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Maternal Cytomegalovirus Infection and Congenital Cytomegalovirus Disease: Laboratory Diagnosis, Antiviral Therapy, and Maternal–Pediatric Management.

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Abstract

Background: Congenital cytomegalovirus (CMV) infection is the most common congenital viral infection and a major cause of sensorineural hearing loss and neurodevelopmental impairment in children. Maternal infection frequently remains undiagnosed because most women are asymptomatic or present with nonspecific manifestations.

Aim: This review examines the epidemiology, virology, pathogenesis, maternal risk factors, diagnostic approaches, preventive strategies, and clinical management of congenital CMV infection.

Methods: Relevant literature was reviewed to summarize current evidence on maternal primary and non-primary infections, viral latency, placental transmission, serological and molecular diagnosis, secondary prevention, neonatal assessment, antiviral treatment, and emerging vaccine strategies.

Results: Maternal primary and non-primary infections can result in fetal transmission, although the risk varies according to infection type and timing. Diagnosis remains challenging because of the limitations of maternal serological and molecular tests. Neonatal CMV PCR testing using urine or saliva collected within the first three weeks of life remains the diagnostic standard. High-dose valaciclovir may reduce fetal transmission following early maternal primary infection, while valganciclovir is recommended for selected symptomatic newborns, particularly those with central nervous system involvement. Long-term audiological and neurodevelopmental follow-up is necessary because complications may develop after birth, even in initially asymptomatic infants. Vaccine development remains challenging, and no licensed CMV vaccine is currently available.

Conclusion: Early maternal screening, accurate diagnosis, evidence-based preventive interventions, and appropriate neonatal management are essential to reduce the burden of congenital CMV infection. Further research should focus on improving diagnostic methods, understanding protective maternal immunity, and developing effective vaccines.

Keywords: Cytomegalovirus; congenital infection; pregnancy; maternal infection; fetal transmission; valaciclovir; valganciclovir; neonatal diagnosis.

Introduction

Human cytomegalovirus (CMV), also known as human herpesvirus 5 (HHV-5), belongs to the Herpesviridae family and the Betaherpesvirinae subfamily. It is one of the largest human viruses, measuring approximately 200 nm in diameter, and has a global seroprevalence exceeding 80% among women of reproductive age [1]. Congenital CMV infection represents an important public health concern, with an estimated prevalence of 0.64% worldwide. Approximately 17–20% of infected children may develop permanent complications, including hearing loss and neurodevelopmental impairment [2,3]. CMV has a complex icosahedral structure consisting of four components: an outer lipid envelope, a tegument, a nucleocapsid, and an inner nucleoprotein core containing linear double-stranded DNA. The viral envelope contains lipoproteins and numerous structural proteins that facilitate attachment and entry into host cells. The

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tegument contains several viral proteins, including pp65, which serves as an important target in laboratory diagnosis. The viral genome encodes more than 230 proteins, including DNA polymerase, an essential enzyme involved in viral replication and the primary target of currently approved antiviral medications [4]. Transmission occurs through contact with infected bodily fluids across mucosal surfaces, blood transfusion, and organ transplantation. CMV infection is classified as primary or non-primary, the latter resulting from viral reactivation or reinfection with a different strain. Primary infection in immunocompetent individuals is usually asymptomatic but may cause fever, lymphadenopathy, and lymphocytosis. Following initial infection, CMV establishes lifelong latency in various cell types, including leukocytes, endothelial cells, and epithelial cells, as well as organs such as the salivary glands and kidneys. Although active replication becomes undetectable during latency, residual viral gene expression may persist. This phenomenon is described as sleepless latency [5].

CMV may reactivate periodically, allowing viral dissemination and prolonged shedding through saliva, urine, breast milk, and genital secretions. Non-primary infections are generally asymptomatic in healthy individuals but may cause severe complications in immunocompromised patients. Congenital infection occurs when maternal CMV crosses the placenta and reaches the developing fetus. Fetal injury may result from direct viral damage or inflammation at the maternal–fetal interface, which can interfere with normal development [6,7]. The risk of significant fetal complications is particularly high following primary maternal infection during the first trimester [8]. CMV can also be transmitted during delivery through exposure to infected genital secretions or after birth, primarily through breastfeeding. Although postnatal infection is usually asymptomatic in term infants, it may cause substantial morbidity in preterm and very-low-birth-weight neonates, whose immune systems are less developed [9]. Understanding CMV structure, transmission, and latency is essential for developing effective diagnostic strategies, guiding antiviral treatment, and preventing congenital and neonatal complications.

CMV Latency and Congenital Infection

Following primary cytomegalovirus (CMV) infection, the host immune system produces specific immunoglobulin M (IgM) antibodies, followed by immunoglobulin G (IgG) antibodies that generally persist throughout life. However, antibody development does not eliminate the virus, which establishes lifelong latency within host cells. The mechanisms regulating CMV latency and reactivation remain incompletely understood. During pregnancy, latent infection is clinically important because viral reactivation or reinfection with a different strain can result in maternal viral replication and subsequent fetal exposure. Consequently, congenital CMV infection can occur in women with pre-existing immunity, particularly in populations with high seroprevalence [7]. Maternal CMV seroprevalence varies considerably across geographical regions and populations. Reported rates include approximately 60% in France, 72% in Finland, and 98% in Brazil [10–12]. These differences influence the epidemiological distribution of congenital infection. In highly seropositive populations, a substantial proportion of congenital CMV cases results from maternal non-primary infection. For example, non-primary infections account for approximately 90% of congenital cases in Brazil, compared with 53% in Finland and 48% in France [13]. Unlike several other viral infections, previous maternal CMV exposure does not provide complete protection against subsequent fetal transmission. Pre-existing immunity may reduce the risk or severity of infection but cannot reliably prevent viral reactivation, reinfection, or placental transmission. This characteristic represents a major challenge for vaccine development because effective immunization must provide protection against both primary and non-primary infections. Recent advances in messenger RNA (mRNA) technology have introduced potential approaches to CMV prevention. Experimental studies in rodent models demonstrated that transamniotically administered mRNA could cross the placenta, reach fetal circulation, and induce CMV-specific antibody responses that persisted into the neonatal period. No apparent adverse effects on maternal, fetal, or neonatal morbidity and mortality were reported in the experimental model [14]. Although further investigation is required to establish safety, efficacy, and clinical applicability, this strategy offers a potential direction for developing preventive interventions against congenital CMV infection.

CMV Infection in Pregnancy and the Role of the Placenta

Transplacental transmission is a major determinant of congenital cytomegalovirus (CMV) infection and its associated complications. Following primary maternal infection, fetal transmission occurs in approximately 30–40% of pregnancies, with the probability increasing as pregnancy progresses [15]. In women with pre-existing CMV immunity, transmission is less frequent, occurring in approximately 1–2% of cases. Nevertheless, maternal IgG positivity does not provide complete protection against reinfection with different viral strains or reactivation of latent infection [16,17]. Primary infection during early pregnancy has been associated with spontaneous abortion in approximately 15% of cases, whereas infection later in pregnancy may contribute to preterm delivery and intrauterine growth restriction. These outcomes suggest that placental infection and dysfunction may precede fetal infection [18]. The placenta provides structural and immunological protection through the chorionic villi,

trophoblast layers, and resident immune cells [19]. The syncytiotrophoblast forms the principal barrier between maternal blood and fetal tissues, while cytotrophoblasts contribute to placental development and invasion of the uterine wall. Hofbauer cells, which are fetal-derived macrophages within the chorionic villi, participate in phagocytosis, antigen presentation, cytokine production, and regulation of local immune responses [20]. Although these cells contribute to placental defense, their susceptibility to viral infection may provide an opportunity for CMV persistence and dissemination. They may also participate in maternal antibody transfer through Fc receptors, supporting neonatal immunity [21].

Several maternal immune responses appear to reduce transplacental transmission. These include neutralizing antibodies against CMV glycoprotein B, high-avidity IgG, and antibody-dependent cellular cytotoxicity [22–25]. However, CMV may exploit antibody-mediated transport to cross the placental barrier. Studies by Maidji and Pereira demonstrated that IgG–virion immune complexes can undergo transcytosis through neonatal Fc receptors expressed by syncytiotrophoblasts. This mechanism may facilitate viral passage through chorionic villi and allow subsequent infection of fetal vessels, particularly when maternal antibody responses are insufficient [26–28]. Although administration of CMV hyperimmune globulin has been investigated as a preventive strategy, its clinical efficacy remains controversial because large randomized trials have not established consistent benefit [29]. Cellular immunity also contributes to protection at the maternal–fetal interface. Peripheral CD4+, CD8+, and memory T-cell responses have been associated with reduced fetal transmission. In an ex vivo model, Alfi et al. identified decidual tissue-resident memory CD8+ T cells as important mediators of protection against CMV transmission. These cells were associated with resistance to non-primary infection in tissues from seropositive women, whereas this protective response was absent in tissues from seronegative women with primary infection [30]. Nevertheless, peripheral immune measurements may not accurately represent local immune activity within the placenta and decidua.

Placental studies have detected CMV in fibroblasts, villous endothelial cells, macrophages, lymphocytes, and trophoblasts. Greater chronic villitis and villous structural alterations have been reported in mothers of symptomatic infants, while non-primary infections have also been associated with decidual damage [31]. Experimental investigations by Fisher et al. demonstrated that first-trimester cytotrophoblasts could support CMV infection, whereas syncytiotrophoblasts appeared relatively resistant under the studied conditions [32]. Viral replication in cytotrophoblasts may impair their differentiation, proliferation, and invasive capacity, resulting in abnormal villous architecture and compromised placental development [33]. CMV also employs immune-evasion mechanisms that interfere with antigen presentation, cytokine signaling, and natural killer (NK) cell recognition. These mechanisms may reduce the elimination of infected placental cells and promote local viral persistence. Decidual NK cells normally regulate trophoblast invasion, vascular remodeling, and immune tolerance. Viral interference with their activity may therefore disrupt placental homeostasis and facilitate fetal transmission [34]. Placental injury and inflammation may further compromise oxygen delivery to the developing fetus. Hypoxia can stimulate compensatory vascular remodeling through changes in angiogenic mediators, particularly vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Experimental hypoxic conditions have been associated with increased VEGF expression and vascular dilation around chorionic villi, potentially representing an adaptive response to reduced oxygen availability. However, persistent placental dysfunction may impair fetal growth and contribute to low birth weight [35]. Collectively, these findings demonstrate that congenital CMV disease involves not only direct fetal infection but also disruption of placental structure, immune regulation, and vascular function.

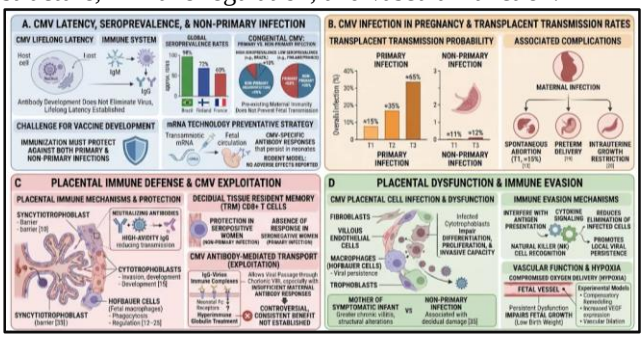


Figure-1: CMV Latency and Congenital Infection in Pregnancy and the Role of the Placenta.

Which Women Are at High Risk of Transmitting the Infection to the Fetus?

All pregnant women are susceptible to cytomegalovirus (CMV) infection, regardless of their previous exposure or serological status. Identifying women at risk of fetal transmission can be challenging, particularly in the absence of routine prenatal serological screening. Maternal CMV infection is frequently asymptomatic or associated with mild, nonspecific manifestations. Approximately one-third of infected pregnant women develop symptoms, which commonly resemble a flu-like illness, including fever, malaise, and myalgia. Consequently, clinical presentation alone is insufficient to establish the diagnosis [36]. Laboratory abnormalities are also nonspecific and may include mild lymphocytosis and elevated serum transaminases. Therefore, confirmation requires

virological and serological investigations [37]. Serological assessment includes CMV-specific IgM and IgG antibodies, while IgG avidity testing can help distinguish recent primary infection from previous exposure. Detection of CMV DNA using polymerase chain reaction (PCR) in blood, saliva, urine, or other biological specimens provides additional diagnostic evidence. PCR performance depends on the specimen type, timing of collection, and whether infection is primary or non-primary [18]. Certain clinical and laboratory findings may indicate an increased probability of congenital transmission. Maternal primary infection during pregnancy is particularly important because it carries a substantially higher transmission risk than non-primary infection. Nevertheless, women with pre-existing CMV immunity may still transmit the virus following reactivation or reinfection. Fetal ultrasound abnormalities can provide additional evidence of possible congenital infection. Tanimura et al. identified both abnormal fetal ultrasound findings and positive CMV PCR results in uterine cervical secretions as independent predictors of congenital infection among pregnant women with positive CMV IgM results [38]. Combining maternal serology, molecular testing, and fetal imaging is therefore essential for identifying pregnancies requiring further evaluation and monitoring.

Maternal Primary Infections (MPI), Serological and Molecular Tests

Maternal primary cytomegalovirus (CMV) infection is generally characterized by the absence of CMV-specific IgG, the presence of IgM, and variable results from molecular testing. The risk of transplacental transmission and long-term neonatal complications is particularly important when infection occurs around conception or during the first trimester. A meta-analysis by Chatzakis and Ville reported late sequelae in 23% of children following first-trimester maternal infection, compared with 0.1% and 0% following second- and third-trimester infections, respectively [39]. Similarly, Faure-Bardon et al. reported sensorineural hearing loss and/or neurological sequelae in 32.4% of children following first-trimester infection, compared with no reported cases following infection in later trimesters [40]. These findings emphasize the importance of early maternal screening and appropriate neonatal follow-up. Preconception or early-pregnancy CMV serological assessment can identify women without previous exposure who remain susceptible to primary infection. In seronegative women, repeated testing during early pregnancy may help detect seroconversion [2]. Diagnosis relies primarily on CMV-specific IgM and IgG measurements. Although modern IgM assays have high sensitivity, their specificity is limited because IgM may persist for months after primary infection. Therefore, a positive IgM result should be interpreted alongside IgG avidity testing [41]. IgG avidity helps estimate the timing of primary infection. Low avidity generally supports recent infection, whereas high avidity during the first trimester strongly suggests previous exposure and makes recent periconceptional infection less likely. However, interpretation requires consideration of assay-specific thresholds, gestational age, and the persistence of low-avidity antibodies. Intermediate avidity may persist for up to six months, while low avidity can occasionally remain detectable for more than 18 weeks. These factors may lead to misclassification of infection timing [42,43]. When results are inconclusive, repeat testing in a specialized laboratory can improve diagnostic interpretation. Molecular testing provides complementary evidence. Detection of CMV DNA in maternal blood may support recent infection, particularly during its early phase. However, DNAemia is transient, and viral DNA may become undetectable over time. Furthermore, CMV detection in blood or urine cannot reliably distinguish primary from non-primary infection or establish the exact timing of infection because viral shedding may persist for months [44]. Consequently, accurate diagnosis requires combining serological findings, IgG avidity, molecular results, and clinical timing to guide pregnancy monitoring and fetal assessment.

Maternal Non-Primary Infections (MNPI)

Diagnosing maternal non-primary CMV infection remains challenging, particularly when previous serological results are unavailable [2]. Unlike primary infection, no single laboratory marker can reliably identify seropositive pregnant women at risk of fetal transmission [45]. Serological testing has limited diagnostic value because CMV IgM is detected in only a proportion of non-primary infections. Moreover, IgM may persist after the initial infection or reappear during viral reactivation or reinfection. Changes in CMV IgG concentrations are also unreliable because antibody titers may increase inconsistently and cannot independently establish active infection. Molecular testing has similar limitations. CMV DNA may be detected intermittently in maternal blood and other biological fluids, reflecting transient viremia and variable viral shedding. Consequently, negative molecular results do not exclude non-primary infection, while positive results do not necessarily establish the timing or clinical significance of viral reactivation. Diagnosis therefore often relies on clinical assessment and serial serological or virological findings, although these provide supportive rather than definitive evidence [8,46]. When fetal infection is suspected, amniocentesis followed by CMV DNA detection using polymerase chain reaction provides the principal method of prenatal confirmation. This distinction is important because maternal infection does not necessarily indicate fetal transmission, and identifying fetal infection is essential for subsequent assessment and pregnancy management.

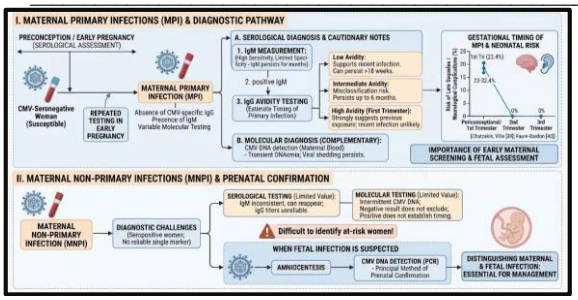


Figure-2: CMV Maternal primary and non-primary infections.

Secondary Prevention of Maternal–Fetal Infections

Administration of Hyperimmune Immunoglobulins

Intravenous administration of CMV-specific hyperimmune immunoglobulins has been investigated as a strategy to reduce maternal–fetal transmission following primary maternal infection [47]. This approach aims to provide passive immunity by neutralizing circulating virus, limiting placental infection, and reducing viral passage to the fetus. Its rationale is partly supported by observations that most women with pre-existing CMV immunity do not transmit the virus to the fetus following reactivation or reinfection. However, clinical evidence has not established consistent preventive efficacy. An Italian randomized controlled trial involving 124 pregnant women found that monthly administration of hyperimmune immunoglobulins at 100 IU/kg, initiated six weeks after infection onset, did not significantly reduce congenital CMV infection compared with placebo [48]. Subsequent studies examined whether dosing intervals influenced antibody exposure. Buxmann et al. adopted monthly administration based on an estimated terminal IgG half-life of 22.4 days [49,50]. However, pharmacokinetic observations by Hamprecht et al. demonstrated more rapid reductions in CMV-specific IgG concentrations, with an estimated half-life of approximately 11 days. They also reported fluctuations in antibody avidity and epithelial-cell neutralizing activity during four-week dosing intervals [51]. These findings raised questions about whether monthly administration maintains sufficient antiviral antibody activity. A 2019 observational study reported more favorable outcomes with biweekly administration of 200 IU/kg in women with primary infection during the first trimester. The reported fetal transmission rate was 2.5% among treated women, increasing to 7.5% when cases with late-onset symptoms were included, compared with 35.2% in untreated controls. All infected newborns in the treated group were asymptomatic [29]. Nevertheless, these findings were not confirmed by a subsequent double-blind multicentre trial conducted in 2021. This study found no reduction in congenital transmission or in the composite outcome of neonatal infection or death. Treatment was also associated with adverse outcomes, including prematurity, low birth weight, severe allergic reactions, chills, and headaches. The trial was stopped for futility after analysis of 394 participants [52]. Overall, differences in study design, patient selection, treatment timing, and dosing schedules may explain some variation in reported outcomes. However, the available randomized evidence does not support routine administration of CMV hyperimmune immunoglobulins during pregnancy. Most obstetricians therefore do not recommend this intervention for preventing congenital CMV infection following primary maternal infection [53].

Prevention of Fetal Infection with Valaciclovir

Valaciclovir has emerged as a potential intervention for reducing vertical CMV transmission in pregnant women with primary infection acquired during the periconceptional period or first trimester. Clinical studies have evaluated high-dose oral treatment at 8 g/day, based on its ability to inhibit viral replication. Valaciclovir is an antiviral prodrug with approximately 55% oral bioavailability. Following absorption, it is rapidly converted in the liver to acyclovir, which undergoes intracellular phosphorylation to form acyclovir triphosphate. This active metabolite inhibits viral DNA polymerase, terminates DNA chain elongation, and prevents viral DNA synthesis. Although commonly used against herpes simplex and varicella-zoster viruses, this mechanism also provides a rationale for its use against CMV. A meta-analysis of randomized and quasi-randomized studies reported that high-dose valaciclovir reduced vertical CMV transmission by approximately 71%. Three studies involving 527 pregnant women demonstrated lower rates of congenital infection and fewer pregnancy terminations following severe fetal findings. Earlier treatment initiation was associated with better outcomes, suggesting that prompt antiviral intervention may limit placental viral replication and subsequent fetal exposure. Severe adverse effects were relatively uncommon, occurring in approximately 2.1% of treated women [54–56]. Based on these findings, oral valaciclovir at 8 g/day has been recommended for women with primary CMV infection during the periconceptional period or first trimester. Treatment should begin as soon as possible after diagnosis and continue until amniocentesis, generally performed at approximately 20 weeks of gestation. Early maternal screening is therefore important. CMV serological testing during the first trimester, followed by repeat testing at 14–16 weeks in initially seronegative women, may facilitate timely diagnosis and treatment.

Evidence from a multicentre Italian observational study involving 447 pregnant women further supported this approach. Among these participants, 205 received valaciclovir and 242

remained untreated. Treatment was associated with a significant reduction in congenital CMV diagnosis at amniocentesis, as well as lower rates of pregnancy termination and symptomatic congenital infection at birth. The study also reported good treatment tolerability [2,57]. However, high-dose treatment requires attention to adverse effects. Approximately 21% of women experienced symptoms such as nausea or headache. Acute renal impairment occurred in around 2% of participants, including three reported cases, but resolved after treatment discontinuation [54]. Renal function monitoring is therefore important during therapy. Preventive treatment should be discontinued when amniocentesis confirms the absence of fetal infection. If fetal infection is detected, management should include serial targeted ultrasonography and third-trimester magnetic resonance imaging. These examinations provide complementary information about fetal abnormalities and help assess the potential severity of congenital CMV disease [58].

Congenital Cytomegalovirus Infection in the Newborn

Congenital cytomegalovirus (CMV) infection affects approximately 1 in 200 neonates in high-income countries, making it the most common congenital infection [59]. Around 11–13% of infected newborns present with clinical manifestations at birth, and 40–58% of symptomatic infants develop permanent sequelae. These complications include sensorineural hearing loss (SNHL), intellectual disability, and neurodevelopmental impairment. Importantly, approximately 8–15% of infected children who are asymptomatic at birth may also develop long-term complications, particularly hearing loss and developmental abnormalities [60]. Congenital CMV should be suspected in newborns whose mothers have confirmed infection, indicated by seroconversion or positive CMV PCR in amniotic fluid. Suspicion is also warranted when maternal infection is suspected based on flu-like symptoms during pregnancy or positive CMV IgM results that were not further investigated. Prenatal ultrasound abnormalities, including ventriculomegaly, cerebral hyperechogenicity, subependymal cysts, hyperechogenic bowel, and hepatic calcifications, also support further investigation. In addition, newborns presenting with compatible clinical manifestations, laboratory abnormalities, or imaging findings should undergo diagnostic testing [2]. The diagnostic gold standard is real-time PCR detection of CMV DNA in urine or saliva collected within the first 21 days of life. Saliva and urine PCR demonstrate high sensitivity (93–100%) and negative predictive value (98–99%), although specificity ranges from 91% to 99.7% and positive predictive value from 49% to 73% [2]. Saliva testing may produce false-positive results because of contamination with maternal genital secretions or recent breastfeeding, particularly when viral loads are low. Therefore, positive saliva results should be confirmed using urine PCR. Testing after the first three weeks cannot reliably distinguish congenital infection from postnatal acquisition. In older infants, dried blood spots (DBS) collected during the neonatal period can support retrospective diagnosis. Although DBS PCR has high specificity, its sensitivity varies, with pooled estimates ranging from 84.4% to 99.9%. Consequently, a positive result strongly supports congenital infection, whereas a negative result does not exclude it. This limitation reflects the relatively low CMV concentration and small blood volume available in DBS samples [61]. Neonatal IgM testing is also unsuitable because approximately 30% of infected infants lack detectable IgM at diagnosis, resulting in low sensitivity [62].

The risk of long-term complications depends partly on the timing of maternal infection. Primary maternal infection (MPI) during the first trimester is an important risk factor for adverse neurological outcomes. A clinical virologist should assess maternal serological findings to establish the timing of infection as accurately as possible. However, long-term outcomes following maternal primary and non-primary infections may be broadly comparable [45]. Clinical examination, laboratory investigations, and specialized assessments help classify newborns as symptomatic or asymptomatic, as summarized in Table 3 [2]. Because individual findings at birth have variable prognostic significance, treatment and follow-up decisions should consider the overall clinical and imaging profile. Current management emphasizes risk stratification and long-term surveillance. Children with confirmed congenital infection following first-trimester maternal infection, or with an unknown timing of transmission, should receive specialized follow-up for at least six years. This prolonged surveillance may not be necessary for children whose mothers had documented primary infection during the second or third trimester [2]. Microcephaly is particularly important because it has high specificity for adverse neurological outcomes, especially when head circumference is disproportionately reduced relative to birth weight (HC z-score minus weight z-score < -2). In contrast, isolated symmetric intrauterine growth restriction (IUGR) in otherwise asymptomatic newborns does not necessarily predict an unfavorable outcome [44]. Brain magnetic resonance imaging (MRI) is recommended for newborns with clinical manifestations of CMV infection, SNHL, chorioretinitis, or cranial ultrasound abnormalities. It is also indicated when maternal primary infection occurred during the first trimester or when its timing is unknown. Normal neuroimaging generally predicts normal or near-normal neurodevelopment, whereas significant structural abnormalities indicate a less favorable prognosis [63–65].

According to the 2024 European consensus, antiviral treatment is recommended for symptomatic

congenital CMV, particularly when central nervous system involvement, microcephaly, or chorioretinitis is present. Treatment is generally continued for six months in these cases. Selected infants with isolated hepatitis or thrombocytopenia may receive a shorter six-week course. Antiviral therapy is not recommended for asymptomatic newborns or infants presenting only with IUGR [2]. Oral valganciclovir at 16 mg/kg twice daily is the preferred treatment, while intravenous ganciclovir is reserved for selected clinical circumstances. Therapy should begin as early as possible, preferably within the first month after birth, although initiation up to 12 weeks may be considered in selected infants [66]. Evidence regarding hearing outcomes remains mixed. Early treatment may reduce hearing deterioration in some affected children, but treatment initiated beyond the neonatal period has not consistently improved hearing outcomes. Prolonged antiviral therapy provides only modest long-term benefits and requires regular monitoring because of potential hematological and hepatic toxicity [66,67].

Vaccines and Future Perspectives

The development of an effective vaccine against cytomegalovirus (CMV) remains a major priority for preventing congenital infection and its associated complications. Although several vaccine candidates have progressed through clinical trials, a licensed vaccine is unlikely to become available in the immediate future. Until an effective vaccine is established, hygiene-based behavioral interventions remain the principal strategy for primary prevention. These measures include regular handwashing, avoiding the sharing of food and utensils with young children, and limiting contact with saliva and urine, particularly among pregnant women who are seronegative. Vaccine development remains challenging because of the complex CMV life cycle, its ability to establish lifelong latency, its mechanisms of immune evasion, and the absence of clearly defined immune correlates that reliably predict protection against infection and fetal transmission [68]. Several vaccine platforms have been investigated, including live-attenuated vaccines, recombinant protein subunits, viral vectors, DNA vaccines, and mRNA-based formulations. These approaches target viral antigens involved in host-cell entry and immune recognition. Glycoprotein B (gB) and the pentameric complex are major targets for inducing neutralizing antibodies, whereas phosphoprotein 65 (pp65) is considered an important target for CMV-specific cellular immune responses, particularly cytotoxic T lymphocytes [69]. Combining humoral and cellular immune responses may be necessary to achieve broader protection because antibodies alone may not prevent viral reactivation, reinfection, or transmission across the placenta.

Despite substantial research, several vaccine candidates have failed to demonstrate sufficient clinical efficacy in phase III trials, highlighting the difficulty of translating immunogenicity into meaningful clinical protection [70]. One important example is Moderna's mRNA-1647 vaccine, which was developed using an mRNA platform targeting gB and the pentameric complex. In October 2025, Moderna announced that the candidate failed to meet its primary efficacy endpoint in the phase III trial, leading to the discontinuation of its development [71]. This outcome emphasizes the need to reassess vaccine targets, immune-response requirements, dosing strategies, and the populations most likely to benefit from vaccination. Future vaccine strategies may need to induce both strong neutralizing antibody responses and durable CMV-specific T-cell immunity. Antibodies directed against gB and the pentameric complex may interfere with viral attachment and entry into susceptible cells, while cellular immunity may help control infected cells and limit viral replication. Understanding the relative contribution of these immune mechanisms is essential for identifying reliable correlates of protection and improving the design of subsequent vaccine candidates [69]. Vaccination of young children represents another potential preventive approach. Because young children frequently shed CMV in saliva and urine, reducing infection and viral shedding in this population could indirectly decrease exposure among pregnant women. This strategy may provide community-level protection, particularly in households and childcare settings where close contact facilitates viral transmission [72]. However, the effectiveness of this approach will depend on vaccine efficacy, duration of protection, coverage, and the extent to which vaccination reduces viral shedding.

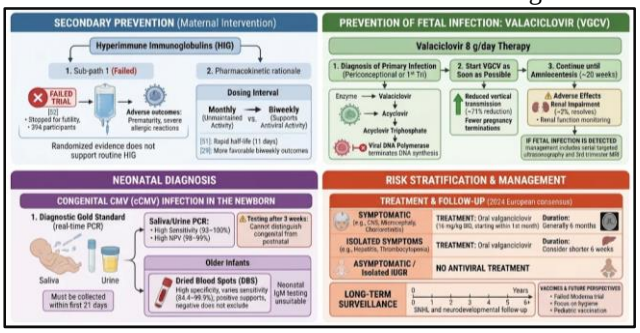


Figure-3: Secondary prevention of maternal CMV infection.

An important unresolved issue is the incomplete protection provided by naturally acquired immunity. Women with pre-existing CMV antibodies may still experience reinfection with different viral strains or reactivation of latent infection, resulting in possible fetal transmission. The immunological mechanisms responsible for this susceptibility remain insufficiently understood. Further studies are needed to identify the immune deficiencies that permit reinfection and reactivation in seropositive

individuals, particularly during pregnancy [73,74]. Future research should therefore integrate vaccine development with investigations of CMV latency, immune evasion, maternal immunity, and placental transmission. Defining protective antibody functions and cellular immune responses may support the development of vaccines capable of preventing both primary and non-primary maternal infections. Until such interventions become available, early maternal screening, hygiene education, appropriate prenatal assessment, and timely management of confirmed maternal infection remain central to reducing the burden of congenital CMV.

Conclusion:

Congenital CMV infection remains a major public health concern because of its potential to cause permanent hearing loss and neurodevelopmental impairment. Its diagnosis is complicated by asymptomatic maternal infection, limitations in serological testing, and the narrow diagnostic window during the first three weeks of neonatal life. Early maternal identification, appropriate fetal assessment, and timely neonatal PCR testing are essential for effective management. High-dose valaciclovir offers a preventive option following early maternal primary infection, whereas antiviral treatment with valganciclovir benefits selected symptomatic newborns. However, uncertainties remain regarding non-primary infection, long-term outcomes, and optimal preventive strategies. Future research should prioritize the development of effective vaccines, improved diagnostic biomarkers, and a better understanding of maternal and placental immunity. Integrating prenatal screening, evidence-based interventions, and long-term pediatric follow-up may reduce the clinical and developmental consequences of congenital CMV.

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