NEW YORK STATE

Department of Health
Wadsworth Center

A Pilot Study in NYS to Screen Newborns for Congenital Cytomegalovirus

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CYTOMEGALOVIRUS INFECTION

- Cytomegalovirus (CMV) is a member of the Herpesviridae family and has a double-stranded DNA genome
- CMV seroprevalence in immunocompetent adults ranges from 40 to 100%
- Approximately 1 in 200 babies is born with congenital CMV (cCMV)
- Approximately 10% of babies with cCMV have symptoms at birth. Symptoms may include:
  - Hearing loss
  - Visual impairment
  - Microcephaly
  - Premature birth
  - Jaundice
  - Seizures
  - Low birth weight
  - Petechiae
  - Pneumonia
- Approximately 10-15% of newborns with cCMV develop hearing loss later in life

CMV, cytomegalovirus; DNA, deoxyribonucleic acid; cCMV, congenital cytomegalovirus

RATIONALE FOR SCREENING FOR cCMV

- Common disease (leading non-genetic cause of hearing loss in the US)
- A subset of infected babies may not present symptoms at birth but will present symptoms later in life
- Babies with cCMV disease may pass their newborn hearing screen
- Screening tests are available
- Treatment is available
- Treatment must be started early in life to be effective

https://www.cdc.gov/hearing-loss-children-guide/parents-guide/understanding-hearing-loss.html

US, United States; cCMV, congenital cytomegalovirus

NEWBORN SCREENING FOR cCMV

Since the 1990s there have been publications on detecting CMV in dried blood spots (DBS) from newborns. Availability of a test facilitated NBS for CMV.

Year	NBS Program
2019	Ontario
2022	Saskatchewan
2023	Minnesota
2023	NYS with funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to perform screening of all newborns born in NYS for 1 year
2025	Connecticut

cCMV, congenital cytomegalovirus; DBS, dried blood spots; NBS, newborn screening; NYS, New York State; NICHD, National Institute of Child Health and Human Development

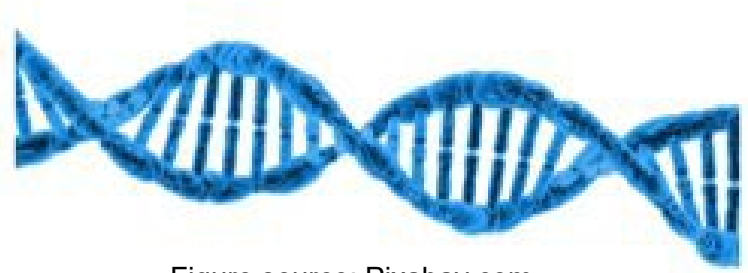
SCREENING TESTS FOR NEWBORNS

- Detection of CMV in dried blood spots (DBS) by quantitative polymerase chain reaction (qPCR)
    - Convenient, but sensitivity is an issue. A recent study indicates sensitivity of approx. 75% in DBS (Dollard et al., JAMA Pediatrics, 2021;175(3):e205441)
- Detection of CMV in urine by qPCR (Gold standard diagnostic test)
- CMV is also detected in saliva, but this could be complicated by presence of CMV in breast milk
- Effective cCMV screening requires detection in a specimen collected within three weeks of birth

CMV, cytomegalovirus; DBS, dried blood spots; qPCR, quantitative polymerase chain reaction

TEST FACTORS TO CONSIDER

- Nucleic acid extraction method
- Number of dried blood spots
- qPCR method
- Automation
- Sensitivity/specificity
- Throughput/practicality
- Cost



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qPCR, quantitative polymerase chain reaction

KNOWN CHALLENGES

- Lack of sensitivity of the qPCR test will lead to missed cases (possible ~25% false negative screening rate)
- Most babies with cCMV will not have any symptoms and do not need treatment
- Creates stress in families by referring newborns with asymptomatic cCMV, who will not need treatment and follow-up
- May cause unnecessary medicalization of infected newborns
- Costly to perform audiology tests and other follow-up tests if they are not needed
- Treatment is not 100% effective and may have serious side effects

qPCR, quantitative polymerase chain reaction; cCMV, congenital cytomegalovirus

TASKS PERFORMED PRIOR TO START OF PILOT

- Hired 3 staff members to perform screening and follow-up
- Set up Advisory committee
- Collaborated with NYS EHDI (Early Hearing Detection & Intervention) Program
- Obtained IRB approval
- Performed NIH training
- Obtained control material for assay
- Compared multiple extraction methods and qPCR assays
- Collaborated with kit/instrument manufacturer
- Developed SOPs and worksheets
- Validated method and obtained CLEP-approval
- Collaborated and certified 11 NYS Specialty Care Centers (SCC) who set up PROACTIVE NYS Registry
- Created educational material for providers and parents
- Developed opt-out method for parents

NYS, New York State; EHDI, Early Hearing Detection and Intervention; IRB, Institutional Review Board; NIH, National Institutes of Health; qPCR, quantitative polymerase chain reaction; SOP, standard operating procedure; CLEP, Clinical Laboratory Evaluation Program; SCC, specialty care center

FINAL CMV SCREENING ASSAY

- Number of 3 mm DBS: 2
- Extraction method: Extracta DBS Buffer (Quantabio)
- qPCR method: NeoMDx cCMV Real-time PCR Assay (Revvity)
- Internal control: RPP30 (Ribonuclease P/MRP Subunit P30, RNase P)
- qPCR instrument: EonisQ
- Automation: Janus Liquid Handler Workstation

Figure source: Revvity, Inc

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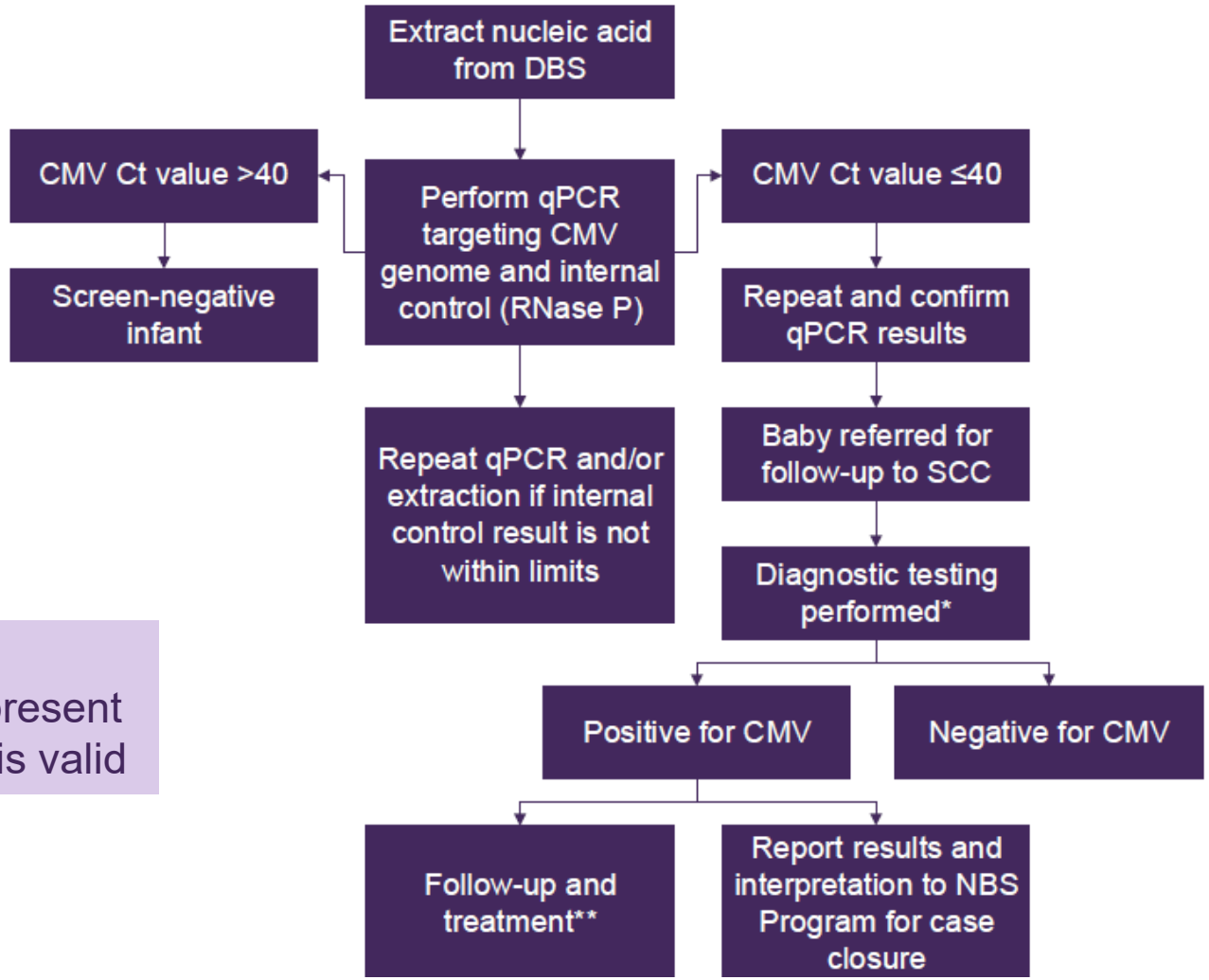
DBS, dried blood spot; qPCR, quantitative polymerase chain reaction; RNase P, Ribonuclease P

WORKFLOW DIAGRAM



DBS, dried blood spot
CMV, cytomegalovirus
Ct, cycle threshold
qPCR, quantitative polymerase chain reaction
RNaseP, ribonuclease P
SCC, specialty care center
NBS, newborn screening
DNA, deoxyribonucleic acid

Cut-off Values
Ct ≤ 40 cCMV DNA is present
Ct ≤ 30 RNaseP assay is valid

*PCR of urine
**As determined by Specialty Care Center (SCC)

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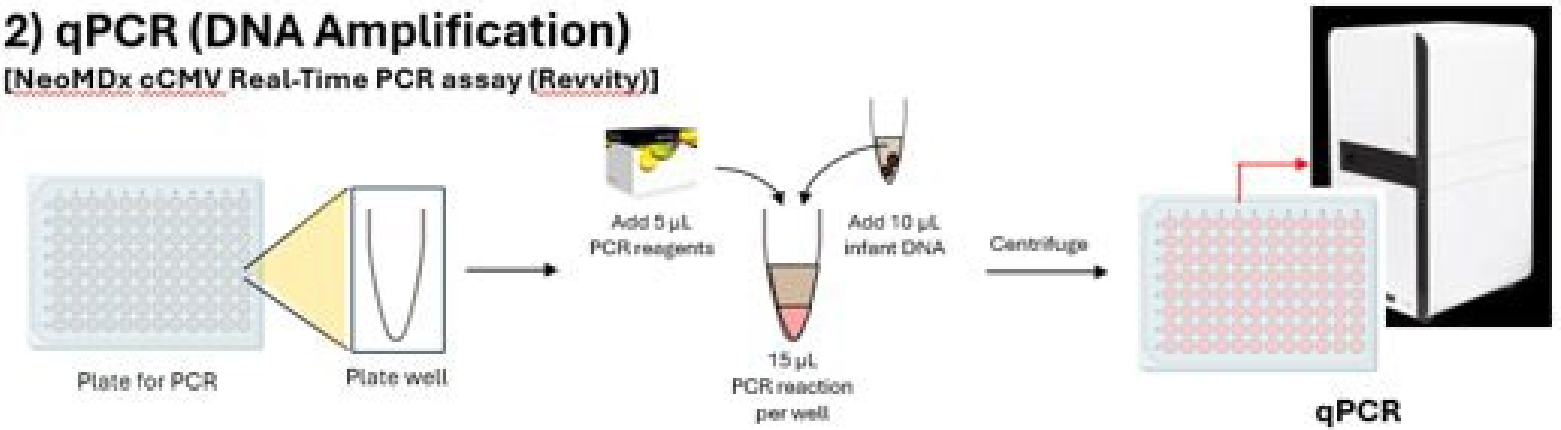
EXTRACTION AND qPCR

1) Extraction of DNA

[Extracta DBS (Quantabio)]

2) qPCR (DNA Amplification)

[NeoMDx cCMV Real-Time PCR assay (Revvity)]



qPCR protocol

Step	Temperature (°C)	Time	
1	37	2 min	
2	94	10 min	
3	93	10 sec	40x
4	60	30 sec	
5	69	40 sec	

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qPCR, quantitative polymerase chain reaction; DNA, deoxyribonucleic acid; DBS, dried blood spot; cCMV, congenital cytomegalovirus

POPULATION SCREENED (10/2/23-12/31/24)

	Total screened (%)	Referred (%)
No. specimens	247,471	-
No. babies screened	208,322 (84.2)	529
No. babies opted-out	223 (0.1)	-
Male babies	106,157 (51.0)	282 (53.3)
Female babies	101,255 (48.6)	247 (46.7)
Specimens collected ≤3 weeks of age	237,411 (95.9)	349 (66.0)
Specimens collected >3 weeks of age	10,059 (4.1)	180 (34.0)
Specimens from low birth weight (<2500 g) babies	36,262 (14.7)	-
Specimens from normal birth weight (≥2500 g) babies	211,144 (85.3)	-
Low birth weight (<2500 g) babies	18,175 (8.7)	143 (27.0)
Normal birth weight (≥2500 g) babies	190,090 (91.2)	382 (72.2)
NICU babies	21,478 (10.3)	178 (33.6)
Non-NICU babies	186,844 (89.7)	351 (66.4)

No., number; g, gram; NICU, neonatal intensive care unit

OUTCOME OF REFERRED INFANTS

Outcome/Description of case closure	Number (%)	Incidence	Number of babies whose specimens were collected at ≤ 3 weeks of age (%)	Number of babies whose specimens were collected at > 3 weeks of age (%)
Referred cases	529	1 : 393	349	180
Total cCMV cases	279 (52.7)	1 : 746	273 (78.2)	6 (3.3)
cCMV disease	68* (12.9)	1 : 3,060	68* (19.5)	0 (0)
cCMV infection	200 (37.8)	1 : 1,040	196 (56.2)	4 (2.2)
cCMV infection with isolated SNHL	11 (2.1)	1 : 18,918	9 (2.6)	2 (1.1)
Likely acquired CMV	131**(24.8)	1 : 1,589	9 (2.6)	122** (67.8)
Specimen was collected at >3 weeks of age but no earlier specimen was available for testing	40 (7.6)	1 : 5,202	1*** (0.3)	39 (21.7)
Parents refused follow-up	26 (5.0)	1 : 20 referred cases	18 (5.2)	8 (4.5)
Lost to follow-up	36 (6.8)	1 : 15 referred cases	32 (9.2)	4 (2.2)
False-positive	17 (3.2)	1 : 31 referred cases	16 (4.6)	1 (0.6)

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*The percentage includes one deceased case. **The percentage includes two deceased cases. ***Specimen was collected at 20 days. cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss

PROBABLE FALSE-POSITIVE CASES

In 17 cases, urine PCR, saliva PCR or urine culture were negative, and babies had no clinical symptoms.

Number	Description
4	NBS card was contaminated
8	<50% PCR results of DBS were positive (possible qPCR contamination)
5	>50% PCR results of DBS were positive (possible NBS card or qPCR contamination)

qPCR, quantitative polymerase chain reaction; NBS, newborn screening; DBS, dried blood spot

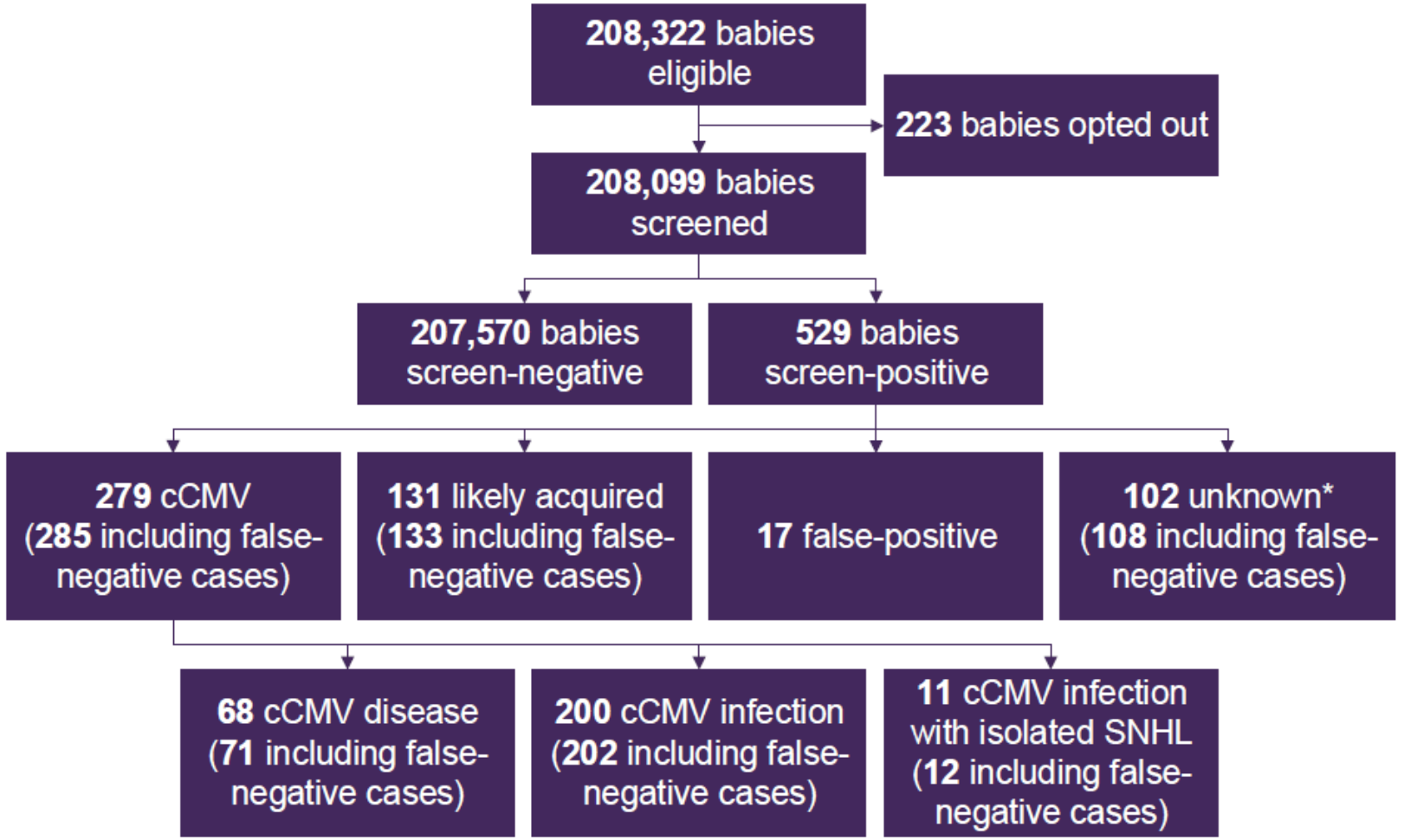
PROBABLE FALSE-NEGATIVE CASES

We are aware of 25 probable false-negative test results.

Number	Description	Case Outcome
11	Initial qPCR was negative, but baby was referred	2 cCMV disease 6 cCMV infection 2 likely acquired CMV 1 lost to follow-up
5	Initial qPCR was negative. After we were Informed of a false-negative case, qPCR was repeated and was positive	2 cCMV disease 1 cCMV infection 1 lost to follow-up 1 unknown
9	Initial and retest were negative. Urine PCR was positive	1 cCMV disease 1 cCMV infection 1 cCMV infection with SNHL 2 likely acquired CMV 1 lost to follow-up 3 unknown

qPCR, quantitative polymerase chain reaction; cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss

CASE OUTCOMES



* Unknown babies include babies whose specimens were collected at >3 weeks of age but no earlier specimen was available for testing (40), parents declined follow-up (26), or family was lost to follow-up (36).
cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss

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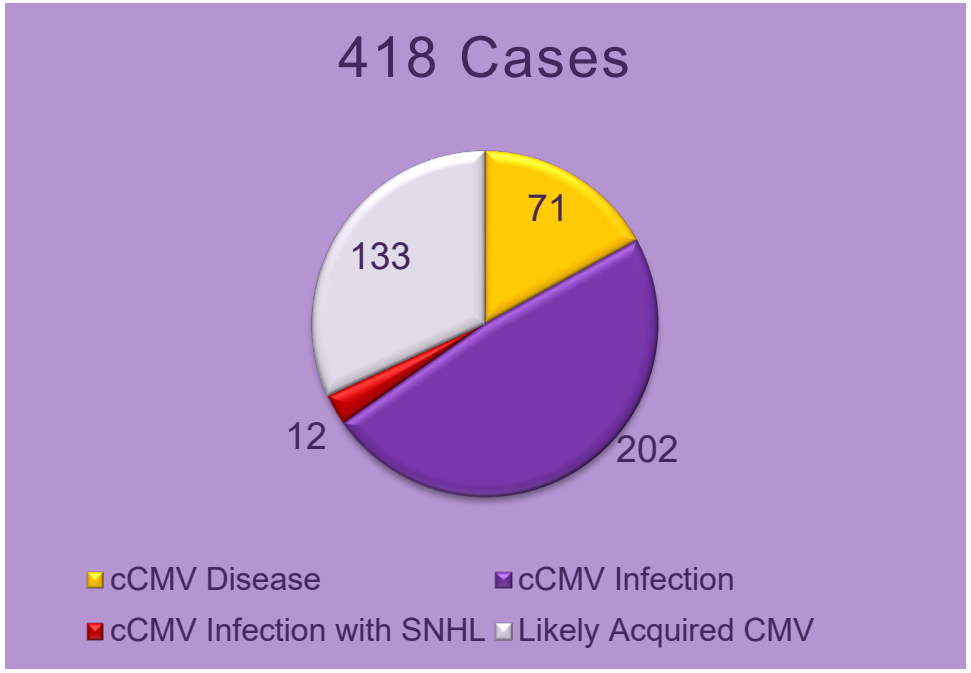
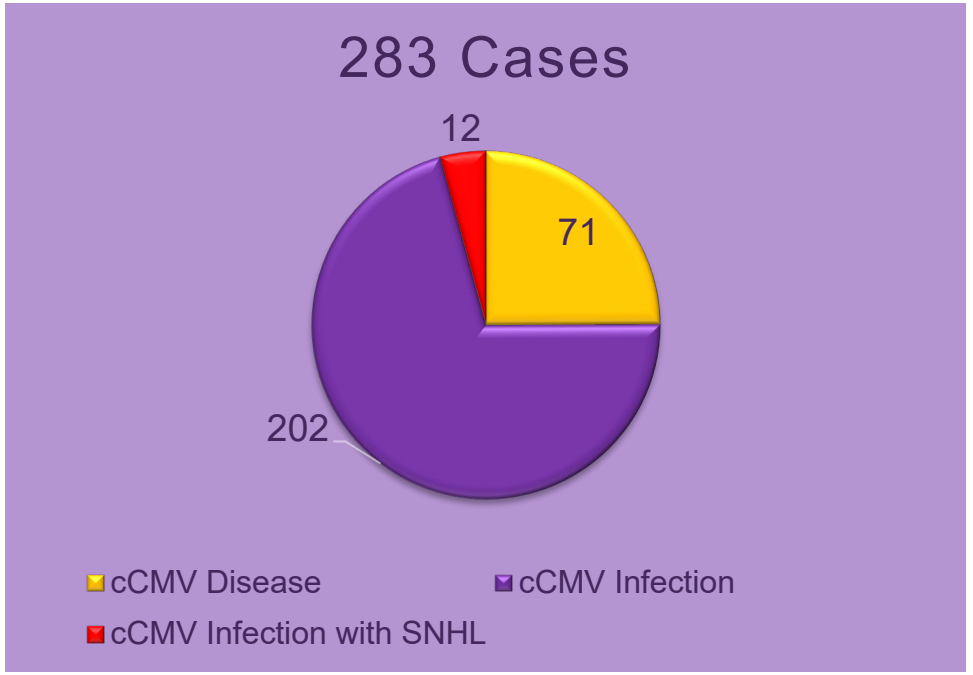
cCMV CASE OUTCOMES





Ratio of cCMV disease + cCMV infection with isolated SNHL : cCMV infection is 1 : 2.4

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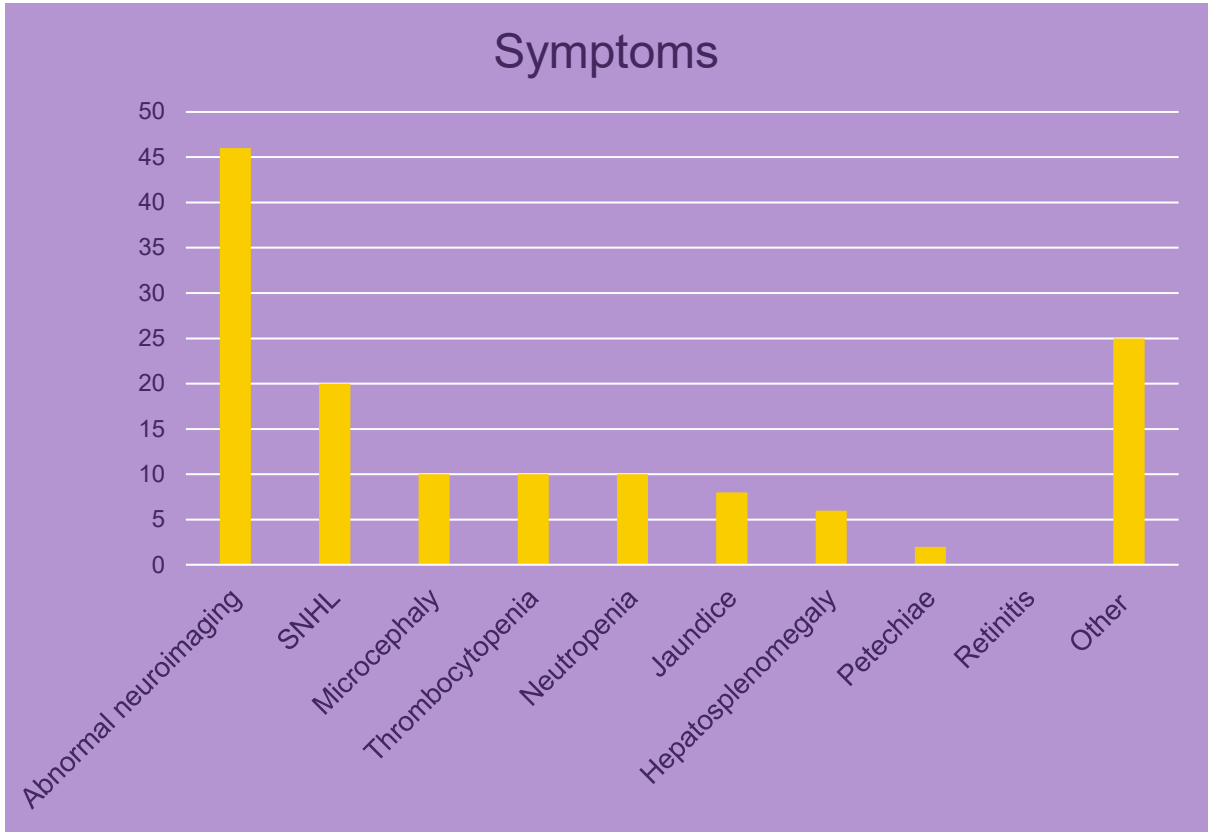
cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss

SYMPTOMS OF cCMV



"Other" includes: small for gestational age, intrauterine growth restriction, elevated liver enzyme levels, hepatitis. SNHL, sensorineural hearing loss

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INCIDENCE

- CMV was detected in 0.25% (1 in 393) babies
- cCMV was confirmed in 0.14% (1 in 730) babies
- cCMV disease was confirmed in 0.034% (1 in 2,931) babies
- Hearing loss caused by cCMV infection occurred in 0.01% (1 in 10,405) babies
- 0.06% (1 in 1,565) babies likely acquired CMV postnatally

https://www.wadsworth.org/programs/newborn/screening

cCMV, congenital cytomegalovirus

CONCLUSIONS

- From October 2023 to September 2024, 208,322 newborns were screened for cCMV
- 223 babies (1 in 934) were opted out of the study
- We referred 529 babies (1 in 393) for follow-up
- Turn-around time for results was generally 3 days
- False-positive rate was 0.008%
- False-negative rate was >5.9%
- Symptoms of cCMV included abnormal neuroimaging, SNHL, microcephaly, thrombocytopenia, neutropenia, jaundice, hepatosplenomegaly
- Of the 68 babies with cCMV disease, 48 (70.6%) were treated with antiviral medication
- Follow-up of referred newborns will continue for 2-3 years by infectious disease physicians at specialty care centers

cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss;

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https://www.linkedin.com/posts/nys-office-of-children-and-family-services_thank-you-suzanne-e-miles-gustave-esq-activity-7181680256137756672-ppGX/

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