Establishing standardized case definitions for congenital cytomegalovirus (cCMV) infection and disease in the United States

Max Sidesinger, MPH
Stephanie McVicar, Au.D., CCC-A
Jacinda Merrill, MPH, CHES

Utah Early Hearing Detection and Intervention Program

Utah Department of Health & Human Services

Learning objectives

1. Describe the laboratory and clinical criteria for each of the three proposed cCMV case classifications

2. Explain the process of drafting a CSTE standardized case definition position statement

3. Summarize the reasons for inclusion and exclusion of various cCMV laboratory and clinical criteria for both reporting and case classification purposes

Birth Defects Research

Society for Birth Defects Research & Prevention
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RESEARCH ARTICLE

Congenital cytomegalovirus surveillance in the United States

Kelley Raines, Kristen Nichols Heitman, Jessica Leung, Kate R. Woodworth, Van T. Tong, David E. Sugerman, Tatiana M. Lanzieri

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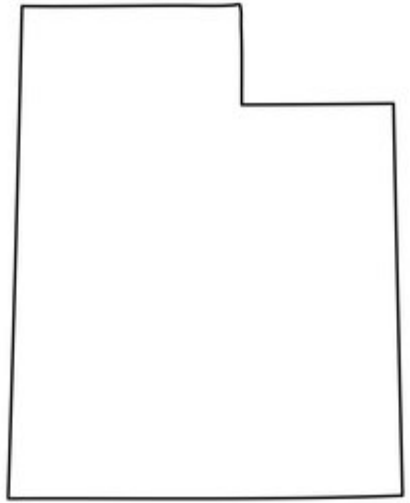
- January - June 2022, all 50 state health departments were assessed regarding their cCMV surveillance case ascertainment methods

- Authors also gauged jurisdiction's interest in joining a working group for forming a standardized case definition for cCMV

Utah

- cCMV surveillance is part of the state's Early Hearing Detection and Intervention (EHDI) program
- First state to adopt legislation mandating hearing-targeted screening for cCMV (2013)
- CMV added to the state's communicable disease reporting rule (2015)



Position statement background

- Published by the Council of state and territorial epidemiologists (CSTE)
  - Position statement archive - 700+ position statements, beginning in 1980s
    - Policy statements
    - Standardized surveillance - can be driven by variability in jurisdictional case definitions, unknown disease burden, need for monitoring trends in incidence, effective use of public health surveillance resources, and more
      - Nationally notifiable conditions - can be driven by morbidity/mortality, availability of public health intervention, need for a national picture, and more - shouldn't be driven solely for increased awareness
- Voted on at CSTE's annual business meeting
- Authors must be CSTE members

Position statement (PS) contributors

Submitting author

- Leads discussion and writing of PS
- Presents PS on formal discussion webinars
- Presents PS at roundtable and voting session at annual CSTE Conference

Co-authors

- Participate in discussions, writing, and revisions of PS

Subject matter experts

- Don’t have to be CSTE members
- Advise authors on content development
- Participate in discussions and review edits made to PS

Position statement (PS) contributors

Utah team

- Stephanie McVicar (presenting and submitting author), Max Sidesinger, and Jacinda Merrill

CDC team

- Kristen Nichols Heitman, Tatiana Lanzieri, Kelley Raines, Ashrita Rau, and Jessica Leung

SMEs

- 24 nationwide researchers, clinical practitioners, and professionals working on CMV

Core working group (CWG)

- 13 public health officials in jurisdictions conducting active CMV surveillance

Large working group (LWG)

- 65 individuals, including all listed above, plus additional jurisdictional partners with experience or interest in CMV surveillance

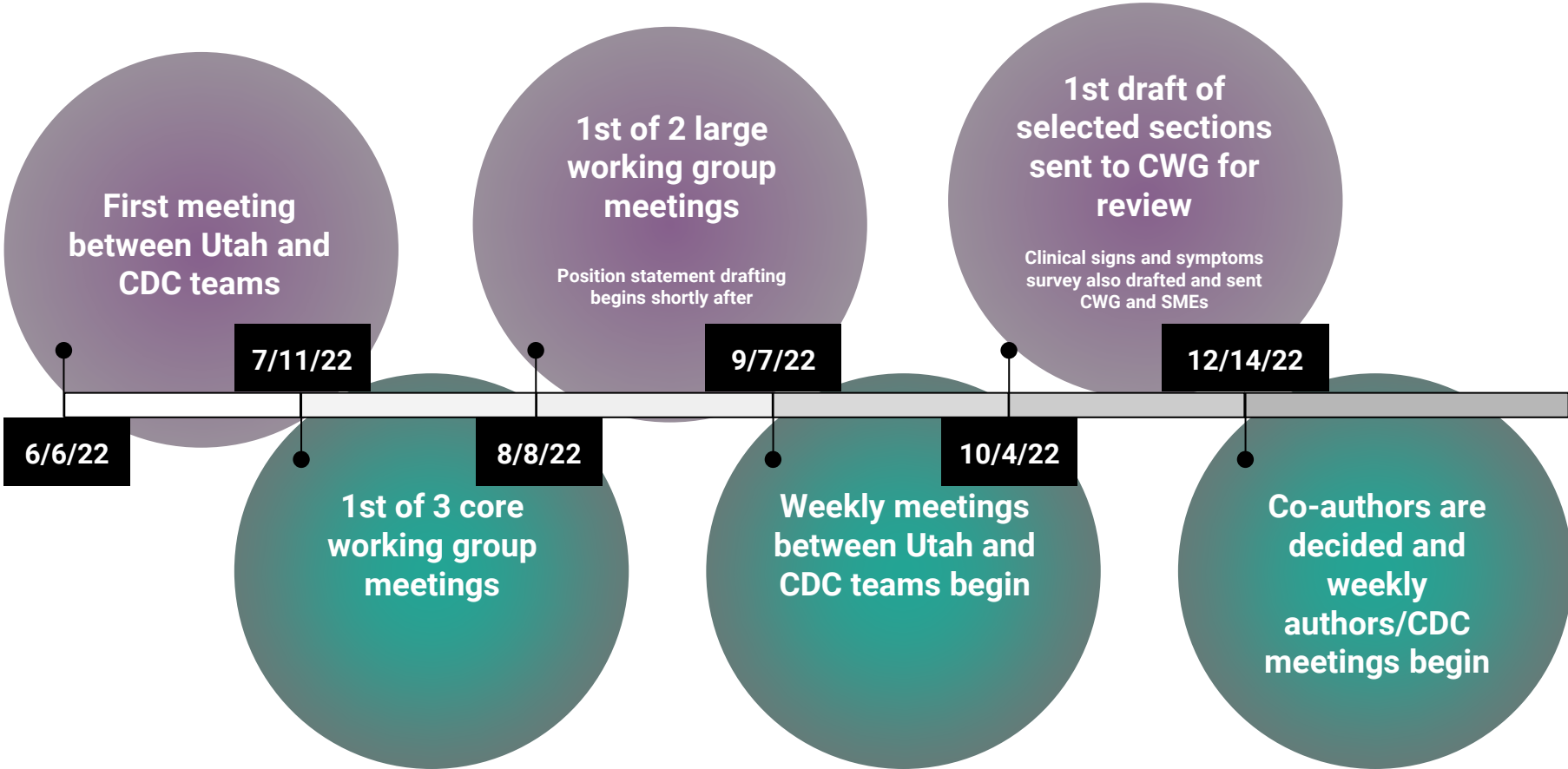
Position statement (PS) authors

Co-authors
Max Sidesinger, MPH **(UT)**
Chas DeBolt **(WA)**
Elizabeth Dufort, MD **(MN)**
Tory Kaye, MPH **(MN)**
Jessica Kumar, DO, MPH **(NY)**
Nicole Longcore, MPH **(NY)**
Maryrose McInerney, PhD, CCC-A **(NJ)**
Sondra Rosendahl, MS, LCGC **(MN)**
Presenting and submitting author
Stephanie McVicar, Au.D., CCC-A **(UT)**

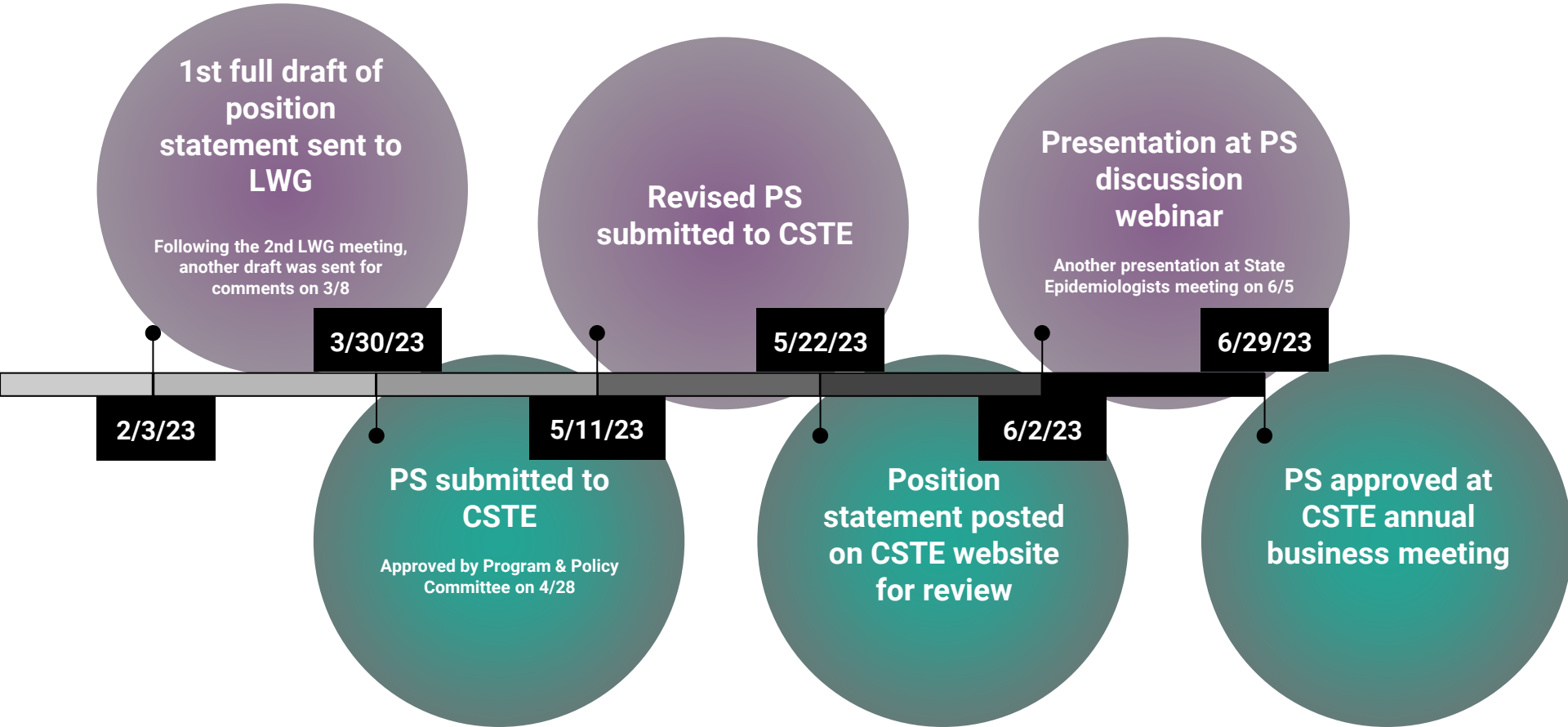
CDC team
Tatiana Lanzieri, MD, MPH **(Primary SME)**
Kristen Nichols Heitman, MPH **(SME)**
Jessica Leung, MPH
Kelley Raines, MPH
Kate Russell Woodworth, MD, MPH

SMEs
Suresh Boppana, MD
Gail Demmler-Harrison, MD
Karen Fowler, DrPH
David Kimberlin, MD
Pablo Sanchez, MD
Mark Schleiss, MD

Timeline


First meeting between Utah and CDC teams
6/6/22
1st of 3 core working group meetings
7/11/22
1st of 2 large working group meetings
Position statement drafting begins shortly after
8/8/22
Weekly meetings between Utah and CDC teams begin
9/7/22
1st draft of selected sections sent to CWG for review
Clinical signs and symptoms survey also drafted and sent CWG and SMEs
10/4/22
Co-authors are decided and weekly authors/CDC meetings begin
12/14/22

Timeline


1st full draft of position statement sent to LWG
Following the 2nd LWG meeting, another draft was sent for comments on 3/8
2/3/23
PS submitted to CSTE
Approved by Program & Policy Committee on 4/28
3/30/23
5/11/23
Revised PS submitted to CSTE
Position statement posted on CSTE website for review
5/22/23
6/2/23
Presentation at PS discussion webinar
Another presentation at State Epidemiologists meeting on 6/5
PS approved at CSTE annual business meeting
6/29/23

I. Statement of the problem
II. Background and justification
III. Statement of the desired actions to be taken
IV. Goals of surveillance
V. Recommended data sources and methods for surveillance
    - Table V - recommended sources of data, surveillance methods, and extent of coverage for ascertainment of cases

I. Criteria for case ascertainment
    A. Narrative - includes clinical, laboratory, epidemiologic linkage, and other reporting criteria
    B. Disease-specific data elements to be included in the initial report
    - Table VI - table of reporting criteria

I. Case definition for case classification
    A. Narrative - includes clinical, laboratory, epidemiologic linkage, and other classification criteria
    B. Criteria to distinguish new cases from recurring, duplicate, or relapse cases
    - **Table VII - classification table**

I. Period of surveillance
II. Data sharing and release criteria

X - XIII. Revision history, references, coordination, and author information

Position statement contents

Table VI

Table VI. Table of criteria to determine whether a case should be reported to public health authorities.

Criterion	Reporting cCMV infection or disease
Clinical Criteria for Reporting	
N/A	
Laboratory Criteria for Reporting	
Detection of CMV DNA by NAAT from infant† urine, saliva, whole blood (including DBS), or CSF specimen	S
Detection of CMV DNA by NAAT from amniotic fluid specimen	S
Isolation of CMV in viral culture from infant† urine, saliva, whole blood, or CSF specimen	S
Isolation of CMV in viral culture from amniotic fluid specimen	S
Demonstration of CMV antigen in a biopsy from umbilical cord or autopsy specimen by IHC	S
Detection of CMV antigen by antigenemia test in infant† whole blood specimen	S
Epidemiologic Linkage Criteria for Reporting	
N/A	
Vital Record Criteria for Reporting	
An infant aged one year or less whose death certificate lists cCMV or CMV as an underlying cause of death or significant condition contributing to death.	S
Healthcare Record Criteria for Reporting	
A child aged 6 years or younger whose healthcare record contains a diagnosis* of cCMV infection	S
An infant aged 45 days or younger whose healthcare record contains a diagnosis* of CMV disease.	S

Table VII

Table VII.A. Classification Table: Criteria for defining a case of cCMV infection or disease.

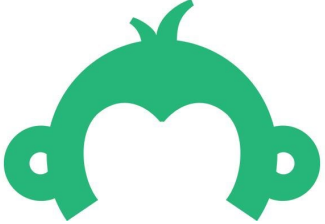
Criterion	Case Classification				
	cCMV Infection	cCMV Disease			
	Confirmed	Confirmed		Probable	
Clinical Evidence					
Hepatomegaly		O		O	
Splenomegaly		O		O	
Petechial rash or purpura ("blueberry muffin rash")		O		O	
Microcephaly††			O		O
Brain imaging abnormalities*			O		O
Sensorineural hearing loss			O		O
Seizures			O		O
Cerebral palsy			O		O
Chorioretinitis			O		O
Vision impairment¶			O		O
Absence of a more likely alternative etiology		N	N	N	N
Infant in neonatal period		N		N	
Child aged 6 years or younger			N		N
Laboratory Evidence					
Absence of a negative test (CMV DNA by NAAT or culture) on a urine specimen collected within 21 days of life	N	N	N	N	N
Detection of CMV DNA by NAAT from urine, whole blood (including DBS), or CSF collected within 21 days of life	O	O	O		
Detection of CMV DNA by NAAT from amniotic fluid specimen	O	O	O		
Isolation of CMV in viral culture from urine, whole blood, or CSF collected within 21 days of life	O	O	O		
Isolation of CMV in viral culture from amniotic fluid specimen	O	O	O		
Demonstration of CMV antigen in an autopsy specimen by IHC	O	O	O		
Detection of CMV antigen by antigenemia test in whole blood collected within 21 days of life	O	O	O		
Detection of CMV DNA by NAAT from saliva collected within 42 days of life§				O	O
Isolation of CMV in viral culture from saliva collected within 42 days of life§				O	O
Detection of CMV DNA by NAAT from urine, whole blood or CSF collected at 22–42 days of life				O	O
Isolation of CMV in viral culture from urine, whole blood, or CSF collected within 22–42 days of life				O	O
Epidemiologic Linkage Evidence					
N/A					

N = All “N” criteria in the same column are NECESSARY to classify a case.

O = At least one of these “O” (ONE OR MORE) criteria in each category (categories=clinical evidence, laboratory evidence, and epidemiologic evidence) in the same column—in conjunction with all “N” criteria in the same column—is required to classify a case.

1. Which is the best way to categorize cCMV cases?

- *Symptomatic/Asymptomatic or Infection/Disease*



2. Please rank the following CMV laboratory results based on the definitions below:

Confirmed laboratory evidence - Specified laboratory results that are consistent with the diagnosis of a cCMV infection and are part of the confirmed case classification.
Presumptive laboratory evidence - Specified laboratory results that are consistent with the diagnosis of a cCMV infection and are part of the probable case classification.
Supportive laboratory evidence - Specified laboratory results that are consistent with the diagnosis of a cCMV infection and are part of the suspect case classification.

- *23 different laboratory results to classify*

3. Please rank the following clinical signs/symptoms based on how strongly you feel it aligns with a clinical presentation of cCMV

- *23 different clinical signs to rank on a scale of 1-5*

Clinical signs survey

Clinical criteria

A1. Clinical Criteria

Cases should be assessed according to absence or presence of clinical evidence as defined below and the clinical data should be included in the case investigation.

In the absence of a more likely alternative etiology:

- An infant with at least one of the following clinical signs during the neonatal period:[28,29]
  - Hepatomegaly
  - Splenomegaly
  - Petechial rash or purpura ("blueberry muffin rash"),

OR

- A child aged 6 years or younger with one or more of the following permanent conditions:[28,29,30]
  - Microcephaly (defined as head circumference measurement >2 standard deviations below the average (or <3rd percentile) for the same age and sex, notation in the medical record, or diagnostic code of microcephaly (e.g., ICD-10 code Q02),
  - Brain imaging abnormalities consistent with cCMV, such as intracranial calcifications, periventricular calcifications, leukomalacia, polymicrogyria, lissencephaly, pachygyria, schizencephaly, or ventriculomegaly
  - Sensorineural hearing loss
  - Seizures
  - Cerebral palsy
  - Chorioretinitis
  - Vision impairment, resulting from conditions consistent with cCMV, such as retinitis, retinal scarring, optic neuritis, optic atrophy, or brain damage resulting in cortical vision impairment

Laboratory criteria

A2. Laboratory Criteria*

Confirmatory Laboratory Evidence[†]*:*

- Absence of a negative test (CMV DNA by NAAT or culture) on a urine specimen collected within 21 days of life, **AND**
- Detection of CMV DNA by NAAT from urine, whole blood (including dried blood spot [DBS]), or cerebrospinal fluid (CSF) collected from an infant within 21 days of life, **OR**
- Detection of CMV DNA by NAAT from amniotic fluid specimen, **OR**
- Isolation of CMV in viral culture from urine, whole blood, or CSF collected from an infant within 21 days of life, **OR**
- Isolation of CMV in viral culture from amniotic fluid specimen, **OR**
- Demonstration of CMV antigen in an autopsy specimen by IHC, **OR**
- Detection of CMV antigen by antigenemia test in whole blood collected from an infant within 21 days of life.

Presumptive Laboratory Evidence:

- Absence of a negative test (CMV DNA by NAAT or culture) on a urine specimen collected within 21 days of life, **AND**
- Detection of CMV DNA by NAAT from saliva collected from an infant within 42 days of life[§], **OR**
- Isolation of CMV in viral culture from saliva collected from an infant within 42 days of life[§], **OR**
- Detection of CMV DNA by NAAT from urine, whole blood, or CSF collected from an infant within 22–42 days of life[¶], **OR**
- Isolation of CMV in viral culture from urine, whole blood, or CSF collected from an infant within 22–42 days of life[¶].

** Note: The categorical labels used here to stratify laboratory evidence are intended to support the standardization of case classifications for public health surveillance. The categorical labels should not be used to interpret the utility or validity of any laboratory test methodology.*

[†] *Only valid in the absence of a subsequent negative test on a urine specimen that was completed for confirmatory purposes.*

[§] *If CMV is detected in saliva, repeat testing should be performed using urine.*

[¶] *Only valid in the absence of a prior negative test on a urine specimen collected within 21 days of life.*

Case classification summary

Confirmed:

- cCMV infection: meets confirmatory laboratory evidence
- cCMV disease: meets clinical criteria AND confirmatory laboratory evidence

Probable:

- cCMV disease: meets clinical criteria AND presumptive laboratory evidence

CSTE

Council of State and Territorial Epidemiologists

23-ID-02

Committee: Infectious Disease

Title: Standardized Surveillance Case Definitions for Congenital Cytomegalovirus (cCMV) Infection and Disease

☐Check this box if this position statement is an update to an existing standardized surveillance case definition and include the most recent position statement number here: N/A.

Synopsis:

- This position statement creates standardized case definitions for cCMV infection and disease.
- Standardized case definitions for cCMV infection and disease are needed because multiple jurisdictions in the United States are conducting cCMV screening and surveillance activities but are using various methods and inclusion criteria for case ascertainment, reporting, and classification. As more jurisdictions pass legislation for newborn screening for cCMV, standardized case definitions for cCMV infection and disease can be used to understand the epidemiology of cCMV and compare trends across the United States.
- Case ascertainment criteria include laboratory criteria (the detection of CMV in neonatal urine, saliva, whole blood, or cerebrospinal fluid specimens, in amniotic fluid specimens, or umbilical cord or autopsy specimens), vital records criteria (infant death certificates), and healthcare records criteria (e.g., using ICD-10 diagnostic codes).
- Case classification criteria include clinical and laboratory criteria.
- Case classifications include confirmed cCMV infection, confirmed cCMV disease, and probable cCMV disease.

I. Statement of the Problem

Cytomegalovirus (CMV) infection during pregnancy can cause stillbirth, infant death, and a myriad of birth defects.[1-3] In the United States (U.S.), approximately 1 in 200 babies is born with congenital CMV (cCMV) infection; one out of 5 of these babies will present with clinical signs of cCMV disease in the neonatal period and/or have long-term health conditions.[4] cCMV is the most common infectious cause of developmental disabilities and non-genetic sensorineural hearing loss (SNHL) in U.S. children.[5-8] Nonetheless, the burden of cCMV disease is not fully understood.[9-11]

Surveillance of cCMV in the U.S. is complicated by several factors. First, most newborns with cCMV infection have no clinical signs at birth and, without universal cCMV screening, are not identified.[12,13] Second, neonatal clinical signs of cCMV disease are nonspecific and may be attributed to other conditions.[14] Third, postnatal CMV infection is common among infants, and a reliable diagnosis of cCMV infection or disease may not be possible unless specimens are collected within the first three weeks of life.[15] Finally, not all newborns with a laboratory diagnosis of cCMV infection receive a diagnostic code that would allow cases to be ascertained through a review of administrative data.[16]

II. Background and Justification

cCMV infection is responsible for an estimated 5-10% of cases of prelingual hearing loss among children less than 2 years of age, and an estimated 15-20% of moderate to profound bilateral SNHL among all U.S. children.[7,17] A substantial proportion of cCMV-related SNHL cases occur in children with cCMV infection who do not have apparent clinical signs at birth, including those who pass the newborn hearing screen.[18] Early identification and timely and appropriate intervention services are critical for improving developmental outcomes of deaf or hard-of-hearing children.[19-22] Consequently, the Joint Committee on Infant Hearing recommends that all infants who test positive for cCMV receive periodic audiologic monitoring beginning no later than three months of age to allow for the provision of appropriate amplification, early intervention, and family support.[23] Jurisdictional programs that monitor children with

Thank you!

Stephanie McVicar, Au.D., CCC-A

Tatiana Lanzieri, MD, MPH

Kristen Nichols Heitman, MPH

All SMEs, Co-Authors, working group members

Contact us

ehdi@utah.gov
cmv@utah.gov
msidesinger@utah.gov
smcvicar@utah.gov
jmerrill@utah.gov
801-273-6600

health.utah.gov/cmv
health.utah.gov/ehdi

Utah Department of Health & Human Services