ACIP CMV Vaccine Workgroup
Cytomegalovirus (CMV) and congenital CMV (cCMV) Epidemiology and Disease Burden

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Measles, Rubella and CMV Epidemiology Team
Viral Vaccine Preventable Diseases Branch
Division of Viral Diseases

Objectives

- Review epidemiology and disease burden of CMV and cCMV

More than 16,000 children born with cCMV infection in the U.S. every year – 4.5 per 1,000 live births

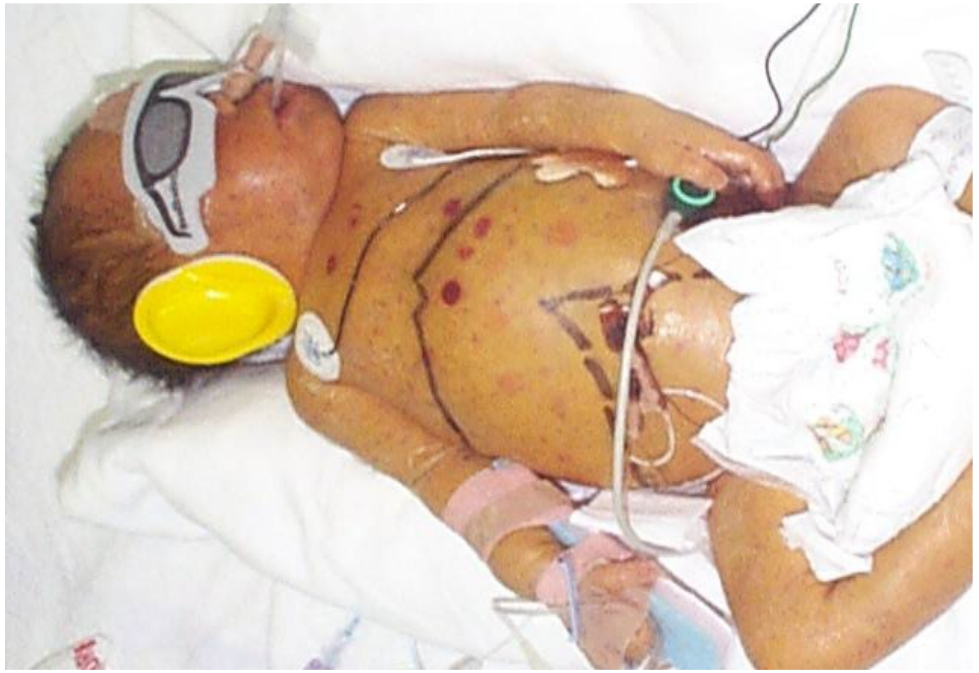
Outcome	Annual number of affected children	%
Neonatal death	80	0.5
cCMV disease†	2800	17
Long-term outcomes *(selected)*		
Sensorineural hearing loss	825	5
Cognitive impairment	495	3
Motor impairment	165	1

Frequencies based on unpublished review of 30 unique cohorts of children with cCMV identified through newborn screening followed up through childhood.

cCMV disease

Neonatal signs

- Rash (purpura/petechiae)
- Enlarged liver and/or spleen (hepatosplenomegaly)
- Small head (microcephaly)



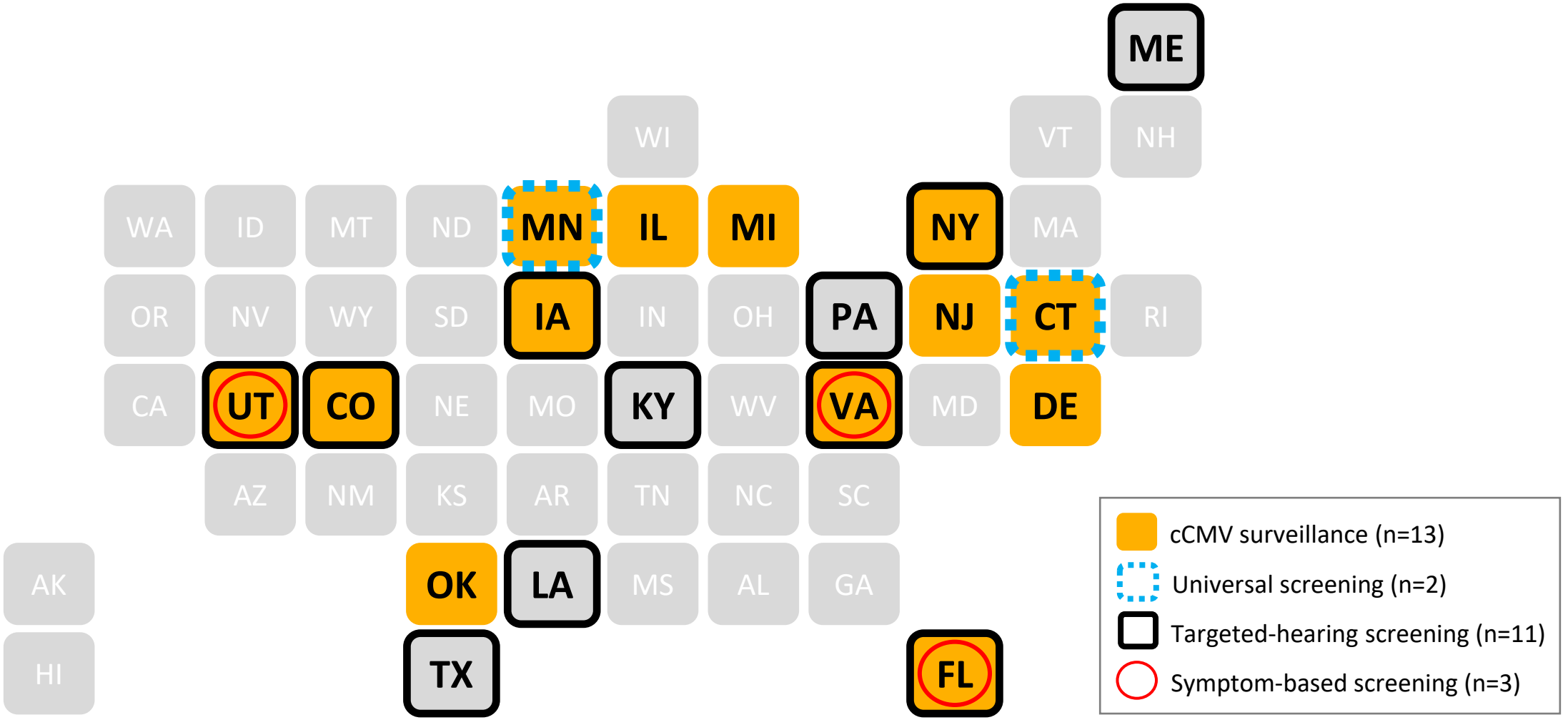
Laboratory diagnosis

- PCR or culture positive on urine, blood, cerebrospinal fluid collected within 21 days of life

Most newborns with cCMV infection have no clinical signs at birth and are not diagnosed

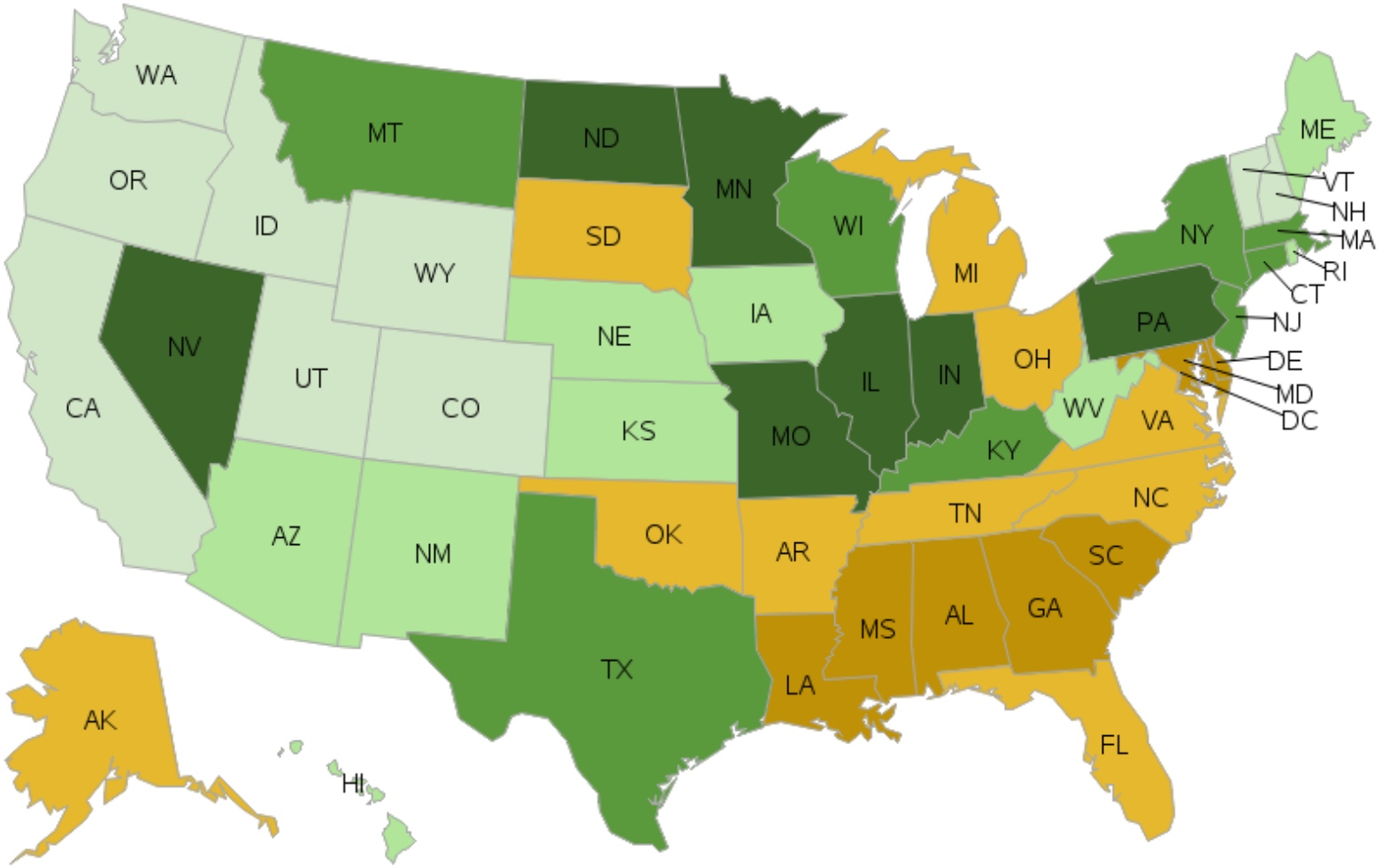
Congenital Cytomegalovirus (cCMV) Infection and Disease 2024 Case Definition | CDC

US landscape on cCMV screening and surveillance



Last updated February 2025

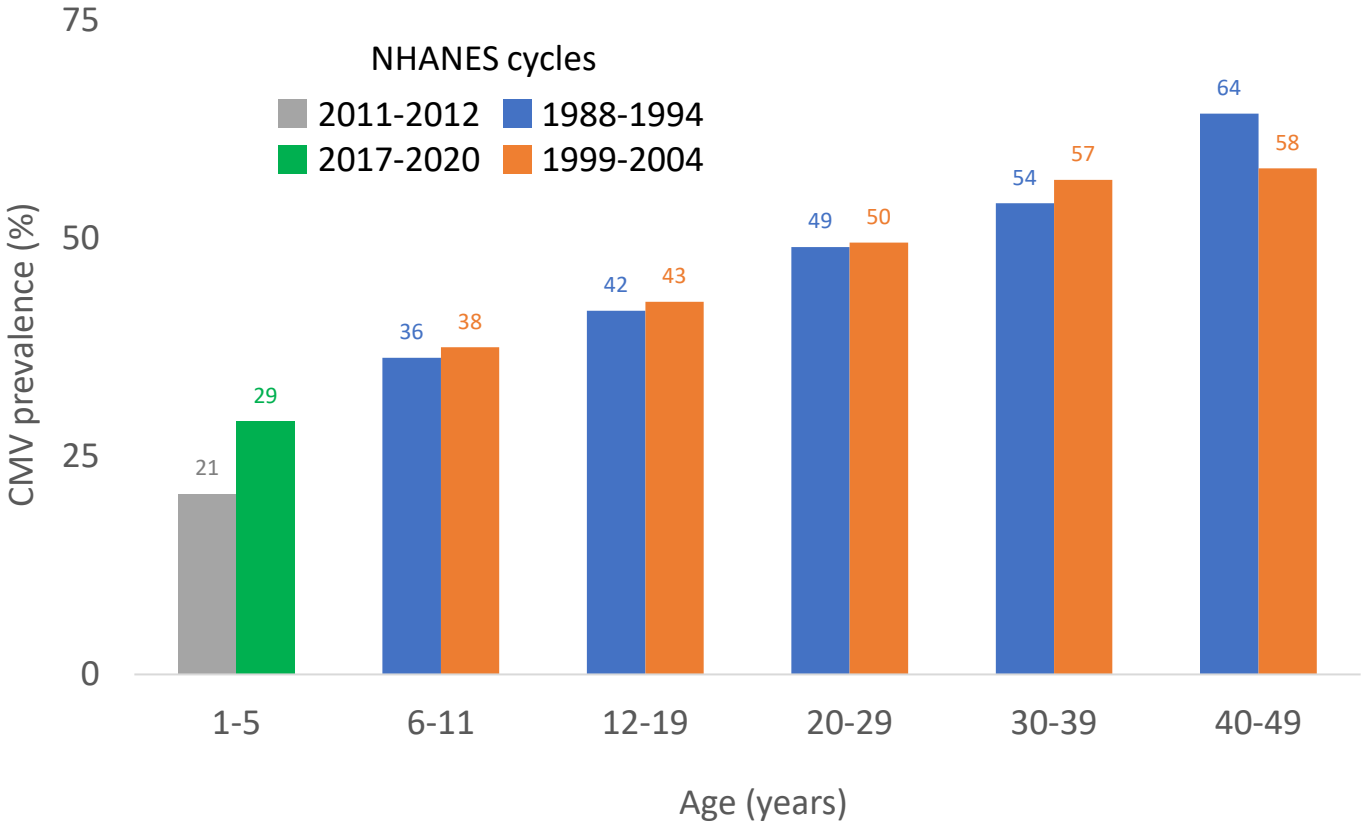
State-specific cCMV prevalence estimates, United States



Adapted from Lutz et al. Updated National and State-Specific Prevalence of Congenital Cytomegalovirus Infection, United States, 2018-2022. J Public Health Manag Pract. 2024

CMV IgG Seroprevalence, United States

National Health and Nutrition Examination Surveys (NHANES)



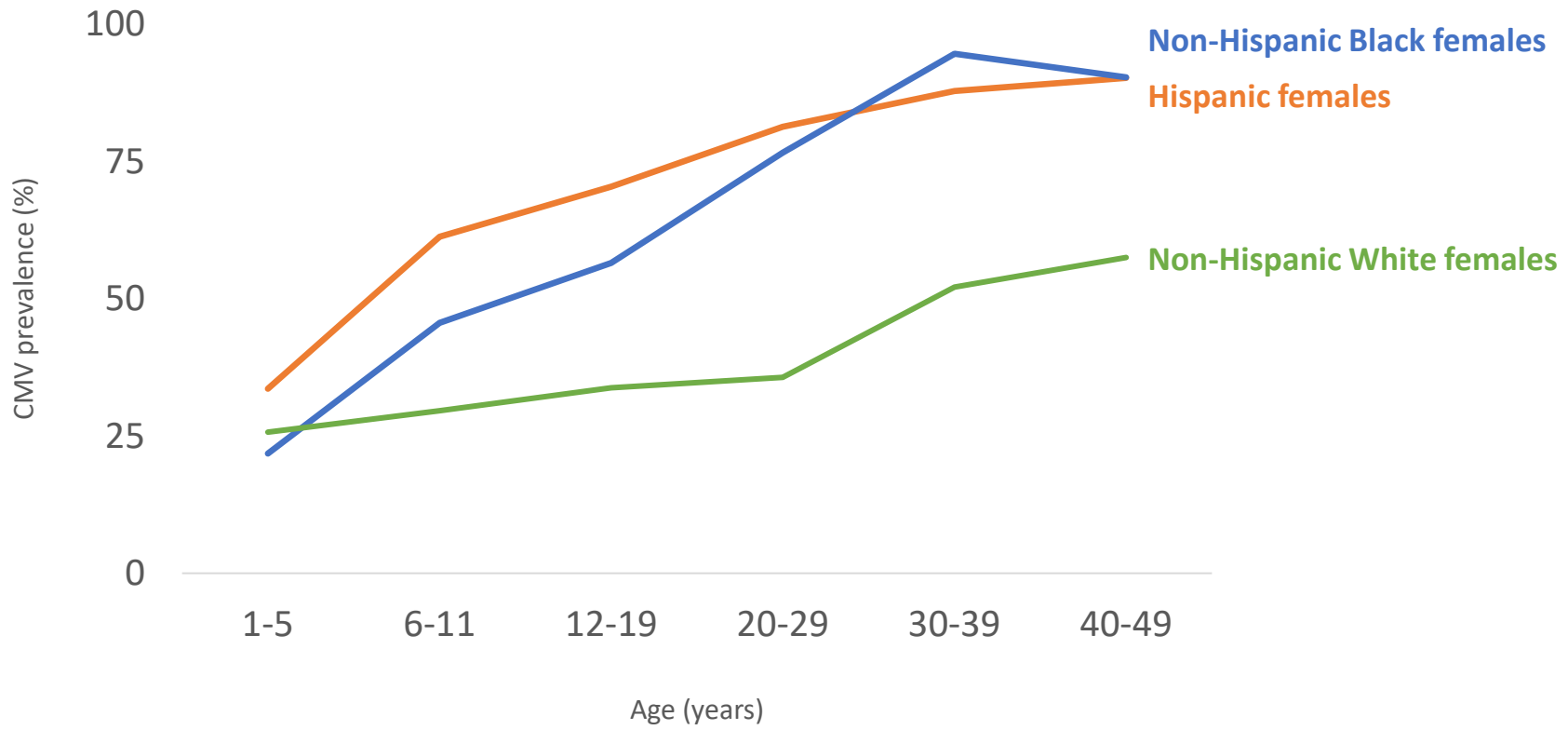
- **Increase with older age**
- **Persons 6-49 years:**
  - No significant changes from 1988-1994 to 1999-2004
- **Children 1-5 years:**
  - Increased from 21% to 29% between 2011-2012 and 2017-2020 pre-pandemic

Lanzieri et al. Seroprevalence of cytomegalovirus among children 1 to 5 years of age in the United States from the National Health and Nutrition Examination Survey of 2011 to 2012. Clin Vaccine Immunol 2015

Lanzieri et al. Cytomegalovirus Seroprevalence Among US Children Aged 1 to 5 Years: The National Health and Nutrition Examination Surveys, 2017-March 2020 Pre-Pandemic Dataset. Clin Infect Dis 2022

Bate et al. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. Clin Infect Dis 2010

CMV IgG Seroprevalence, United States, NHANES, 1999-2004*



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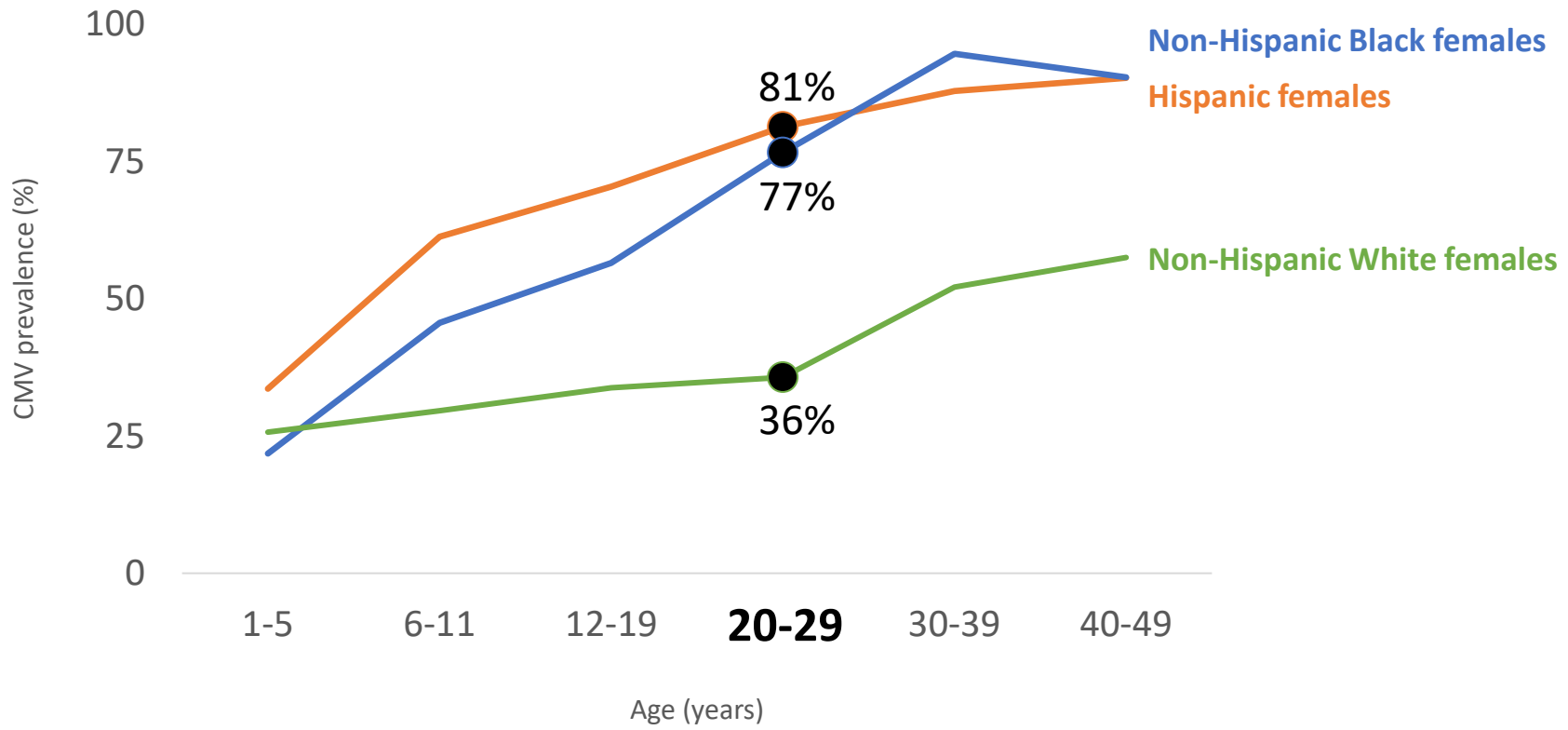

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Risk of vertical transmission and cCMV disease according to timing and type of maternal infection

	Transmission rate (%)	Symptomatic at birth* (%)	SNHL or neurodevelopmental abnormality* (%)
Primary infection†			
Periconception	21.0	1.3	-
First trimester	36.8	9.1	22.8
Second trimester	40.3	0.3	0.1
Third trimester	66.2	0.4	0.0
Non-primary infection	3.4§	3 of 7§§	3 of 7§§

†Primary maternal infection in CMV-seronegative women was defined as seroconversion or low avidity IgG; pooled rates of vertical transmission following primary maternal infection from 10 studies, 2942 fetuses
*Pooled rates of cCMV disease from 10 studies, 796 infected fetuses
§ Transmission rate from 1 study including 205 pregnant women diagnosed with non-primary infection
§§ Sample too small, 6 in the first trimester and 1 unknown timing

Chatzakis et al. Timing of primary maternal cytomegalovirus infection and rates of vertical transmission and fetal consequences. AJOG 2020
Simonazzi et al. Perinatal outcomes of non-primary maternal CMV infection: a 15-year experience. Fetal Diagn Ther 2017.

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Incidence of CMV primary infection and reinfection varies across populations

Country	Annual rate		Population (Assessment)
	Primary (PI) IgG seroconversion	Reinfection (R) IgG seroconversion to new CMV strains	
US	**0.4-7%**	**10%**	PI: pregnant women, IgG seroconversion, low IgG avidity or viral shedding in clinical trials and other studies [1,2,3,4] R: post-partum women, IgG seropositive with seroconversion to new strains [5]
Brazil	**20%**	**9-35%**	Pregnant women, IgG seronegative during 1st trimester or seropositive at first prenatal visit [6,7] R: range for non-transmitters vs. transmitters mothers

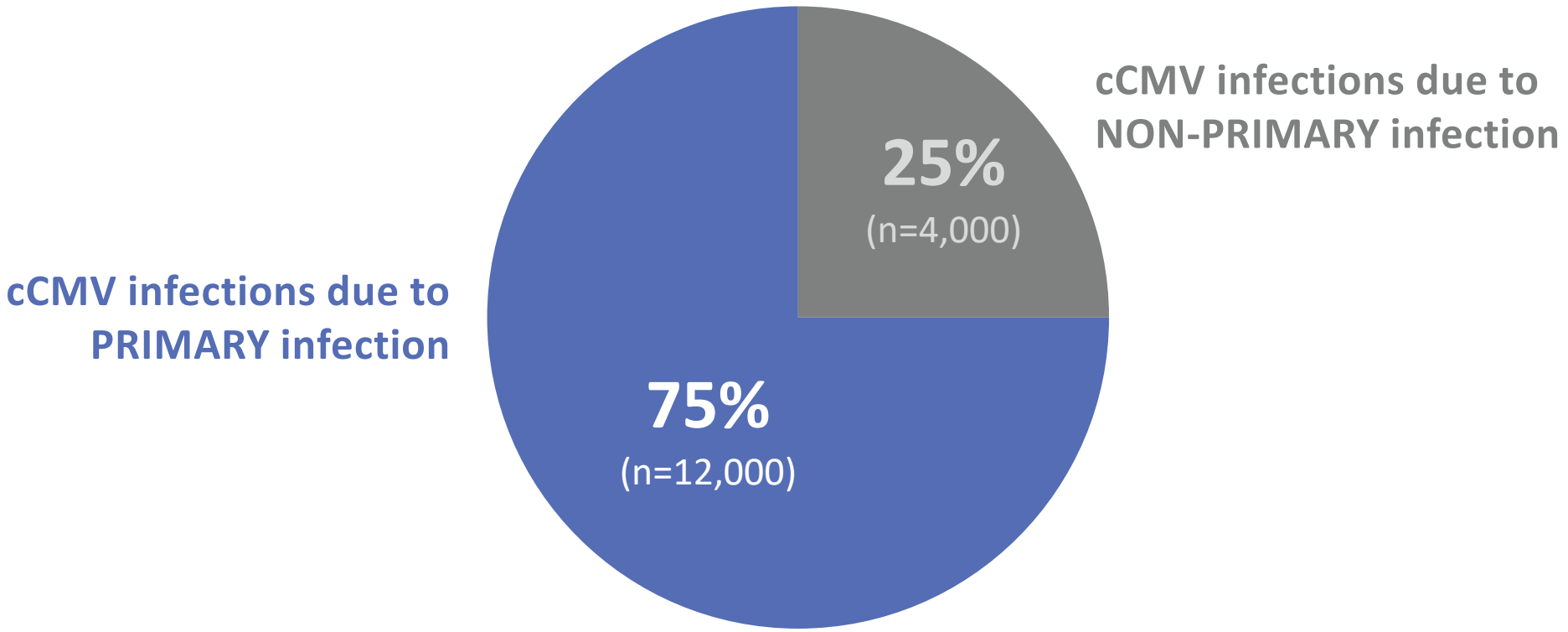
1 Hughes et al. A Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus Infection. N Engl J Med 2021
2 Hyde et al. Cytomegalovirus seroconversion rates and risk factors: implications for congenital CMV. Rev Med Virol 2010
3 Colugnati et al. Incidence of cytomegalovirus infection among the general population and pregnant women in the United States. BMC Infect Dis 2007
4 Das et al. Safety, efficacy, and immunogenicity of a replication-defective human cytomegalovirus vaccine, V160, in cytomegalovirus-seronegative women: a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Infect Dis 2023
5 Ross et al. Cytomegalovirus reinfections in healthy seroimmune women. JID 2010
6 Mussi-Pinhata et al. Seroconversion for cytomegalovirus infection during pregnancy and fetal infection in a highly seropositive population: "the BraCHS study." JID 2018
7 Yamamoto et al. Human cytomegalovirus reinfection is associated with intrauterine transmission in a highly cytomegalovirus-immune maternal population. AJOG 2010

Proportions of cCMV infections due to non-primary maternal infection (NPI) vary with maternal seroprevalence but risk of cCMV infection is higher when mother is CMV seronegative before pregnancy

Country, years (n° infants screened)	Maternal CMV IgG seroprevalence	cCMV infection prevalence per 1,000 live births	Risk of cCMV among seronegative vs. seropositive mother	Proportion attributable to NPI
France, 2013-2015 (12,000)	61%	3.7	0.86% vs. 0.2% (4x)	52%
Brazil, 2013-2017 (12,000)	97%	5.7	2.8% vs. 0.5% (6x)	90%

Leruez-Ville et al. Risk Factors for Congenital CMV Infection Following Primary and Nonprimary Maternal Infection: A Prospective Neonatal Screening Study Using PCR in Saliva. CID 2017
Yamamoto et al. Contribution of Congenital CMV Infection to Permanent Hearing Loss in a Highly Seropositive Population: The Brazilian CMV Hearing and Maternal Secondary Infection Study. CID 2020
Mussi-Pinhata et al. Seroconversion for Cytomegalovirus Infection During Pregnancy and Fetal Infection in a Highly Seropositive Population: "The BraCHS Study". JID 2018

About 12,000 cCMV infections in the U.S. every year may be attributable to primary maternal infections*



* Using 3,667,758 live births in US 2022 NVSS - Birth Data (cdc.gov), stratified by maternal age group and birth order
Unpublished estimates based on CMV seroprevalence data from NHANES; other studies 25-50% cCMV infections attributed to primary maternal infections.

Young children play a critical role in CMV transmission

- **Children with CMV infection excrete large amounts of virus in saliva and urine for months**

- **CMV excretion peaks at 1-2 years of age**
  - 1/3 of first-time mothers will be pregnant again, with a second birth within <18 months of the first
  - More likely with day care attendance (2x)
  - Higher risk of cCMV in second-born children

Stowell et al. Cross-sectional study of cytomegalovirus shedding and immunological markers among seropositive children and their mothers. BMC Infect Dis. 2014.
Cannon et al. Repeated measures study of weekly and daily cytomegalovirus shedding patterns in saliva and urine of healthy cytomegalovirus-seropositive children. BMC Infect Dis. 2014.
Cannon et al. Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. Rev Med Virol 2011.
Schleiss et al. Assessment of congenital cytomegalovirus prevalence among newborns in Minnesota during the COVID-19 pandemic. JAMA Network Open 2022.

Modeling suggest that short-duration of protection in infants can impact transmission to pregnant mothers and decrease cCMV infections

Model	Population	Vaccine efficacy (%)	Duration of protection (years)	Vaccine coverage (%)	Effect 50 years post-vaccination
Byrne*	2m	35	1	67	85% ↓cCMV infections
Lanzieri§	<1y	60	5	50	Elimination
	12-18m and 15-19y	70	5	60	30% ↓cCMV infections
	20-29y	60	5	50	10% ↓cCMV infections
Alfaro-Murillo†	19-20y (CMV neg. F)	95	25	90	4% ↓cCMV disease
	<1y (CMV neg. F)	95	4	90	2% ↓cCMV disease

*Protection estimated for primary infection (35% for up to 1 year)
†Screening coverage, all CMV-seronegative vaccinated
§Potential for increase in congenital CMV infections due to primary maternal infections predicted in high seroprevalence settings (Brazil) without booster at 15-19y

Models predict different impact of vaccine in US

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Summary

- **The epidemiology of CMV and cCMV is complex**
- **In the United States, nearly 75% of cCMV infections due to primary maternal infection**
  - Globally, most cCMV infections due to non-primary maternal infection
- **An effective CMV vaccine could reduce cCMV disease burden**
  - Long-lasting immunity to ensure women are protected *before pregnancy* and *throughout childbearing years*
  - Vaccination of toddlers could provide *indirect protection* to pregnant women

Acknowledgments - ACIP CMV WG Members

ACIP Members

- Denise Jamieson (WG chair)
- Bonnie Maldonado

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- Leisha Nolen (CSTE)
- Ajit Limaye (IDSA)
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Acknowledgments - ACIP CMV WG CDC Participants

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