Congenital Cytomegalovirus: New Screening Strategies and Clinical Management

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Global Product Manager, MDx

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Content

What is CMV?
Who is at risk?
What can we do if we identify CMV?
How should we manage an infection?
How and when should we screen for it ?

What is CMV?

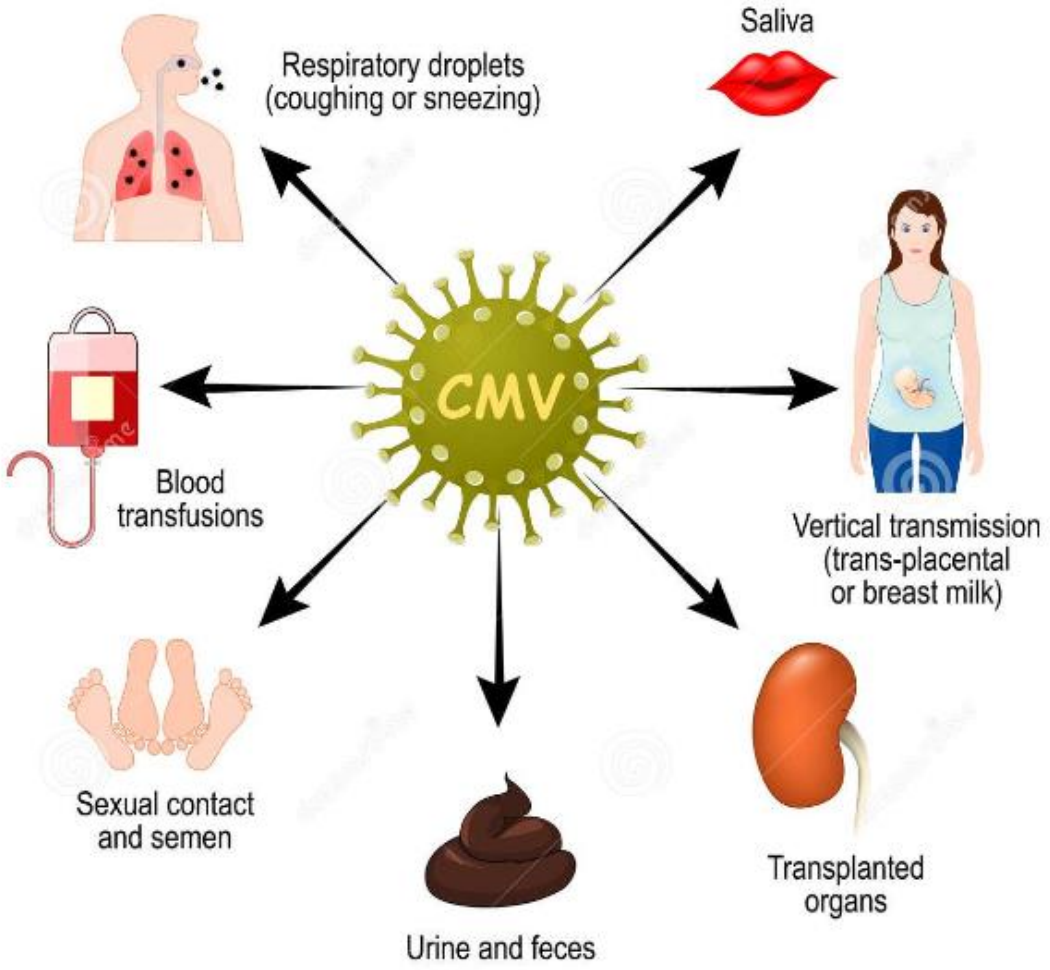
Who is at risk?

What can we do if we identify CMV?

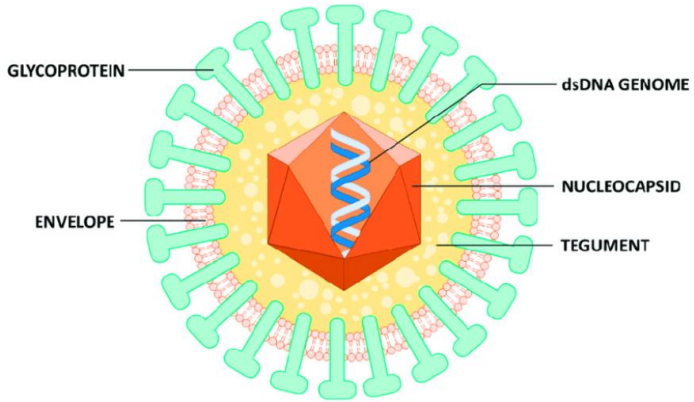
How should we manage an infection?

How and **when** should we screen for it ?

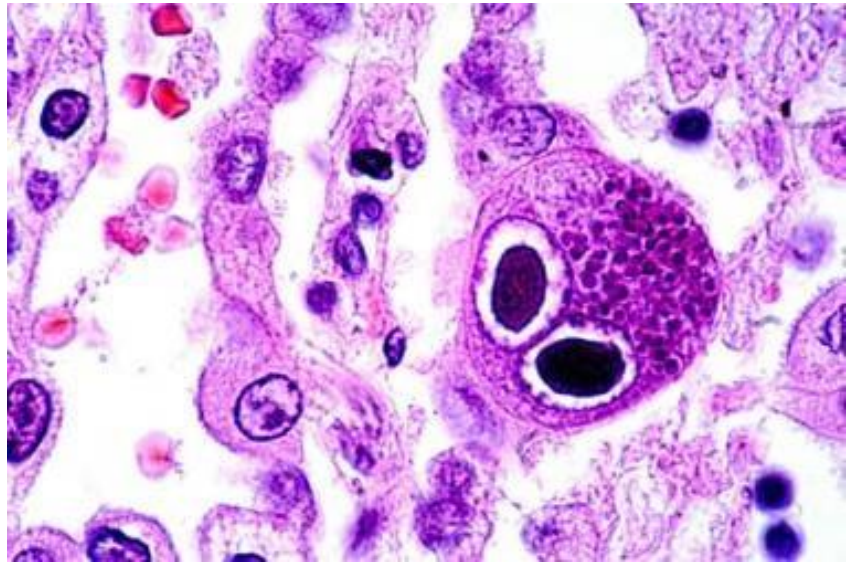
Cytomegalovirus has the biggest reported viral genome



Transmission of Cytomegalovirus Infection Stock Vector - Illustration of blood, human: 191399866

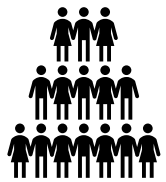


https://www.researchgate.net/figure/Structure-of-HCMV-virion-Mature-virions-are-coated-by-an-envelope-from-which-viral_fig1_341253731



https://emedicine.medscape.com/article/215702-overview?form=fpf

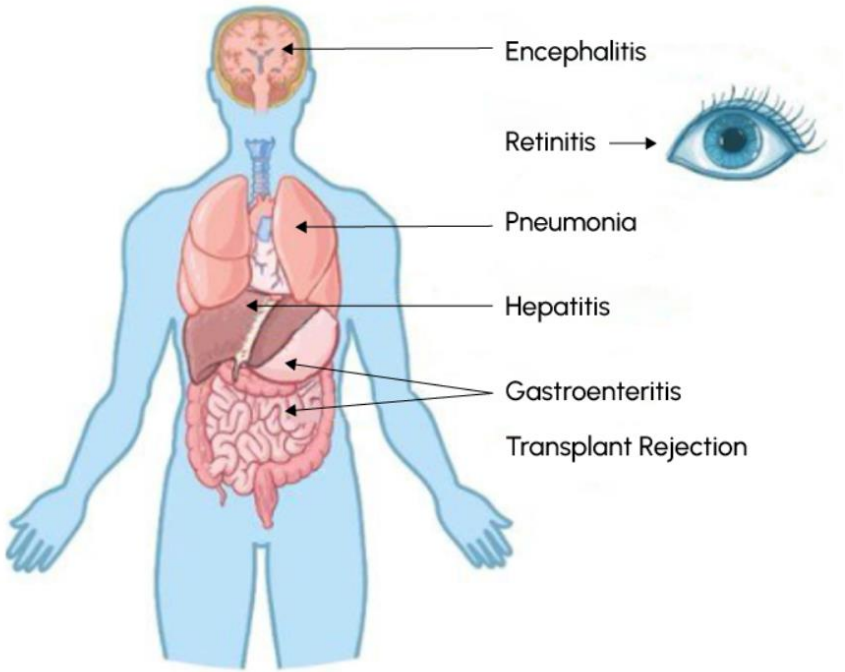
80% of all adults and 0.7% of all newborns are CMV positive



83% of adult population positive

1:200 newborns positive (0.7% of all newborns)

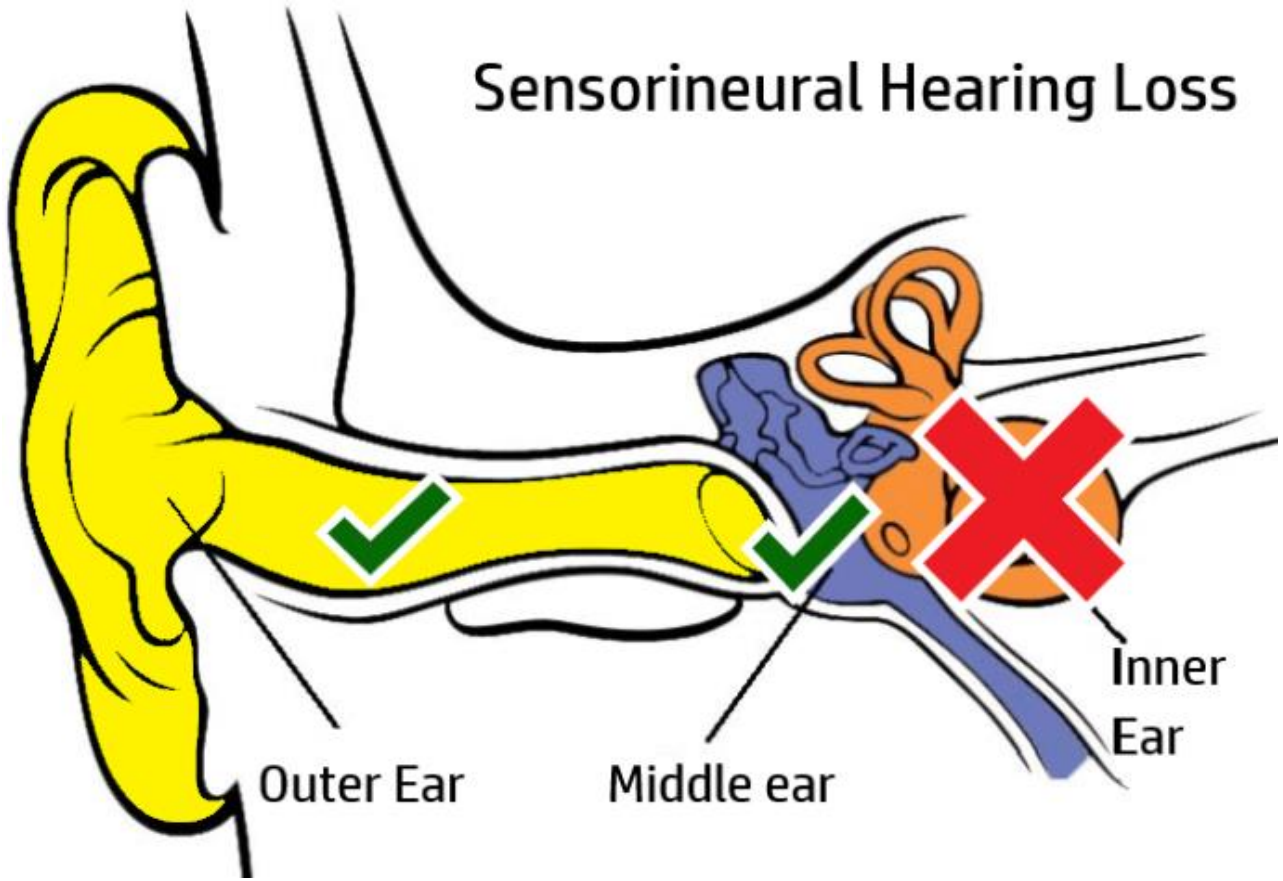
1:5 health problems

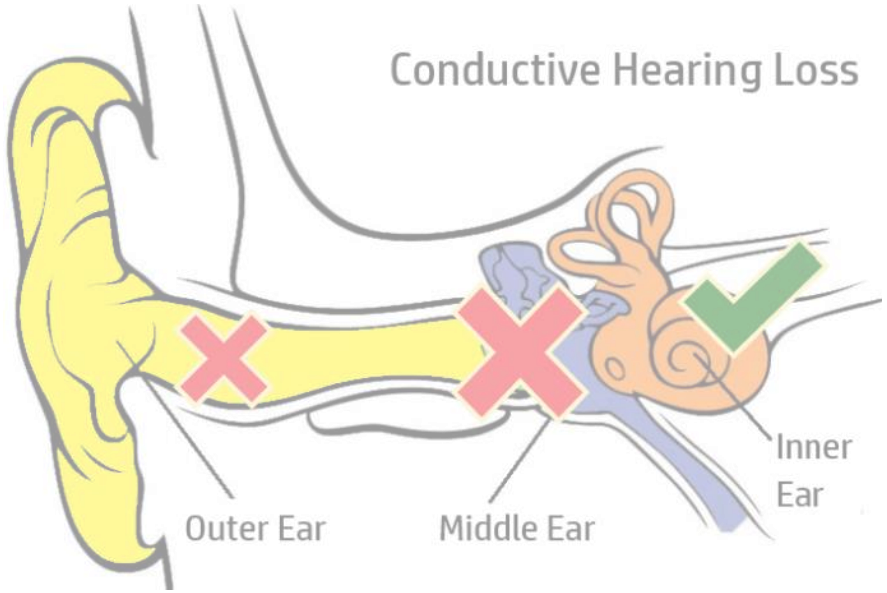


https://vitrosens.com/what-is-cytomegalovirus-cmv-infection-how-to-use-cmv-detection-qpcr-kit/

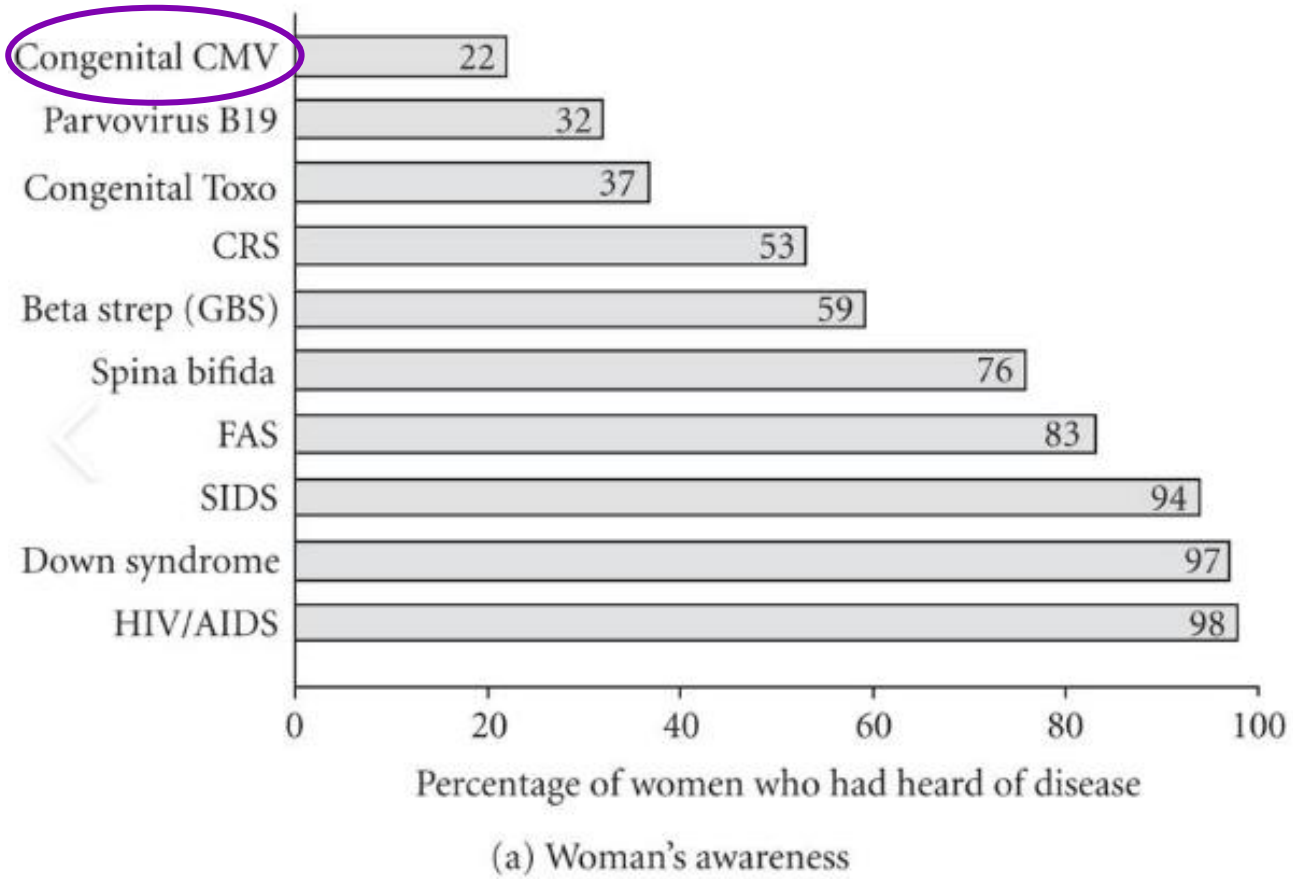
https://uoflhealth.org/articles/what-is-congenital-cytomegalovirus/

Congenital CMV is the leading cause of hearing loss in infants - Sensorineural hearing loss SNHL

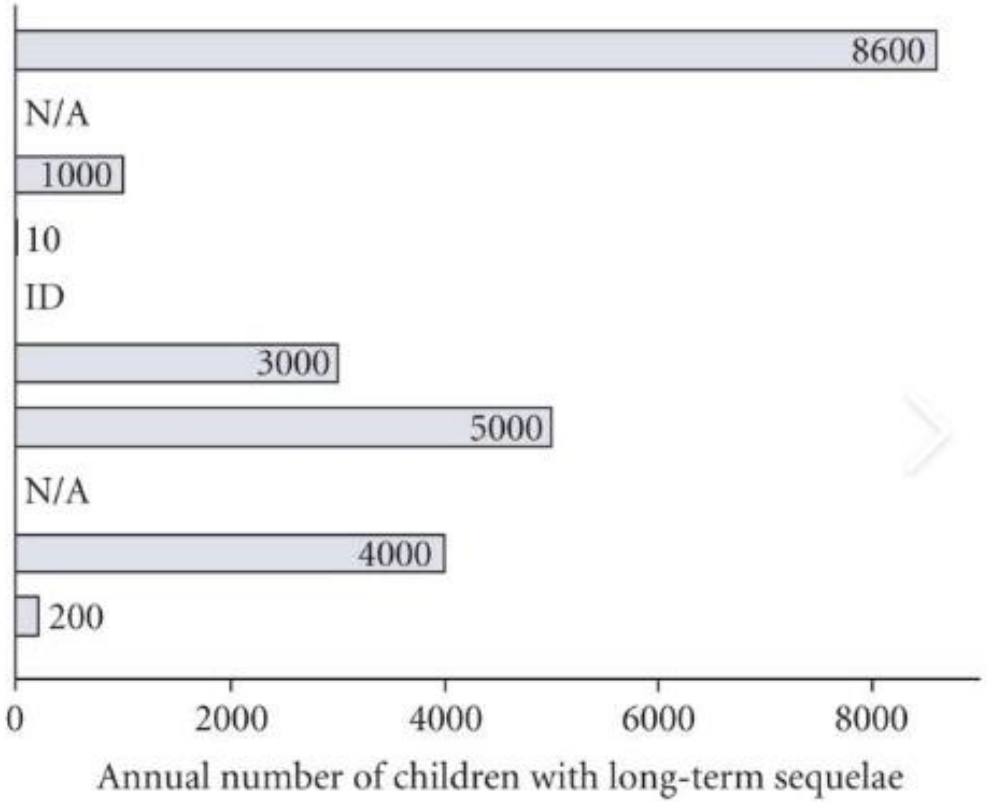




Cytomegalovirus - The unknown enemy of newborns



(a) Woman's awareness



(b) Estimated disease burden

What is CMV?

Who is at risk?

What can we do if we identify CMV?

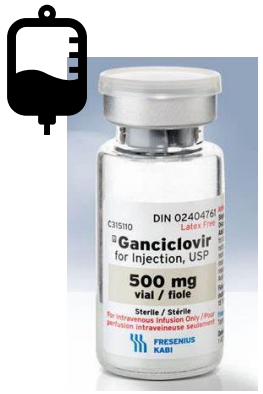
How should we manage an infection?

How and **when** should we screen for it ?

Treatment Options and Outcomes

TREATMENT OPTIONS

- Treatment for congenital CMV infection should start at the latest at 1 month of age and should last for 6 months
- Early treatment is recommended for symptomatic newborns
- Benefit for treatment of asymptomatic newborns has not been shown



TREATMENT OUTCOMES

- Early intervention with antiviral treatment is shown to yield better neurological outcomes
- Language development of children with impaired hearing is positively affected by the age of hearing loss identification

Original article

Neurological outcomes in symptomatic congenital cytomegalovirus-infected infants after introduction of newborn urine screening and antiviral treatment

Kosuke Nishida [a 1], Ichiro Morioka [a 1], Yuji Nakamachi [b], Yoko Kobayashi [b], Takamitsu Imanishi [b], Seiji Kawano [b], Sota Iwatani [a], Tsubasa Koda [a], Masashi Deguchi [c], Kenji Tanimura [c], Daisuke Yamashita [d], Ken-ichi Nibu [d], Toru Funakoshi [e], Masanobu Ohashi [f], Naoki Inoue [g], Kazumoto Iijima [a], Hideto Yamada [c]

Conclusions

This is the first Japanese report of neurological assessments in infants with symptomatic congenital CMV infection who received early diagnosis and antiviral treatment. Urinary screening, resulting in early diagnosis and treatment, may yield better neurological outcomes in symptomatic congenital CMV-infected infants.

From Screening to Early Identification and Intervention: Discovering Predictors to Successful Outcomes for Children With Significant Hearing Loss

Get access

Christine Yoshinaga-Itano

The Journal of Deaf Studies and Deaf Education, Volume 8, Issue 1, January 2003, Pages 11–30, https://doi.org/10.1093/deafed/8.1.11

Published: 01 January 2003 **Article history**

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Abstract

This article summarizes the research findings from a longitudinal study of the language, speech, and social-emotional development of children who are deaf and hard of hearing, all of whom have hearing parents. This series of studies, from 1994 to the present, investigated predictors of successful developmental outcomes. The article provides information about how the findings of these studies relate to the existing literature. A description of the Colorado Home Intervention Program (CHIP) in which the participants were enrolled is also provided. During the course of these investigations, universal newborn hearing screening programs were established in Colorado, changing the age of identification of hearing loss and initiation into intervention in this program geared to families with infants and toddlers, birth through three years of age, from an average of 20 months of age to 2 months of age. Language development is positively and significantly affected by the age of identification of the hearing loss and age of initiation into intervention services. Both speech development and social-emotional variables are highly related to language development.

Current options for preventing CMV infections - Vaccines

- The first phase 2 vaccine trial provided only 50% protection from CMV
- A new mRNA vaccine candidate from Moderna targets CMV glycoprotein B and is now in phase 3 clinical trials with promising results
- The vaccine is targeted to women of child-bearing age with no previous CMV infection

A Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1647 Cytomegalovirus (CMV) Vaccine in Healthy Participants 16 to 40 Years of Age

ClinicalTrials.gov ID NCT05085366

Sponsor ModernaTX, Inc.

Information provided by ModernaTX, Inc. (Responsible Party)

Last Update Posted 2024-04-24

Study Details | A Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1647 Cytomegalovirus (CMV) Vaccine in Healthy Participants 16 to 40 Years of Age | ClinicalTrials.gov

What is CMV?

Who is at risk?

What can we do if we identify CMV?

How should we manage an infection?

How and **when** should we screen for it ?

Why CMV screening?

Hearing Loss and Congenital CMV Infection:
A Systematic Review

AUTHORS: Julie Goderis, MD,[a] Els De Leenheer, MD, PhD,[a] Koenraad Smets, MD, PhD,[b] Helen Van Hoecke, MD, PhD,[a] Annelies Keymeulen, MD,[b] and Ingeborg Dhooge, MD, PhD[a]

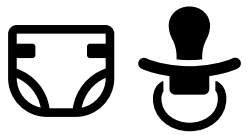
www.pediatrics.org/cgi/doi/10.1542/peds.2014-1173
doi:10.1542/peds.2014-1173
Accepted for publication Aug 27, 2014

RESULTS:

Thirty-seven studies were included: 10 population-based natural history studies, 14 longitudinal cohort studies, and 13 retrospective studies. The prevalence of cCMV in developed countries is 0.58% (95% confidence interval, 0.41–0.79). Among these newborns 12.6% (95% confidence interval, 10.2–16.5) will experience hearing loss: 1 out of 3 symptomatic children and 1 out of 10 asymptomatic children. Among symptomatic children, the majority have bilateral loss; among asymptomatic children, unilateral loss predominates. In both groups the hearing loss is mainly severe to profound. Hearing loss can have a delayed onset, and it is unstable, with fluctuations and progression. Among hearing-impaired children, cCMV is the causative agent in 10% to 20%. Despite strict selection criteria, some heterogeneity was found between selected studies.

Two approaches of Neonatal CMV screening - Targeted vs Universal screening

Targeted newborn screening



Universal newborn screening

Two approaches of Neonatal CMV screening - Targeted vs Universal screening

Targeted CMV screening

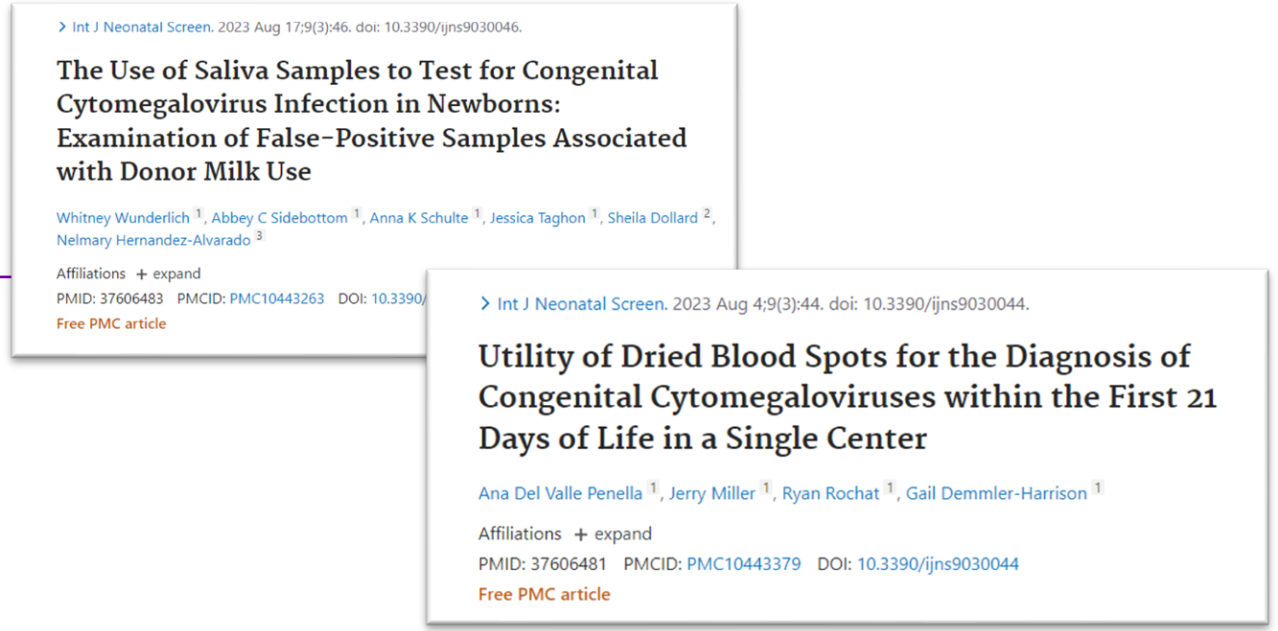
From saliva/urine

- Sensitivity of test is very good
- Only newborns with confirmed hearing loss are screened
- Treatment is started after 28 days of age
- Are the positive cases congenital? Late testing can result in postnatal infection through breast-feeding
- Asymptomatic newborns are missed

Universal CMV screening

From DBS

- All newborns are tested for CMV
- Easy to implement as DBS infrastructure is available
- Treatment is started early before 28 days of age
- Sensitivity of DBS test is not as good as saliva/urine



> Int J Neonatal Screen. 2023 Aug 17;9(3):46. doi: 10.3390/ijns9030046.

The Use of Saliva Samples to Test for Congenital Cytomegalovirus Infection in Newborns: Examination of False-Positive Samples Associated with Donor Milk Use

Whitney Wunderlich [1], Abbey C Sidebottom [1], Anna K Schulte [1], Jessica Taghon [1], Sheila Dollard [2], Nelmary Hernandez-Alvarado [3]

Affiliations + expand

PMID: 37606483 PMCID: PMC10443263 DOI: 10.3390/

Free PMC article

> Int J Neonatal Screen. 2023 Aug 4;9(3):44. doi: 10.3390/ijns9030044.

Utility of Dried Blood Spots for the Diagnosis of Congenital Cytomegaloviruses within the First 21 Days of Life in a Single Center

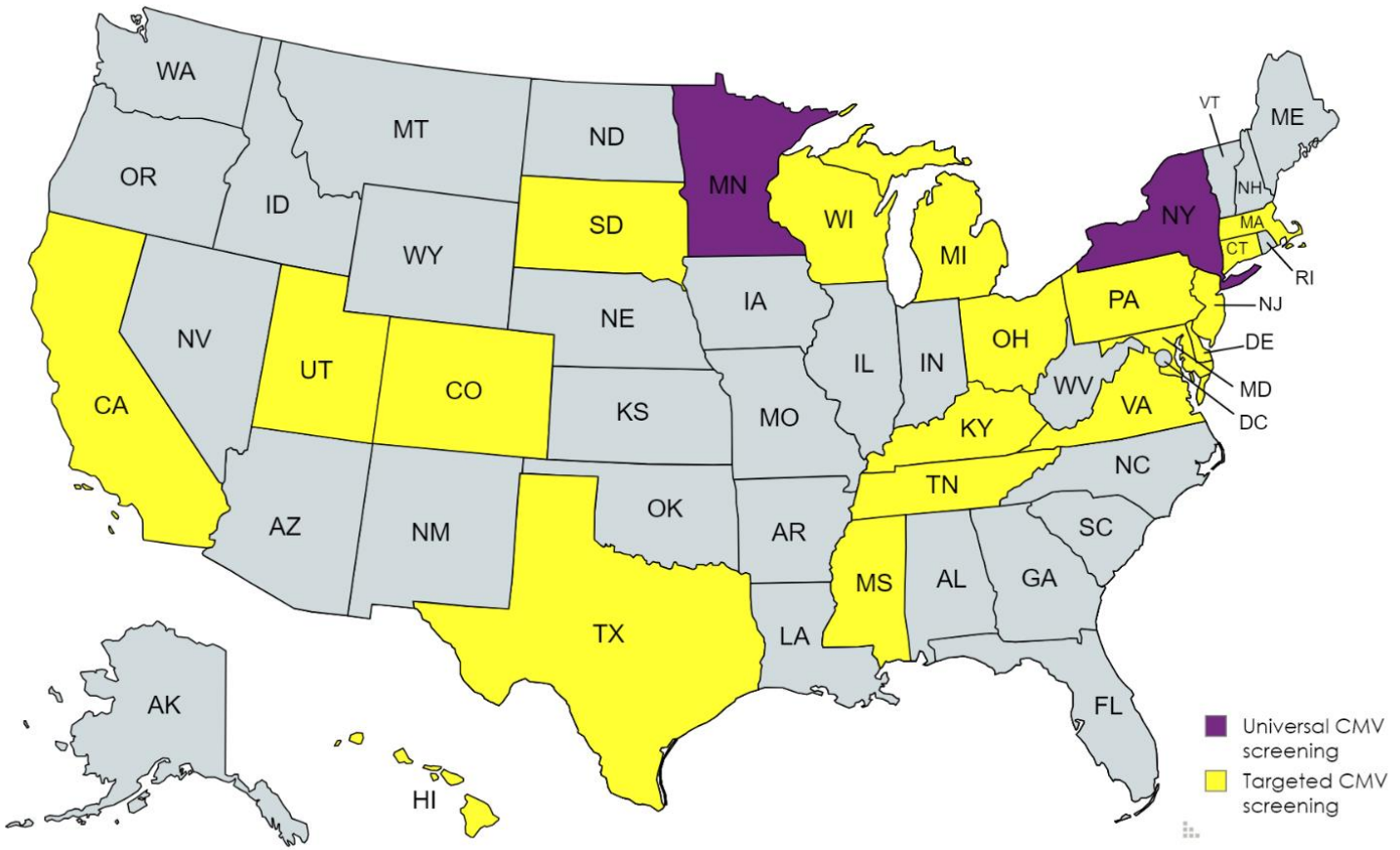
Ana Del Valle Penella [1], Jerry Miller [1], Ryan Rochat [1], Gail Demmler-Harrison [1]

Affiliations + expand

PMID: 37606481 PMCID: PMC10443379 DOI: 10.3390/ijns9030044

Free PMC article

Who is screening?

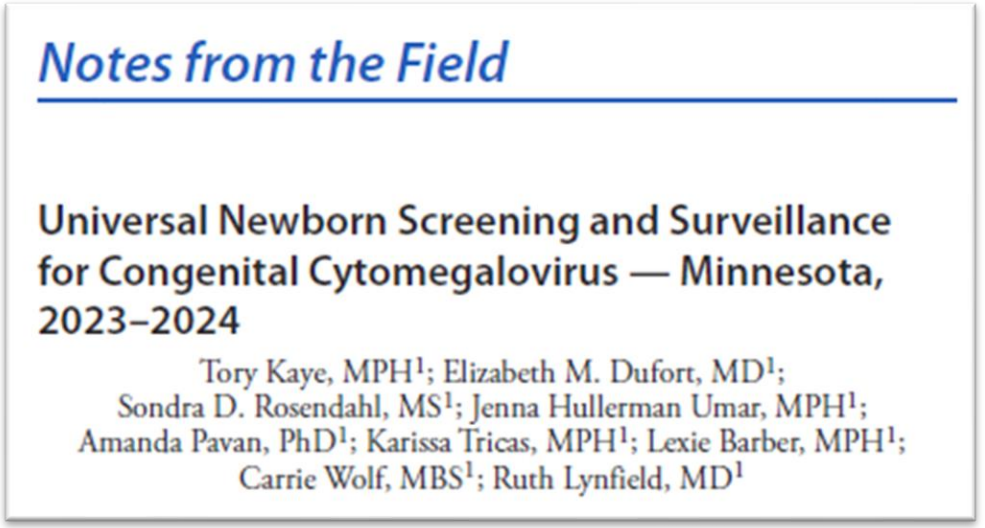


What are the treatment outcomes of patients detected through screening?

176 confirmed cases of congenital CMV disease was detected in one year in Minnesota.

Of these 176:

- 160 (91%) had neuroimaging, audiology, and ophthalmology assessments
- 59 (34%) infants had one or more clinical findings identified, most frequently nonspecific neuroimaging abnormalities
- 7 (4%) had CMV findings that were not detected through routine newborn clinical care but through newborn screening
- 29 (16%) had nonpassing results for newborn hearing screening
- 4 (2.3%) received passing results for newborn hearing screening
- 11 (6.3%) had permanent hearing loss
- 15 (8.5%) infants received antiviral therapy
- 2 infant deaths, both with causes other than cCMV listed


Notes from the Field

Universal Newborn Screening and Surveillance for Congenital Cytomegalovirus — Minnesota, 2023–2024

Tory Kaye, MPH[1]; Elizabeth M. Dufort, MD[1]; Sondra D. Rosendahl, MS[1]; Jenna Hullerman Umar, MPH[1]; Amanda Pavan, PhD[1]; Karissa Tricas, MPH[1]; Lexie Barber, MPH[1]; Carrie Wolf, MBS[1]; Ruth Lynfield, MD[1]

Why are we not yet screening universally for CMV?

- Who is eligible for antiviral treatment?
- Viral load & treatment need
- Overuse of antivirals
- Cost issues
- RUSP not there yet

CMV PCR tests - design and performance

CMV PCR from DBS

Year 2010

Published in final edited form as:
JAMA. 2010 April 14; 303(14): 1375–1382. doi:10.1001/jama.2010.423.

DRIED BLOOD SPOT REAL-TIME POLYMERASE CHAIN REACTION ASSAYS TO SCREEN NEWBORNS FOR CONGENITAL CYTOMEGALOVIRUS INFECTION

Suresh B. Boppana, M.D., Shannon A. Ross, M.D., Zdenek Novak, M.D., Masako Shimamura, M.D., Robert W. Tolan Jr., M.D., April L. Palmer, M.D., Amina Ahmed, M.D., Marian G. Michaels, M.D., Pablo J. Sánchez, M.D., David I. Bernstein, M.D., M.A., William J. Britt, M.D., and **Dr. Karen B. Fowler, P.H. for the National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study**
Departments of Pediatrics (SBB, SAR, ZN, MS, WJB, KBF), Epidemiology & International Health (KBF), Microbiology (SBB, WJB), and, Neurobiology (WJB) University of Alabama at Birmingham, Birmingham, AL; Department of Pediatrics, Saint Peter's University Hospital, New Brunswick, NJ (RWT); Department of Pediatrics, University of Mississippi Medical Center, Jackson, MS (ALP);

Conclusions—Among newborns, CMV testing with DBS real-time PCR compared with saliva rapid culture had low sensitivity, limiting its value as a screening test.

Year 2023

Notes from the Field

Universal Newborn Screening and Surveillance for Congenital Cytomegalovirus — Minnesota, 2023–2024

Tory Kaye, MPH[1]; Elizabeth M. Dufort, MD[1]; Sondra D. Rosendahl, MS[1]; Jenna Hullerman Umar, MPH[1]; Amanda Pavan, PhD[1]; Karissa Tricas, MPH[1]; Lexie Barber, MPH[1]; Carrie Wolf, MBS[1]; Ruth Lynfield, MD[1]

Congenital cytomegalovirus (cCMV) is the most frequent infectious cause of birth defects and the most frequent nongenetic cause of permanent hearing loss in U.S. children; cCMV affects approximately 0.5% of U.S. births. Among infants with cCMV infection, approximately 10% have clinical findings at birth (*1*). Early identification of cCMV infection could improve outcomes through the use of antiviral therapy when indicated, and audiology and developmental screenings (*1*). A recent Minnesota study found average dried blood spot sensitivity of 75% for detection of cCMV infection (*2*). In February 2023, Minnesota became the first U.S. state to implement universal newborn screening for cCMV. To evalu-

Summary

What is already known about this topic?

Congenital cytomegalovirus (cCMV) is the most frequent infectious cause of birth defects and the most common nongenetic cause of permanent hearing loss in U.S. children.

What is added from this report?

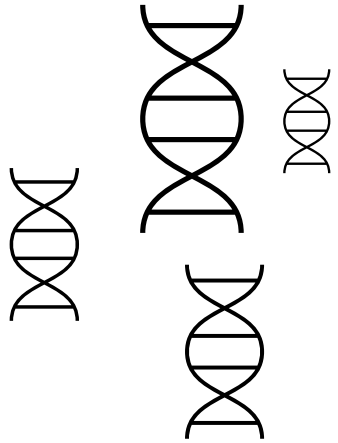
Universal newborn screening and population-based surveillance for cCMV, implemented in Minnesota in 2023, identified an observed cCMV prevalence of 0.3% of Minnesota live births. Nearly all cCMV cases detected through newborn screening were confirmed with diagnostic testing; most infants received comprehensive evaluations and linkage to care, leading to the detection of unapparent cCMV-specific findings among seven infants.

What are the implications for public health practice?

Universal newborn screening identified infants with neurologic abnormalities and those with or at risk for cCMV-associated permanent hearing loss and other sequelae, who might have been missed by routine care or targeted screening.

Revvity CMV assays are *qualitative* CMV assays

PCR is looking for a specific gene, and if present/not present → baby has a positive screening result



Is the target gene present in the sample?

How many target DNA copies does the sample have?

Qualitative assays

Fixed cutoff value (+ / -)

E.g. direct Cq value reporting

Quantitative assays

Relative quantification (ΔC_q calculation where target C_q values are adjusted by internal control C_q values)

(Absolute) quantification via a standard curve

Revvity CMV offerings

NEO MDX WET CMV RUO ASSAY

Liquid

- From 1-punch DBS or 2-punch DBS (and Saliva)
- Conventional wet qPCR workflow, can be combined with NeoMDx SCID-SMA workflow
- 96- and 384-well versions available
- Compatible with several qPCR cyclers

Punching → DNA Extraction → Mastermix prep → Sample addition → qPCR and analysis

EONIS DRY CMV RUO ASSAY

Dry

- From 1-punch DBS (and Saliva, Urine)
- Simple dry qPCR workflow
- 96 –well version available
- Compatible with Eonis Q, AJ and BioRad CFX qPCR cyclers

Punching → DNA Elution → Sample addition → qPCR and analysis

Eonis™ dry CMV qPCR kit's analytical sensitivity with DBS, saliva and urine samples

Dry

DBS

97 % detection rate at 3000 CMV IU/ml of blood

Dried urine spots

100 % detection rate at 7500 CMV IU/ml (3 CMV IU/reaction)

Diluted urine

100 % detection rate at 250 CMV IU/ml

Dried saliva spots

100 % detection rate at 1000 CMV IU/ml

Saliva

100 % detection rate at 200 CMV IU/ml

Sample type	CMV IU/mL Blood	CMV IU/reaction	RPP (Cy5)				CMV (ROX)			
			Ct average	SD	Replicates	Detection rate %	Ct average	SD	Replicates	Detection rate %
DBS	0	0	28.72	0.71	36	100	No ct	0	36	0
	1000	0.68	26.35	1.61	19	100	39.92	1.01	19	74
	3000	2.04	27.24	1.68	31	100	37.8	1.18	31	97
	5000	3.4	27.37	2	31	100	37.49	0.79	31	100
	10000	6.8	26.02	1.25	19	100	36.36	0.66	19	100
	500000	340	25.23	0.39	19	100	30.48	0.21	19	100

Sample type	Sample concentration CMV IU/ml	RPP (Cy5)				CMV (ROX)			
		Ct average	SD	Replicates	Detection rate %	Ct average	SD	Replicates	Detection rate %
Dried urine spots	0	35.2	0.52	6	100	No Ct	-	6	0
	7500*	35.0	0.57	10	100	36.80	35.56	10	100
	12500*	34.7	0.37	10	100	34.75	0.66	10	100
	25000*	33.48	0.16	10	100	34.85	0.48	10	100
Direct urine samples	250	29.66	2.32	8	100	36.71	36.82	8	100

* Estimation

Sample type	Sample concentration CMV IU/ml	RPP (Cy5)				CMV (ROX)			
		Ct average	SD	Replicates	Detection rate %	Ct average	SD	Replicates	Detection rate %
Raw saliva	200	25.9	0.40	12	100	33.61	1.35	12	100
Dried saliva spots	1000	27.2	0.06	6	100	36.80	0.65	6	100
	3000	27.2	1.68	31	100	37.80	1.18	31	97

NeoMDx™ liquid CMV qPCR kit's accuracy and sensitivity with DBS samples

Liquid

Performance Metrics

- 98.6% Accuracy
- PPV = 100%
- 100% Specificity
- 95.2% Sensitivity

Sample Type	CMV Call	Sample ID	Viral Loads	CMV (FAM)			RPP30 (Cy5)		
				Mean	Std Dev	N	Mean	Std Dev	N
DBS Sample	Negative	DBS Sample	Negative	-	-	0	23.00	1.222	180
Proficiency Panel	Negative	CMVDBS20S-03	CMV Negative	-	-	0	22.97	0.928	12
	Positive	CMVDBS20S-01	CMV (AD169)	33.72	0.468	12	22.84	0.794	12
		CMVDBS20S-02	CMV clinical	35.75	3.132	12	23.13	0.909	12
		CMVDBS20S-04	CMV (AD169)	35.95	0.676	10	23.11	0.997	12
		CMVDBS20S-05	CMV clinical	37.28	0.498	10	23.12	1.093	12
		CMVDBS20S-06	CMV (AD169)	36.51	0.778	12	22.96	0.839	12
		CMVDBS20S-07	CMV clinical	36.68	1.132	12	22.97	0.978	12
		CMVDBS20S-08	CMV (AD169)	34.93	0.582	12	22.96	0.843	12

2x 3.2 mm DBS punch Input, 65 µL Elution, 10 µL qPCR Sample Input for a 15 µL reaction

*Out of 276 Proficiency Panel Samples and DBS Samples, with 80 true positive, 0 false positive, 192 true negative, and 4 false negative. CMV panel from QCMD (Quality control for molecular diagnostics by Randox)

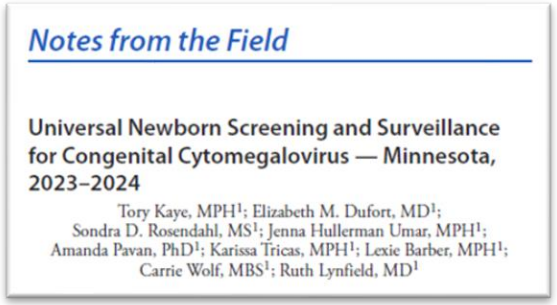
Published user experiences of Revvity CMV solutions

Liquid

MINNESOTA DEPARTMENT OF HEALTH – ROUTINE UNIVERSAL SCREENING

Universal newborn screening of 60 115 infants (February 6, 2023–February 5, 2024):

- 174 positive cases → 0.29%
- 170/174 cases were confirmed positive with urine confirmatory testing → 98% (false positives 4/174)
- 3 infants with cCMV who had a negative test result during CMV newborn screening were identified by clinician or laboratory reporting → False negative rate 0.005%



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Universal Newborn Screening and Surveillance for Congenital Cytomegalovirus — Minnesota, 2023–2024

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Liquid Dry

NEW YORK STATE DEPARTMENT OF HEALTH – PILOT UNIVERSAL SCREENING

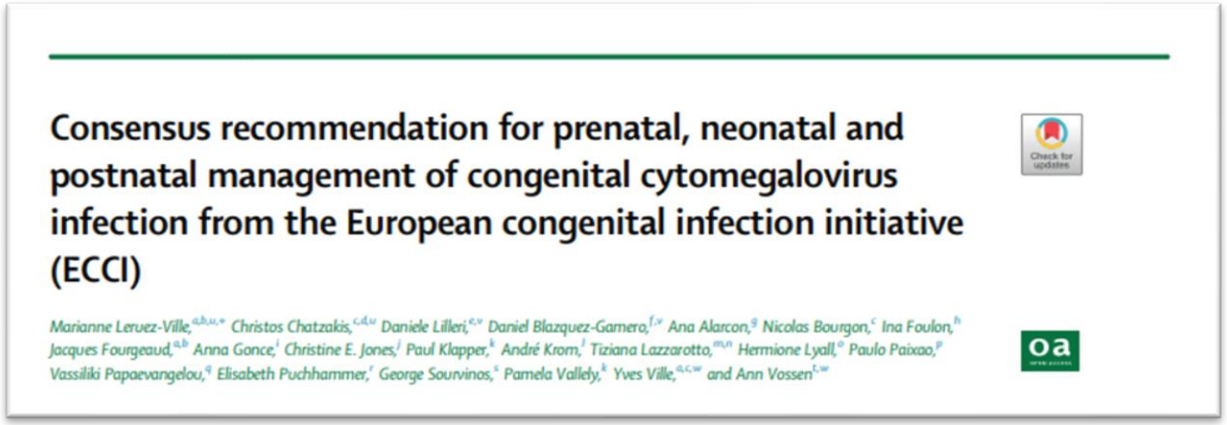
Over 5000 random specimens were screened using liquid NeoMDx and dry Eonis method:

- 26 positive cases (both methods)→ 0.52%
- 21/26 cases were confirmed positive with urine confirmatory testing → 81% (false positives 5/26)
- 16 infants with cCMV who had a negative test result during CMV newborn screening were identified by clinician or laboratory reporting → False negative rate 0.32%

Modification and Comparison of Two Revvity qPCR Assays for the Detection of Congenital Cytomegalovirus in Newborns

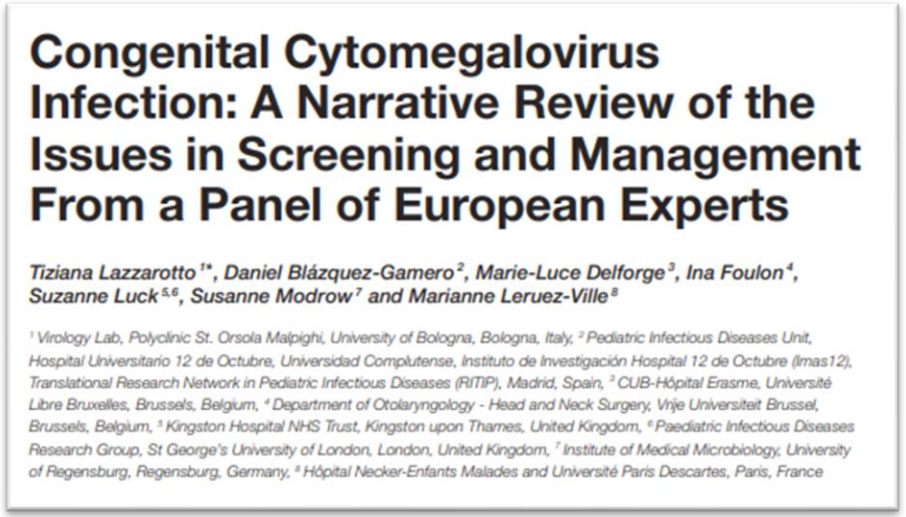
Norma P. Tavakoli PhD, Melissa Pearce, Alyssa Giacinto, Ifeyinwa Ojukwu, Michele Caggana ScD FACMG
Newborn Screening Program, Wadsworth Center, New York State Department of Health, Albany, NY

The current status: Prenatal, hearing-targeted neonatal or universal neonatal screening – Which way is the right way?



Consensus recommendation for prenatal, neonatal and postnatal management of congenital cytomegalovirus infection from the European congenital infection initiative (ECCI)

Marianne Leruez-Ville,[a,b,u,v,*] Christos Chatzakis,[c,d,v] Daniele Lilleri,[e,v] Daniel Blazquez-Gamero,[f,v] Ana Alarcon,[g] Nicolas Bourgon,[c] Ina Foulon,[h] Jacques Fourgeaud,[a,b] Anna Gonce,[i] Christine E. Jones,[j] Paul Klapper,[k] André Krom,[l] Tiziana Lazzarotto,[m,n] Hermione Lyall,[o] Paulo Paixao,[p] Vassiliki Papaevangelou,[q] Elisabeth Puchhammer,[r] George Sourvinos,[s] Pamela Vallely,[k] Yves Ville,[a,c,w] and Ann Vossen[t,w]



Congenital Cytomegalovirus Infection: A Narrative Review of the Issues in Screening and Management From a Panel of European Experts

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"Well-designed clinical trials to address several facets of CMV treatment (in pregnant women, CMV-infected fetuses and both symptomatic and asymptomatic neonates and children) are required. Prevention (vaccines), biology and transmission factors associated with non-primary CMV, and the cost-effectiveness of universal screening, all demand further exploration to fully realize the ultimate goal of preventing cCMV. In the meantime, prevention of primary infection during pregnancy should be championed to all by means of hygiene education."

“The era of cCMV screening is here! Of the cCMV screening options before us – universal, targeted, expanded-targeted, or none-of-the-above – the only alternative that is not acceptable is ”none-of-the-above” “

Dr. M. Schleiss, University of Minnesota Medical school

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