NCHAM Webinar Series

Congenital CMV 101: From Prevention to Treatment

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NCHAM
National Center for Hearing Assessment and Management
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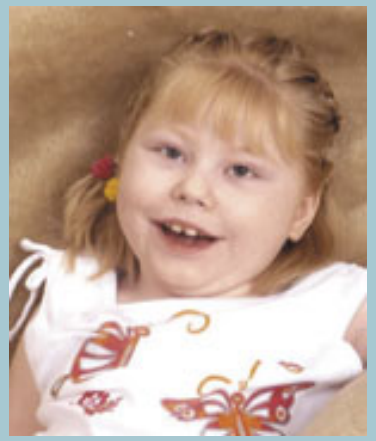
Possible Outcomes of Congenital CMV Infection

Transient outcomes	Permanent outcomes
Hepatomegaly	Hearing loss
Splenomegaly	Intellectual disability
Jaundice	Vision loss
Petechia and purpura	Microcephaly
Seizures	Motor disabilities
Fetal growth retardation	Seizures
Pneumonitis	Death



Child with cerebral palsy, hearing loss, and mental retardation

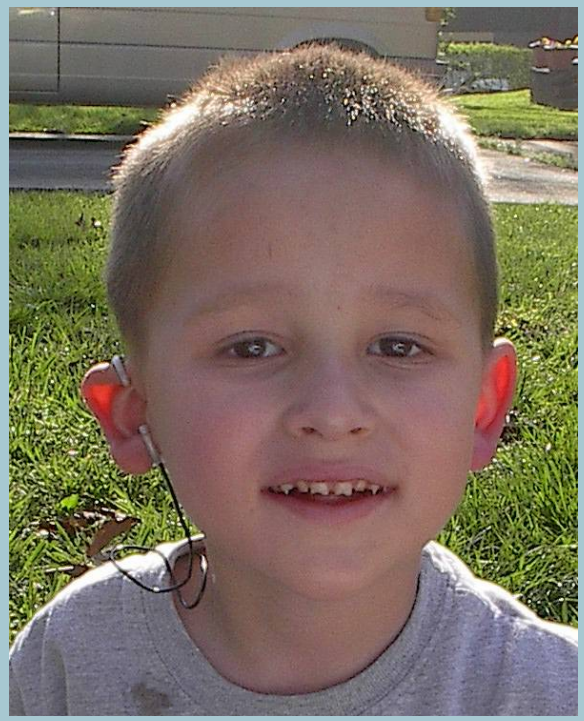
Infant with microcephaly

Child with spastic quadraplegic cerebral palsy, vision loss, microcephaly, intracranial calcifications, and epilepsy

Adapted from Stagno, 2001

US Estimated Annual Congenital CMV Disease Burden

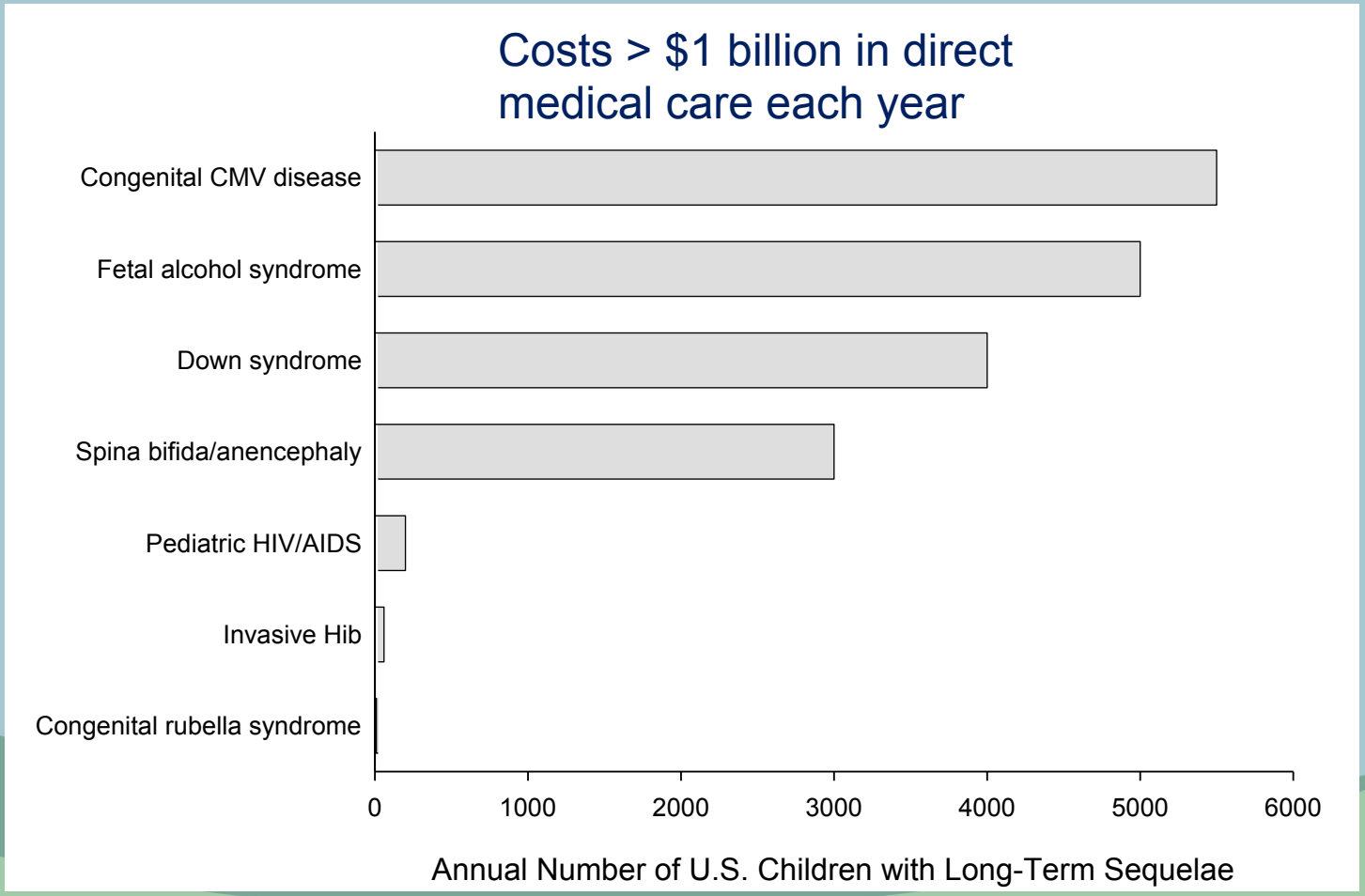
- 30,000 congenital CMV infections
- 3,500 symptomatic infections
- 140 deaths
- ≥ 5500 children with permanent sequelae



Dollard, Grosse, & Ross, Rev Med Virol, 2007

Relative Burden of Congenital CMV

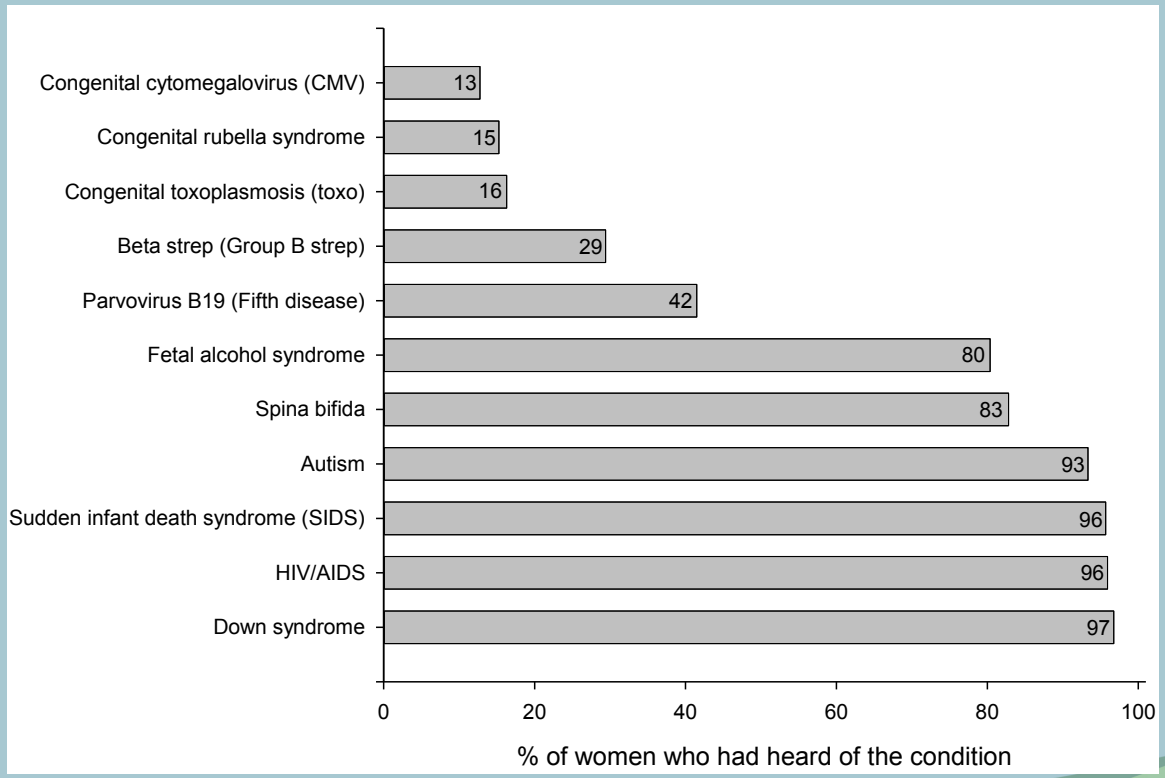
Long-term sequelae



Adapted from Cannon & Davis, BMC Public Health, 2005

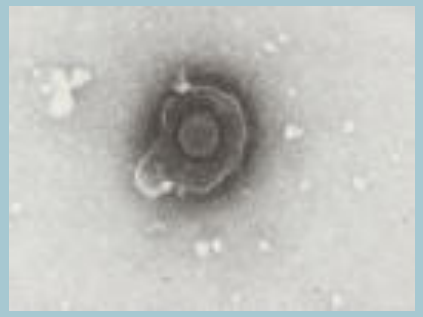
Congenital CMV is an Invisible Disease

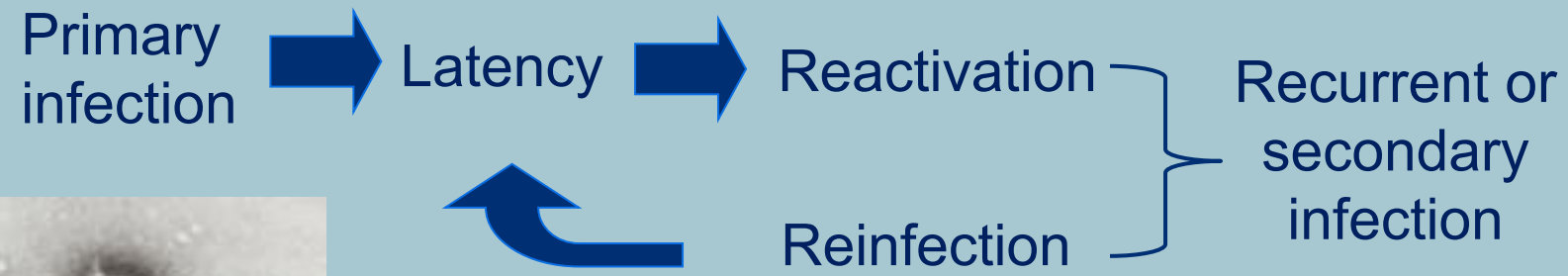
- Mothers do not know when they are infected
- Many infected babies are asymptomatic at birth
- When babies have symptoms, they are often non-specific
- Congenital CMV usually cannot be diagnosed retrospectively



Cannon, Prev Med, 2012

CMV Natural History

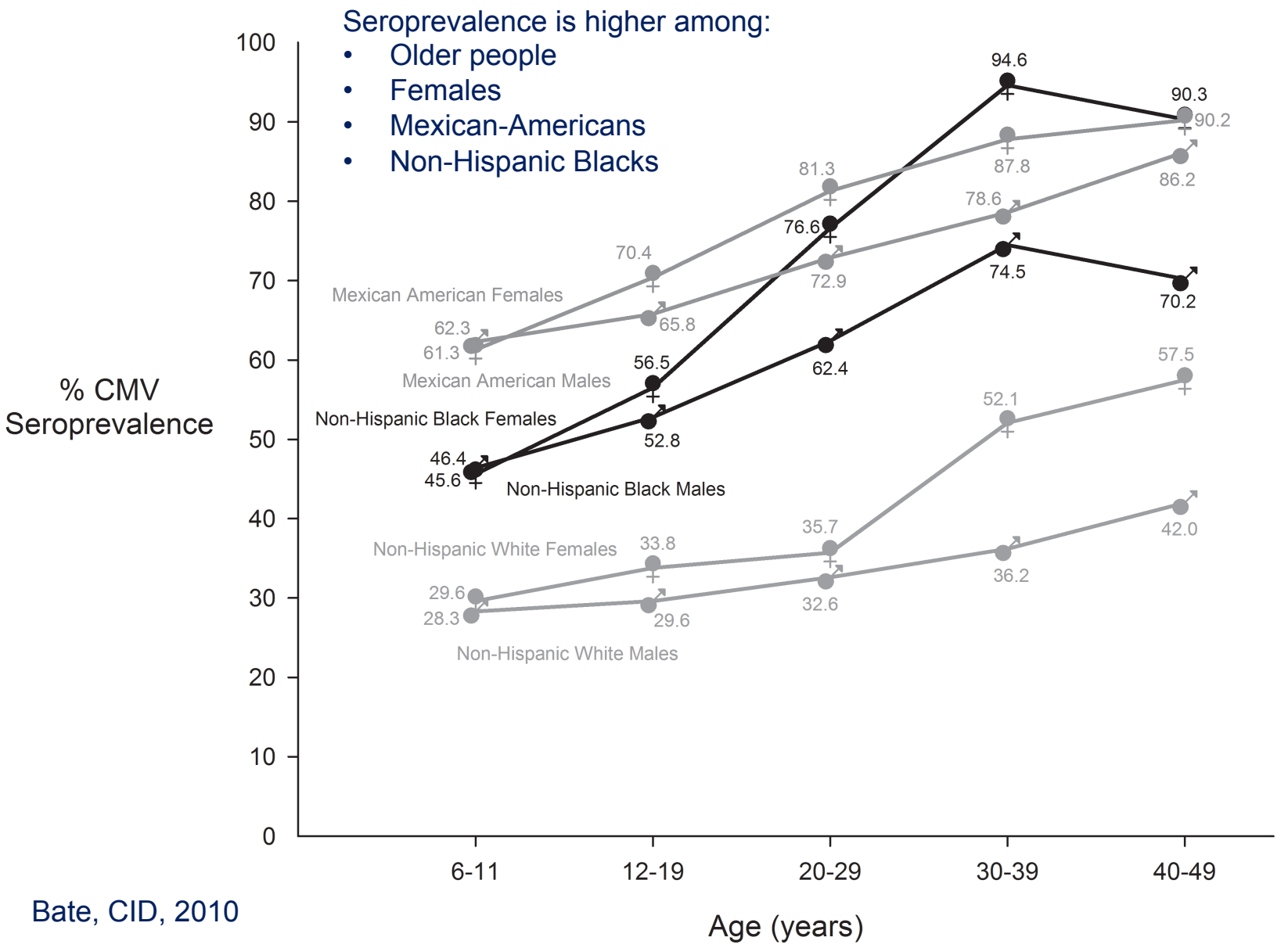




The Laboratory Vocabulary

Measurement	Labelled	Detects	Test format
Ever been infected	Seropositive	Antibody	ELISA
At risk for transmission	Shedding or excreting	Virus or viral DNA	PCR or culture

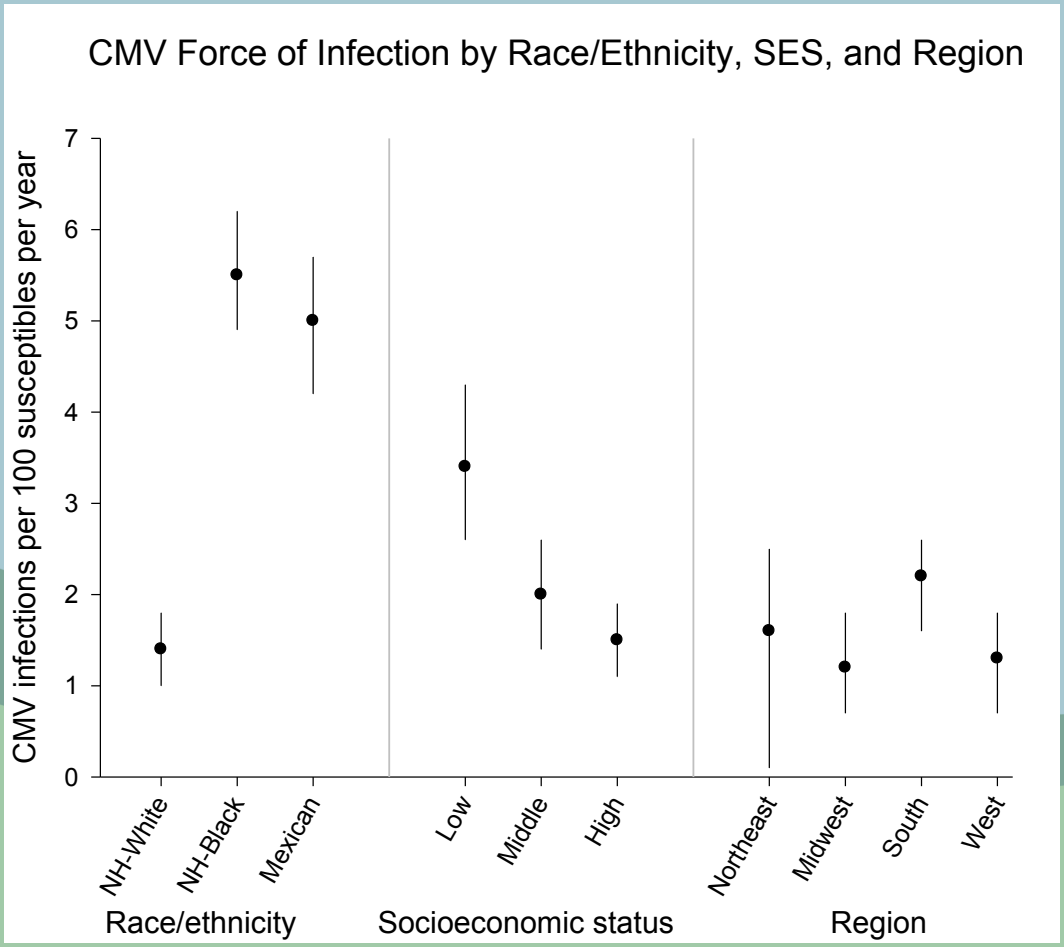
1999-2004 CMV Seroprevalence in the US



Bate, CID, 2010

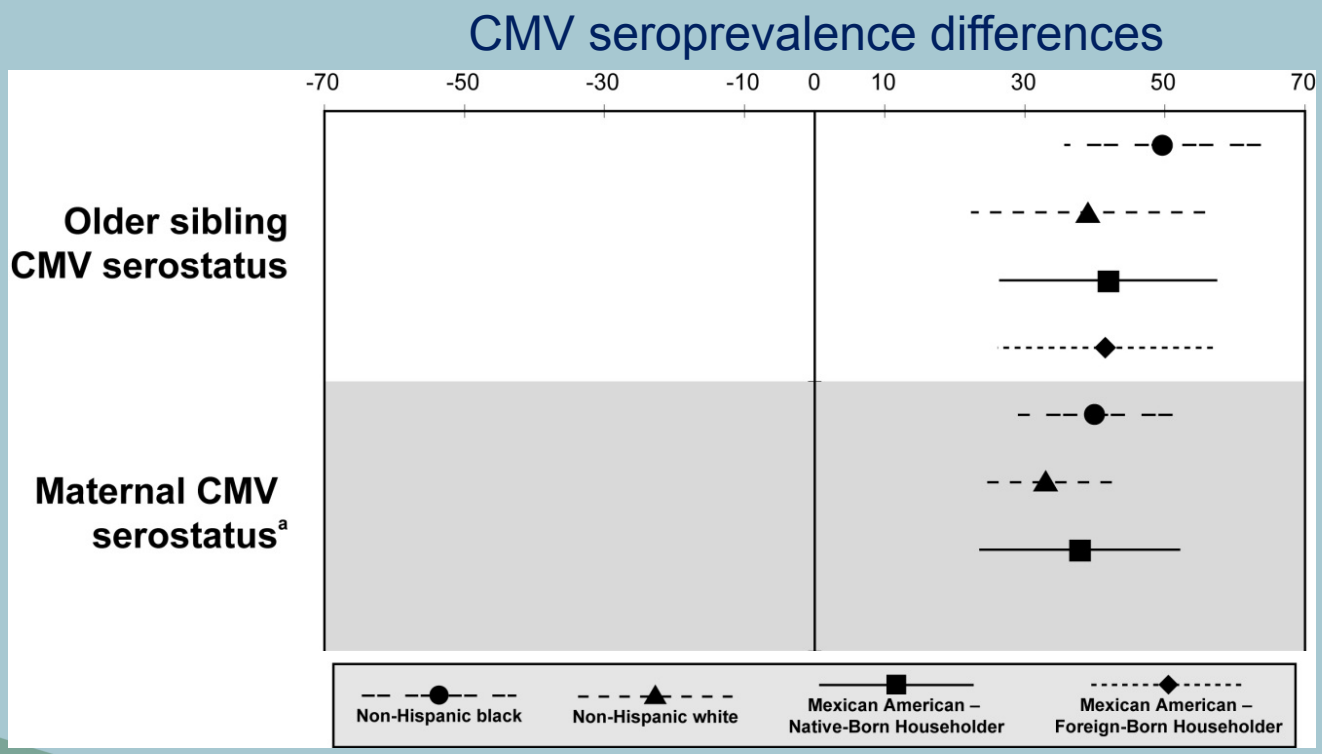
Demographic Risk Factors for Seroconversion

- In the U.S., rates of new CMV infections in susceptibles are much higher in disadvantaged populations such as racial/ethnic minorities and persons of low SES



Adapted from Colugnati, 2007, BMC Infect Dis

Household Transmission Risk



- Seroprevalences among family members of seropositive children are 30-50 percentage points higher than among family members of seronegative children

Staras, J Clin Virol, 2008

Summary CMV Annual Seroconversion

Risk group	Summary annual seroconversion rate (%)	95% confidence interval (%)
Pregnant women	2.2	2.1 - 2.4
Parents with child not shedding CMV	2.1	0.3 - 6.8
Healthcare workers	2.7	2.3 - 3.2
Day care providers	8.5	6.1 - 11.6
Women attending STD clinics	13	10 - 17
Parents with child shedding CMV*	24	18 - 30

*Annual infection rate of less 25% in this high risk group suggests that CMV is not easily transmitted.

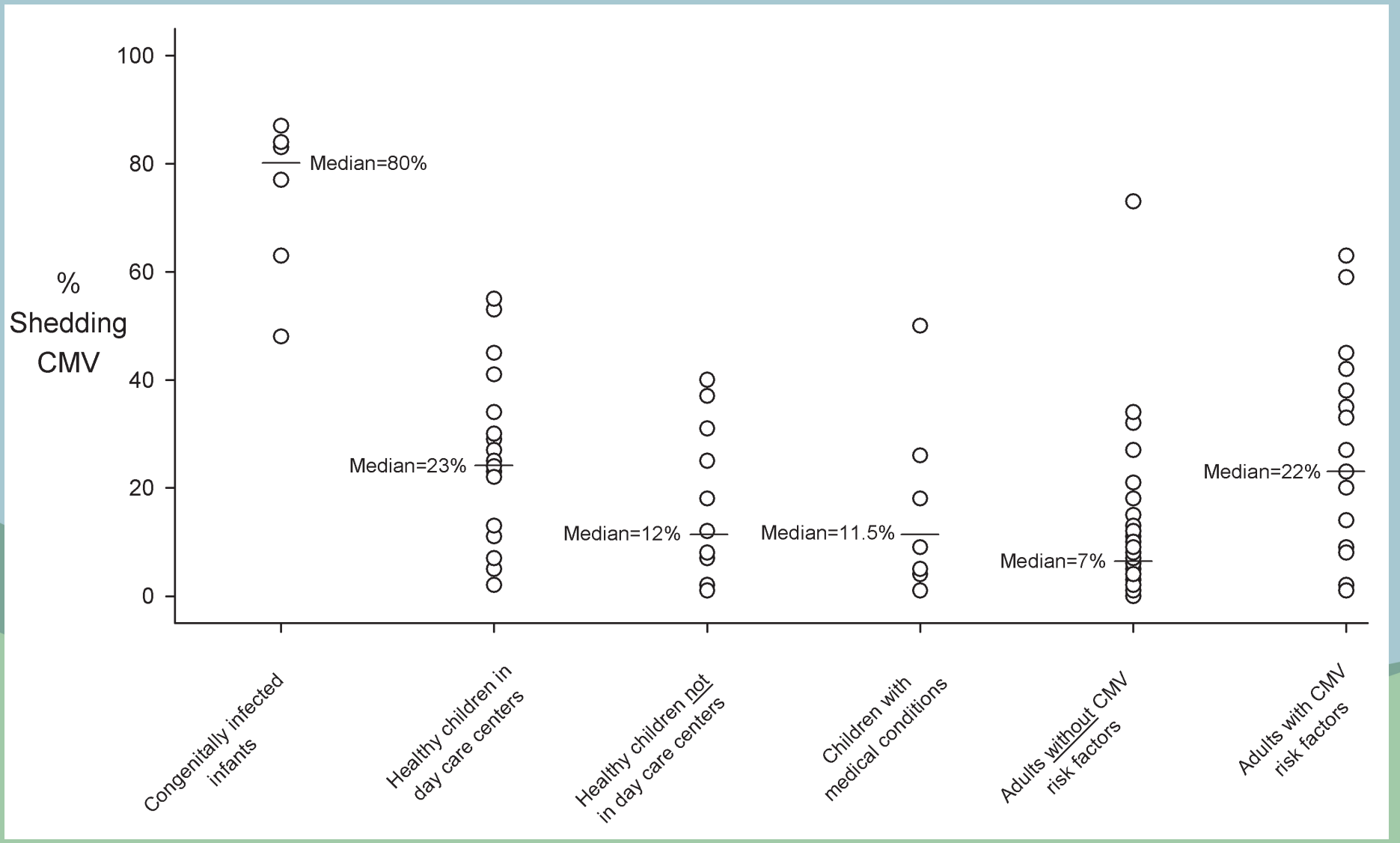
Adapted from Hyde, Rev Med Virol, 2010

Comparison of Models of Contagiousness

Study	Design	Force of infection (100 p-y)	Basic reproductive rate	Age of infection (years)
Measles Mumps Rubella	Review Ages 11-17	20 12 10		
Varicella	Convenience Ages ≥10	6		
CMV Griffiths (2001)	Hospital-based Ages 16-40	3.1 and 3.5	2.4 and 2.7	29 and 32 (median)
CMV Colugnati (2007)	Pop.-based Ages 12-49	1.8	1.7	28.7 (mean)
HSV-2	Pop.-based Ages ≥12	0.84		
Hepatitis A	Pop.-based Ages ≥10	0.2-1.0		
Hepatitis B	Pop.-based Ages 6-39	0.15		

Adapted from Colugnati, BMC Infect Dis, 2007

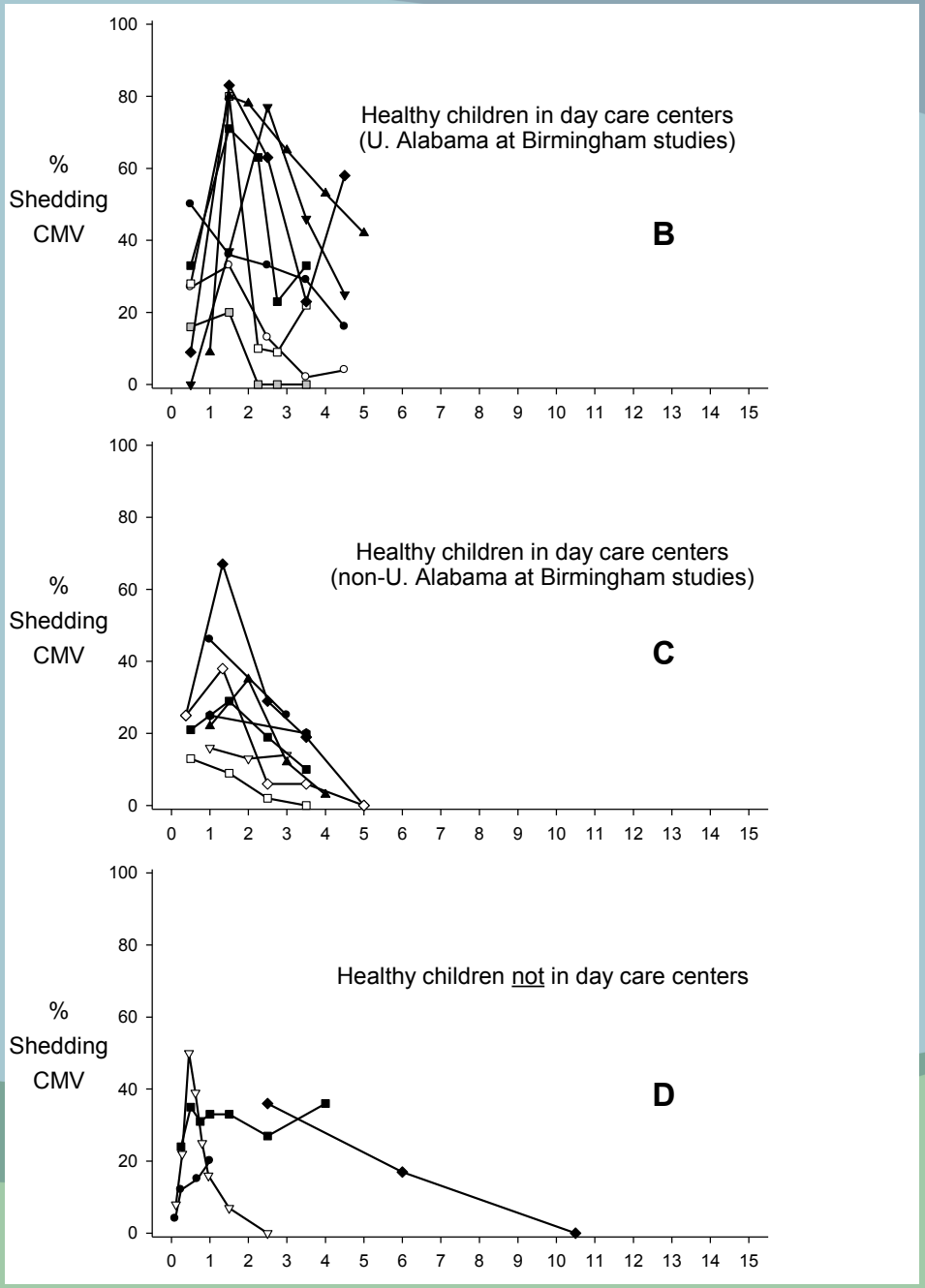
CMV Shedding Prevalences by Risk Group



Cannon, Rev Med Virol, 2011

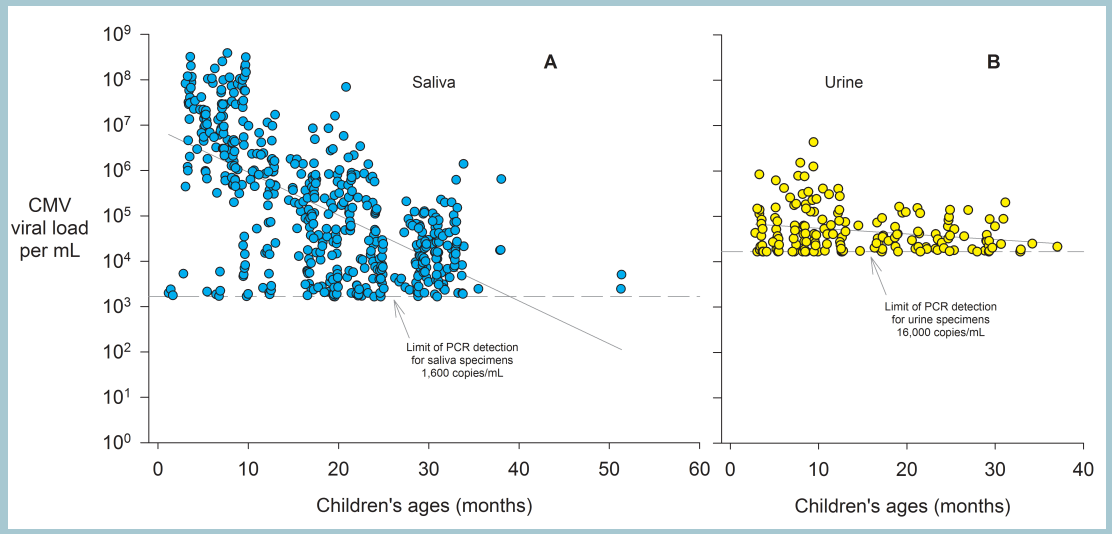
Among children, shedding prevalence peaks at ages 1-2 years

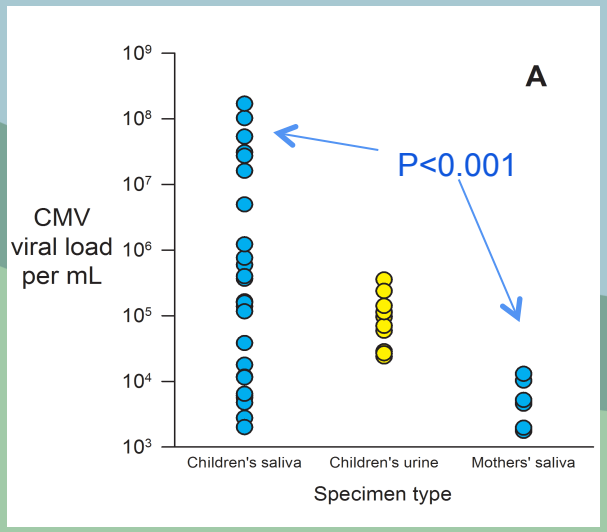
These are the ages at which children are putting the most fluids into the environment



Cannon, Rev Med Virol, 2011

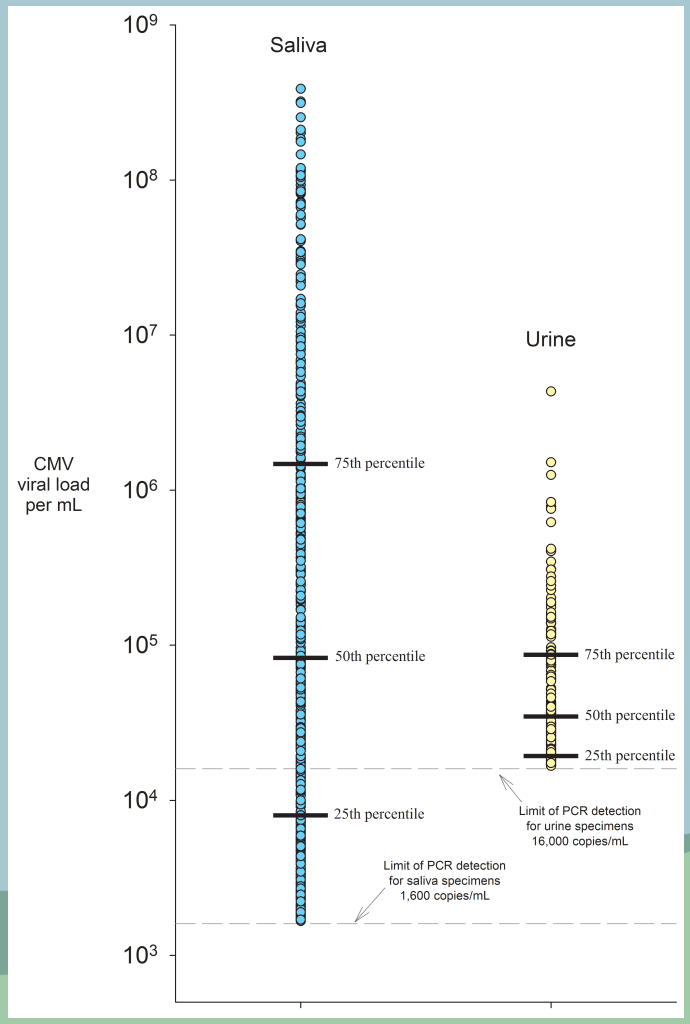
CMV Viral Load Data





Viral loads higher in:

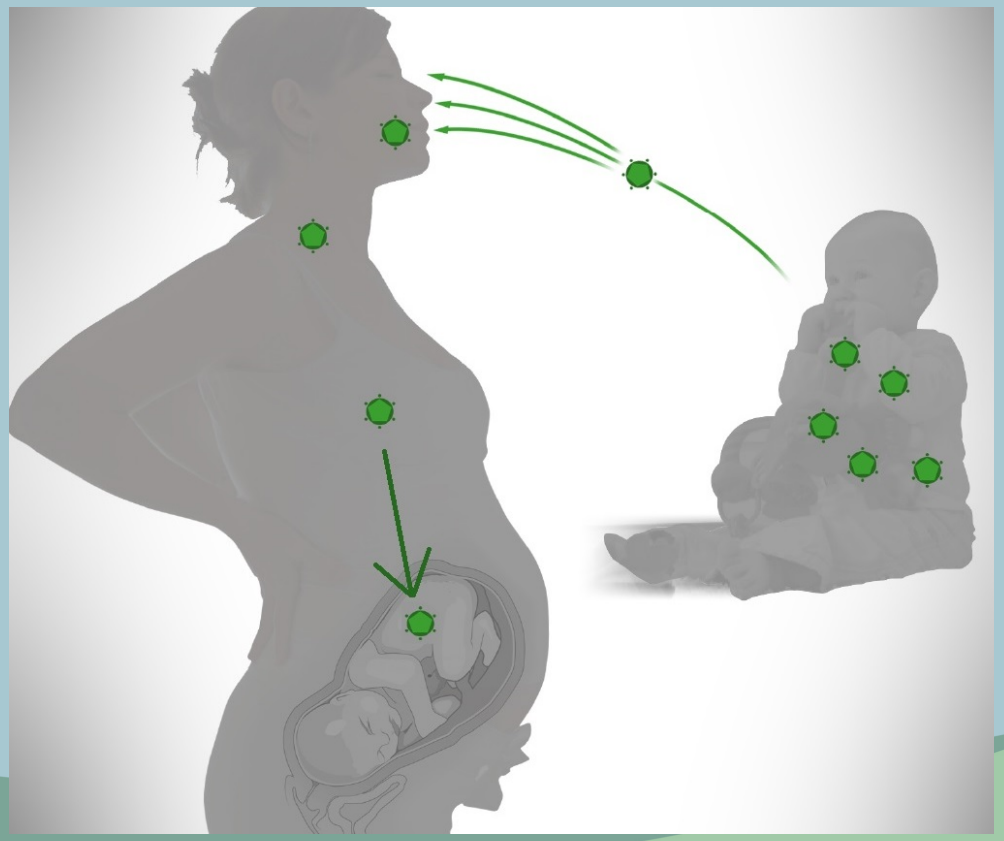
- Saliva than in urine
- Children than in adults
- Younger children than in older children

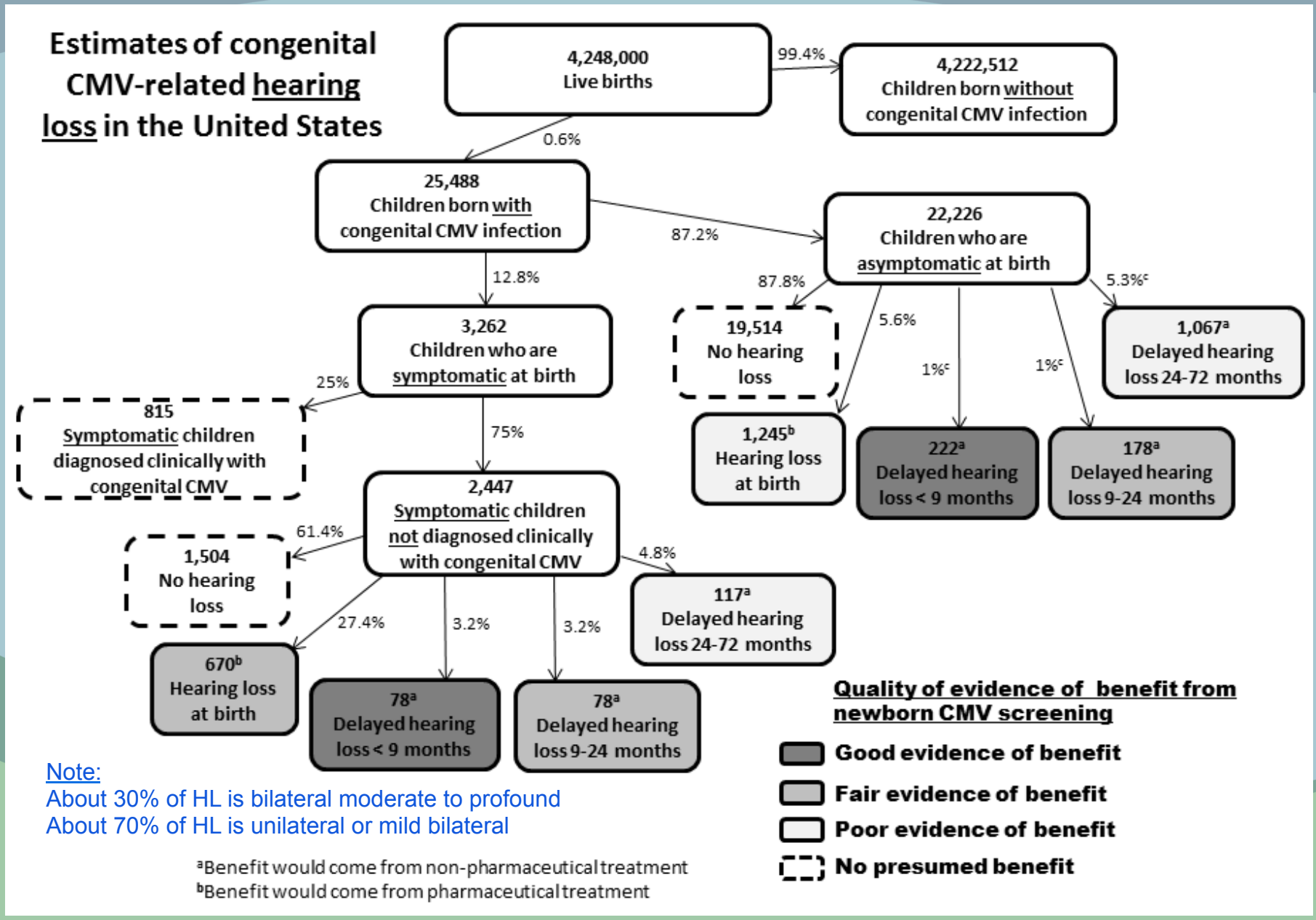


Cannon et al., unpublished data

Summary of CMV Transmission

- CMV is transmitted through direct contact with body fluids
- CMV is not transmitted easily
- Saliva and urine are important fluids for transmission
- Saliva has higher viral loads than urine
- Young children are a major source of infection
- CMV can be transmitted through intimate adult contact





Note:
About 30% of HL is bilateral moderate to profound
About 70% of HL is unilateral or mild bilateral

[a]Benefit would come from non-pharmaceutical treatment
[b]Benefit would come from pharmaceutical treatment

Cannon, Rev Med Virol, 2014

Timing of Hearing Loss

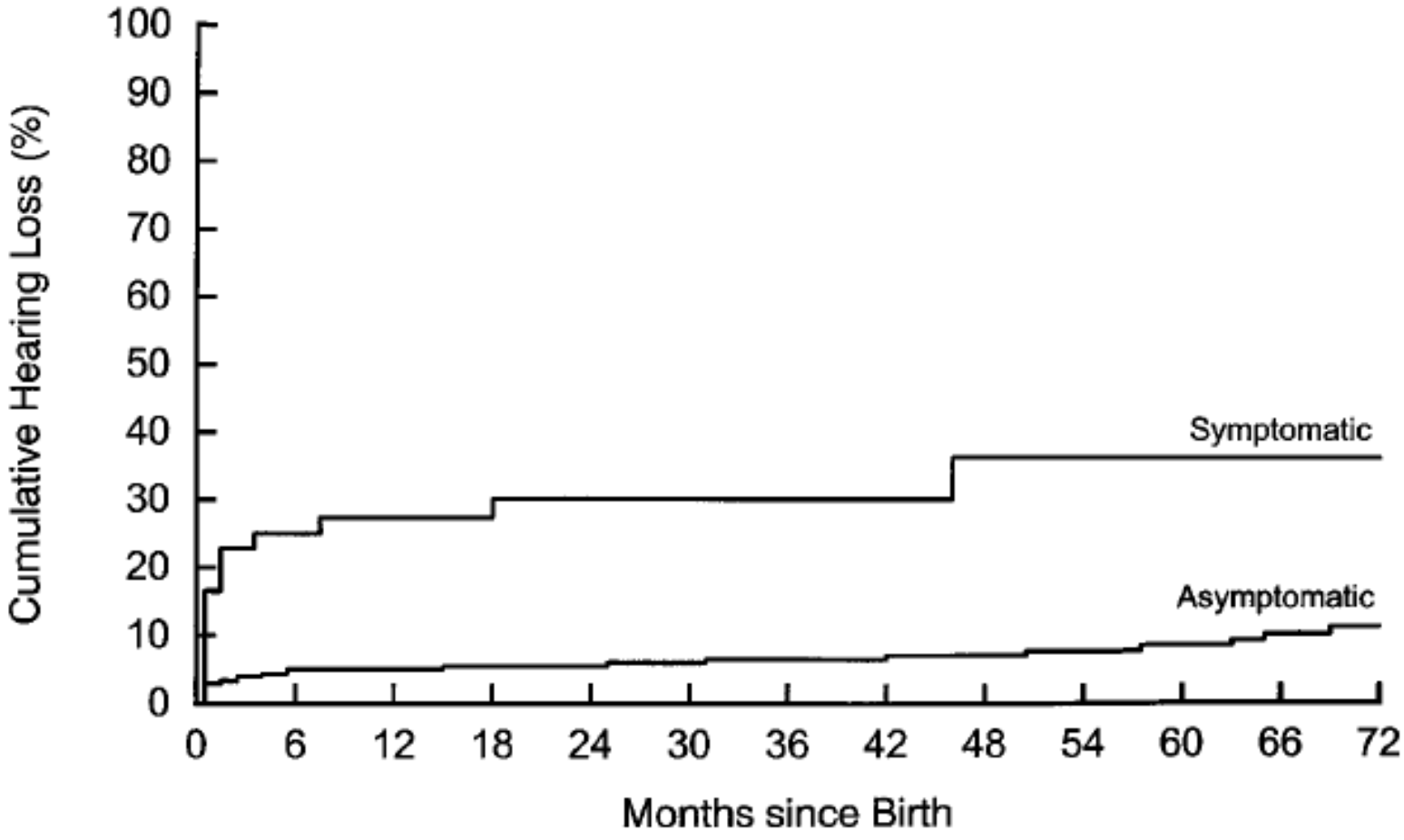
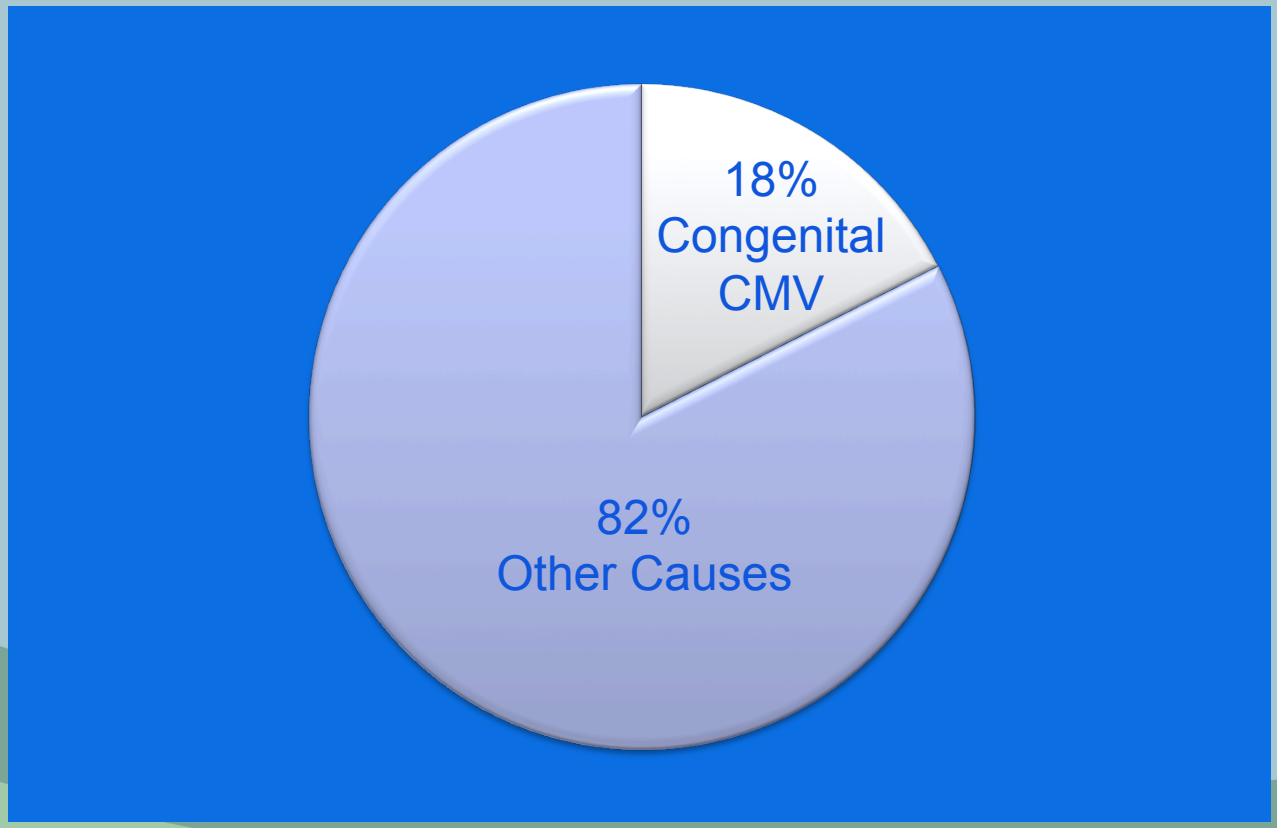


Figure. Cumulative SNHL >20 dB thresholds in children with congenital CMV infection according to symptomatic and asymptomatic status at birth ($P < .0001$).

Fowler, J Peds, 1999

Bilateral Moderate to Profound Hearing Loss Attributable to Congenital CMV

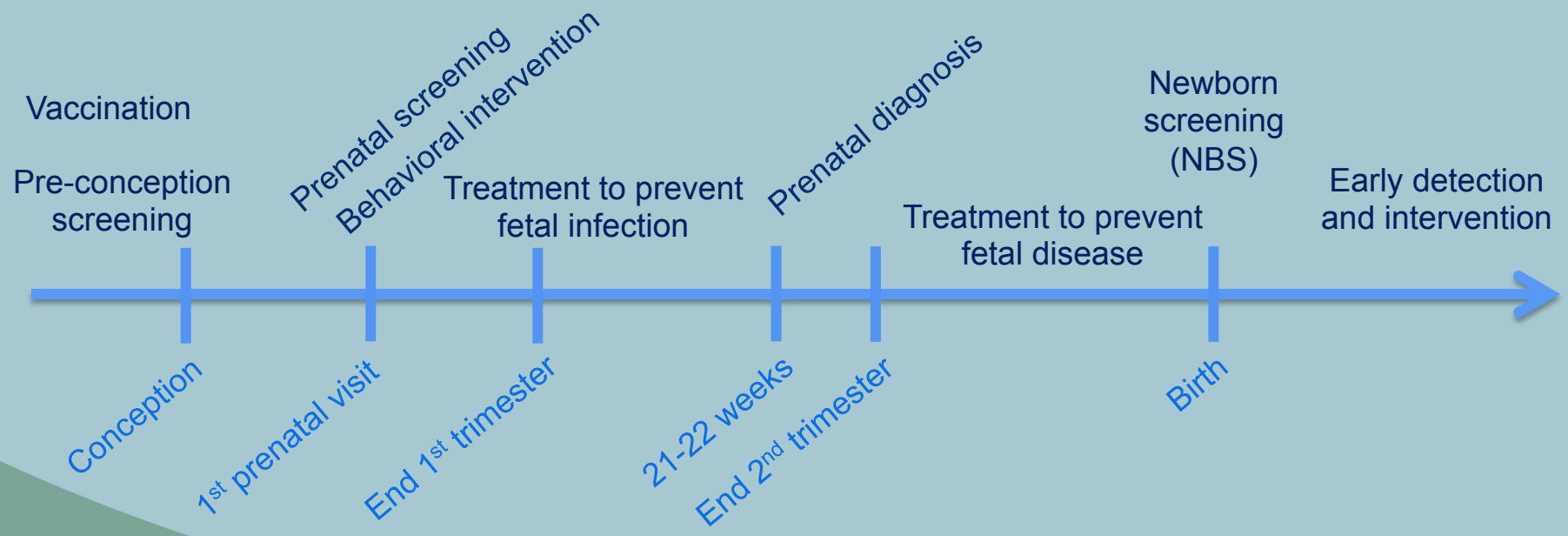


Adapted from Grosse, J Clin Virol, 2008

Takeaway Points for Congenital CMV Infection and Outcomes

- Non-primary maternal infection is a major source of congenital infection
- Congenital infection occurs in 0.5%-1% of newborns in the U.S.
- Disabilities occur or develop in 15%-20% of infected newborns
- Congenital CMV is a major cause of childhood hearing loss

Potential Clinical and Public Health Interventions for Congenital CMV



Currently, none of these interventions is routine in the U.S.

Utility of Newborn CMV Screening

Probably satisfies

- Important health problem
- Recognizable latent or early symptomatic stage
- Natural history adequately understood

May not yet satisfy

- Suitable test available
- Test acceptable to population
- Agreed on policy on whom to treat
- Facilities for diagnosis and treatment available
- Cost-effective

Grosse, J Clin Virol, 2009

Laboratory Approaches to Newborn CMV Screening

Specimen	Method	Advantages	Disadvantages
Dried blood spot	PCR from DBS	NBS program already in place	CMV viral load lower in blood, less available specimen
Saliva	PCR from cheek swab	CMV viral load higher in saliva	Not part of existing NBS program
Urine	PCR from bagged urine or diaper insert	CMV viral load higher in urine	Not part of existing NBS program

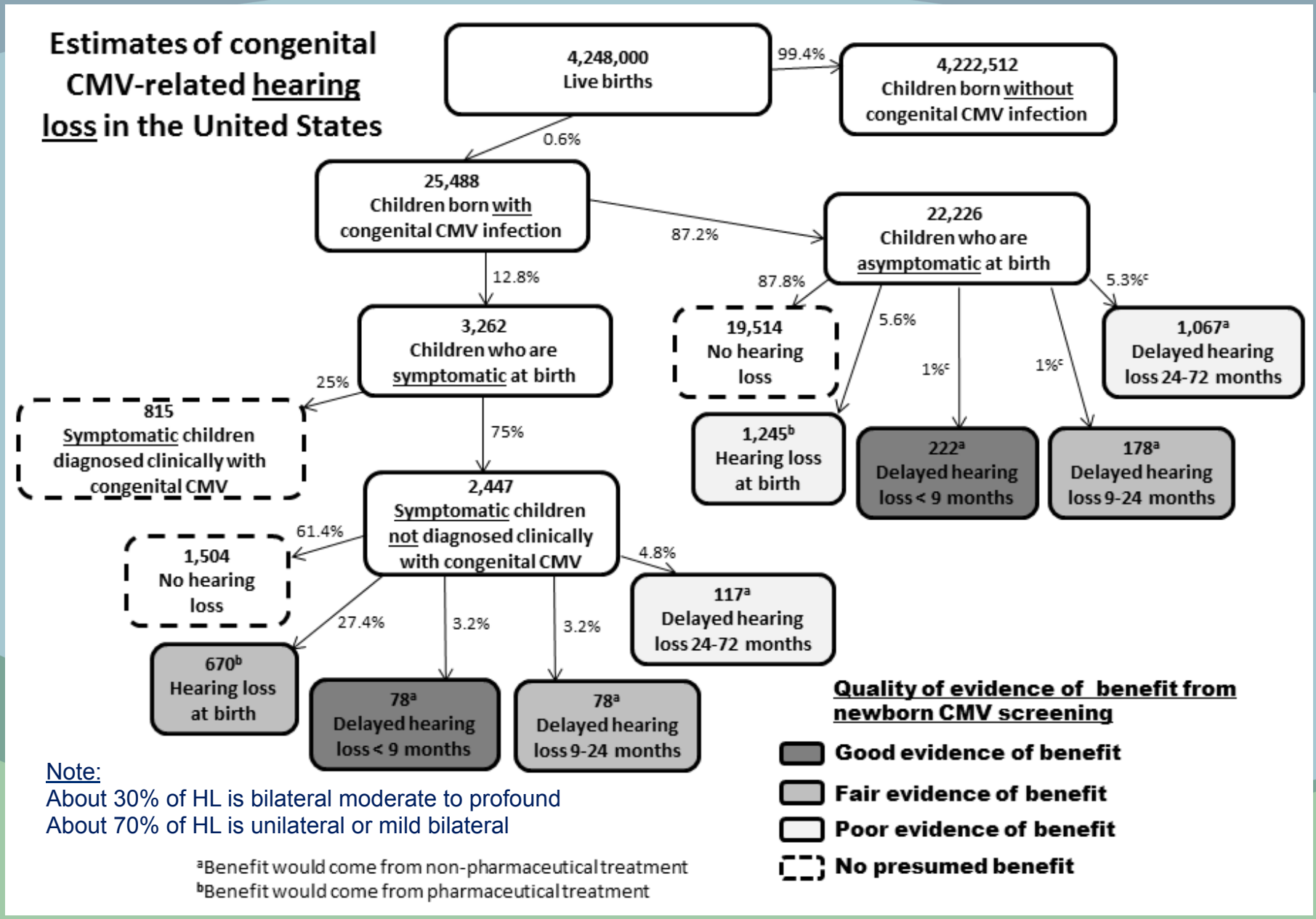
Dollard, J Inherit Metabol Dis, 2010

Pharmaceutical Treatment of Infants with Congenital CMV

- 42 symptomatic infants with central nervous system (CNS) deficits were evaluated for hearing loss.
- 6 weeks IV ganciclovir vs. no treatment
- Ganciclovir recipients were significantly less likely to experience worsening in hearing.
- Two thirds of treated infants had significant neutropenia during therapy.

- Current multi-site trial underway with oral valganciclovir
- Infants need not have CNS deficits to be enrolled

Kimberlin, J Ped, 2003; Kimberlin, J Infect Dis, 2008



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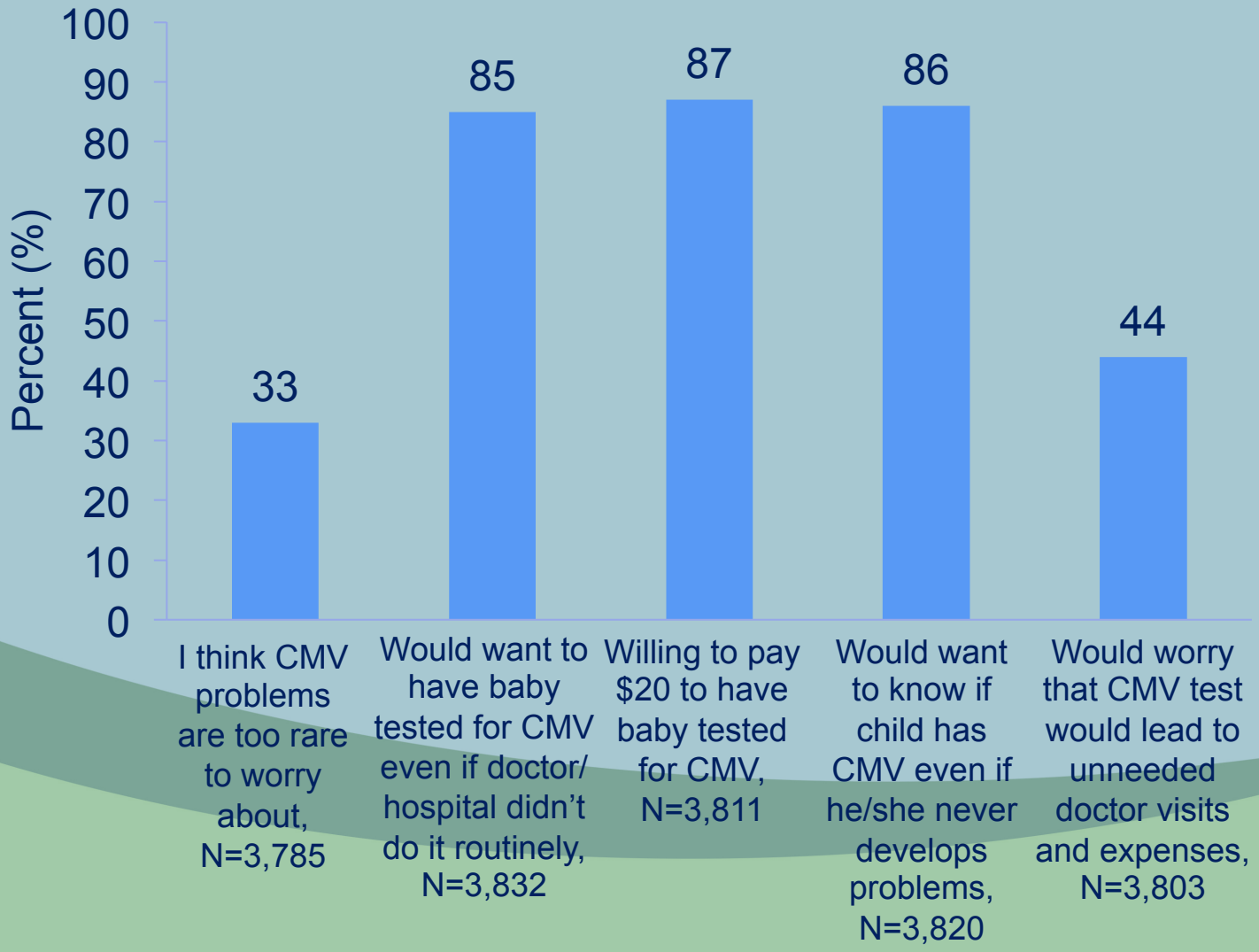
Cannon, Rev Med Virol, 2014

Proportion of Respondents who Somewhat/ Strongly Agreed by CMV Statement



Din, Pediatrics, 2011

Future Directions for Newborn CMV Screening

- Further assessments of DBS assays
- Development of point-of-care assays for saliva and urine
- Evaluation of saliva or urine collection on filter paper cards
- Assessments of psychosocial impacts of screening
- Develop protocols for monitoring and treatment of children who screen positive for CMV at birth
- Pilot studies for feasibility of universal screening
- Pilot studies of targeted CMV screening (e.g., infants who fail hearing screen)

Selected Additional References

- Vaccines
  - Griffiths et al., Vaccine, Vol. 31, p. B197-B203 (2013)
  - Krause et al., Vaccine, Vol. 32, p. 4-10 (2013)
- Prenatal screening/prenatal diagnosis
  - Lazzarotto, Clin Microbiol Newsletter, Vol. 32, p. 9-15 (2010)
- Behavioral intervention
  - Vauloup-Fellous, J Clin Virol, Vol. 46, p. S49-S53 (2009)
- Prenatal treatment
  - Nigro, N Engl J Med, Vol. 353, p. 1350-1362 (2005)
  - Revello, N Engl J Med, Vol. 370, p. 1316-1326 (2014)
  - Jacquemard, BJOC, Vol. 114, p. 1113-1121 (2007)

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Questions?

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For more information about CMV please visit www.cdc.gov/cmv

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