

# Cognitive outcomes of children with asymptomatic congenital cytomegalovirus infection: Houston Congenital CMV Longitudinal Study

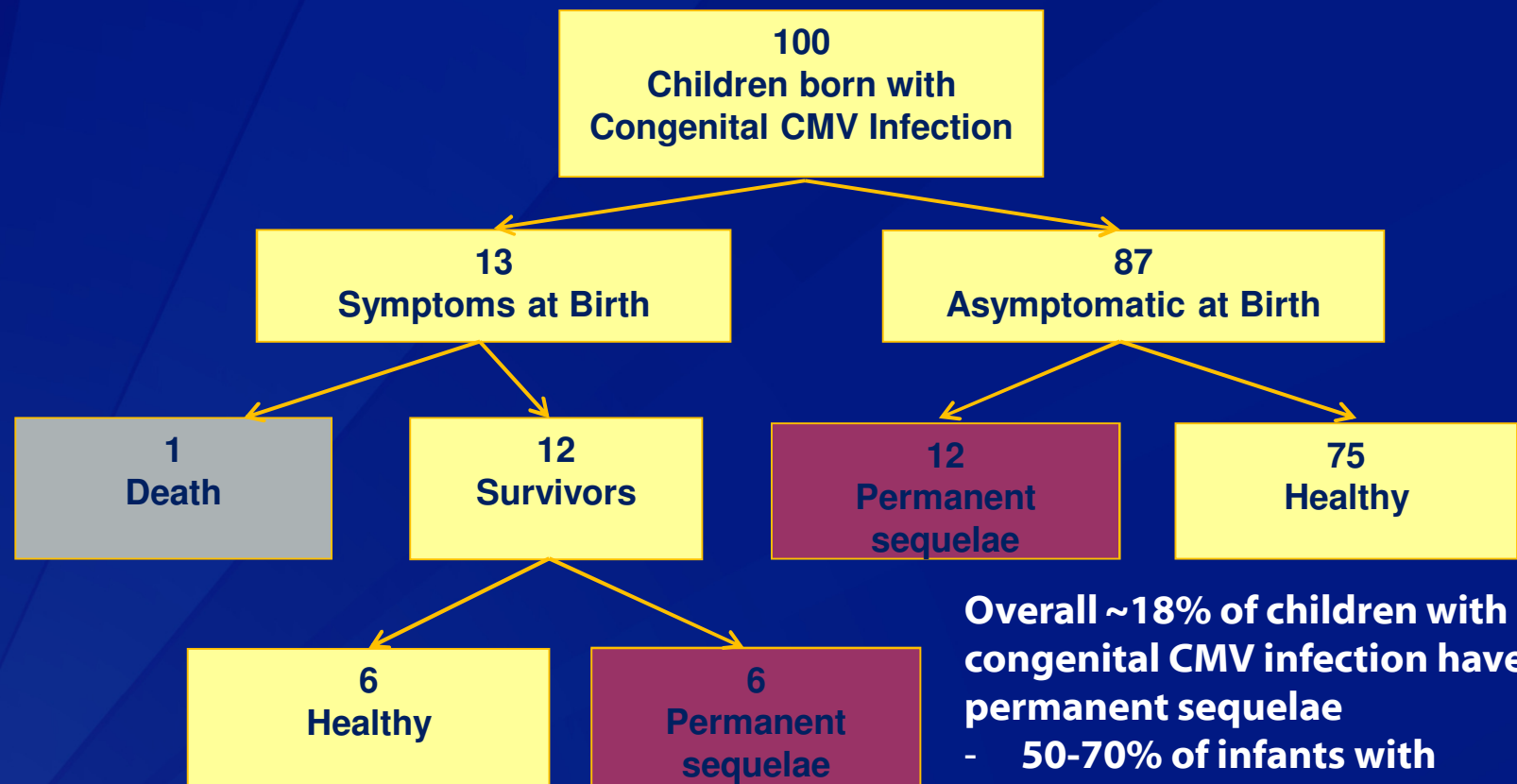
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# Permanent Sequelae in Children with Congenital CMV Infection



**Overall ~18% of children with congenital CMV infection have permanent sequelae**

- 50-70% of infants with symptomatic cCMV infection
- 15% of infants with asymptomatic cCMV infection

## **Permanent Sequelae in Children with Congenital CMV (cCMV) Infection**

- ❑ **Infants with cCMV infection that is symptomatic at birth are more likely than those with cCMV infection that is asymptomatic at birth to:**
  - experience sequelae
  - have disabling sequelae
- ❑ **Among infants with cCMV infection that is asymptomatic at birth**
  - over half with sequelae have hearing loss
  - spectrum of other neurologic sequelae not fully described

## **Congenital CMV Infections and Intellectual Disability**

- ❑ Occurrence of profound intellectual disability in children with cCMV infections that are symptomatic at birth is well documented**
- ❑ Extent to which infants with cCMV infection that is asymptomatic at birth are at risk of intellectual disability or cognitive deficits is not fully understood**
- ❑ Important to understanding full spectrum of sequelae associated with cCMV infections to plan for appropriate follow-up and intervention in setting of CMV testing or screening of newborns**

## Studies of Cognitive Impairments in Children with Asymptomatic cCMV Infection

Authors	# Total participants	Mean length of follow-up	Cognitive impairments (yes/no)
Kumar et al NEJM 1973	38	7.6 years	No
Reynolds et al NEJM 1974	36	38 months	No
Hanshaw et al NEJM 1976	88	3.5-7 years	Yes
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## **Why is more data needed on cognitive outcomes in children with asymptomatic cCMV infection?**

- ❑ **Small number of studies**
- ❑ **Small numbers of participants**
- ❑ **Limited follow-up time**
- ❑ **Although several studies suggest that intellectual disability is not common in children with cCMV infection that was asymptomatic at birth, questions remain**
  - Is there a risk of significant intellectual disability that previous studies were not powered to capture?
  - Are there more subtle cognitive effects that were overlooked in previous studies?
  - Are there late onset cognitive effects not captured by studies with limited follow-up time?

# Objectives

- ❑ **To determine if cognitive outcomes of children cCMV infection that is asymptomatic at birth differ from children without cCMV infection**
  - Intellectual ability
  - Intellectual achievement
  - Language

# **METHODS**



# Study Population

- ❑ **Participants identified through comprehensive hospital-based screening during 1982-1992**
  - All infants born at Women's Hospital of Texas were screened for cCMV infection within 3 weeks of birth using urine culture
  - Population served by hospital was largely privately insured
- ❑ **Participants in this analysis were infants identified with a CMV-positive urine culture who had no clinical manifestations of CMV**
- ❑ **Infants selected as controls had a urine culture that was negative for CMV**
  - identified through the hospital-based screening or referrals
- ❑ **Follow-up is ongoing**
- ❑ **Analyzed data collected through 2012.**

# Methods: Cognitive and Language Testing

Test	Measure of Intellectual Ability or Language	Age range (years)	Purpose
<b>COGNITIVE TESTS</b>			
<b>Bayley Scales of Infant Development</b>	Mental score	1	Measure of physical, motor, sensory, and cognitive development
<b>McCarthy Scales of Children's Abilities</b>	General cognitive index	2-5	Measure of cognitive capabilities
<b>Wechsler Intelligence Scale for Children, 3<sup>rd</sup> edition (WISC-III)</b>	Full scale IQ Performance IQ Verbal IQ	6-17	Measure of cognitive capabilities
<b>Wechsler Abbreviated Scale of Intelligence (WASI)</b>	Full scale standard score Performance standard score Verbal standard score	6-17	Measure of cognitive capabilities
<b>Woodcock-Johnson Tests of Achievement</b>	Broad math scores Broad reading scores Broad skills scores Broad written language scores	3-17	Measure of developed skill or knowledge
<b>LANGUAGE TESTS</b>			
<b>Pre-school Language Scale (PLS-3)</b>	Auditory comprehension Expressive communication Total language	2-5	Measure of auditory comprehension, expressive communication, and total language
<b>Expressive One Word Picture Test – revised (EOWPT-R)</b>	Standard score	2-17	Measure of expressive vocabulary
<b>Peabody Picture Vocabulary Test – revised (PPVT-R)</b>	Standard score	2-17	Measure of receptive (understood) vocabulary

## **Cognitive and Language Testing**

- ❑ **All tests had mean scores of 100 and standard deviations of 15 or 16**
- ❑ **Participants with IQ or language scores <85 categorized as at risk for cognitive or language impairments**
- ❑ **Participants with achievement test scores <75 categorized as at risk for school failure**

# Methods: Hearing Evaluations

- ❑ **Auditory brainstem response (ABR) test for children <4 years**
  
- ❑ **Behavioral audiometry for children 4-18 years of age**
  - Pure Tone Auditory (PTA) thresholds based on the average score of 500, 1000, 2000 and 4000 Hz exams
  - Excluded exams with abnormal tympanograms
  
- ❑ **Definitions of hearing loss**
  - >25 dB threshold for one ear = unilateral hearing loss
  - >25 dB threshold for both ears = bilateral hearing loss



## Methods: Data Analysis

- ❑ **Comparison of cognitive, language and achievement scores between children with AcCMV infection (cases) and controls**
  - Children with at least one cognitive test were included in analysis
  - Data analyzed by age groups
    - 1 yr, 2-5 yrs, 6-12 yrs, 13-17 yrs
  - Mean scores compared using Kruskal-Wallis or Wilcoxon Rank Sum Test
  - Growth curve model
    - Longitudinal analysis technique used to estimate change in scores over time
    - Utilizes all cognitive and language testing data available from each participant



# RESULTS

# Characteristics of children with cCMV infection that was asymptomatic at birth and control children

Demographic characteristics	Asymptomatic (N= 110), n (%)	Controls (N= 42), n (%)	P-value
<b>Gender</b>			0.07
Male	53 (57.6)	31 (73.8)	
Female	39 (42.4)	11 (26.2)	
<b>Mother's age at delivery</b>			0.5
<20 years	1 (1.1)	0 (0)	
20-29 years	57 (62)	23 (56.1)	
30-39 years	33 (35.9)	18 (43.9)	
40-49 years	1 (1.1)	0 (0)	
<b>Mother's race</b>			0.3
White	82 (89.1)	36 (85.7)	
Black	10 (10.9)	4 (9.5)	
Asian	0 (0)	0 (0)	
Other/Unknown	0 (0)	2 (4.8)	
<b>Mother's ethnicity</b>			0.8
Non-Hispanic	83 (90.2)	39 (92.9)	
Hispanic	6 (6.5)	1 (2.4)	
Unknown	3 (3.3)	2 (4.8)	
<b>Mother's marital status</b>			0.8
Single	4 (4.4)	0 (0)	
Married	84 (91.3)	40 (95.2)	
Unknown	4 (4.4)	2 (4.8)	
<b>Insurance</b>			<0.001
None	3 (3.3)	1 (2.4)	
Private/HMO	70 (76.1)	17 (40.5)	
Medicaid	1 (1.1)	0 (0)	
Other/Unknown	18 (19.6)	24 (57.1)	

## Length of follow-up

- ❑ Overall, cohort followed for a median of 16.3 years as of 2012
- ❑ The numbers of children with evaluations at each age group varied

# children evaluated at each age group	Children with asymptomatic cCMV infection N=110	Control Children N= 42
1 year	82	22
2-5 years	74	18
6-12 years	80	26
13-17 years	73	29



## **IQ scores at age 13-17 among children with asymptomatic cCMV infection and control children**

	<b>Asymptomatic cCMV Infection</b>	<b>Controls</b>	<b>P-Value</b>
<b>Mean IQ score (range)</b>	109 (75-134)	109 (87-132)	1.0
<b>Number with score &lt;85/total number evaluated, n/N (%)</b>	3/73 (4)	0/29 (0)	0.3

## Language scores at 13-17 years of age among children with asymptomatic cCMV infection and control children

Subject status	Asymptomatic cCMV Infection	Controls	P-Value
	n=43	n=18	
EOWPT-R score (range)	96 (74-132)	102 (82-135)	0.2
	n=75	n=34	
PPVT-R score (range)	105 (64-134)	107 (75-135)	0.4

## Mean broad achievement scores among children with asymptomatic cCMV infection and control children

Tests	Asymptomatic cCMV Infection Score (range)	Controls Score (range)
<b>Math</b>	107 (58-142)	113 (91-136)
# with score <75/total # evaluated, n/N	3/75	0/33
<b>Reading</b>	111 (61-154)	108 (48-144)
# with score <75/total # evaluated, n/N	1/75	1/33
<b>Writing language</b>	105 (47-163)	102 (82-138)
# with score <75/total # evaluated, n/N	2/73	0/32

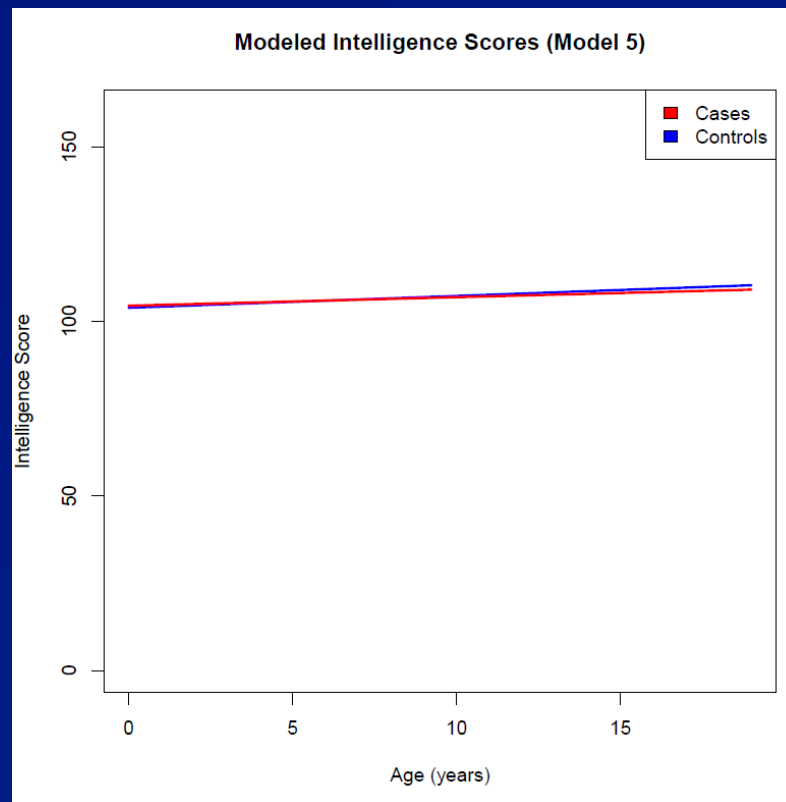
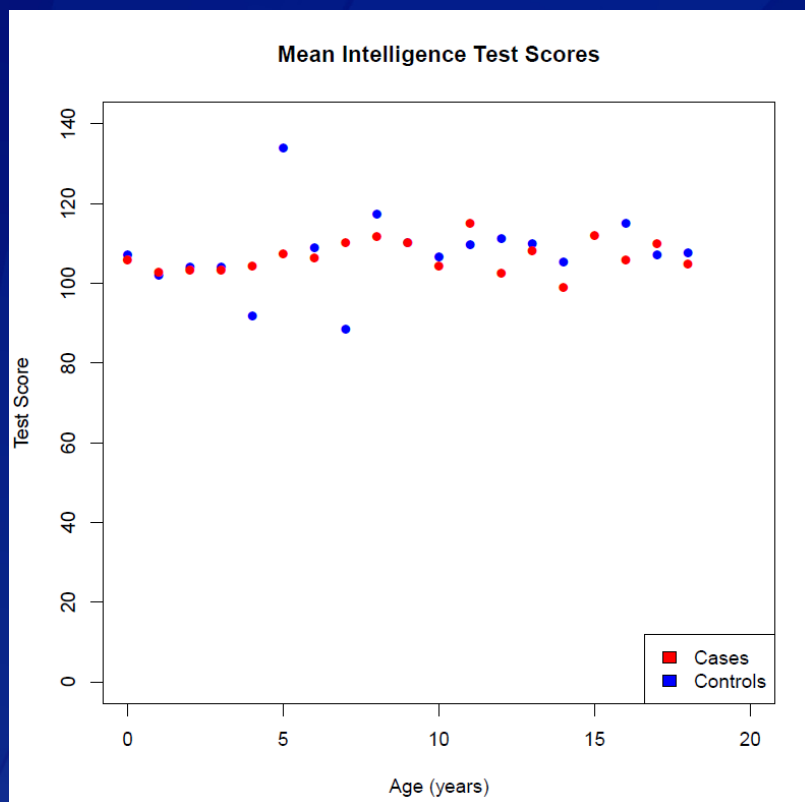
\*No statistically significant differences between proportion of children with scores <75 among asymptomatic and control groups.

# IQ scores among children with asymptomatic cCMV infection and control children over time

Subject status	Age Group			
	1 year	2-5 years	6-12 years	13-17 years
<b>Asymptomatic</b>				
Mean age (range)	18.5 months (3-30 months)	3 years (2-5 years)	8.7 years (6-10 years)	16.2 years (13-17 years)
Mean score (range)	105 (64-133)	104 (70-130)	109 (76-132)	109 (75-134)
# with score <85/total number evaluated, n/N	5/82 (6%)	8/74 (11%)	3/80 (4%)	3/73 (4%)
<b>Control</b>				
Mean age (range)	18.2 months (5-27 months)	3 years (3-4 years)	9.3 years (6-12 years)	16 years (13-17)
Mean score (range)	104 (66-140)	106 (74-126)	112 (81-134)	109 (87-132)
# with score <85/total number evaluated, n/N	4/22 (18%)	2/18 (11%)	1/26 (4%)	0/29 (0%)

# IQ scores over time among children with asymptomatic cCMV infection and control children

CU11



## Slide 21

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### CU11

Not sure if you want to include these figures but I think they show nicely how the scores remain stable over time. These also include all scores, not just those in the specific age groups we analyzed for the primary analysis.

CDC User, 9/22/2014

## **IQ scores among children with children with cCMV infection that was asymptomatic at birth**

- ❑ Proportion of asymptomatic children with hearing loss who underwent testing ranged from 12%-20% across age groups**
- ❑ Overall, hearing loss (HL) did not appear to impact IQ scores at any age among children with asymptomatic cCMV infection**

## Next steps

- ❑ **Analyze data using refined age categories**
  - 6-12 years may be too broad
  - IQ scores may not be stable until 9 years of age
- ❑ **Estimate risk for learning disability by examining discrepancies between IQ and achievement scores**
- ❑ **Analyze sub-scores indicative of ADHD**
- ❑ **Estimate socioeconomic status of participants**



## Limitations

- ❑ **Not all children with asymptomatic cCMV infection had cognitive, hearing, and language tests performed at every time point**
- ❑ **Data on interventions provided to children with AcCMV infection not captured systematically**
  - interventions may have ameliorated impaired and interfered with ability to detect subtle cCMV-related cognitive deficits; however, very few children had scores that would have met criteria for offering accommodations or interventions
- ❑ **Results may not be generalizable to all populations, particularly those with lower socioeconomic status**



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## Conclusions

- ❑ **This study describes cognitive outcomes into adolescence among a cohort of children identified through comprehensive hospital-based screening for cCMV infection**
- ❑ **Consistent with the majority of previous studies, children with asymptomatic cCMV do not appear to be at disproportionate risk of cognitive or language impairments**
- ❑ **Based on results from our study, cCMV infection does not appear to be associated with late onset of cognitive impairments among children who were asymptomatic at birth**

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# THANK YOU

**For more information please contact Centers for Disease Control and Prevention**

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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# **IQ scores among children with asymptomatic cCMV infection and hearing loss**

## **□ At 1 year of age**

- n=25 children
- 5 (20%) had any hearing loss (HL)
  - 3 unilateral, 2 bilateral
- All 5 with HL had IQ scores  $\geq 85$

## **□ At 2-5 years of age**

- n=51 children
- 8 (16%) had any HL
  - 7 unilateral, 1 bilateral
- 1 with unilateral HL had IQ score  $< 85$

## **□ At 6-12 years of age**

- n=73 children
- 10 (14%) had any HL  $\rightarrow$  9 unilateral, 1 bilateral
- 1 with bilateral HL had IQ score  $< 85$

## **□ At 13-17 years of age**

- n=72 children
- 9 (12%) had any HL  $\rightarrow$  7 unilateral, 2 bilateral
- All 9 with HL had IQ scores  $\geq 85$