Advancing Clinical Practice Guidelines for cCMV Prevention and Care: A Targeted Literature Review

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Background

CMV infection during pregnancy can result in cCMV infection and 1 in 200 babies in the United States and Canada are born with cCMV[1, 2]

cCMV can cause serious lifelong health complications in newborns, including SNHL, microcephaly, low birth weight, rash, jaundice, hepatosplenomegaly, seizures, and retinitis[2]

Currently, there are no effective prevention or treatment interventions approved for cCMV in the United States[3]

Evidence-based clinical practice guidelines have been published; however, recommendations for prenatal and newborn screening and care vary, and most have not been updated recently[4-7]

cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; SNHL, sensorineural hearing loss.

1. CMV Canada. About CMV. https:/cmvcanada.com/about-cmv/. 2. Centers for Disease Control and Prevention. Babies Born With Congenital CMV. https://www.cdc.gov/cmv/congenital-infection.html. 3. Centers for Disease Control and Prevention. CMV Clincal Overview. https://www.cdc.gov/cmv/clinical/overview.html. 4. Luck SE, et al. *Pediatr Infect Dis J.* 2017;36(12):1205-1213. 5. Boucoiran I, et al. *J Obstet Gynaecol Can*. 2021;43(7):893-908. 6. Rawlinson WD, et al. *Lancet Infect Dis.* 2017;17(6):e177-e188. 7. Kalb S, et al. *Int J Neonatal Screen*. 2023;9(3):37.

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Phase 1: Completion of our Framework for Advancing Clinical Practice Guidelines (CPGs) for cCMV

Phase 1

Semi-structured qualitative interviews conducted with 8 cCMV experts

Objective

To understand clinical practice guidelines and patterns for CMV and cCMV care in the United States

Phase 1 Lessons Learned: Examples to Drive Change in Clinical Guidelines and Practice Patterns

Raise Awareness Among Providers and the Public

- Engage with national foundations in the CMV and cCMV area, pharmaceutical stakeholders, providers, and patient advocates to support existing awareness campaigns
- Support broader education for providers and patients
- Advocate for inclusion of CMV- and cCMV-specific learning in continued medical education
- Leverage unique messaging and informational tactics to increase education
- Advocate for universal screening programs and increase awareness of screening opportunities
- Emphasize patient voice and knowledge to increase engagement
- Support the publication of reports and studies through formal and informal avenues

Show Evidence of Treatment and Prevention

- Support evidence generation on CMV and cCMV, including:
  - Burden of disease
  - Patient perspectives
  - Treatment, screening, and prevention efforts

Phase 2: A Targeted Literature Review (TLR) Summarized Evidence on cCMV Clinical Care

Phase 1

Semi-structured qualitative interviews conducted with 8 cCMV experts

Objective

To understand clinical practice guidelines and patterns for CMV and cCMV care in the United States

Phase 2

TLR to summarize evidence on CMV/cCMV disease and clinical care

Objective

To assess recent cCMV-related research, synthesize evidence, and identify gaps that may inform advancement of clinical practice guidelines

cCMV, congenital cytomegalovirus; CMV, cytomegalovirus.

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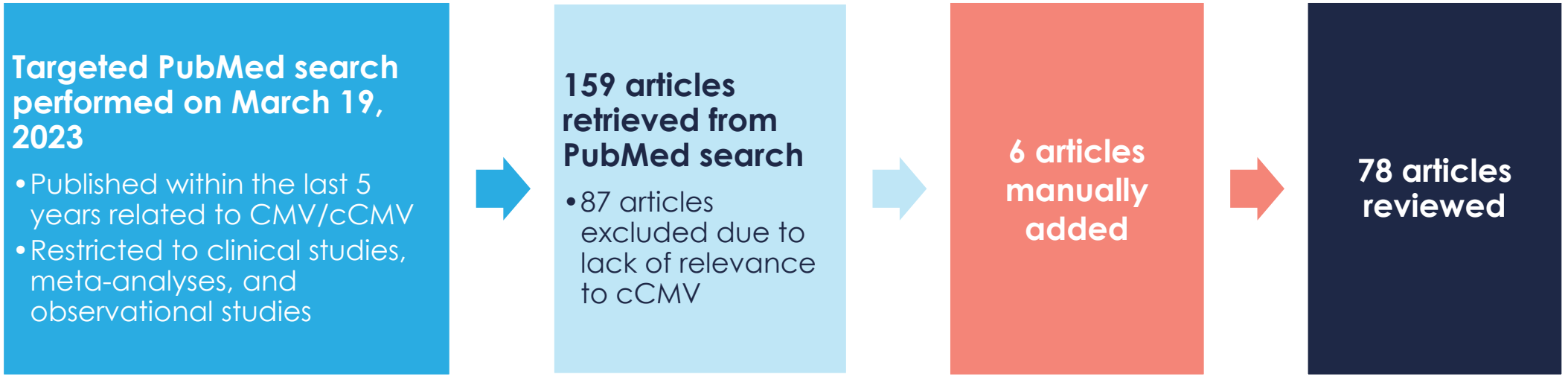
The TLR of Recent cCMV-Related Research Was Conducted to Identify Gaps That May Inform CPG Development



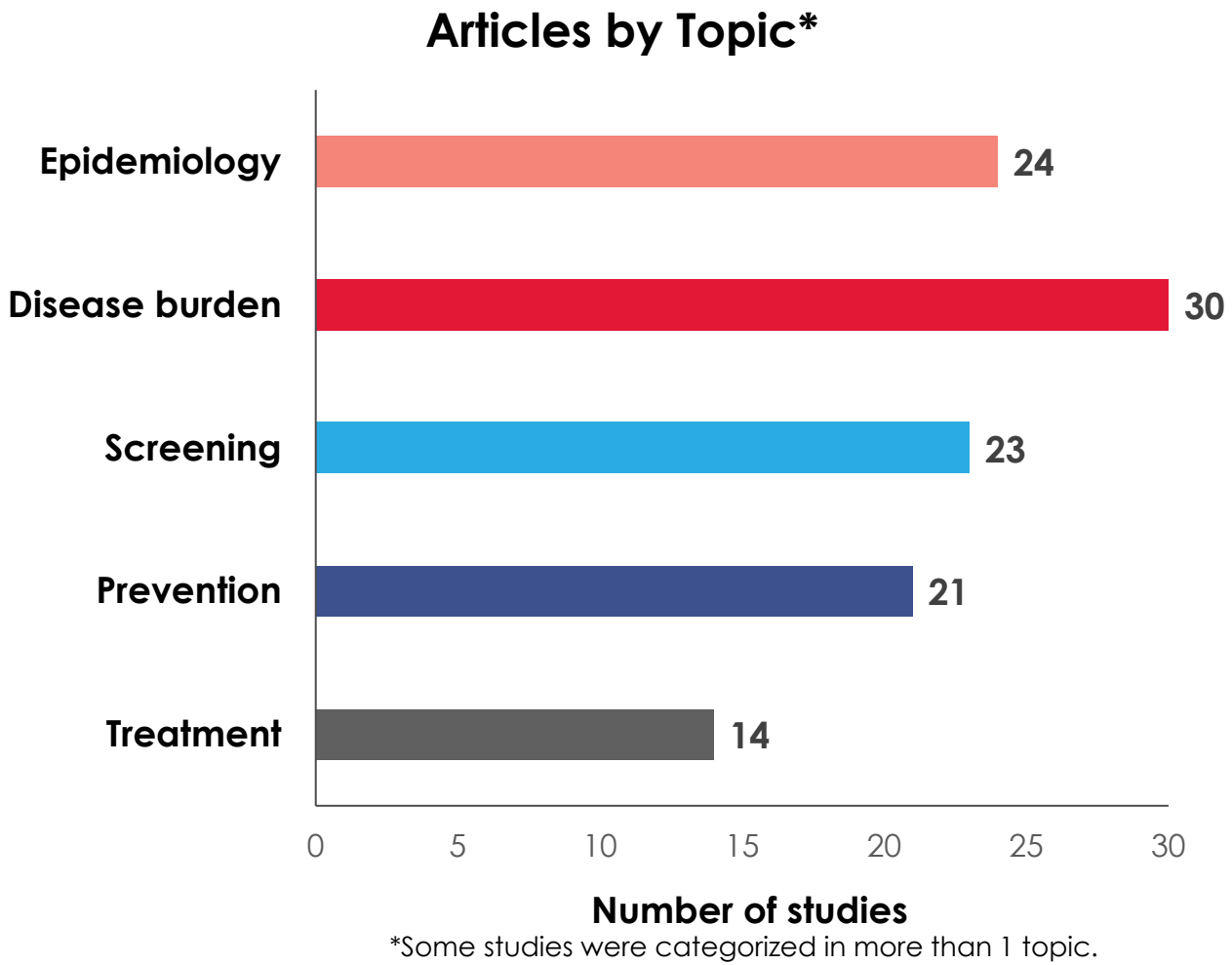
Articles were evaluated in the context of 3 published clinical practice or recommendation guidelines

- ***Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy***[1]
- ***European expert consensus statement on diagnosis and management of cCMV***[2]
- ***SOGC guideline for CMV infection during pregnancy***[3]

SOGC, Society of Obstetricians and Gynaecologists of Canada.

1. Rawlinson WD, et al. *Lancet Infect Dis*. 2017;17(6):e177-e1885. 2. Luck SE, et al. *Pediatr Infect Dis J*. 2017;36(12):1205-1213. 3. Boucoiran I, et al. *J Obstet Gynaecol Can*. 2021;43(7):893-908.

Key Findings From Review of 78 Articles Across Multiple Topics Are Presented Today



*Some studies were categorized in more than 1 topic.

- **Disease burden** and **epidemiology** were the most common topics among articles reviewed
- SLR and/or meta-analyses and retrospective observational studies represented more than half of the articles retrieved
- Other article types included clinical trials, and sub-studies or secondary analyses of clinical trials

SLR, systematic literature review.

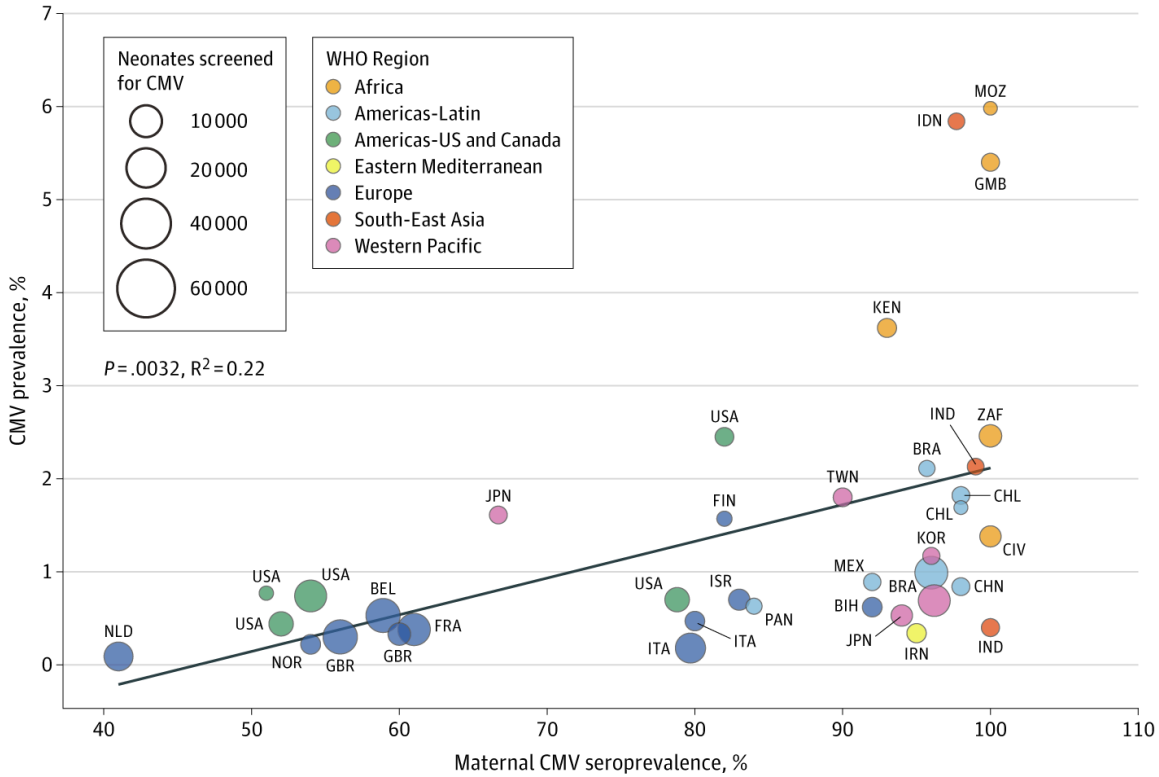
Epidemiology

Global Prevalence of cCMV Has Remained Consistent for 6 Decades

A large meta-analysis of 77 studies reported on risk factors associated with **higher cCMV rates**:[1]

- **Low- and middle-income vs high-income** countries (3-fold higher at 1.42% and 0.48%, respectively
- **Black race (in the United States and Canada), HIV infection, and younger maternal age**

Global cCMV Prevalence, 1970-2020[1]



HIV, human immunodeficiency virus.
1. Ssentongo P, et al. *JAMA Network Open*. 2021;4(8):e2120736.
Linear fit from linear regression model. Circles represent countries and are labeled by their International Organization for Standardization (ISO) code. The size of the circle is proportional to the sample.
Figure from: Ssentongo P, et al. Congenital cytomegalovirus infection burden and epidemiologic risk factors in countries with universal screening : a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(8):e2120736. doi:10.1001/jamanetworkopen.2021.20736, an open access article distributed under the terms of the CC-BY license.

Disease Burden

Understanding the Full Spectrum of cCMV-Related Clinical Manifestations is Essential to Informing Practice Guidelines

- Several studies have highlighted the complexity of identifying cCMV-associated clinical manifestations, many of which are **not detectable during routine newborn exams**

cCMV is associated with increased risk of **spontaneous abortion, stillbirth, preterm birth, and growth impairment**, and the mechanism(s) are still unknown[1,2]

Meta-analyses confirm the **clear risk for hearing loss** in babies with cCMV infection[3-5]

Additional risks that may be associated with cCMV infection include **cerebral palsy, congenital heart disease, fetal echogenic bowel, low weight and length at 2 years, reduced olfactory performance,** and **microcephaly**[6-12]

1. Shi TL, et al. *J Clin Virol.* 2018;104:48-55. 2. Njue A, et al. *Viruses.* 2020 24;13(1):20. 3. Liu PH, et al. *Medicine (Baltimore)*. 2021;100(36):e27057. 4. Wood JW, et al. *Laryngoscope*. 2021;131(2):425-434. 5. Zhang L, et al. *Behav Neurol.* 2021;15;2021:9603660. 6. Ong LT, et al. *J Paediatr Child Health*. 2022;58(12):2156-2162. 7. Ye Z, et al. *J Am Heart Assoc*. 2019;8(9):e011264. 8. D'Amico A, et al. *Prenat Diagn.* 2021;41(4):391-399. 9. Magai DN, et al. *PLoS One.* 2020;15(4):e0231947. 10. Tagarro A, et al. *Pediatr Infect Dis J.* 2019;38(12):1230-1235. 11. Lazarini F, et al. *Eur J Pediatr.* 2022;181(5):1859-1869. 12. Messinger CJ, et al. *JAMA Pediatr.* 2020;174(12):1159-1167.

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Disease Burden

Identifying Maternal Risk Factors for cCMV Transmission and Related Outcomes Could Enable More Effective CMV Screening Strategies

- **Maternal factors evaluated for association with risk of cCMV infection or transmission in recent studies:**

Maternal HIV infection

Babies **infected with HIV or HIV-exposed in utero had a higher prevalence of cCMV** compared with the global cCMV prevalence[1-4]

Occupational exposure to children

Pregnant childcare workers, but not healthcare workers, had an increased risk of transmission[5]

Timing of maternal infection

Risk of transmission increased with **gestational age,** while risk of severity decreased; most cCMV cases occurred from maternal infection **early in gestational age**[6,7]

Primary vs nonprimary maternal infection

Similar outcomes were observed in babies with symptomatic cCMV whether mothers had primary or nonprimary infection[8,9]

1. Prieto LM, et al. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2022;40(10):557-561. 2. Purswani MU, et al. *J Pediatr*. 2020;216:82-87.e2. 3. Pathirana J, et al. *Clin Infect Dis*. 2019;69(10):1789-1796. 4. Adachi K, et al. *Pediatr Infect Dis J*. 2018;37(10):1016-1021. 5. Balegamire SJ, et al. *Syst Rev*. 2022;11(1):131. 6. Huang Y, et al. *Emerg Microbes Infect*. 2021;10(1):1824-1831. 7. Chatzakis C, et al. *Ultrasound Obstet Gynecol*. 2023;61(2):158-167. 8. Kobas M, et al. *Swiss Med Wkly*. 2018;148:w14627. 9. Maltezou PG, et al. *J Clin Virol*. 2020;129:104518.

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Current Guidelines Highlight the Need for More Evidence on Newborn cCMV Screening

Current Recommendations for Newborn cCMV Testing in Clinical Practice Guidelines	
2017 European consensus guidelines[1]	**Clinical indications for newborn cCMV testing:** • Fetal ultrasound/MRI consistent with cCMV disease • Maternal history of primary CMV infection • Newborns with clinical signs/symptoms • Children with SNHL
2017 International cCMV recommendations group[2]	**Universal neonatal CMV screening should be considered** to enable early detection of cCMV-infected infants allowing early intervention for SNHL and developmental delay where appropriate **(Level 2b evidence)**
2021 SOGC guidelines[3]	Although cCMV testing of newborns who fail the newborn hearing screen has become widely adopted in Canada, **targeted CMV screening misses more than half of all infants with cCMV who develop SNHL after birth** • Ontario added CMV to the universal newborn screening panel in 2019

MRI, magnetic resonance imaging.

1. Luck SE, et al. *Pediatr Infect Dis J*. 2017;36(12):1205-1213. 2. Rawlinson WD, et al. *Lancet Infect Dis*. 2017;17(6):e177-e1885. 3. Boucoiran I, et al. *J Obstet Gynaecol Can*. 2021;43(7):893-908.

Screening

Expanding cCMV Testing Options Could Enable More Widespread Newborn Screening and Identification of Missed Cases

- Targeted screening, which is the focus of current clinical practice guidelines, has resulted in improved cCMV diagnosis rates[1,2]
  - Following the implementation of the Newborn Hearing Screening Programme in England in 2006, detection of **cCMV cases increased from 4.6 to 22.7 per 100,000 infants**[1]
- However, recent evidence suggests that commonly used targeted screening approaches based on **early clinical symptoms** may miss many cCMV cases[3-8]

Targeted screening may fail to detect nearly **24%** of babies with cCMV and **83%** of those with asymptomatic cCMV[3,4]

30% of newborns who pass newborn hearing screening may develop late-onset SNHL[5]

60% of newborns with positive genetic screening for deafness may still pass hearing screening[6]

49% of babies with asymptomatic cCMV may develop SNHL by 3 years of age[7]

43% of infants who develop CMV-related SNHL may not be diagnosed by targeted newborn hearing screening[8]

1. Kadambari S, et. *Lancet Infect Dis.* 2020;20(2):220-222. 2. Chung PK, et al. *Arch Dis Child Fetal Neonatal Ed.* 2023;108:F302-308. 3. Bartlett AW, et al. *J Clin Virol*. 2018;108:121-125. 4. Masarweh K, et al. *Isr Med Assoc J.* 2021;23(5):318-322. 5. Ouellette CP, et al. *Nat Commun*. 2020;11(1):3548. 6. Lu CY, et al. *J Pediatr*. 2018;199:144-150.e1. 7. Lin C, et al. *Medicine (Baltimore)*. 2020;99(10):e19419. 8. Fowler KB, et al. *Pediatrics.* 2017;139(2):e20162128.

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Screening

Direct CMV Testing (Maternal and Newborn) Remains the Most Reliable Tool to Identify Those at Risk

Pre- and post-natal imaging

- **Ultrasound** and **MRI did not reliably identify risk** of cCMV transmission and outcomes[1-4]

Amniocentesis

- **Amniocentesis** testing for CMV was an **accurate predictor of cCMV infection**, but not severity[5]
  - However, amniocentesis is not without risk of fetal loss in healthy women[6]

Serological testing

- **No robust studies** to support recommendations **for serological testing** for CMV in pregnant women[7]

1. Escobar Castellanos M, et al. *Neurologia (Engl Ed).* 2022;37(2):122-129. 2. de Juan Gallach A, et al. *An Pediatr (Engl Ed).* 2020;93(2):111-117. 3. Kyriakopoulou A, et al. *J Infect.* 2020;80(4):407-418. 4. Buca D, et al. *Ultrasound Obstet Gynecol.* 2021;57(4):551-559. 5. Dinsmoor MJ, et al. *Am J Obstet Gynecol MFM.* 2022;4(4):100641. 6. Odibo AO, et al. *Obstet Gynecol.* 2008;111(3):589-595. 7. Xie M, et al. *Prenatal Diag.* 2023;43:959-967.

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Prevention

Multiple cCMV Prevention Approaches Continue to be Investigated

- **Among the articles retrieved from the literature search, there was limited evidence supporting effectiveness of preventative therapies and vaccines**

Prophylactic antiviral medications

Valaciclovir associated with a **reduction in vertical transmission** of CMV versus placebo, and most effective if taken soon after infection was acquired[1]

Hyperimmunoglobulin

Variable effect of hyperimmunoglobulin on cCMV transmission compared with placebo (100 IU/kg monthly or 200 IU/kg biweekly)[2-8]

Vaccines

Exploratory analyses of gB/MF59 mechanisms of immune response and viral dynamics,[9,10] and V160 cellular immune responses[11,12]

Recent phase 2b results for V160 reported that the primary efficacy endpoint was not met[13]

Behavioral interventions

Risk reduction behavior and **educational strategies** may increase awareness in patients and HCPs[14-18]

gB, glycoprotein B; HCP, health care provider.

1. Shahar-Nissan K, et al. *Lancet*. 2020;396(10253):779-785. 2. Hughes BL, et al. *N Engl J Med*. 2021;385(5):436-444. 3. Devlieger R, et al. *Fetal Diagn Ther*. 2021;48(8):611-623.4. Kagan KO, et al. *Ultrasound Obstet Gynecol*. 2019;53(3):383-389. 5. Kagan KO, et al. *Ultrasound Obstet Gynecol*. 2021;57(4):560-567. 6. Blázquez-Gamero D, et al. *J Matern Fetal Neonatal Med*. 2019;32(4):617-625. 7. Seidel V, et al. *Arch Gynecol Obstet*. 2020;302(6):1353-1359. 8. El-Qushayri AE, et al. *Expert Rev Anti Infect Ther*. 2021;19(5):661-669. 9. Nelson CS, et al. *Proc Natl Acad Sci U S A*. 2018;115(24):6267-6272. 10. Nelson CS, et al. *J Virol*. 2019;93(5):e01695-18. 11. Cox KS, et al. *J Infect Dis*. 2021;223(11):2001-2012. 12. Liu Y, et al. *J Virol*. 2019;93(23):e00747-19. 13. Das R, et al. *Lancet Infect Dis*. 2023 Aug 31:S1473-3099(23)00343-2. 14. Villaverde S, et al. *Pediatr Infect Dis J*. 2022;41(7):590-592. 15. Montague A, et al. *Midwifery*. 2022;106:103249. 16. Vena F, et al. *J Perinat Med*. 2020;49(3):327-332. 17. Calvert A, et al. *BMC Pregnancy Childbirth*. 2021;21(1):565. 18. Butler SK, et al. *South Med J*. 2020;113(11):531-537.

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Treatment

Current Guidelines Recommend Antiviral Medications for Symptomatic cCMV Treatment

Current Recommendations for Neonatal cCMV Treatment in Clinical Practice Guidelines		
2017 European consensus guidelines[1]	**Clinical indications for treatment:** 1. Symptomatic cCMV in babies aged <28 days 2. Babies with life-threatening disease	**Recommended treatment/duration or follow up:** 1. Oral valganciclovir for 6 months; if not tolerated, IV ganciclovir 2. Oral valganciclovir (no consensus on duration); if not tolerated, IV ganciclovir should be used
2017 International cCMV recommendations group[2]	**Clinical indications for treatment:** • Neonates with moderately to severely symptomatic cCMV	**Recommended treatment/duration or follow up:** • Valganciclovir for no longer than 6 months • Initiate treatment within the first month of life
2021 SOGC guidelines[3]	• A detailed discussion of the care of infants with cCMV is outside the scope of this guideline	• However, there is level I evidence for the benefit of antiviral treatment for selected infants with symptomatic cCMV, which is now the standard of care

IV, intravenous.

1. Luck SE, et al. *Pediatr Infect Dis J*. 2017;36(12):1205-1213. 2. Rawlinson WD, et al. *Lancet Infect Dis*. 2017;17(6):e177-e1885. 3. Boucoiran I, et al. *J Obstet Gynaecol Can*. 2021;43(7):893-908.

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Treatment

However, Optimizing Dose and Timing of Antiviral Treatment for cCMV Remains an Ongoing Research Need

Antiviral medications have shown some clinical benefit for hearing recovery relative to placebo in people aged <30 days to 56 years with hearing loss[1]

However, **evidence related to timing and duration of antiviral treatment varies**[2-5]

Key considerations for treatment with antivirals include **drug resistance, lack of viral load relevance to outcome, and individualized dosing approaches** for increased efficacy of treatment[6-8]

1. LM Liu, LL Xia. *Front Neurol.* 2022;13:1027615. 2. Pasternak Y, et al. *J Pediatr.* 2018;199:166-170. 3. Dorfman L, et al. *Eur J Pediatr.* 2020;179(5):807-812. 4. Suganuma E, et al. *J Infect Chemother.* 2021;27(2):185-191. 5. Tanimura K, et al. *J Reprod Immunol.* 2021;143:103263. 6. Marsico C, et al. *J Infect Dis.* 2019;219(9):1398-1406. 7. Torii Y, et al. *BMC Infect Dis.* 2022;22(1):568. 8. Dong Q, et al. *Antimicrob Agents Chemother.* 2018;62(5):e00075-18.

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After Considering all 78 Articles Across Each Topic, We Drew Four Conclusions:

Although specific recommendations differed, stakeholders agreed that additional evidence related to CMV and cCMV infection and disease are needed and could shift practices and standards of care

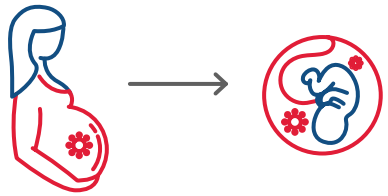
Lack of routine surveillance and screening for CMV limits our understanding of causal pathways between CMV infection, disease, and clinically diagnosed outcomes that are critical for improving patient outcomes

Current targeted cCMV screening approaches based on early clinical symptoms can miss many cases, highlighting the importance for broader cCMV screening and diagnostic methods

Recent studies provide some evidence to support advancing clinical practice guidelines for cCMV, but more robust studies are needed

Our Analysis Identified Gaps That Can Inform Research on the Advancement of Clinical Practice Guidelines

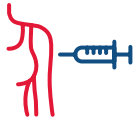
Evaluating maternal risk factors for CMV transmission to enable more effective screening strategies



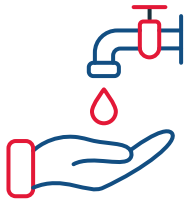
Optimizing use of antiviral treatments

Alternative cCMV testing methods to support more widespread implementation of screening

Identifying effective preventive therapies and vaccines



Refining behavioral strategies for prevention and educational programs to increase patient awareness and HCP confidence



Cost-benefit analyses of universal screening

Recognizing the full spectrum of potential clinical manifestations of cCMV, including those that develop after the postnatal period

The Results of This Review Open the Discussion as to how to Proceed in Phase 3

Phase 1

Semi-structured qualitative interviews conducted with 8 cCMV experts

Objective

To understand clinical practice guidelines and patterns for CMV and cCMV care in the United States

Phase 2

Targeted literature review to summarize emerging evidence on CMV/cCMV disease and clinical care

Objective

To assess recent cCMV-related research, synthesize evidence, and identify gaps that may inform advancement of clinical practice guidelines

Results, report, and study materials available upon request:
stephanie.kalb@modernatx.com

Phase 3

TBD; Academia-advocacy-industry partnerships

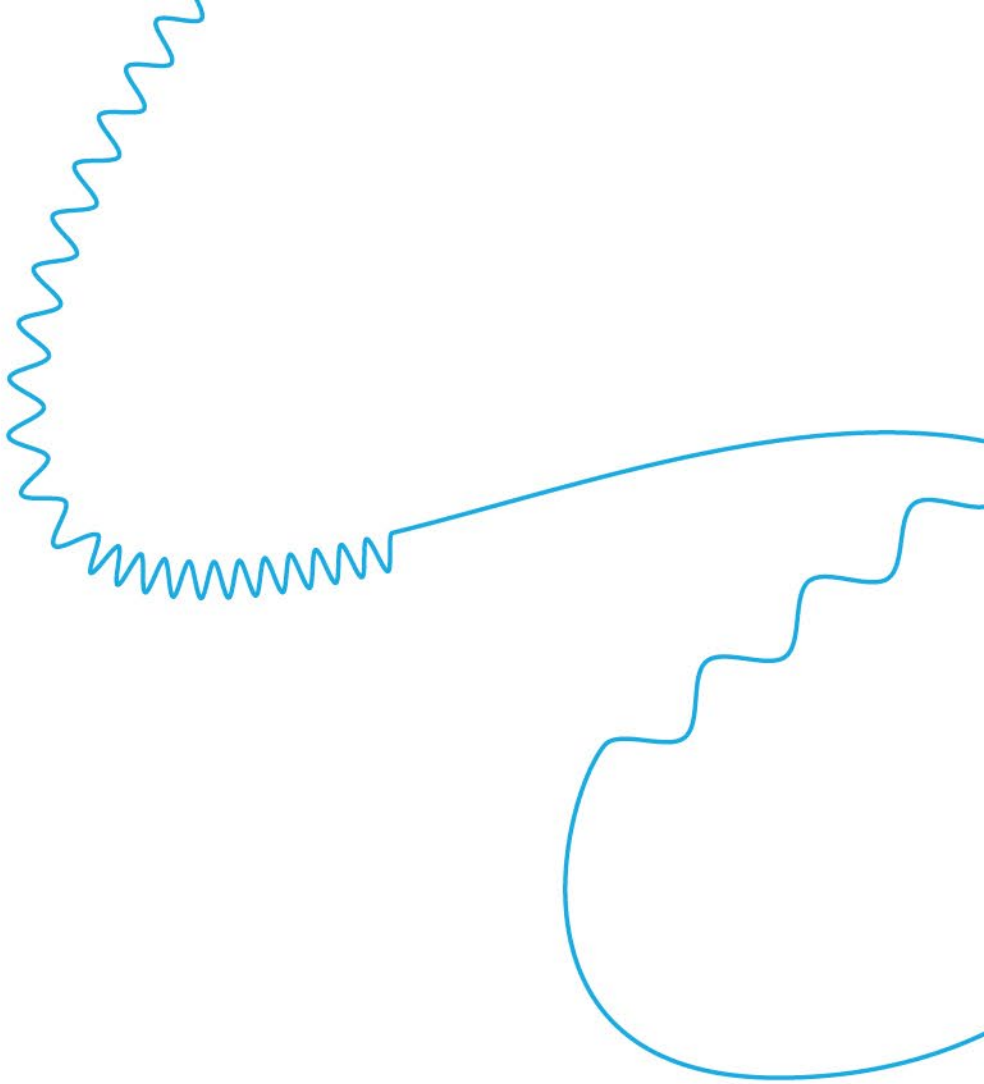
Objective

TBD; To develop unified research agenda, generate evidence, and advance clinical practice guidelines

Discussion Questions

- What are the biggest challenges HCPs face in discussing cCMV with pregnant patients?
- As HCPs, what are the top priorities for advancing cCMV research and guideline updates?
- What are the barriers to implementing universal screening for cCMV in the United States ?
- In what ways can the evidence gaps highlighted here be addressed?

Thank you



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