Congenital CMV Infection – Disease Burden and Prevention Strategies

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UAB MEDICINE
PEDIATRICS

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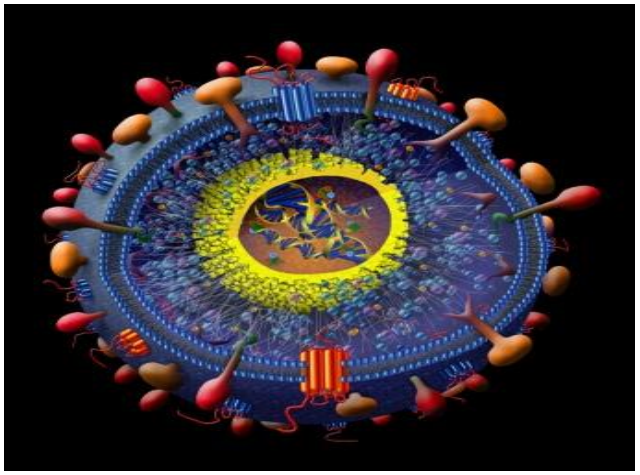
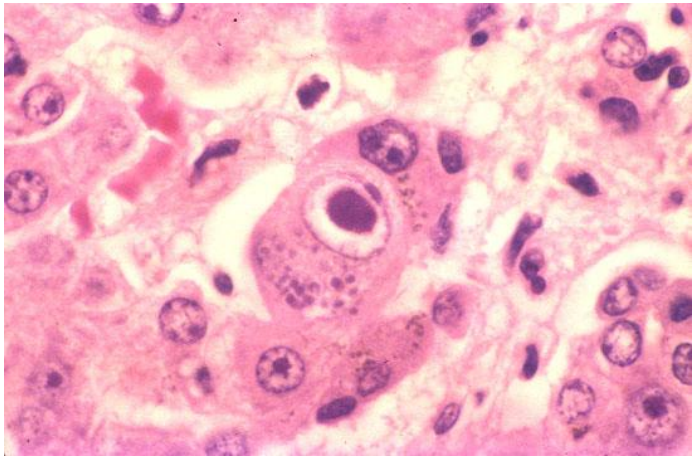
Disclosures

- Research Funding to UAB: NIH, Merck, and Pfizer
- Consulting: GSK CMV Vaccine Scientific Advisory Board
- Member, Board of Directors, National CMV Foundation

Cytomegalovirus

- Belongs to ß-herpesvirus family
- Large ds-DNA (~250 kb size genome)
- Large, inclusion-bearing cells (typical owl's eye appearance)
- Highly species-specific virus
- CMV strains are highly genetically diverse





CMV infection during pregnancy

- Adverse outcomes of pregnancy
  - Still births, intrauterine growth restriction and preterm birth (Iwasenko, JID 2011; Periera, JID 2014)
- Disease burden from congenital CMV
  - Mortality and morbidity during newborn period
  - Long-term sequelae
    - Hearing and balance disorders, vision loss, and neurodevelopmental delays

Congenital CMV infection

- Most frequent congenital infection
- Leading non-genetic cause of sensorineural hearing loss and brain disease in children
- Most (85%) infected newborns have no clinical abnormalities (subclinical or asymptomatic infection)
  - 10-15% with asymptomatic infection develop sequelae (mainly hearing loss)
  - 50-60% of symptomatic children develop sequelae

Public health importance of congenital CMV infection

Congenital CMV infection rates in live births

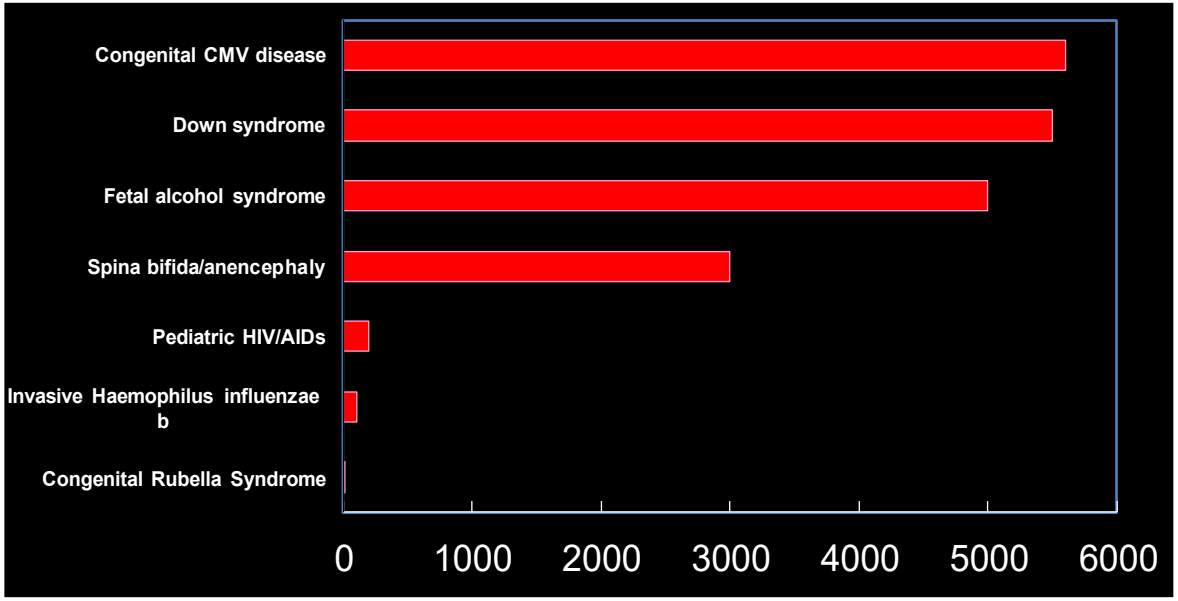
US, Canada, Western Europe, Australia & Japan – 0.5%-0.7%

Latin America, Africa and most countries in Asia – 0.4%-6%

Newborns with congenital CMV infection annually

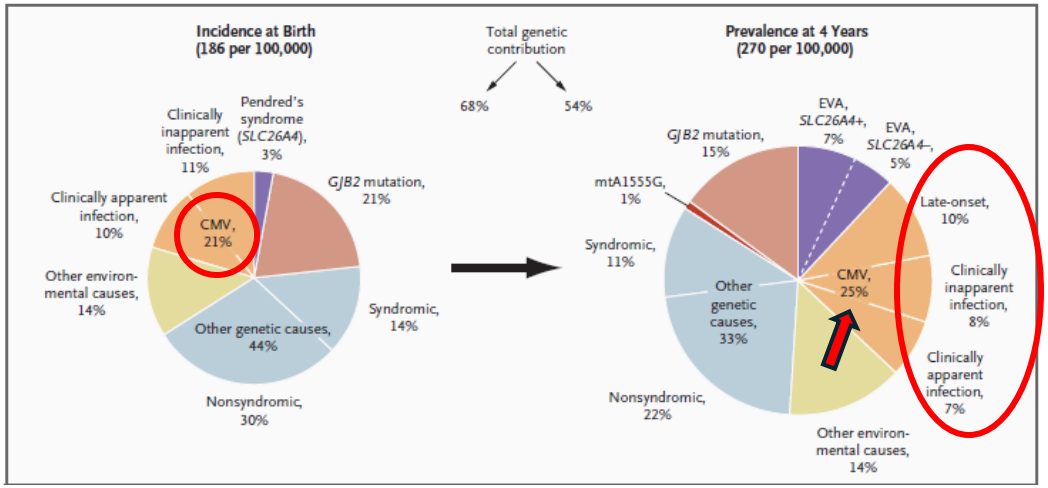
U.S.	20,000 – 30,000
Brazil	15,450 – 25,750
India	~230,000

Congenital CMV Infection – Disease Burden



Annual number of US children with cCMV-related sequelae

- Leading non-genetic cause of SNHL
- Leading cause of neurodevelopmental delays
  - 0.5% mortality
  - 17-20% with ≥ 1 long-term sequelae



Morton 2006; Dollard 2007; Cannon 2009; Manicklal 2013

Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

William D Rawlinson, Suresh B Boppana, Karen B Fowler, David W Kimberlin, Tiziana Lazzarotto, Sophie Alain, Kate Daly, Sara Doutré, Laura Gibson, Michelle L Giles, Janelle Greenlee, Stuart T Hamilton, Gail J Harrison, Lisa Hui, Cheryl A Jones, Pamela Palasanthiran, Mark R Schleiss, Antonia W Shand, Wendy J van Zuylen

Moderate to severe symptomatic cCMV Disease

Multiple cCMV Findings

- Thrombocytopenia
- Petechial rash
- Hepatomegaly
- Splenomegaly
- IUGR
- Hepatitis (elevated LFTs)

CNS involvement

- Microcephaly
- Imaging: (ventriculomegaly, calcifications, cortical or cerebellar malformations)
- Chorioretinitis
- SNHL
- Abnormal CSF indices
- CMV DNA in CSF

Mildly symptomatic cCMV disease

1-2 isolated, mild, transient cCMV manifestations

Asymptomatic cCMV with isolated SNHL

No apparent abnormalities + SNHL

Asymptomatic cCMV infection

No apparent abnormalities + normal hearing

Rawlinson, 2017

Neurodevelopmental Sequelae

Symptomatic cCMV

- 43-64% with global developmental delay
- 30-43% with gross motor delay
- 50% with intellectual/cognitive delays
- Prognostic indicators → microcephaly, radiological findings, chorioretinitis

Asymptomatic cCMV

- No developmental delays compared to controls
- No significant gross/fine motor
- No speech/language delay if corrected for SNHL
- SNHL onset < 2 yrs → low receptive/vocab scores
- Normal intellectual/cognitive development
- No biomarkers or predictors for adverse outcome

Pesch (review) 2024

Sensorineural Hearing Loss (SNHL)

- Association initially described in 1964
- The most common cause of non-hereditary SNHL
- Prevalence of cCMV-associated SNHL → 12.6%
  - 1 of 3 with symptomatic cCMV
  - 1 of 10 with asymptomatic cCMV
- <u>Unique characteristics</u>

Onset → newborn vs late-onset/delayed

Progression → stable vs progressive

Severity → mild – moderate – severe/profound

Fluctuant

Laterality → unilateral vs bilateral

- No definitive virological prognostic indicators

cCMV-associated SNHL

TABLE 1 Results of the Quantitative Approach[3,8,23,27,40,51,63–66]

	Estimated Proportion, %	95% CI	I^2, %	*P* of Heterogeneity
Prevalence of cCMV in population	0.58	0.41–0.79	94.3	<.0001
Proportion of symptomatic cCMV	9.8	5.8–14.6	70	.0004
Proportion of asymptomatic cCMV	90.2	85.4–94.2	70	.0004
Proportion of symptomatic cCMV with hearing loss	32.8	23.2–43.2	0	.6423
Proportion of asymptomatic cCMV with hearing loss	9.9	6.3–14.2	46.9	.0495
Proportion of cCMV with hearing loss	12.6	9.4–16.3	26.7	.198
Prevalence of hearing loss by cCMV in population	0.05	0.03–0.09	79.6	<.0001

TABLE 2 Nature of Hearing Loss Stratified by Symptomatic or Asymptomatic Infection[8,24,25,27–29,34,40,67–72]

Hearing Loss Characteristics	Symptomatic at Birth		Asymptomatic at Birth	
	Estimated Proportion, %	95% CI, I^2, *P* of Heterogeneity	Estimated Proportion, %	95% CI, I^2, *P* of Heterogeneity
Bilateral hearing loss	71.2	64.2–77.8, 0%, .8944	43.1	28.2–58.6, 39.8%, .1024
Unilateral hearing loss	28.8	22.2–35.9, 0%, .8944	56.9	41.4–71.8, 39.8%, .1024
Severe to profound hearing loss	76.8	70.1–83, 0%, .5044	77.7	59.6–91.6, 52.9%, .038
Bilateral severe to profound hearing loss	65.1	54.2–75.2, 0%, .4937	42.6	20.2–66.7, 49%, .0673
Delayed hearing loss	18.1	5.9–36.2, 65.4%, .0051	9	0.8–24.5, 64.8%, .0058
Progressive hearing loss	17.7	3.5–39.4, 80.5%, <.0001	20.3	5.3–41.8, 73.1%, .0002
Fluctuating hearing loss	21.5	9.3–37, 55.6%, .0272	24	2.1–59.6, 86.3%, <.0001

Goderis 2014

Median age of delayed-onset SNHL → 44m (Asx) vs 33 m (Sx)

cCMV-associated Vestibular Insufficiency

Vestibular Follow-up Program for Congenital Cytomegalovirus Based on 6 Years of Longitudinal Data Collection

Cleo Dhondt,[1] Leen Maes,[2,3] Emmely Van Acker,[2] Sarie Martens,[2] Saartje Vanaudenaerde,[3] Lotte Rombaut,[3] Elise De Cuyper,[1] Helen Van Hoecke,[1,3] Els De Leenheer,[1,3] and Ingeborg Dhooge[1,3]

Audiovestibular Consequences of Congenital Cytomegalovirus Infection: Greater Vulnerability of the Vestibular Part of the Inner Ear

Emilien Chebib,[1] Audrey Maudoux,[1,2] Charlotte Benoit,[1,3] Sophie Bernard,[1] Thierry Van Den Abbeele,[1,3] Natacha Teissier,[1,3,4] and Sylvette R. Wiener Vacher,[1,2,3,4]

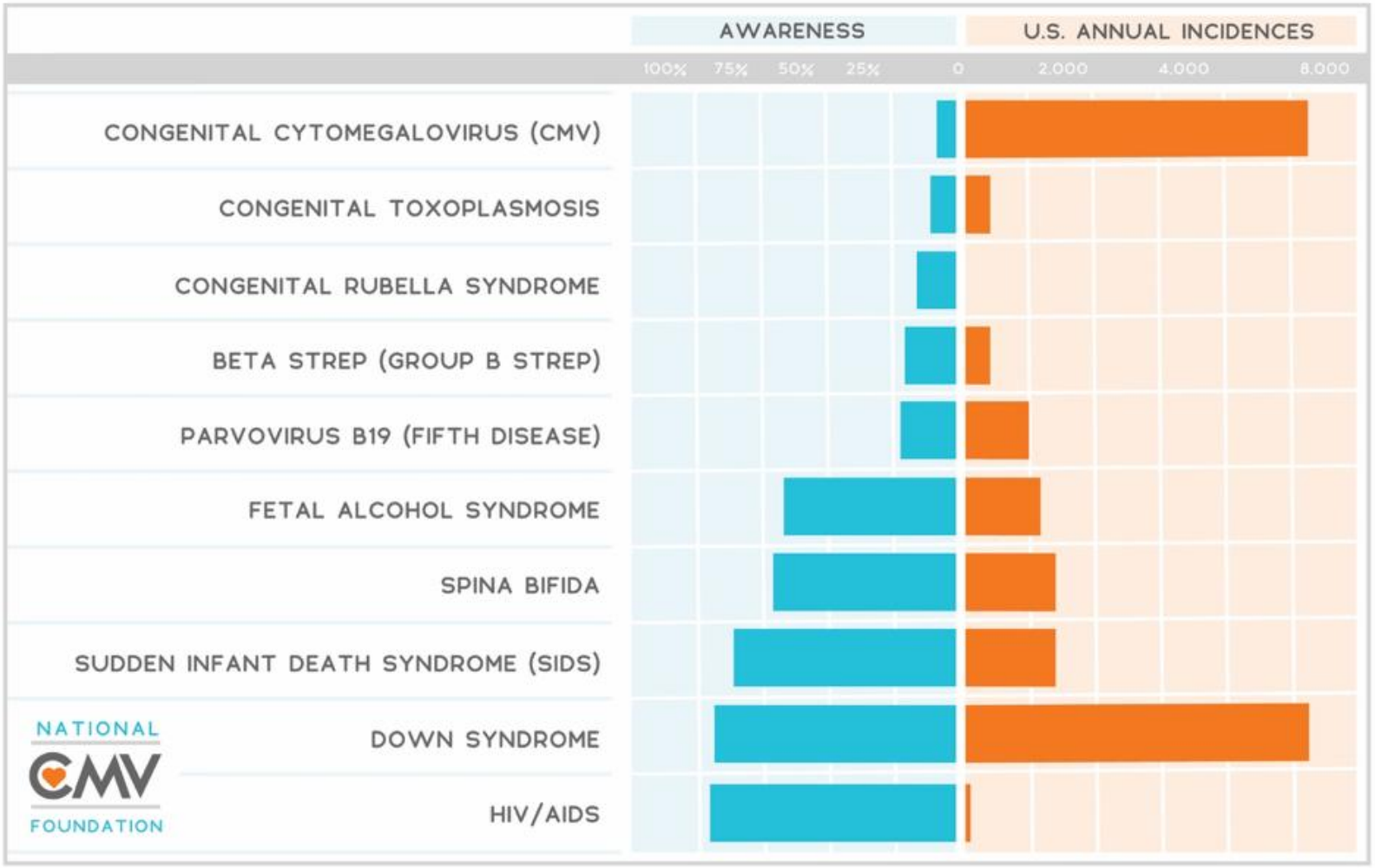
Vestibular, Gaze, and Balance Disorders in Asymptomatic Congenital Cytomegalovirus Infection

Swetha Pinninti, MD,[a] Jennifer Christy, PT, PhD,[b] Anwar Almutairi, PT, PhD,[b] Graham Cochrane, BA,[b] Karen B. Fowler, PhD,[a,c] Suresh Boppana, MD[a,c]

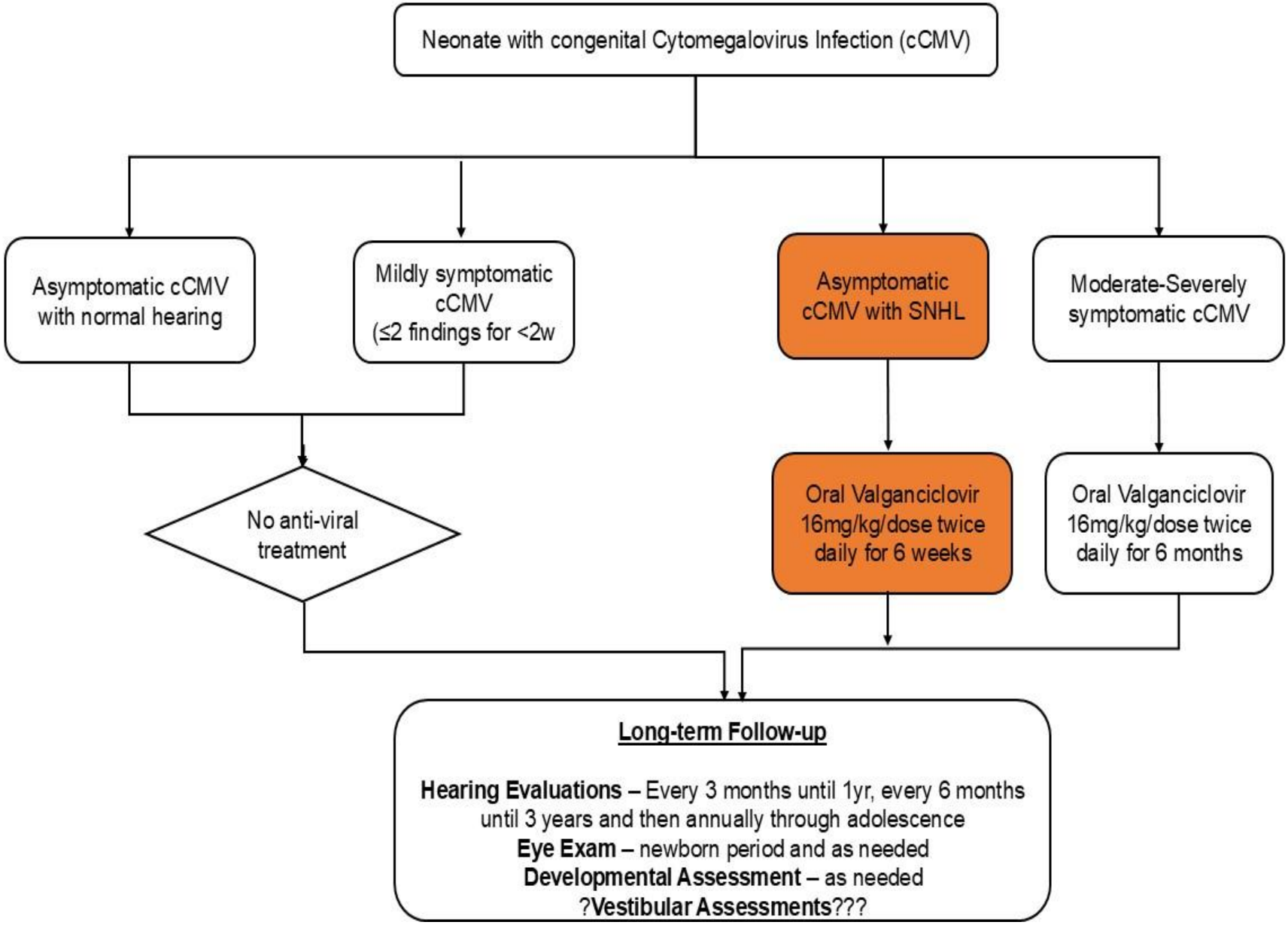
- Incidence 19-92%
- Symptomatic cCMV > Asymptomatic cCMV
- Independent of severity and laterality of SNHL

- ??Most common sequela of cCMV; Vestibular Rehabilitation

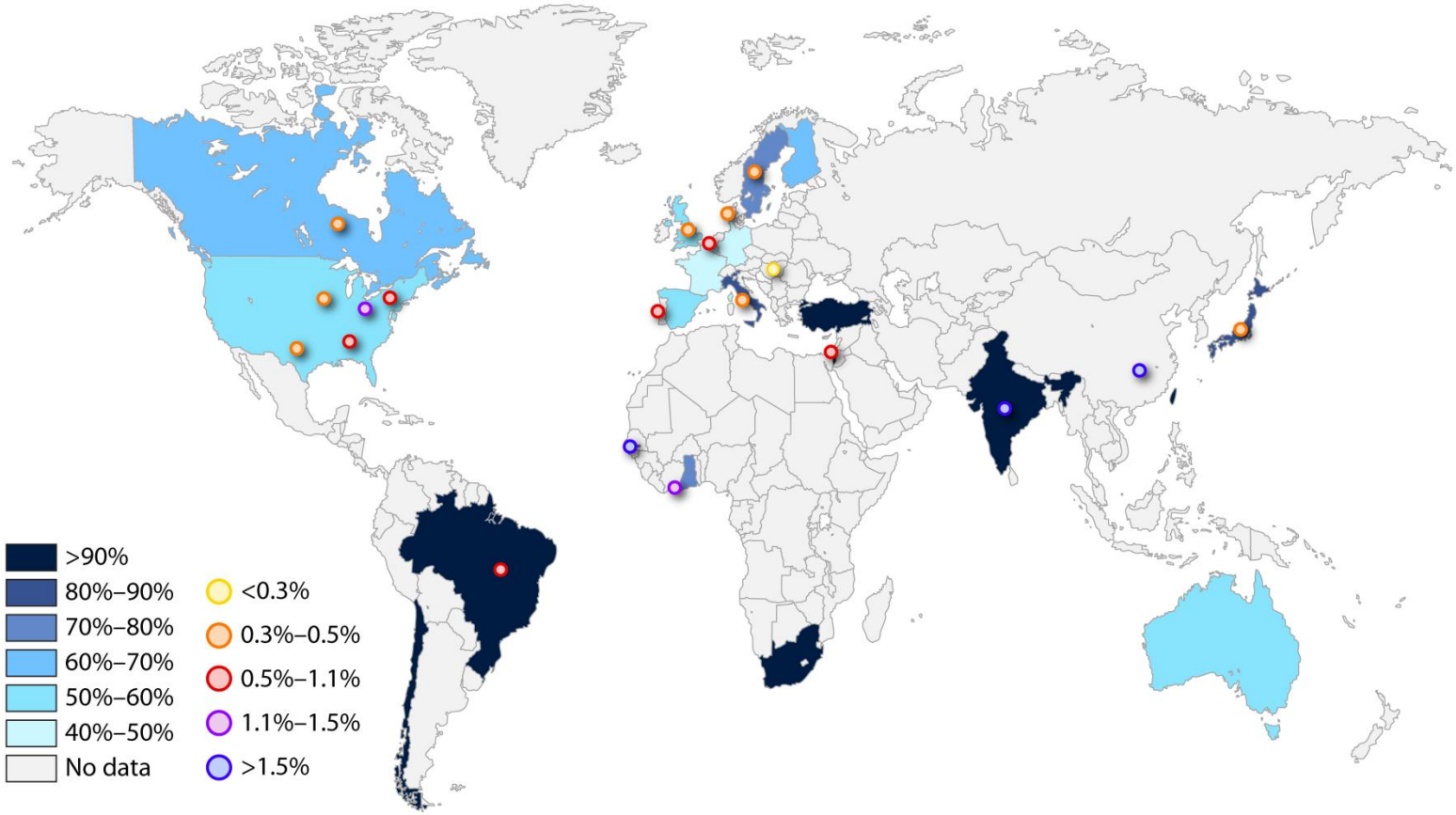
2016 HealthStyles™ surveys



Follow-up


Neonate with congenital Cytomegalovirus Infection (cCMV)
Asymptomatic cCMV with normal hearing
Mildly symptomatic cCMV (≤2 findings for <2w
Asymptomatic cCMV with SNHL
Moderate-Severely symptomatic cCMV
No anti-viral treatment
Oral Valganciclovir 16mg/kg/dose twice daily for 6 weeks
Oral Valganciclovir 16mg/kg/dose twice daily for 6 months
Long-term Follow-up
Hearing Evaluations – Every 3 months until 1yr, every 6 months until 3 years and then annually through adolescence
Eye Exam – newborn period and as needed
Developmental Assessment – as needed
?Vestibular Assessments???

CMV seroprevalence rates among women of reproductive age and birth prevalence of congenital CMV



Manicklal, Clin Microbiol Rev 2013
Cannon, Rev Med Virol 2010

Maternal CMV Infection

- Primary CMV infection - Initial acquisition
  - Seroconversion
  - Positive CMV IgG, IgM and low IgG avidity
  - Intrauterine transmission – ~30%
  - Accounts for 25 - 50% of congenital CMV infections in US

- Non-primary CMV infection – Acquisition prior to pregnancy
  - Positive CMV IgG, negative IgM, and high IgG avidity
  - Intrauterine transmission – ~1%
  - Accounts for majority of congenital CMV infections

CMV Seroconversion Rates

Population group	Annual rate (95% CI)
Pregnant women	2.3% (2.1-2.4)
Healthcare workers caring for children	2.3% (1.9-2.9)
Daycare workers	8.5% (6.1-11.8)
Parents of young children	
Children not shedding CMV	2.1% (0.3-6.8)
Children shedding CMV	24% (18-30)

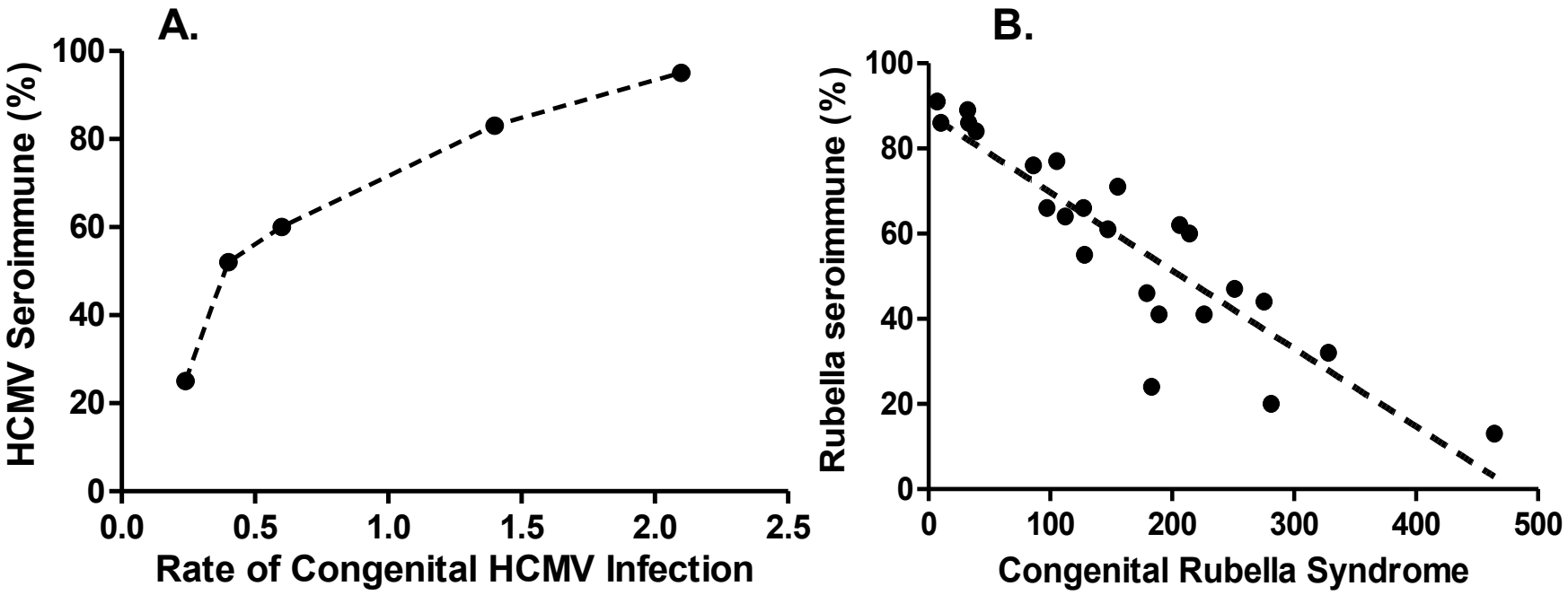
Hyde TB, Schmidt DS, Cannon MJ. Rev Med Virol 2010

Primary CMV infection during pregnancy
Rates of intrauterine transmission

- Preconception period – 5.2%
- Periconceptional period – 16.4%
- First trimester – 36.5%
- Second trimester – 40.1%
- Third trimester – 65%

Picone et al. Prenat Dign 2013

Seroprevalence and congenital CMV and rubella infections



Stagno et al. Semin Perinatol, 1983
Cutts et al. Int J Epidemiol 1999

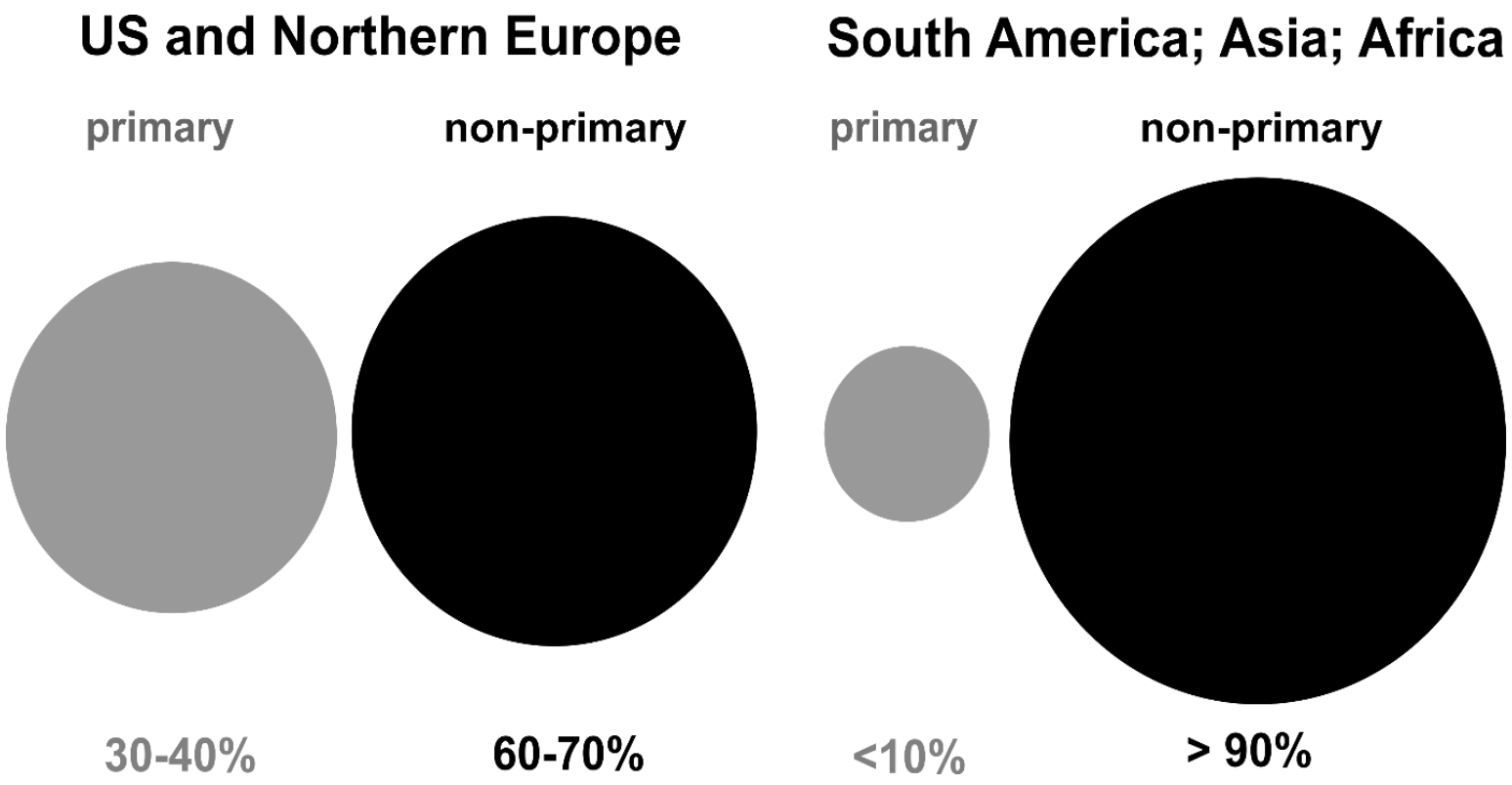
What proportion of congenital CMV infections are attributed to non-primary maternal infections?

Estimated no. of children with congenital CMV in the U.S. from mothers with primary and non-primary infection during pregnancy

Race/ethnicity, age	CMV seropositive proportion	Live-birth pregnancies in the United States	Live-birth pregnancies among CMV seropositive women	Live-born children with congenital infection from mothers with non-primary infection	Previously seronegative women with primary infection during live birth pregnancies	Live-born children with congenital infection from mothers with primary infection
Column calculation	A[a]	B[a]	C=A*B	D=C*1.4%[b](95% CI, 1.1%–1.7%)	E[a]	F=E*32.3%[c](95% CI, 29.8%–34.9%)
Non-Hispanic White						
12–19 Years	0.390	232000	90480	1267 (995–1538)	209 (0–5452)	68 (0–1902)
20–29 Years	0.433	1214000	525662	7359 (5782–8936)	9469 (5220–14204)	3058 (1608–4555)
30–39 Years	0.506	912000	461472	6461 (5076–7845)	6202 (3466–9302)	2003 (1058–2969)
40–49 Years	0.611	51000	31161	436 (343–530)	270 (153–408)	89 (46–129)
Subtotal				15523 (12196–18849)		5218 (2712–9555)
Non-Hispanic Black						
12–19 Years	0.574	133000	76342	1069 (840–1298)	4150 (2008–6211)	1340 (659–2035)
20–29 Years	0.822	306000	251532	3521 (2767–4276)	1867 (1040–2693)	603 (334–877)
30–39 Years	0.866	135000	116910	1637 (1286–1987)	621 (351–891)	201 (113–290)
40–49 Years	0.947	8000	7576	106 (83–129)	14 (8–21)	5 (2–7)
Subtotal				6333 (4976–7690)		2149 (1108–3209)
Mexican American						
12–19 Years	0.699	122000	85278	1194 (938–1450)	805 (0–2135)	264 (0–692)
20–29 Years	0.825	399000	329175	4608 (3621–5596)	2673 (1476–3870)	863 (474–1260)
30–39 Years	0.895	170000	152150	2130 (1674–2587)	680 (374–986)	220 (120–321)
40–49 Years	0.932	10000	9320	130 (103–158)	26 (14–38)	8 (5–12)
Subtotal				8062 (6336–9791)		1355 (599–2285)
Total				29918 (23508–36330)		8722 (4419–16049)

Wang, Clin Infect Dis 2011

Contribution of primary and non-primary maternal CMV infections



Marisa Mussi-Pinhata and colleagues

Primary Maternal Infection

1000 seronegative women

1000 at risk for infection[1]

2) Seroconversion rate 2-4%[2]

3) Intrauterine transmission rate 30%[3]

6-12 congenital infections[4]

Non-Primary Maternal Infection

1000 seroimmune women

1) Unknown number at risk for reinfection/reactivation[1]

2) Reinfection rate 4-17%[2]

3) Intrauterine transmission rate 27.5%-6.5%[3]

9-45 congenital infections[4]

Britt W, Med Microbiol Immunol, 2015

The paradox of cCMV and maternal non-primary CMV Infections

Table 1. Human Cytomegalovirus (HCMV) Seroreactivity and Congenital HCMV Prevalence in Maternal Populations

Location	Maternal Seroreactivity	cCMV Prevalence
Brazil (Mussi-Pinhata, 2018) [29]	98%	6.1
China (Wang, 2011) [28]	96%	7
Japan (Tanimura, 2017) [43]	71%	6.4
France (Leruez-Ville, 2017) [44]	61%	3.7
Finland (Puhakka, 2018) [43][a]	71%	2.0

Britt W 2020

TABLE 3 Hearing Loss According to Type of Infection[24,25,27–29,40,71,72]

Type of Infection	Estimated Proportion, %	95% CI	I^2, %	*P* c Heterogeneity
Hearing loss in case of primary infection	12.1	8.6–16	18.8	.2814
Hearing loss in case of nonprimary infection	11.8	7.5–16.8	21.7	.2568

Goderis 2014

TABLE 3. COMPARISON OF STRAIN-SPECIFIC ANTIBODY RESPONSES AGAINST GLYCOPROTEIN H IN SERIAL SERUM SAMPLES FROM MOTHERS WITH PRECONCEPTIONAL IMMUNITY AGAINST CMV, ACCORDING TO WHETHER THEIR INFANTS HAD CONGENITAL CMV INFECTION.

ACQUISITION OF NEW ANTIBODY SPECIFICITIES BETWEEN PREGNANCIES	MOTHERS OF INFECTED INFANTS (N=16)	MOTHERS OF UNINFECTED INFANTS (N=30)
	no. (%)	
Yes	10 (62)	4 (13)*
No	6 (38)	26 (87)

*P<0.001 for the comparison with the mothers of infected infants.

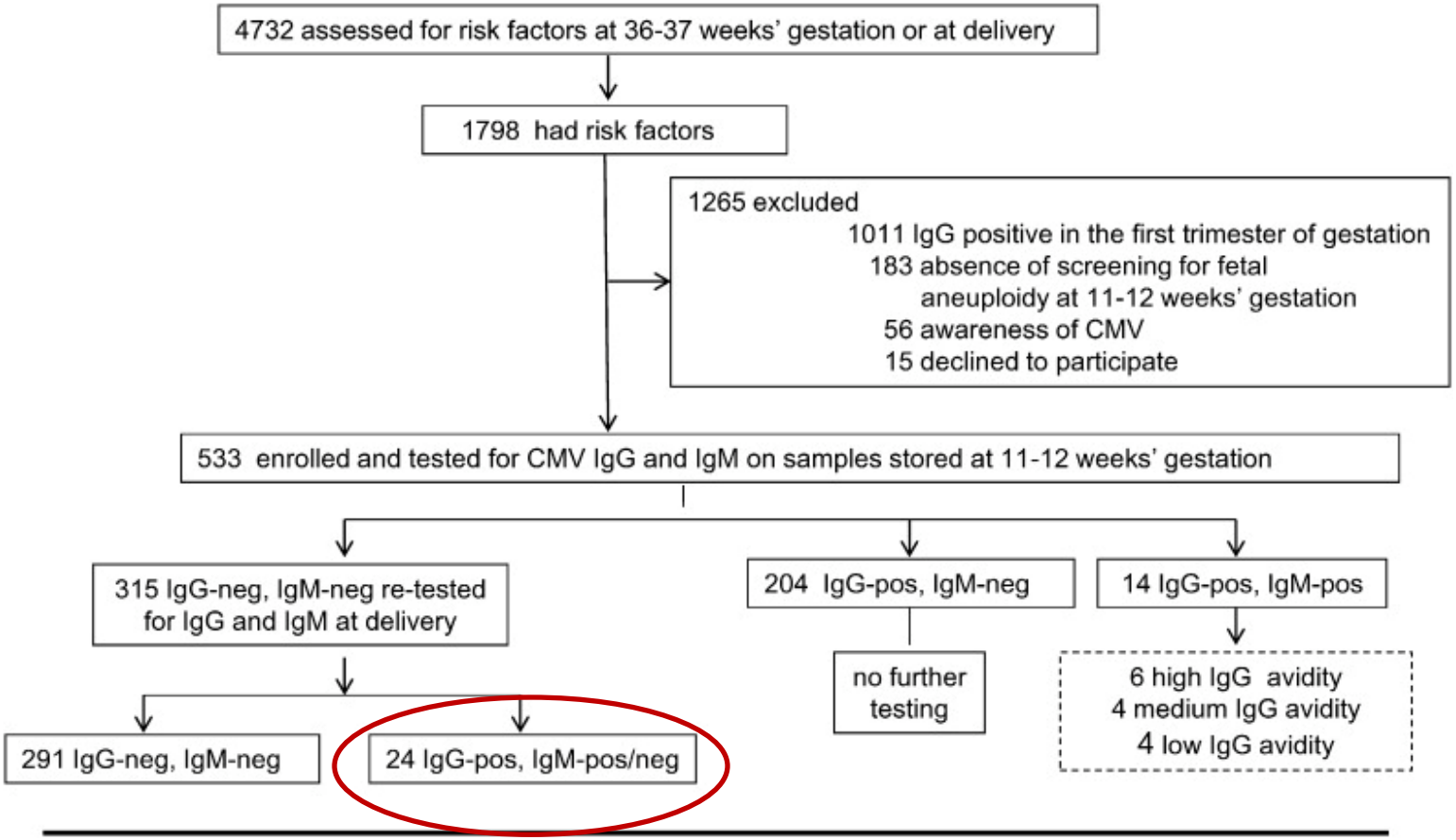
Boppana et al. 2001

- Non-primary >> primary maternal CMV infections
- Similar frequency of sequelae
- CMV reactivation vs re-infections

Boppana 2001;Ross 2006; Mussi-Pinhata 2018; St-Georges 2025

Prevention of Maternal and Fetal Congenital CMV infection

Behavioral intervention trial to prevent primary CMV infection



4/331 (1.2%) vs 24/315 (7.6%) – Delta 6.4, 95% CI 3.2-9.6, p<0.001

Revello MG et al. Ebiomedicine. 2015 Sep; 2(9): 1205–1210.

- Hyperimmune globulin is ineffective

Hughes 2021

- Oral valacyclovir for primary CMV maternal infections
  - 1st trimester infections
  - decreased amniotic fluid CMV PCR positivity
  - decreased incidence of cCMV

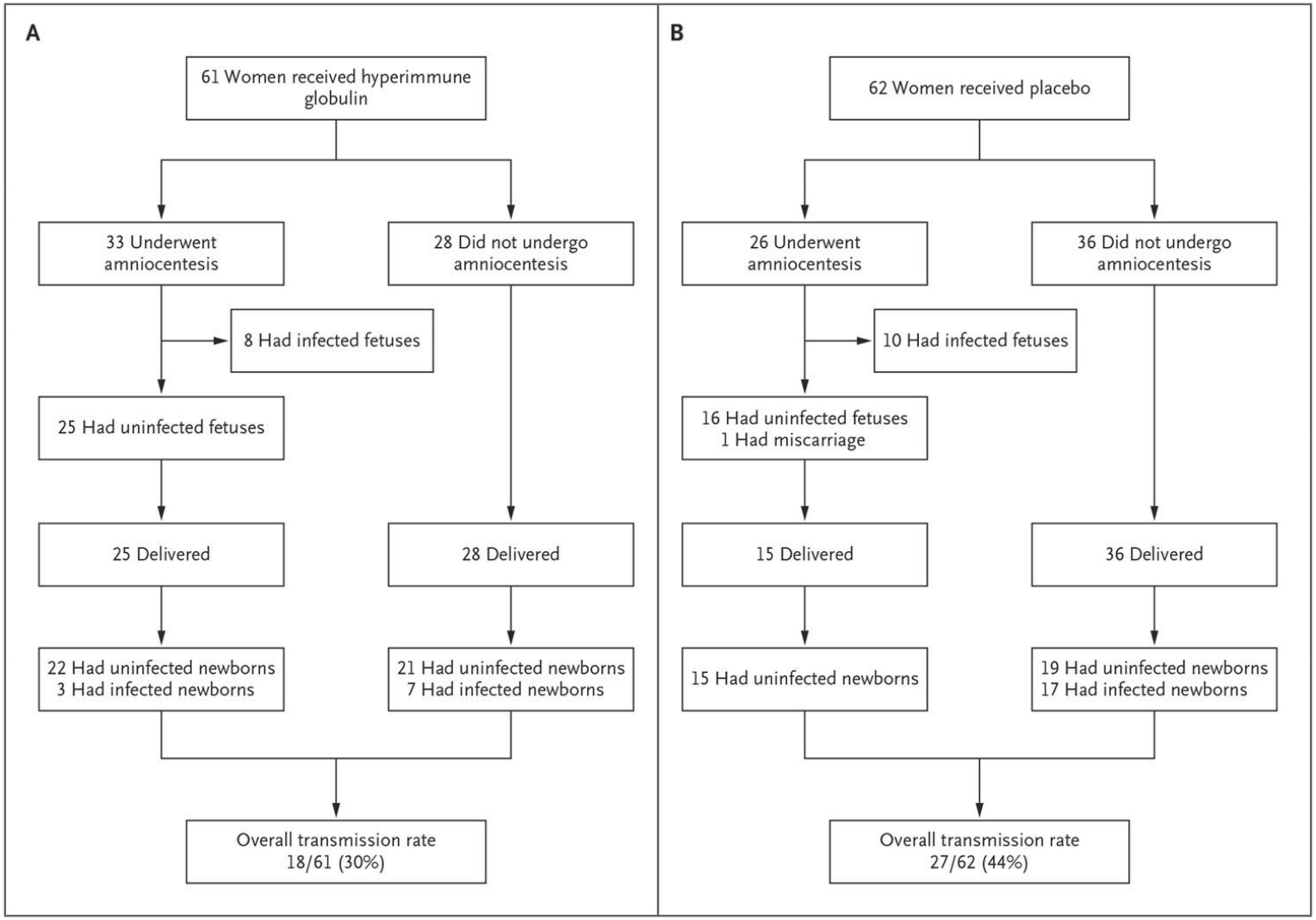
Shahar-Nissan 2020; Faure-Bardon 2021

- Fetal CMV infection – efficacy of treatment unknown

D'Antonio 2023

- US → No systematic CMV screening during pregnancy

Hyperimmune globulin failed to prevent congenital CMV infection



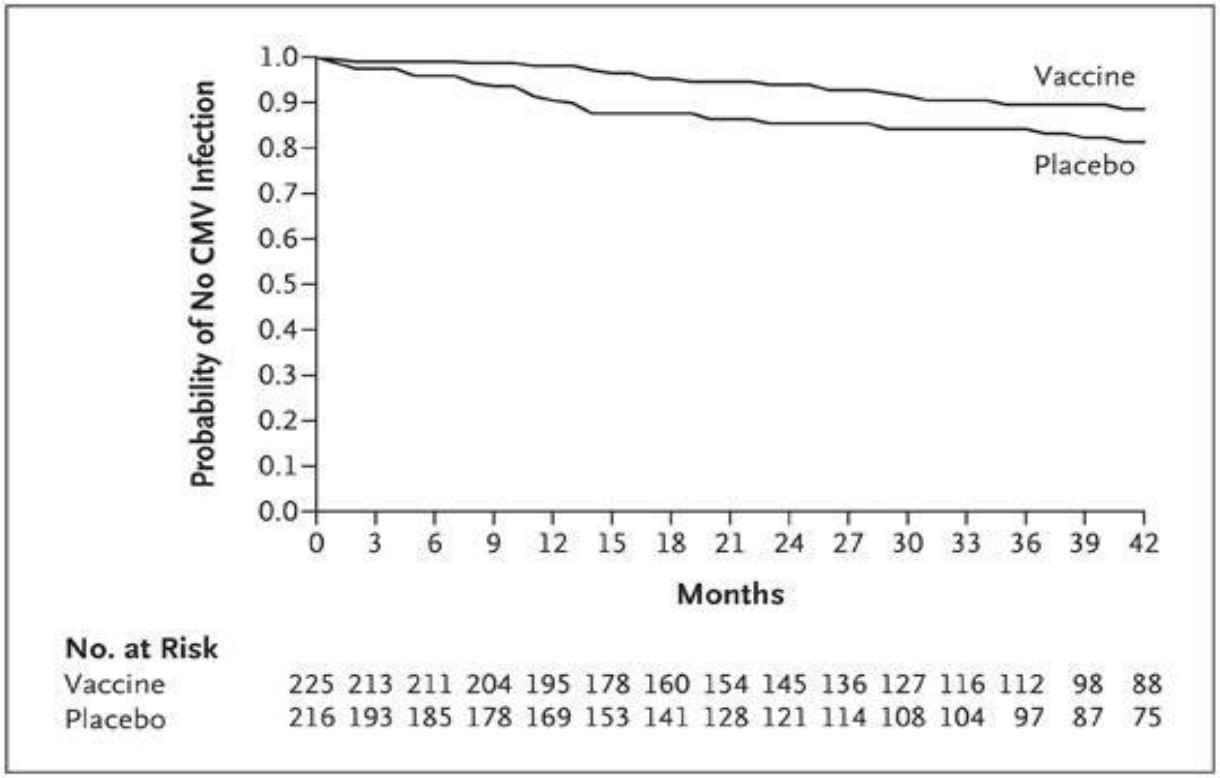
Revello, N Engl J Med, 2014

NICHD MFMU Network CMV Hyperimmune Globulin Trial

Primary and Secondary Outcomes				
	HIG (N=206)	Placebo (N=193)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary outcome	46 (22.7)	37 (19.4)	1.17 (0.80 - 1.72)	0.424
Neonatal CMV infection	37	32		
Neonatal death without evidence of CMV	0	0		
Fetal death with evidence of CMV infection	6	3		
Fetal death without evidence of CMV	3	2		
Fetal/neonatal outcomes				
Fetal death	9 (4.4)	5 (2.6)	1.69 (0.58 - 4.97)	0.330
Neonatal death	1	0	-	-
Fetal growth restriction < 5th percentile	21 (10.7)	10 (5.3)	2.01 (0.97 - 4.16)	0.052
Head circumference < 3rd percentile	6 (3.1)	6 (3.2)	0.97 (0.32 - 2.95)	0.956
Maternal outcomes				
Any side effects	81 (39.3)	62 (32.1)	1.22 (0.94 - 1.60)	0.134
Preterm birth < 37 weeks	25 (12.2)	16 (8.3)	1.47 (0.81 - 2.67)	0.200

Hughes B. 2021

Probability of Remaining Free of CMV Infection following CMV gB immunization

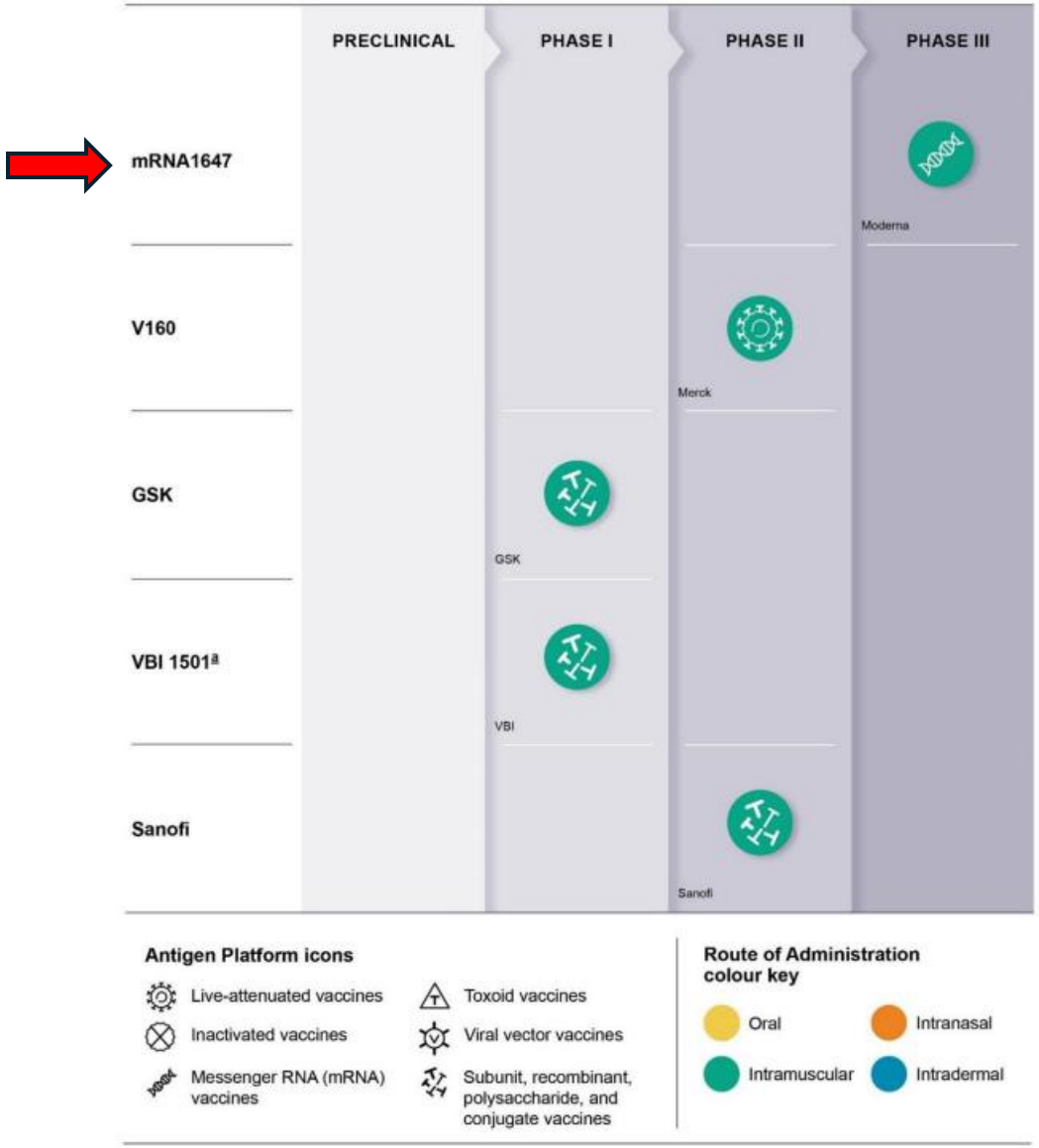


Vaccine efficacy based on infection rates per 100 person-years: 50% (95% CI, 7 to 73)

Pass RF et al. N Engl J Med 2009;360:1191-1199

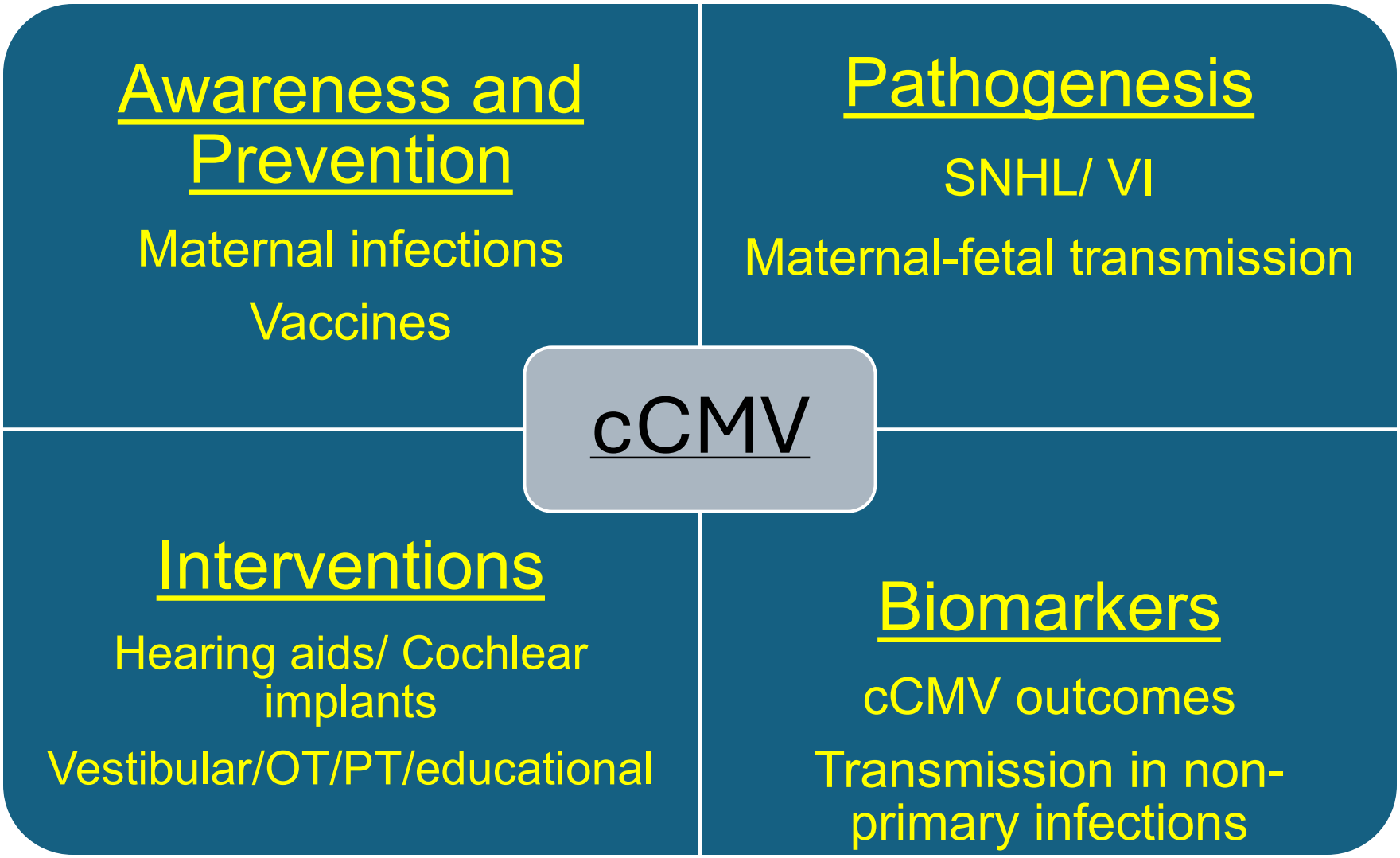
CMV Vaccines

No currently approved CMV vaccine



Boppana 2023

Gaps and Challenges




Questions???
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