"Why Is Our Baby's Head Small?"

The Pathogenesis of Microcephaly Resulting From Zika Virus and Other Congenital Infections

Lawrence D. Frenkel, MD, Professor, Departments of Pediatrics and Microbiology, U. of Illinois College of Medicine, Chicago, USA

Fernando Gomez, MD, Professor, Department of Specialty Medicine
Rocky Vista University School of Osteopathic Medicine, Parker, CO

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Questions to Try to Answer About Congenital Microcephaly

- Why do some women get infected with the responsible pathogens?
- Why are their pathogen loads high enough to cross the placenta and infect their fetus?
- Why are some fetuses merely infected while others are afflicted*?
- What determines the pattern and degree of affliction?

* Congenitally infected infants who demonstrate stigmata at birth

Major Pathogens Associated with Congenital Microcephaly

Microorganism	Risk of Affliction with Primary Maternal Infection (%)*	% of Afflicted Infants with Microcephaly*	Sexual Transmission	Vaccine Availability
Zika Virus	40	20	Yes	In clinical trials
CMV	15	50	Yes	Not in use
Rubella Virus	50	10	No	Routine
HSV	1	<3	Yes	In clinical trials
HVZ	2	rare	No	Routine
Toxoplasma	10	5	No	None available

*Best average estimates of published data at this time

Reported Pathologic Findings

	Zika virus[a]	CMV[b]	Rubella virus[c]	HSV[b]	VZV[b]	*T. gondii*[d]
Microcephaly √	Yes	Yes	Yes	Yes	Yes	Yes
Intrauterine growth retardation √	Yes	Yes	Yes	Yes	Yes	Yes
CNS calcifications √	Yes	Yes	Yes	Yes	Yes	Yes
Sensorineural hearing loss √	Yes	Yes	Yes	Yes	Yes	Yes
Chorioretinal inflammation √, atrophy, or scars	Yes	Yes	Yes	Yes	Yes	Yes
Hydrocephalus, hydranencephaly or ventriculomegaly	Yes	Yes		Yes	Yes	Yes
Malformed gyri	Yes	Yes	Yes			
Cortical dysplasia	Yes	Yes				
Cerebellar hypoplasia or aplasia	Yes	Yes		Yes		
Encephalitis or meningoencephalitis	Yes	Yes	Yes	Yes	Yes	Yes
Microphthalmia	Yes		Yes	Yes		Yes
Optic nerve atrophy	Yes	Yes	Yes	Yes	Yes	Yes
Cataracts	Yes		Yes	Yes	Yes	Yes
Cardiac anomalies			Yes	Yes		
Hepatic dysfunction		Yes	Yes	Yes		Yes

[a]ss+RNA flavivirus, [b]dsDNA herpesvirus, [c]ss+RNA togavirus, [d]intracellular protozoan

√ **Most characteristic findings in TORCH afflicted infants**

Zika Virus Characteristics

- Epidemiology: High attack rate at 70% (data from Yap Island)
- Transmission: ***Aedes aegypti* mosquito** & sexually
- Primary maternal infection resulting in congenital Zika affliction: 1st and 2nd trimester
- Not neurotropic in most individuals; some G-B Syndrome
- Major manifestations

  Maternal: Asymptomatic disease in 80%; rash, headache, arthralgia, myalgia, **conjunctivitis**, and low-grade fever

  Congenital: **Microcephaly**, CNS calcifications and other malformations, intrauterine growth retardation (IUGR), sensorineural hearing loss, chorioretinitis and other eye abnormalities, seizures, developmental delay

Cytomegalovirus Characteristics

- Epidemiology: Very common infection worldwide; most common congenital infection in the US
- Transmission: Sexually and via **oral secretions**
- Primary maternal infection resulting in congenital CMV: 1st or 2nd trimester; however

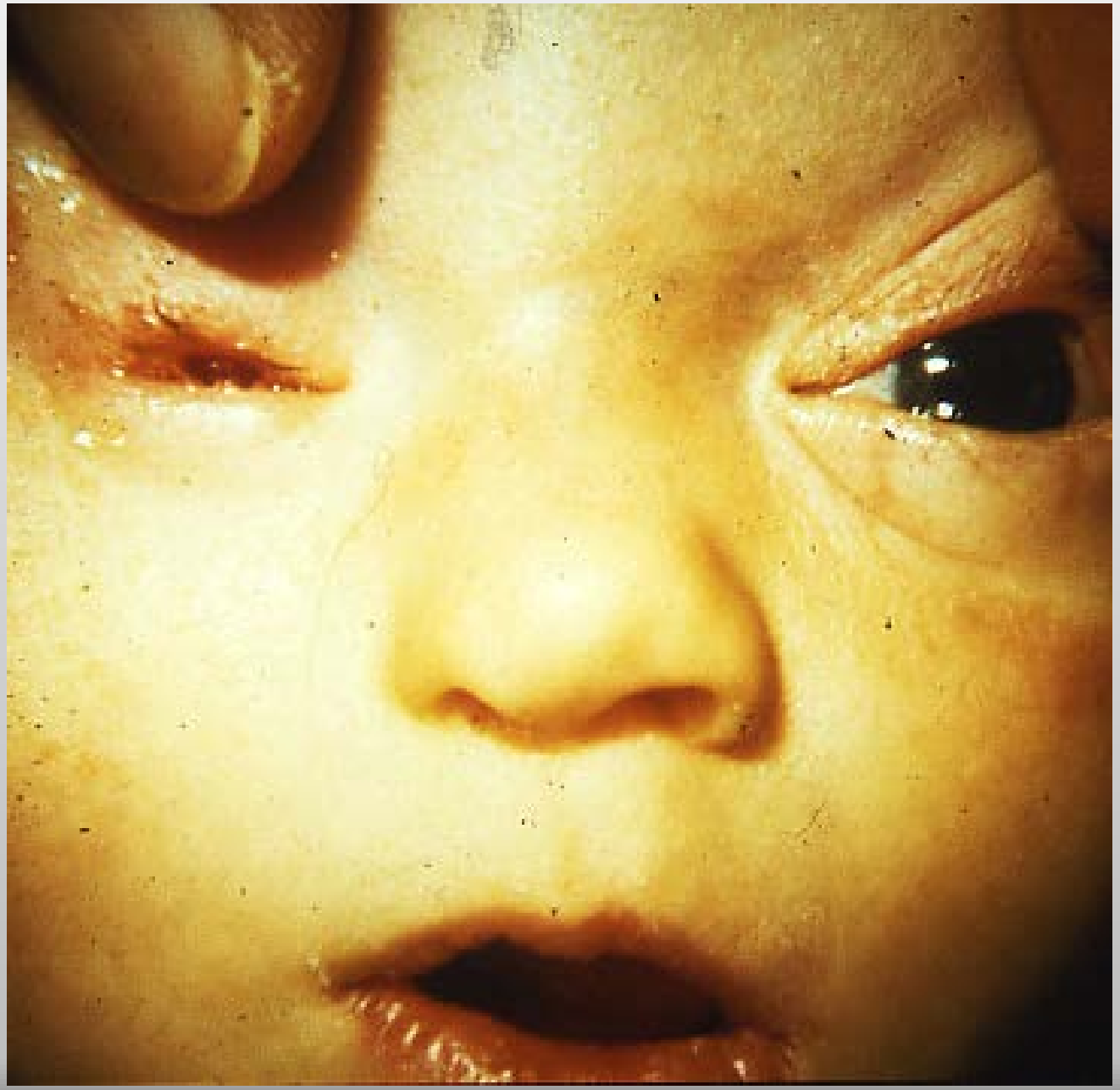
  Fetal infection can occur as reactivation or reinfection in seropositive mothers
- Not neurotropic in immune competent individuals
- Major manifestations

  Maternal: Generally asymptomatic; mild flu-like symptoms

  Congenital: **Microcephaly**, CNS calcifications and other CNS malformations, IUGR, **sensorineural hearing loss**, chorioretinitis and other eye abnormalities, seizures, developmental delay; **petechiae and jaundice indicating fetal dissemination**

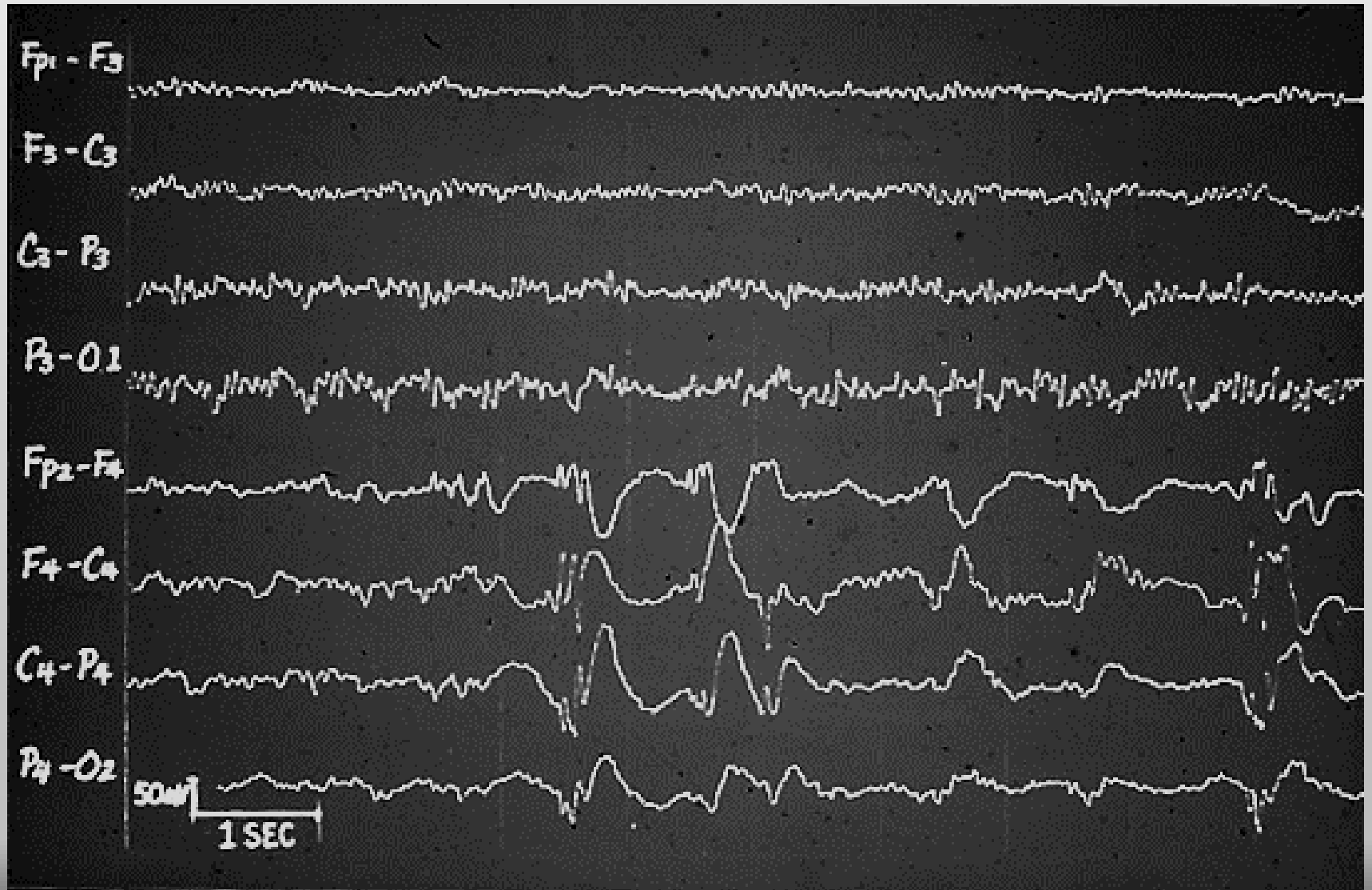

Characteristic
Chorioretinitis
Secondary to
Congenital CMV

Unilateral Microphthalmia in Child With Congenital CMV



“Burst Suppression” Silent Seizures in Congenital CMV

(Same Side as Microphthalmia)



Rubella Virus Characteristics

- Epidemiology: Moderately high attack rate prior to vaccine availability now rare
- Transmission: **Respiratory**
- 1st trimester maternal infection results in congenital affliction in a remarkable 50% of infants
- Neurotropic manifestations: Uncommon, include mild encephalitis
- Major manifestations

  Maternal: Generally mild self limited symptoms, with fever, rash, and adenopathy

  Congenital: Microcephaly, CNS calcifications and other CNS abnormalities, IUGR, sensorineural hearing loss, eye abnormalities, developmental delay, petechiae, and jaundice; **Greg's classic triad from 1941: Deafness, cataracts, cardiac abnormalities**

Herpes Simplex Virus Characteristics

- Epidemiology: Common infection in women, mostly recurrent;
- Transmission: Moderately infectious with sexual or close skin or mucous membrane contact
- Primary maternal infection resulting in congenital HSV is rare but occurs in the: 1st or 2nd trimester
- Neurotropic manifestations: Encephalitis and latency in neural tissues
- Major manifestations

  Maternal: Localized genital lesions, disseminated cutaneous or multi-organ (sometimes fatal) dissemination

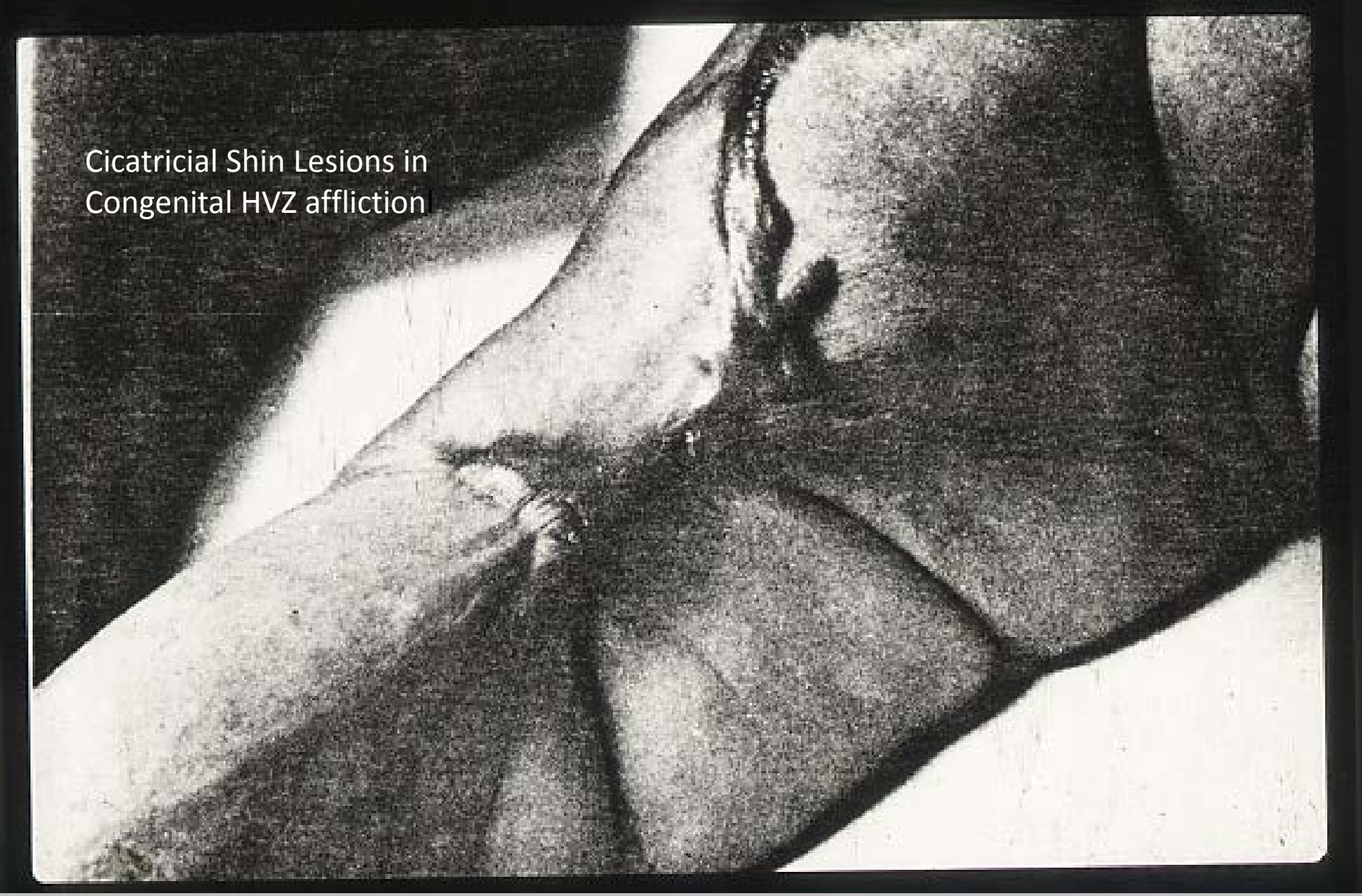
  Congenital: Evidence of necrotizing CNS, pulmonary, hepatic dissemination and DIC; as well as rare microcephaly

Herpes Varicella-Zoster Virus Characteristics

- Epidemiology: The incidence of primary maternal disease is low:
  Most mothers were seropositive historically, because of the highly infectious nature of childhood disease
  And, more recently, because of the widespread use of the vaccine
- Transmission: **Aerosol of respiratory secretions** and fomite contact
- Primary maternal infection resulting in congenital HVZ: 1st or 2nd trimester
- Neurotropic manifestations: Encephalitis, Zoster, and latency in neural tissue
- Major manifestations

  Maternal: Similar to disease in children and others

  Congenital: **Cicatricial skin scarring, limb hypoplasia**, CNS malformations, eye abnormalities, and very rare microcephaly


Cicatricial Shin Lesions in
Congenital HVZ affliction

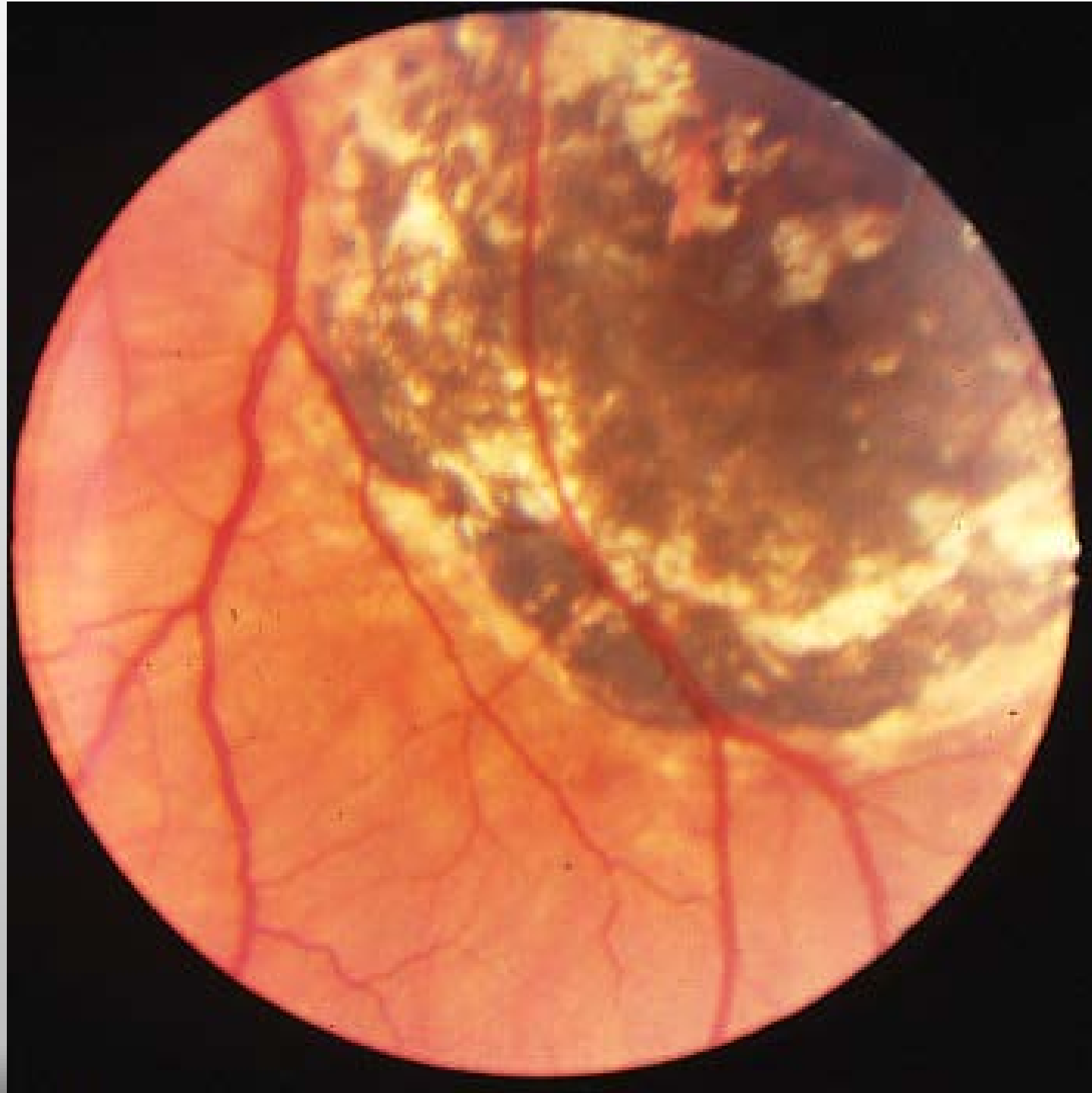
Toxoplasma Characteristics

- Epidemiology: Incidence is dependent on geography and culture; **a major cause of adolescent blindness** via reactivation of silent congenital infection manifest with chorioretinitis
- Transmission: Generally via **cat feces** (e.g. changing cat litter boxes) or by eating **raw meat** (especially lamb)
- Primary maternal infection resulting in congenital toxoplasmosis: 1st or 2nd trimester
- The organisms seem to have a broad tropism for CNS tissue
- Major manifestations

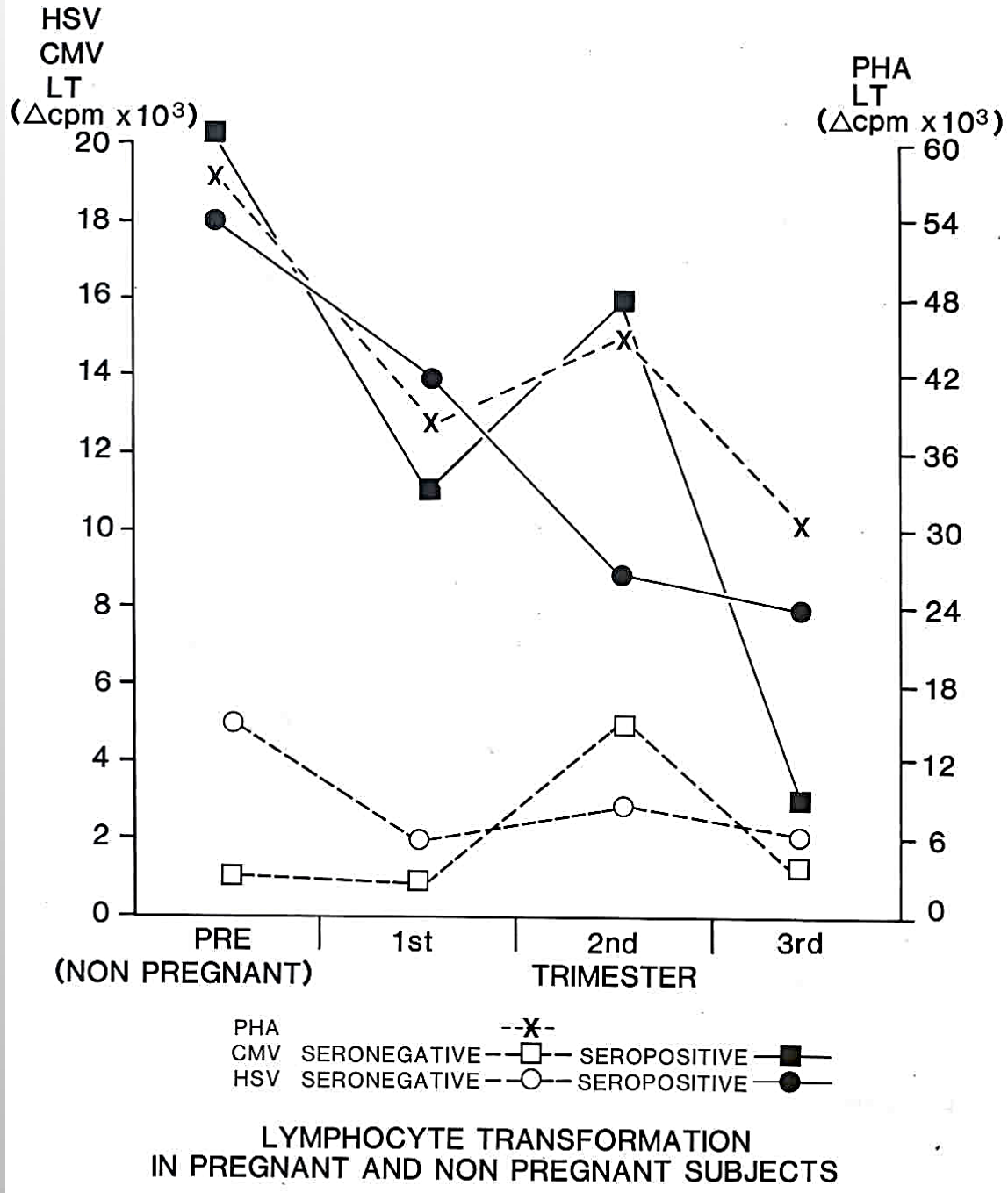
  Maternal: Generally asymptomatic or unrecognized

  Congenital: Microcephaly, CNS calcifications and other CNS abnormalities, IUGR, sensorineural hearing loss, **chorioretinitis** and other eye abnormalities, seizures, developmental delay, jaundice and anemia

Characteristic Chorioretinitis Secondary to Toxoplasma Infection



Depression of Specific and Non-specific Cell Mediated Immunity During Pregnancy



LYMPHOCYTE TRANSFORMATION
IN PREGNANT AND NON PREGNANT SUBJECTS

FIGURE 1

(Frenkel, L.D, et.al. Presented at the Conjoint Meeting on Infectious Diseases, Montreal, Canada, December, 1983)

Specific Immunopathogenic Observations

- Reactivation and reinfection can be associated with congenital **CMV** affliction in seropositive pregnant women
- Reactivation can be associated with delayed blindness in congenital **toxoplasmosis**
- Persistent **CMV and rubella virus** shedding in congenitally infected infants and their mothers is reflective of decreased and delayed viral specific T cell mediated immunity

The Pathology Of Microcephaly (1)

- **Intracellular pathogens** that are **tropic for human fetal CNS tissue**
- Cause neuron infection resulting in death, decreased replication, and abnormal migration
- This causes decreased brain tissue mass and volume reflected in **microcephaly**
- Common findings

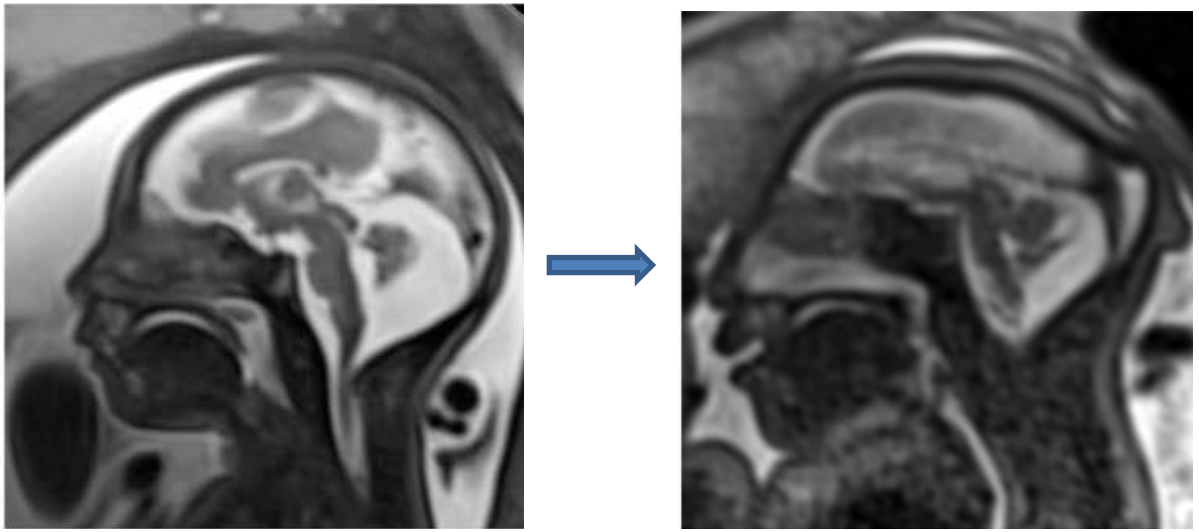
  Increased intracranial fluid

  Lymphohistiocytic inflammation of brain and/or meninges

    Which yields cerebral cortical thinning, cerebral schizencephaly, pachygyria, and/or lissencephaly; and/or hypoplasia or aplasia of cerebellum (e.g. cerebellar vermis aplasia) and/or corpus callosum

The Pathology Of Microcephaly (2)

- The inflammation and decreased brain matter are associated with ventriculomegaly, hydrocephalus and hydranencephaly
- As the fluid levels and brain mass recede there is collapse of the cranial vault, overriding of the cranial bones, flattening of the cranium and redundant scalp skin



Soares de Oliveira-Szejnfeld P, et. al. 2016. Congenital brain abnormalities and Zika virus: what the radiologist can expect to see prenatally and postnatally. Radiology 281:203–218.

The Pathology Of Microcephaly (3)

- The differential neuropathology of microcephaly associated with these pathogens is not clear at this time
- However, the kinetics of CNS tissue destruction may be reflected in the pattern and character of microcephaly (e.g. Zika virus destruction is more severe and rapid than is seen with CMV and other pathogens)

Hypothesis To Explain Congenital Affliction

- Pregnancy leads to a generalized down-regulation of T cell mediated immunity to help preserve the fetal graft.
- Multiple, less understood, factors including primary maternal infection and a more profound immune suppression than is seen in normal pregnancy allow for invasion of maternal circulation and determine the pathogen load delivered to the placenta
- Failure of maternal-fetal barriers allows pathogen dissemination to multiple susceptible developing organs in the fetus

Hypothesis To Explain Congenital Affliction (2)

- The timing of maternal infection (early gestation is when important embryonic events are occurring), and cellular tropism, together, determine the characteristics and degree of affliction
- The pathology of microcephaly is similar regardless of causal pathogen but implies maternal infection early in gestation
- The final step in congenital affliction is chronic destructive inflammation thought to be the result of down-regulation of fetal immune defenses in the face of up-regulation of fetal innate immune responses that promote inflammation

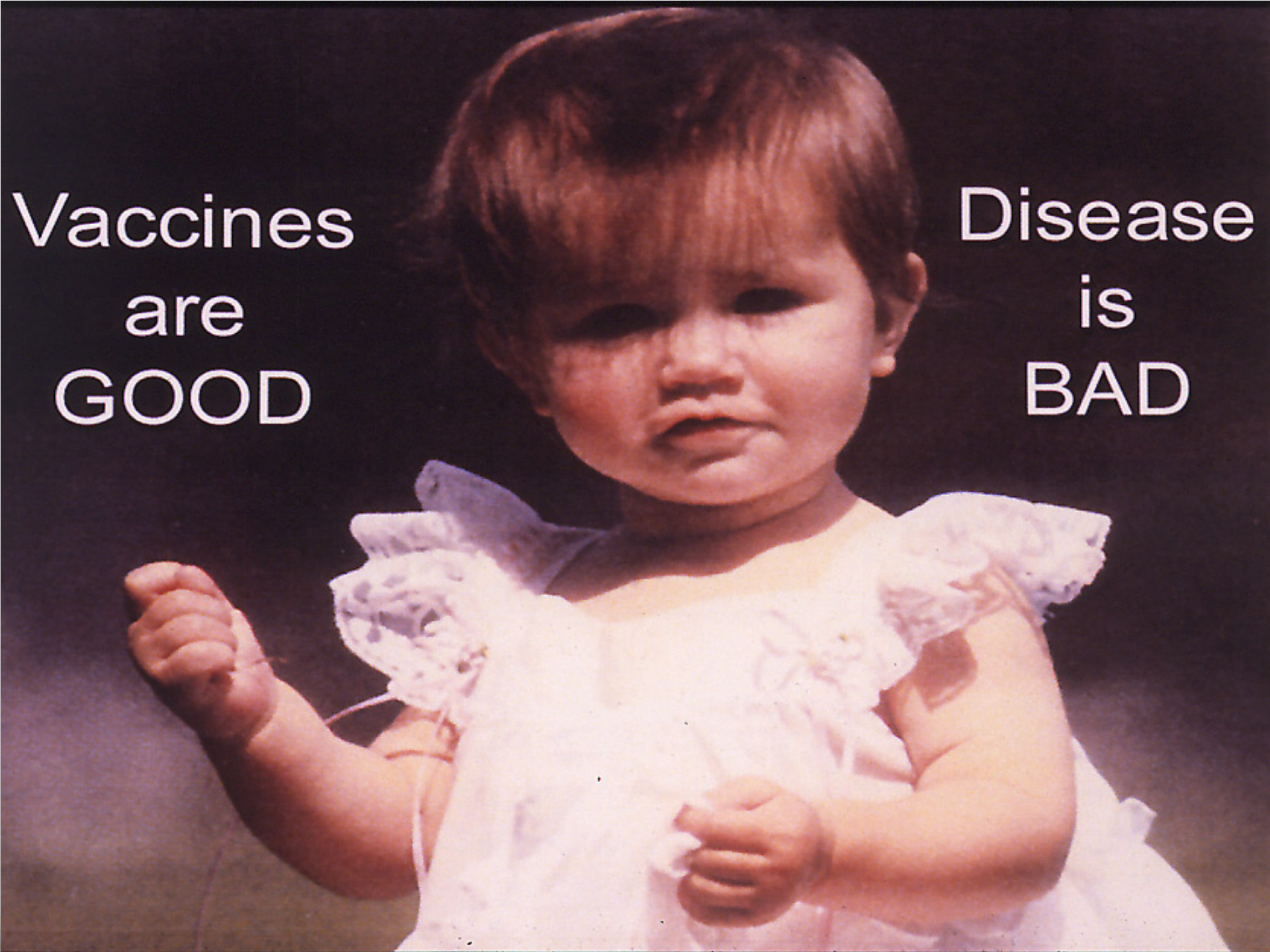
Microcephaly and Flavi/Arbo Viruses

Virus	Documented Intrauterine Transmission (Number of cases/Number studied)	Exposure	Method of Fetal Diagnosis
Dengue	5/34 (15%) disseminated disease; **no microcephaly**	3rd trimester	Specific IgM Ab Viral isolation
Chikungunya	38/7504 (0.5%) CNS lesions on MRI, **5 (0.07%) with microcephaly**, and disseminated disease	Variable	RT PCR Specific IgM antibody
West Nile	1 CNS lesions on MRI, chorioretinitis	Early 3rd trimester	Specific IgM Ab Specific neutralizing Ab, PCR
Yellow Fever	1 disseminated disease	Late 3rd trimester	Specific IgM antibody
Japanese Encephalitis	1 disseminated disease	Early 2nd trimester	Specific IgM Ab Viral isolation

The Incidence of Microcephaly Causally Related to **Non-Zika** Flavi- and Arboviruses Seems to be Very Low

This may be due to pathogen specific differences in:

1. Depression of maternal CMI or innate immune function
2. Effects on maternal-fetal placental barriers
3. Tissue tropism
4. Up regulation of inflammatory responses


Vaccines
are
GOOD
Disease
is
BAD