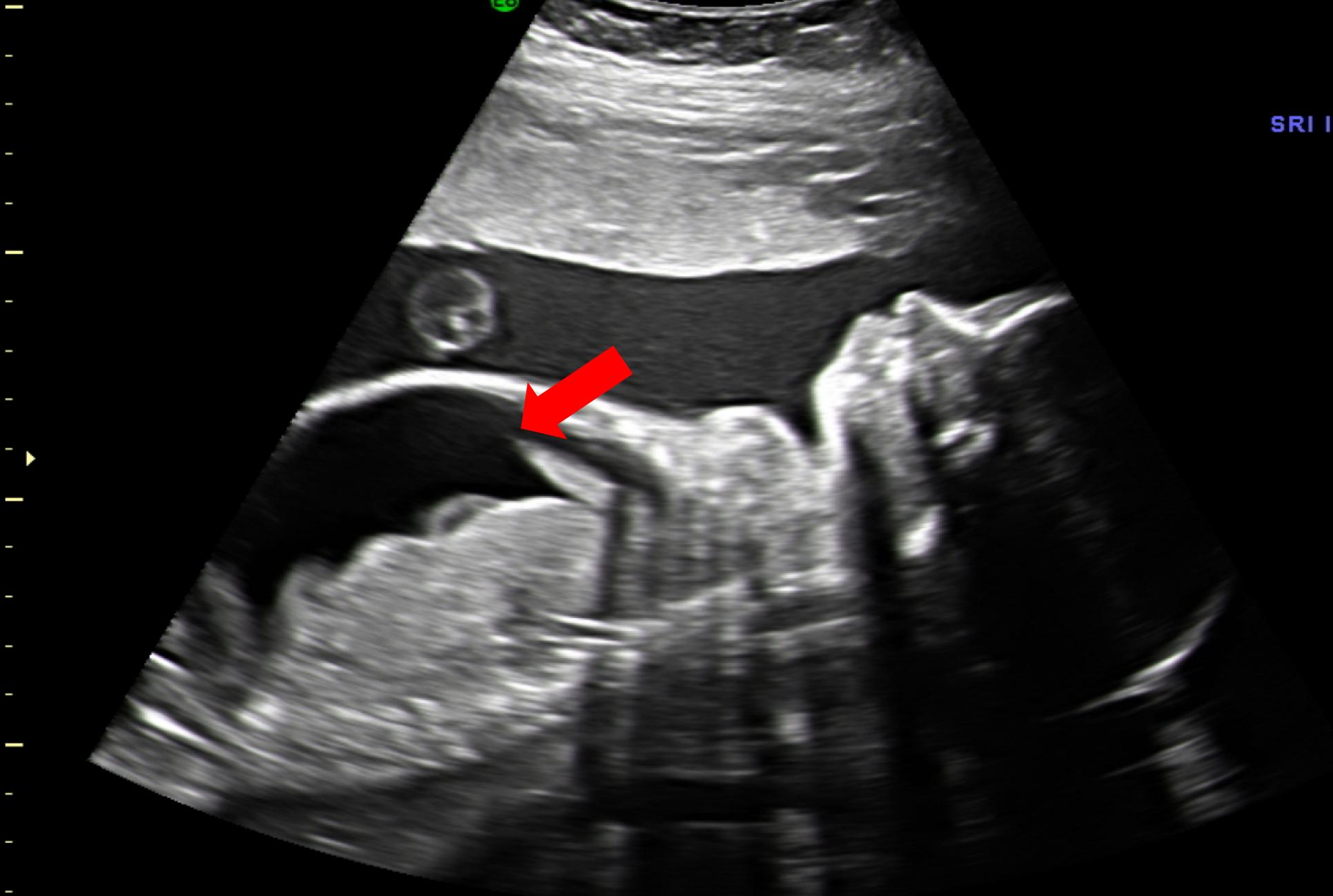
- 24 y.o G2P1Ab0
- Ultrasound 20 and repeat 24 weeks gestation- thickened placenta, cerebral echogenic foci, fetal ascites, hepatosplenomegaly
- Maternal studies: CMV IgG +, CMV IgM +, CMV avidity low - Recent primary infection
- Amniocentesis: + PCR/culture for CMV; viral load > 1 X 10⁶ copies/ml



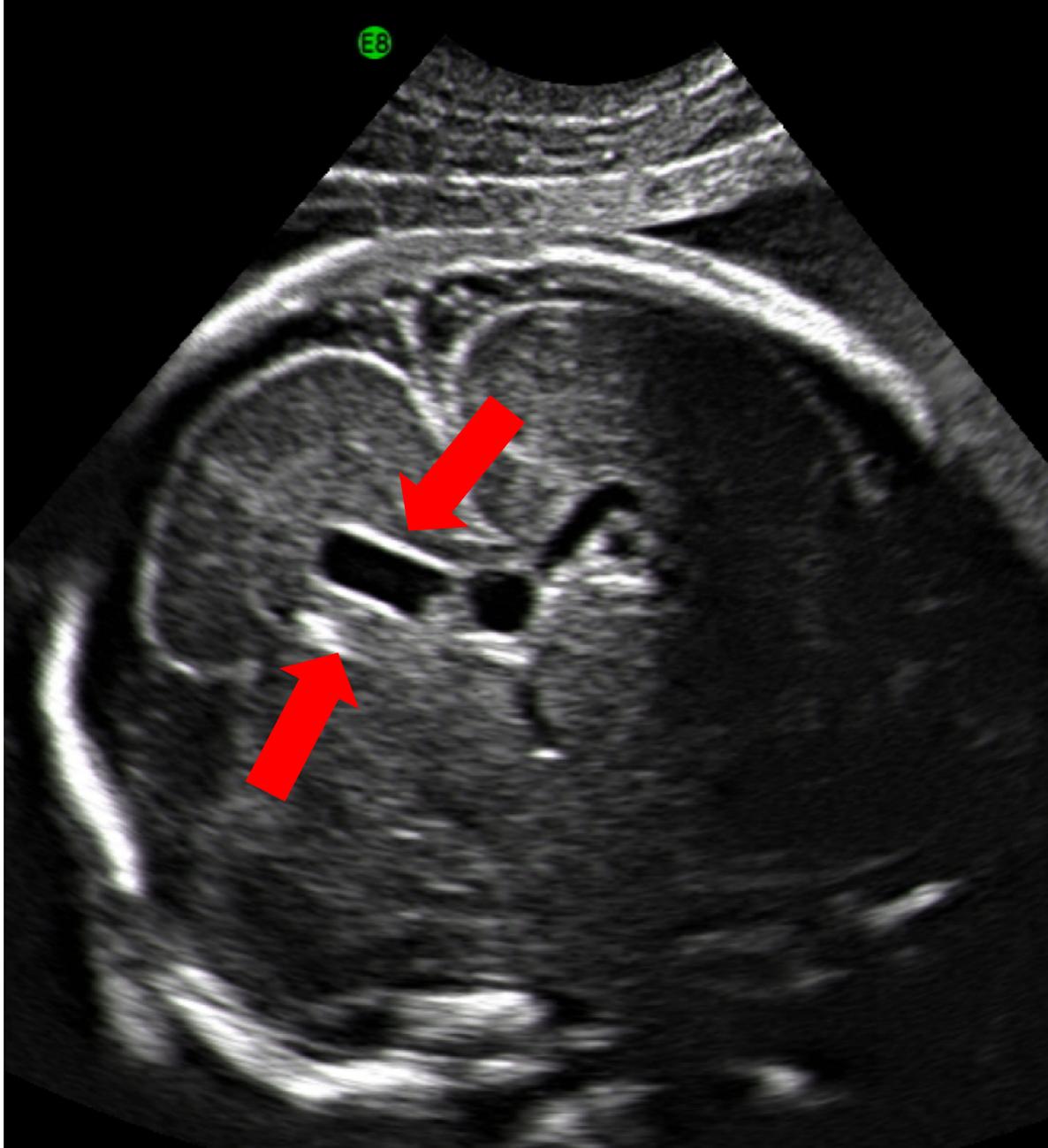
2+3.Trim.
Har-mid
Pwr 100 B
Gn 10
C6 / M8
E3
SRI II 11 / CRI 2

PLACENTA

1 D 4.84cm



SRI I



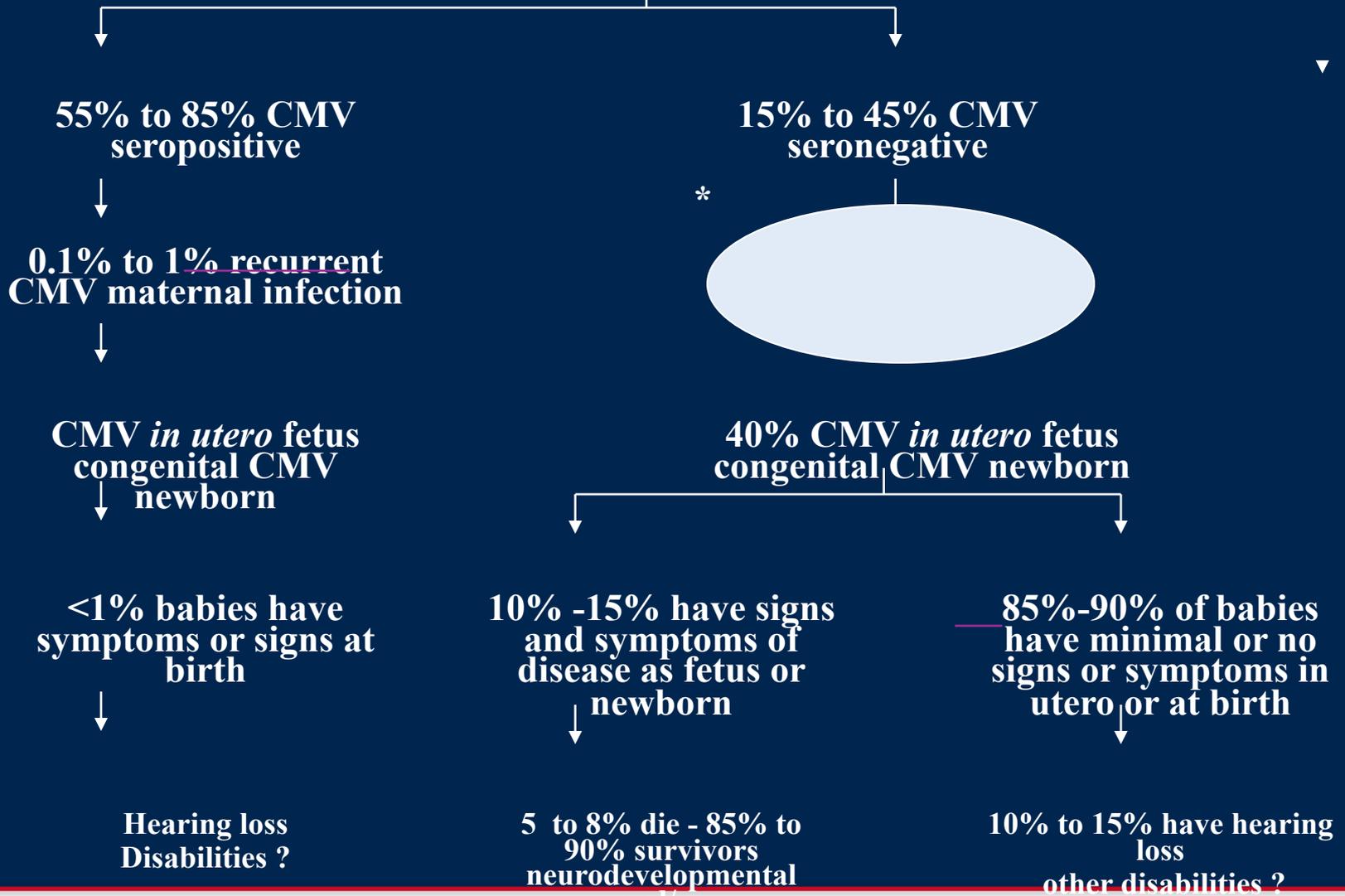
Prenatal Treatment for In UTERO CCMV

- **CMV Hyperimmune Globulin Treatment**
 - Four prospective observational studies were promising and showed reduction in maternal fetal transmission and severity of CCMV disease in baby
 - One RCT did not demonstrate a significant benefit
 - Remains investigational and research
 - It is not standard treatment at this time

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%
 - Safe
 - May be used by some OBs at this time

Pregnant Women In the United States



Pregnant Women In the United States

55% to 85% CMV seropositive

↓

0.1% to 1% recurrent CMV maternal infection

↓

CMV *in utero* fetus
congenital CMV newborn

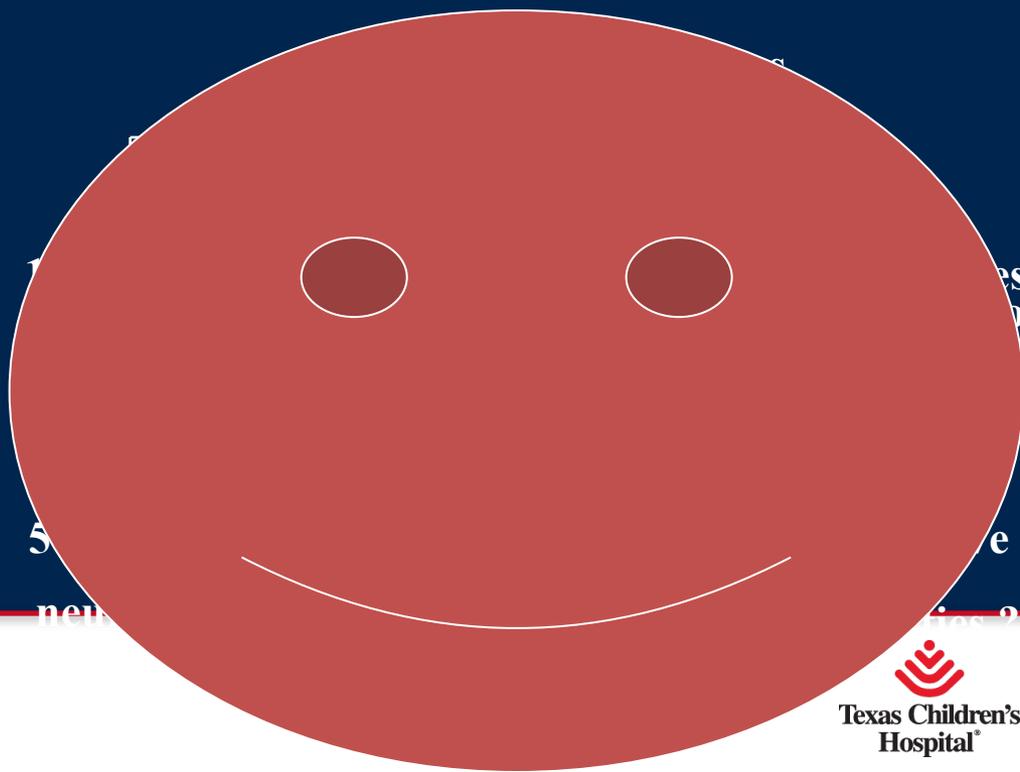
↓

<1% babies have symptoms or signs at birth

↓

Hearing loss
Disabilities ?

15% to 45% CMV seronegative



OBJECTIVES CMV 101- COVER THE BASICS

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

CCMV 101- CMV 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 !**
 - **NO licensed CMV vaccine available yet**

* IOM Committee to Study Priorities for Vaccine Development for 21st Century Nat Academics Press 2000

CCMV 101-

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 101-

“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”

Recommended now by CMV experts, International Consensus Guidelines, AAP, 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; Vauloop-Fellous et al J Clin Virol 2009, Rawlinson et al Lancet ID, 2017

[www.http://www.texaschildrensblog.org/2011/01/cm��-every-pregnant-woman-should-know-about-this-virus/](http://www.texaschildrensblog.org/2011/01/cm��-every-pregnant-woman-should-know-about-this-virus/)



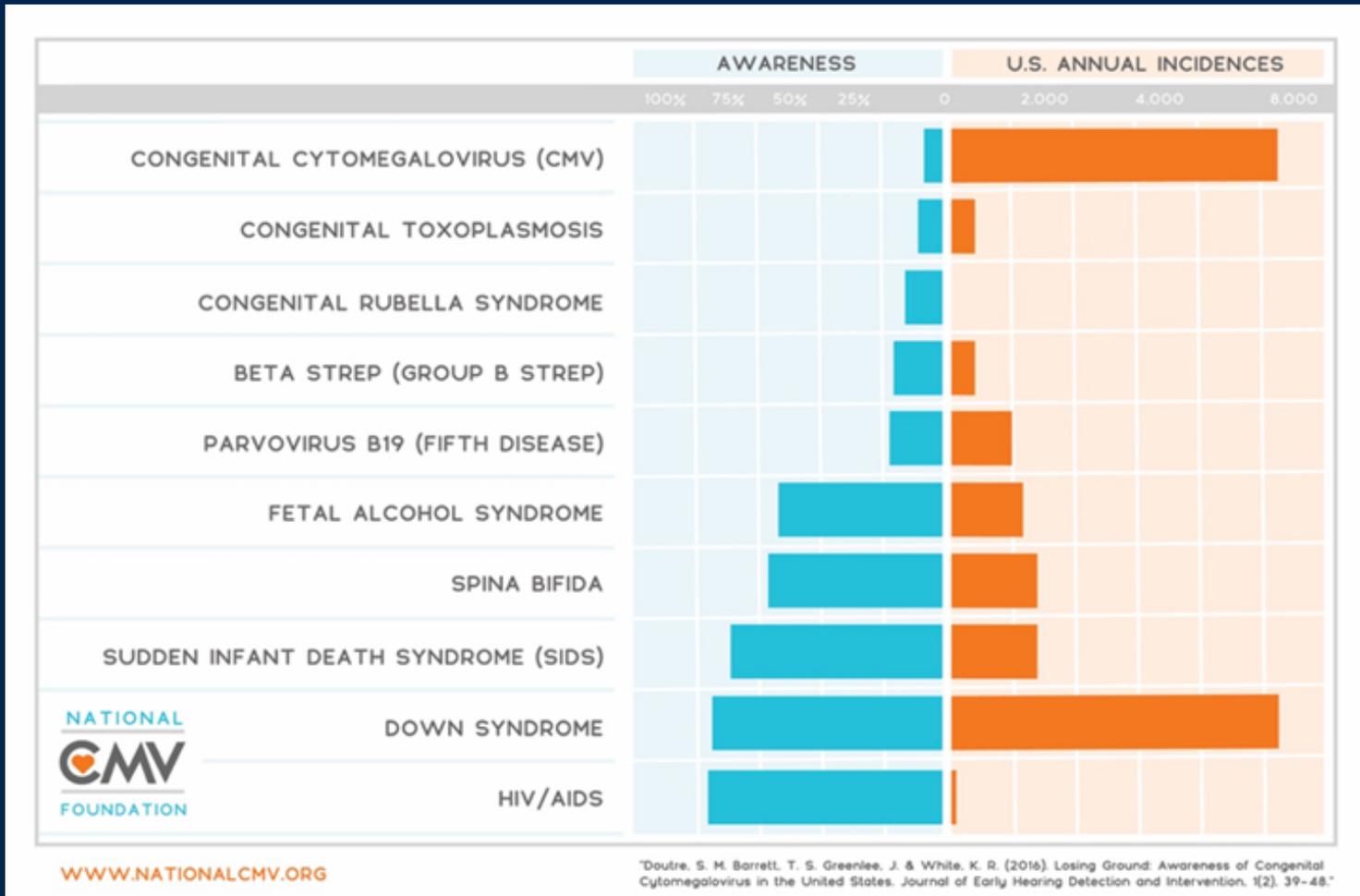
Who should know?

- Pregnant mothers 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

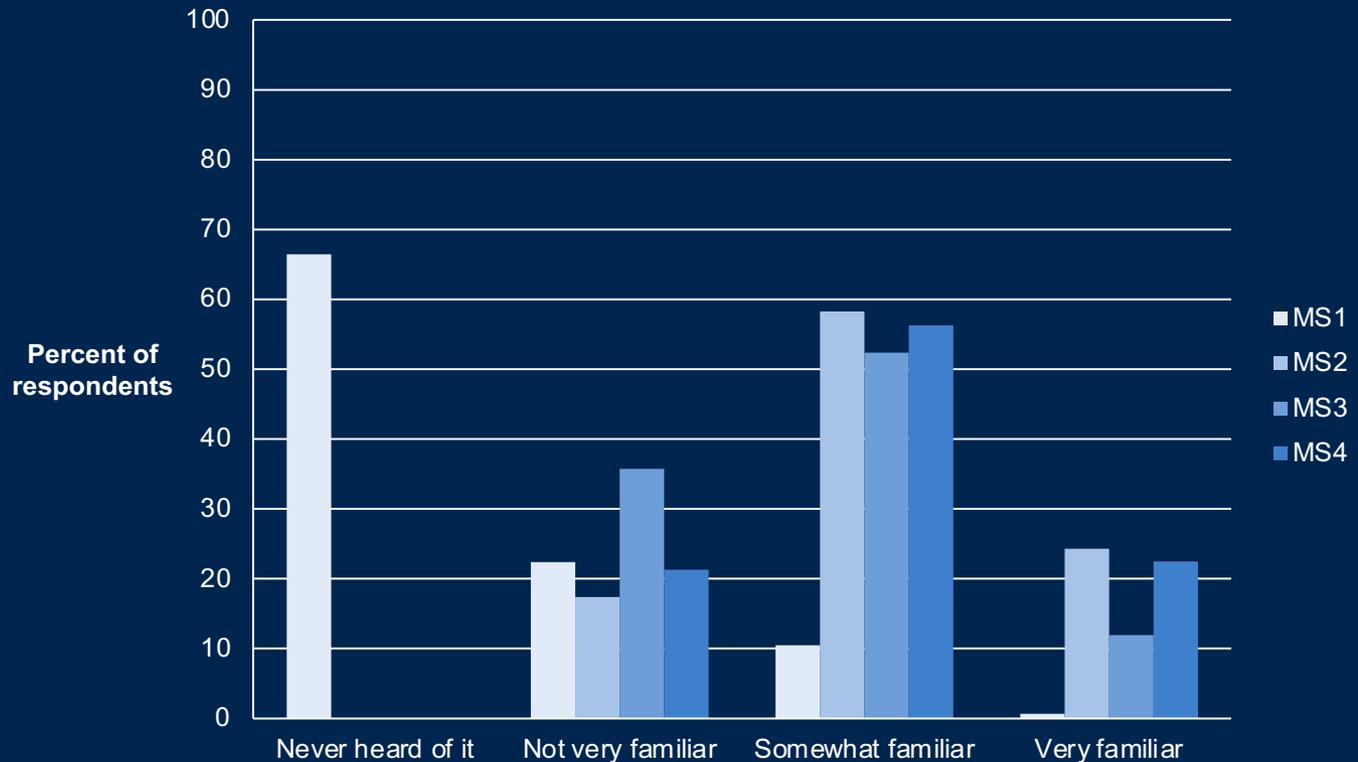


Survey of Congenital Cytomegalovirus (cCMV) Knowledge Among BCM Medical Student, Houston Texas

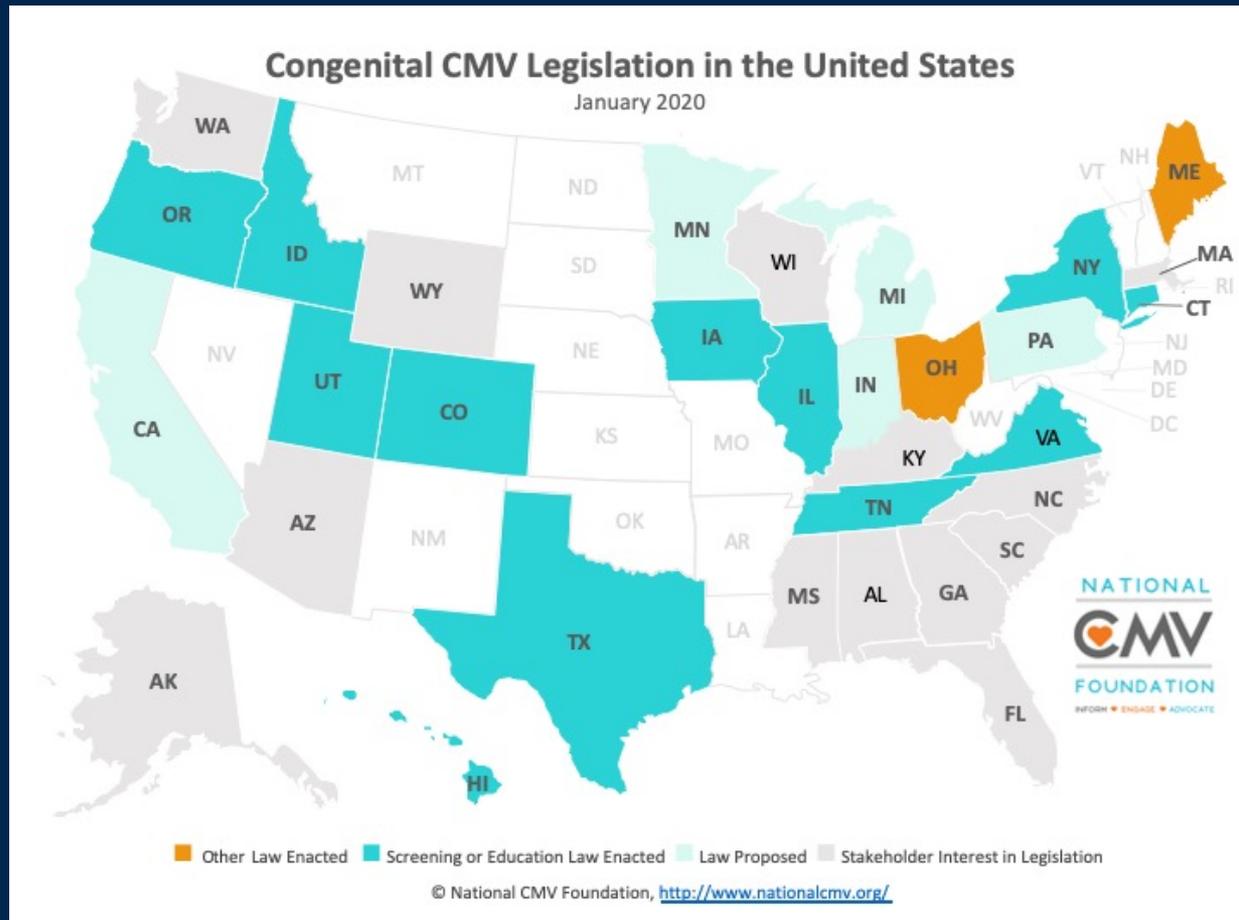
- Most “young doctors to be” have never even heard of CMV !

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

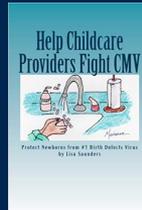
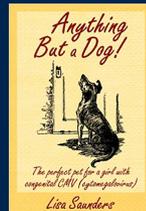
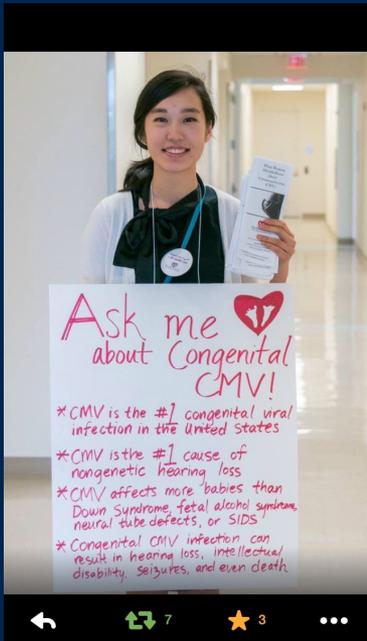
Self-Reported Familiarity With Congenital CMV

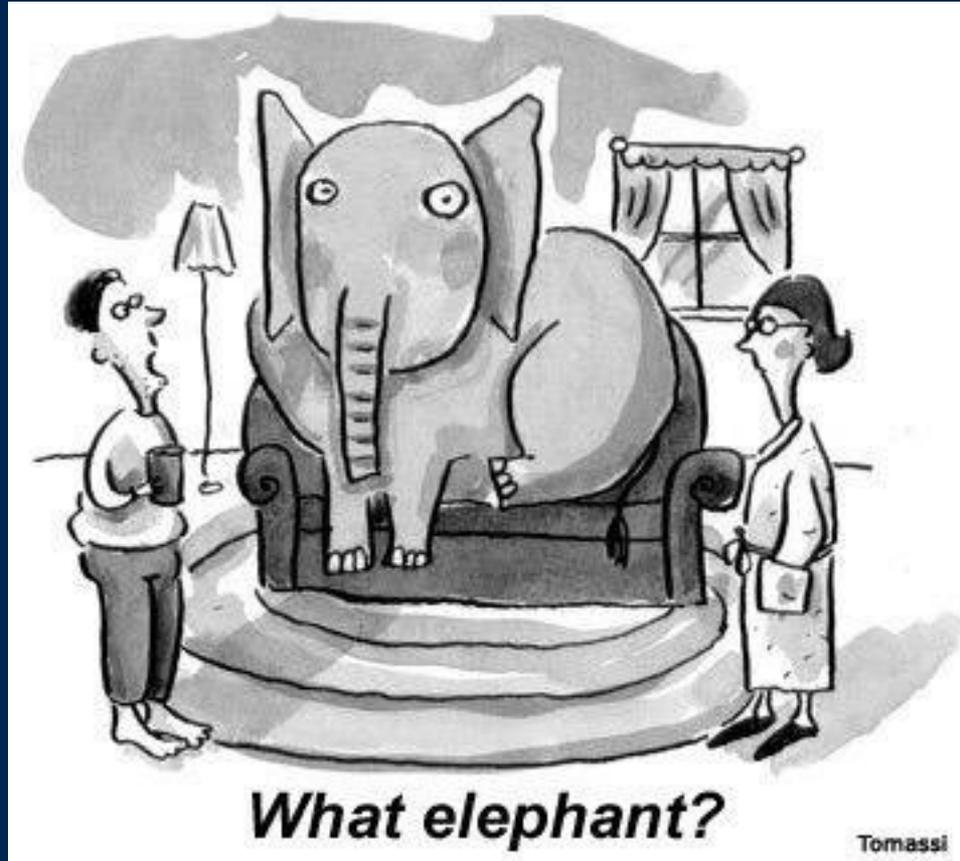


CCMV Legislation in the US. January 2020. www.nationalcmv.org

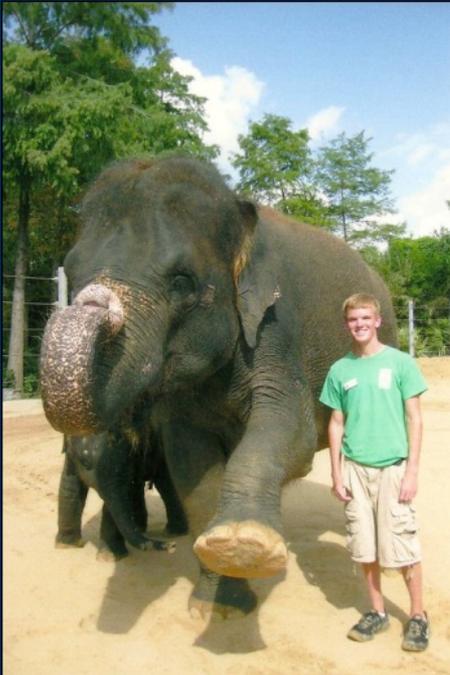


There are many cmv awareness sites on the internet...fueled by parents and professionals... websites, facebook, twitter, instagram, blogs, podcasts, public access TV shows, etc.... there are a few books...but you have to first know CMV exists...to search for them





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