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Vaccine value profile for cytomegalovirus

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ABSTRACT

Cytomegalovirus (CMV) is the most common infectious cause of congenital malformation and a leading cause of developmental disabilities such as sensorineural hearing loss (SNHL), motor and cognitive deficits. The significant disease burden from congenital CMV infection (cCMV) led the US National Institute of Medicine to rank CMV vaccine development as the highest priority. An average of 6.7/1000 live births are affected by cCMV, but the prevalence varies across and within countries. In contrast to other congenital infections such as rubella and toxoplasmosis, the prevalence of cCMV increases with CMV seroprevalence rates in the population. The true global burden of cCMV disease is likely underestimated because most infected infants (85–90 %) have asymptomatic infection and are not identified. However, about 7–11 % of those with asymptomatic infection will develop SNHL throughout early childhood.

Although no licensed CMV vaccine exists, several candidate vaccines are in development, including one currently in phase 3 trials. Licensure of one or more vaccine candidates is feasible within the next five years. Various models of CMV vaccine strategies employing different target populations have shown to provide substantial benefit in reducing cCMV. Although CMV can cause end-organ disease with significant morbidity and mortality in immunocompromised individuals, the focus of this vaccine value profile (VVP) is on preventing or reducing the cCMV disease burden.

This CMV VVP provides a high-level, comprehensive assessment of the currently available data to inform the potential public health, economic, and societal value of CMV vaccines. The CMV VVP was developed by a working group of subject matter experts from academia, public health groups, policy organizations, and non-profit organizations. All contributors have extensive expertise on various elements of the CMV VVP and have described the state of knowledge and identified the current gaps. The VVP was developed using only existing and publicly available information.

1. The global public health need for a vaccine

Human Cytomegalovirus (CMV) is a ubiquitous betaherpesvirus present globally in all populations and a species-specific pathogen

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[1]. Although CMV infection is common throughout the world, it exhibits significant geographic variability. Between 40 and 100 % of people are seropositive, depending on the country and subgroups of the population [2,3].

Infection can be acquired at any age, but in most regions of the world, primary infection is acquired during infancy and childhood. CMV seroprevalence is higher in low- and middle-income countries (LMIC) and in individuals of lower socioeconomic groups/regions at any given age. Table 1 below summarizes currently available evidence of CMV epidemiology and public health impacts.

Congenital CMV infection (cCMV) is a leading cause of birth defects and developmental disabilities, including microcephaly, hearing loss, vision loss, seizures, and cognitive impairment. Approximately 10–15 % of infected neonates have clinical findings at birth (symptomatic infection) which vary widely: petechial rash, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis, thrombocytopenia with or without central nervous system (CNS) involvement (microcephaly, neuroimaging abnormalities, chorioretinitis, and SNHL [4]. Those with moderate to severe symptomatic infection will have sequelae more frequently than those with mild disease [5].

Between 85 % and 90 % of infected neonates have no clinical findings (asymptomatic) at birth, of which about 7–11 % of asymptomatic neonates will develop SNHL during early childhood; hearing loss may fluctuate, or further deteriorate over time. Neurodevelopmental impairment is uncommon in children with asymptomatic cCMV with normal hearing [6]. About one-third of cases of SNHL in Brazil can be attributed to cCMV [7] whereas in high-income countries, cCMV accounts for at least 4–10 % of SNHL [8].

Although CMV can cause end organ disease with significant morbidity and mortality in immunocompromised individuals including allograft recipients and those with HIV/AIDS, this vaccine value profile (VVP) document is focused on preventing or reducing the disease burden from cCMV.

1.1. Current methods of surveillance, diagnosis, prevention, and treatment

CMV antibody screening does not routinely occur in the general population in either HICs or LMICs outside of specific health care settings in HICs (blood banks, solid organ transplantation, in vitro fertilization). A few health care systems in HICs screen pregnant women to identify their risk of intrauterine transmission. Congenital CMV infection can be identified by detecting viral DNA by PCR in urine, saliva, or blood; Population-based screening of newborn dried blood spots for cCMV has been introduced in some programs in Canada and the United States. Culture-based methods may be used for identifying infants with cCMV but are labor intensive and have lower sensitivity than PCR. Congenital CMV surveillance is very limited, and diagnosis of cCMV is mostly made clinically throughout the world.

After birth, infants with moderate to severe symptomatic cCMV can be treated with antiviral agents (ganciclovir and its prodrug valganciclovir). Long-term data on the effectiveness of these antivirals are not known. Also, the safety and efficacy of antiviral therapy has not been demonstrated in children with asymptomatic infection, who nevertheless account for the majority of cCMV-related hearing loss. Without a licensed vaccine, prevention of cCMV focuses on messaging (minimizing contact with saliva and urine of young children) among pregnant women to prevent maternal infection and, therefore, intrauterine transmission [48]. Effectiveness data for preventative interventions and the impact on the population level are unknown. Challenges to this approach are that most women of childbearing age are not aware of cCMV [49], so prevention messaging requires an educational component.

1.2. Summary of knowledge and research gaps in epidemiology, potential indirect public health impact and economic burden

- Burden of disease data including natural history of disease are largely based on studies from a limited number of HICs.
- Immune correlates of protection against intrauterine transmission and disease in infected infants, especially infants born to women with non-primary infection, have not been well defined.
- An understanding of the source(s) of nonprimary CMV infections in seropositive women should be considered a critical parameter in the design and eventual testing of candidate vaccines in seropositive populations.
- Data gaps exist concerning estimates of direct health and non-healthcare costs for those with severe impairment. Other gaps include costs incurred before an established cCMV diagnosis and indirect and intangible costs [47].
- Quality of life data are limited to HICs, so perceived burden at the individual and societal levels are unavailable for other countries.

2. Potential target populations and delivery strategies

2.1. Vaccine delivery

Assessment of target populations, and the related strategies for vaccine delivery to prevent cCMV disease, is influenced by several parameters:

- Clinical trials are likely to evaluate clinical parameters of preventing infection, as this will precede congenital CMV disease in the infant [50].
- Different target populations are not mutually exclusive (Table 2 below).
- Secondary benefits of vaccinating certain populations occur. For example, vaccinating young children will presumably reduce transmission from these children to pregnant mothers, depending upon duration and level of protection [51], and to other children in childcare [52]. Some of these parameters may be measurable.
- Depending on the target population, it will be necessary to consider immunization schedules for other pathogens so that the schedules can be aligned.

2.2. Priority target populations in different scenarios

Since CMV infections are often asymptomatic, target populations would not be based on symptomatology [53]. In addition, the likelihood of fetal damage leading to long-term morbidity is higher when intrauterine transmission occurs in early pregnancy, vaccination would need to be delivered prior to pregnancy [27,54].

Although target populations and mechanisms of vaccine delivery are not yet defined [55], most efforts have focused on protecting seronegative women of childbearing age from primary infection and protecting seropositive women from reinfection and/or reactivation of latent virus to prevent intrauterine transmission and/or reduce the severity of fetal infection during subsequent pregnancies [56].

Targeting children for vaccination as a component of routine childhood immunization has been proposed [57] as a means of reducing adverse consequences of cCMV [58] similar to the current rubella vaccination strategy [59]. This may be the optimal strategy based on the review of different models [60].

Table 1
Summary of epidemiology and potential indirect public health impact.

Feature	Summary and evidence
Epidemiology	
Reservoir	Human cytomegalovirus (CMV) is a ubiquitous betaherpesvirus in all populations and a species-specific pathogen [1]. • There is no natural animal reservoir • Following primary infection, it establishes lifelong latency. • Non-primary infection can occur after viral reactivation or reinfection with a different viral strain. • CMV spreads mainly from human to human through close contact with bodily fluids of individuals shedding infectious virus (urine, saliva, genital secretions, blood, and breast milk) after primary or non-primary infections. Main sources of CMV infection in the general population: • Ingestion of breast milk from an infected mother • Young infants who shed large amounts of virus in saliva and urine after congenital or postnatal infections • Sexual contact with infected individuals • Intrauterine acquisition from a mother with primary or non-primary infection (congenital infection) Other important sources of infection are organs of seropositive donors. CMV infection is common throughout the world but exhibits significant geographic variability [2,3]. • CMV seroprevalence serves as a marker for the size of the population virus reservoir and reflects population-level rates of transmission as well as variations in the environment, host, behavioral, social, and cultural characteristics associated with risk of infection [9]. • Infection can be acquired at any age, but in most regions of the world, primary infection is acquired during infancy and childhood. • CMV seroprevalence is higher in low- and middle-income countries (LMIC) and in individuals of lower socioeconomic groups/regions [9]. Primary or non-primary infections in immunocompetent individuals with CMV are typically asymptomatic or minimally • symptomatic with non-specific findings. CMV can cause severe disease in immunocompromised individuals.
At-risk populations	Overall, lower socioeconomic status (SES) populations are more likely to be CMV seropositive than higher SES populations. Seropositivity among marginalized individuals tends to be higher than in socially advantaged individuals, independent of SES [9]. Living- and work-related environments and selected occupations facilitate exposure, infection, and viral dissemination in the community [9]. • Crowded household • Day-care center workers • Day-care center attendees • Those with multiple sexual partners Persons at risk for developing CMV disease: Immunosuppressed transplant recipients, patients living with AIDS or untreated HIV or other types of T-cell immunodeficiency or receiving immunosuppressive drugs. • Either seronegative or seropositive recipients of organ transplants from seropositive donors can get infected with new strains. Also, 40 % of seropositive stem cell transplant recipients experience reactivation of latent CMV infection. • In untreated HIV infection, CMV is a common opportunistic pathogen. Congenital CMV infection (cCMV) reportedly affects an average of 6.7/1000 live births, but birth prevalence is population-dependent [10,11]. Prevalence of cCMV increases with CMV seroprevalence in women of childbearing age. • In populations with low (≤50 %) or intermediate (50–70 %) maternal CMV seroprevalence, such as in highly industrialized countries, overall cCMV prevalence is estimated to be 4.8 per 1000 live births. • In populations with high (>80 %) maternal seroprevalence, such as in low- and middle-income countries (LMIC), the pooled cCMV prevalence from available data is 14.2 per 1000 live births. • A Brazilian study found that the risk of cCMV was 5–6 times as high for the offspring of seronegative women as for those of seropositive women. However, the majority of infants with cCMV in the study were born to seropositive women [12]. • The exact intrauterine transmission rate of CMV following non-primary maternal infections is unknown because of the difficulty in identifying non-primary infections. However, studies suggest lower intrauterine transmission rates in women with non-primary infection than in women with primary infection. Within a country or region, the prevalence of cCMV can vary according to other population characteristics. • In the US, birth prevalence appears highest (9.5/1000) among black infants [13]. • In Finland, in a population with a maternal seroprevalence of 70 %, cCMV has been reported to be low (2/1000) [14].
Mortality	Primary CMV infection during pregnancy can result in fetal loss or elective pregnancy terminations. CMV has been identified in fetal tissues and placentas in fetal deaths. • In a case-control study in Greece, CMV was detected in 16 % of placental and fetal tissue in cases of intrauterine deaths compared to 3 % of the controls [15]. • In Australia, among 130 stillbirths, CMV was detected in 15 % of fetal tissues and placentas [16]. • CMV has been identified as the most common viral pathogen of infection-related stillbirth in a large US sample [17]. • The 21-year Perinatal Survey in Northern England calculated a rate of 1.1 stillbirths per 100,000 registered births due to CMV [18]. Early infant mortality has been reported in 3–10 % of live born infants with symptomatic cCMV at birth in high-income countries, or 0.3–1.0 % of all infants with cCMV [19]. • A recent study in Brazil reported 4 infant deaths in a prospective cohort of 68 infants [7]. • Among symptomatic neonates in a South African hospital, those with cCMV were more than twice as likely to die as CMV-negative infants, and a much larger difference was observed among infants born to HIV-infected women [20]. • Death certificate data for the United States between 1990 and 2006 reported that cCMV-related deaths were recorded in 0.11 % of all deaths in infants < 1 year old [21]. The overall cCMV infant mortality rate was 8.34 per 1 million infants annually. Native American (aRR = 2.34, 95 % CI, 2.11–2.59) and African American (aRR = 1.89, 95 % CI, 1.70–2.11) infants were more likely to die from cCMV than non-Hispanic white infants. • An analysis of Australian mortality records for 1999–2011 found that infant deaths attributed to cCMV accounted for 0.22 % of all infant deaths [22]. Deaths in early childhood from symptomatic cCMV are also common. Australian children with hospital diagnoses of cCMV had 18.4 times the odds of dying by 5 years of age relative to matched controls [23].

(*continued on next page*)

Table 1 (*continued*)

Feature	Summary and evidence
Morbidity	About 10–15 % of infected neonates are symptomatic at birth. • Congenital CMV disease presents with a wide spectrum of findings at birth. Infants with moderate to severe symptomatic infection can show multisystem abnormalities (thrombocytopenia, petechial rash, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis) with or without central nervous system involvement (microcephaly, neuroimaging abnormalities), chorioretinitis, and SNHL. Infants can be mildly symptomatic with one or two transient findings or isolated hearing loss [4]. • Approximately 40–60 % of those with moderate to severe symptomatic infection will have permanent sequelae such as SNHL, cognitive impairment, cerebral palsy, and vision loss [5]. About 85–90 % of infected neonates have no clinical findings (asymptomatic) at birth. • Approximately 7–11 % will develop SNHL throughout early childhood which may fluctuate or further deteriorate over time [8]. • Neurodevelopmental impairment is uncommon in children with asymptomatic cCMV with normal hearing [6]. Although pre-pregnancy maternal immunity appears to confer substantial protection against intrauterine transmission of CMV, once fetal infection occurs, the cCMV spectrum of clinical presentation and sequela are similar in infants born to mothers with primary or non-primary infection [24]. In LMICs, 18–32 % of cases of SNHL are attributed to cCMV while in HICs, between 4 % and 12 % of SNHL cases in early childhood appear to be due to cCMV [7,8]. Years Lived with Disability associated with cCMV in Belgium, a component of disability-adjusted life years (DALYs) were projected taking into account birth prevalence, life expectancy, and lifelong sequelae [25]. Due to data limitations, some sequelae were not included in the calculations.
Geographical and seasonal distribution	There is no known seasonal distribution of CMV infections. The convergent epidemiology of CMV, HIV, and tuberculosis infections and the ubiquitous and lifelong nature of CMV infection makes these associations of particular interest. Of note, an increased prevalence of cCMV in infants born to women living with HIV has been reported irrespective of whether the infant is infected with HIV. In addition, a worse clinical outcome in infants with HIV-CMV coinfection has been observed [26].
Gender distribution/ Mother to child intrauterine transmission	There is no known gender heterogeneity for any aspect of CMV infection. Both primary and non-primary maternal infections can lead to intrauterine transmission of CMV (cCMV). • The rate of intrauterine transmission to infants born to mothers with primary infection is estimated to be 20–40 %. The exact intrauterine transmission rate after a nonprimary maternal infection is unknown. In one prospective study in Brazil, the prevalence of cCMV among infants born to seropositive women was 0.5 % compared to 2.6 % among seronegative women [27]. During maternal primary infection, intrauterine transmission rates are lower in early than late gestation – 5.5 %, 21.0 %, 36.8 %, 40.3 %, and 66.2 %, during the preconceptional, periconceptional, first, second and third trimesters of pregnancy, respectively. However, the occurrence of sequela (SNHL) is in the opposite direction (22.8 %, 0.1 %, and 0 %, for 1st, 2nd, and 3rd trimesters) [28]. • 50–75 % of cCMV in high income populations and about 90 % of cCMV in less privileged populations, i.e., 40,000 and 600,000 infants, respectively are likely due to non-primary maternal infections [29]. Occurrence of primary and non-primary infection during pregnancy • Well described risks for acquiring CMV infections in seronegative women and transmitting to the fetus include exposure to young children and sexual activity [30]. • Caring for young children and recent onset of sexual activity contribute to an increased risk for cCMV infection following both primary and nonprimary infections in young women [31]. • Nonprimary infections in seropositive women occur due to either reactivation of an existing endogenous virus or after the acquisition of a new virus (reinfection) [32]. • There are limited data demonstrating CMV reactivation in seropositive women. Reinfection with a new variant of CMV by the detection of new antibody reactivities has been described in several maternal populations. • Identifiable factors for cCMV or maternal viral shedding in seropositive pregnant women such as caring for young children, recent onset of sexual activity, crowded household, younger age, black race, and unemployment suggest that exposure to CMV also play a role in nonprimary infection. However, data are still incomplete.

Postnatally acquired CMV infection	CMV can also be transmitted from the mother to child at delivery (perinatally) and through breastfeeding or close contact after birth with people shedding the virus.
	• Breastfeeding is one of the main routes of postnatal CMV acquisition due to CMV reactivation in the breast milk of the vast majority (up to 96 %) of CMV-seropositive lactating women.
	  • Postnatal CMV infections are very frequent (20–60 %).
	  • Acquired CMV infection in full-term newborns rarely causes symptomatic disease. In contrast, extremely preterm and low-birthweight infants, may experience adverse outcomes when infected with CMV.
	• Although CMV can be frequently transmitted postnatally from mother to infant through breastfeeding, the other health benefits of breastfeeding outweigh the risk in general. Although postnatal infection does not have proven long-term consequences for term infants, there may be adverse pulmonary and neurodevelopmental outcomes for extremely preterm infants [33].
	• In populations with high maternal CMV seroprevalence and high breastfeeding rates, postnatal CMV infection is common. It has been reported to reach 55 % within 6 months of age [34] and almost all HIV-exposed African infants by 2 years of age.
	• Due to long-term viral shedding in their fluids and secretions, young infants infected with CMV acquired either in utero or perinatal/postnatally constitute a major source of infection.

Socio-economic status vulnerability (ies) (equity/wealth quintile)	In high-income countries (HIC), cCMV disproportionately affects disadvantaged populations. However, the majority of infants with cCMV around the world live in LMIC.
Natural immunity	After initial infection, a rapid and robust response is mounted involving a wide range of innate, humoral and T-cell mediated immune responses [35]. • The virus is never cleared and establishes a latent infection residing in bone marrow cells for life. • Many virus-encoded immune evasion functions target both innate and adaptive immune responses to CMV resulting in periodical reactivation of latent virus with subclinical infection or disease in immunocompetent and immunodeficient individuals, respectively. There is limited knowledge of the immune responses that protect against intrauterine transmission [36].

Table 1 (*continued*)

Feature	Summary and evidence
	• Potent-neutralizing antibodies targeting the pentameric complex, rapid neutralizing antibody development, and phosphoprotein 65 (pp65)-specific CD4+ T cells have been implicated with reduced risk of intrauterine CMV transmission following primary maternal infection [24]. • CMV trimer- and pentamer-specific neutralizing antibodies in seropositive women during pregnancy did not predict intrauterine transmission in Brazilian women [37].
Pathogenic types, strains, and serotypes	CMV has the largest genome (~235 kb) of all viruses that infect humans. Genetic (high nucleotide variability) and antigenic heterogeneity of circulating CMV strains has been reported with polymorphisms scattered across the virus genome. • High throughput sequencing (HTS) has shown high genetic diversity both within and between hosts [38]. • Infections with multiple CMV strains have been demonstrated in different populations including infants with cCMV and children attending daycare [39]. • However, the significance of this genetic diversity is unclear, but it has been suggested that high diversity may contribute to pathogenesis due to effects on viral immune evasion or dissemination. • It is also unclear whether the genetic diversity has an impact on the development of a CMV vaccine. • A recent study of a small number of HIV-infected mothers and their infants showed compartmentalization of CMV strains between cervical and breast milk [40].
Potential indirect impact	
Anti-microbial resistance (AMR) threat	Resistance of CMV to ganciclovir and valganciclovir has been reported among congenitally infected infants, although data are limited. However, resistance commonly develops during the treatment of immunocompromised patients and negatively impacts outcomes.
Epidemic and outbreak potential	CMV infection is endemic and not considered an epidemic or outbreak-prone infection.
Transmission route/potential	CMV is transmitted by direct contact with the fluids of an infected person. CMV exposure may occur by fomite contamination with CMV, such as toys or surfaces contaminated with CMV-infected saliva in a childcare setting.
Acquired/herd immunity	Little is known about the potential impact of herd immunity by infection or vaccination on the transmission dynamics. It is known that reinfections can and do occur, but the extent to which preexisting immunity protects from reinfection is not known. It is also not clear whether the significant genetic diversity among CMV strains plays a role in limiting the ability of preexisting immunity to provide protection from reinfections.
Co-associated mortality	In patients undergoing allograft transplantation, active CMV infection has been associated with increased rates of bacterial, viral, and fungal diseases, graft loss, and increased mortality and morbidity [41,42]. Intriguing recent data suggest that CMV likely contributes to increasing morbidity and mortality due its potential effect on childhood tuberculosis and long-term health outcomes in infants from areas with high burden of tuberculosis and HIV infection [43].
Economic burden	
Health facility costs/out of pocket costs/ productivity costs	Healthcare costs during early childhood for representative cohorts with cCMV have been estimated as 60–70 % greater than for other children in the Netherlands and Israel [44,45]. However, children with severely symptomatic cCMV will incur much higher costs. A US modeling study projected that children with severe microcephaly and associated brain anomalies resulting from symptomatic cCMV could incur 3.8 million US dollars in costs of care in the first 40 years of life, including skilled home health care [46,47]. Children with disabling sequelae also incur substantial costs to families through out-of-pocket costs and loss of income due to informal care. Costs to the education system, and social services can also be very high, although costs vary across countries.

Studies of potential target populations for CMV vaccination in HIC and LMIC such as universal immunization of infants, adolescent females, and postpartum women are lacking. Therefore, pilot studies are needed, although the outcomes from vaccinating children will take at least 20 years. Studies of vaccination of women of childbearing age will take a shorter time to produce vaccine efficacy data, as the time to pregnancy will be shorter. However, such studies are currently unavailable.

Longer-term assessment of immunologic markers that can serve as surrogates of protection, such as neutralizing antibodies or other immune parameters, need to be assessed as part of such pilot studies, given earlier studies show some reduction in immune parameters with time [62].

3. CMV and its consideration as a public health priority by global, regional or country stakeholders

3.1. Disease burden from cCMV

As described above, cCMV is associated with significant mortality in early childhood and morbidity. Women who acquire primary CMV infection during pregnancy can experience fetal loss or elect to terminate pregnancies. CMV has been identified as the most common viral pathogen of infection-related stillbirth in a large US sample [17]. In HICs, about 3–10 % of live born infants with symptomatic cCMV (0.3–1.0 % of all infants with cCMV) die in early infancy [7,19–22]. Congenital CMV infection is also a leading cause of birth defects and developmental disabilities including hearing loss, vision loss, motor and cognitive deficits. Approximately 40–60 % of those with moderate to severe symptomatic infection will have permanent sequelae such as SNHL, cognitive impairment, cerebral palsy and chorioretinitis [5]. Of the majority of infants with cCMV (85–90 %) with asymptomatic infection, 7–11 % will develop SNHL throughout early childhood which may fluctuate or further deteriorate over time [6]. Therefore, the demand for a CMV vaccine is expected to be significant in HIC based on the disease burden, economic costs (see other sections) and engagement of advocacy groups (see Table 3).

3.2. Screening of newborns and pregnant women for CMV

As most infants with cCMV do not have clinical findings at birth, without universal newborn CMV screening, most infected babies are not identified at birth. In addition, the need for collection of specimens (saliva or urine) within the first 3 weeks of life to distinguish congenital from postnatally acquired CMV infection makes it a challenge to identify infected children. Therefore, numerous US States have mandated cCMV education and/or screening of hearing referred infants (targeted screening program). Recently, Minnesota, US and Ontario and Saskatchewan, Canada began implementing universal newborn CMV screening programs (see Table 3). CMV screening during pregnancy is practiced widely in Israel [63], which also had the world's fastest uptake of COVID-19 immunization [64]. Although this does not address CMV vaccine

Table 2
Overview of potential target and key population(s) and associated delivery strategy (ies).

Target and key population(s)	Delivery strategy(ies)
All children (boys and girls) as part of routine childhood immunization	• Identical to existing rubella immunization program. • The dosing schedule is dependent on vaccine design (1,2,3 or annual vaccination protocols). • Could also reduce transmission to pregnant mothers and other children in childcare (secondary gain). • Most models indicate this to be an effective target population [50,60].
Adolescents as part of routine childhood vaccination consider young women only or all adolescents	• Identical to existing protocols for HPV vaccine. • The dosing schedule is dependent on vaccine design (1,2,3 or annual vaccination protocols) [60]. • Vaccine may also prevent primary infection in young children reducing the number of children shedding the virus.
CMV seronegative women (i.e., CMV IgG negative on Enzyme Immunoassay – EIA or equivalent)	• Prevention of primary CMV infection during pregnancy. • Most women of child-bearing age in LMICs are CMV seropositive and therefore, this approach is only applicable to HICs [56,61].
CMV seropositive women (i.e., IgG positive on EIA or equivalent) who are contemplating pregnancy	• Prevention of non-primary infection from reinfection or reactivation of latent virus. • Most women in LMIC setting are CMV seropositive [56].

support or demand directly, it is indicative that these would be significant markets. Similarly, the high acceptability of newborn or antenatal CMV screening [65–68] while not necessarily indicative of receptivity to immunization, supports the potential for CMV vaccine uptake in these populations (see Table 4).

3.3. Developing and deploying CMV vaccine

Ultimately, recommendations regarding the use of a CMV vaccine will come from the relevant expert advisory bodies (e.g., ACIP in the US, NACI/Provincial immunization committees in Canada, Joint Committee on Vaccines and Immunizations (JCVI) in the UK, Standing Committee on Vaccination (STIKO) in Germany, and National Immunization Technical Advisory Groups (NITAGs) in LMICs). These recommendations, in turn, will affect the funding and uptake of CMV vaccination. Both the recommendations as well as the acceptability and uptake of a CMV vaccine will likely depend on the specific attributes—population/age targeted, safety profile, efficacy, etc.—of the licensed product. Predictions regarding demand for or uptake of a vaccine aimed at girls or women of childbearing age, for example, might be informed by the experience with HPV [69]. Alternatively, a vaccine targeting young children might be expected to have different implications, given the large number of other vaccines administered in the first 2 years of life, and the fact that CMV infection in children is typically asymptomatic or subclinical and would rather primarily provide indirect benefits to pregnant women and their fetuses by reducing transmission. If recommended to be included into the routine childhood immunization schedule, particularly if co-formulated with another vaccine, one might expect a rate of uptake comparable to the rubella vaccine [70,71]. On the other hand, the demand for a CMV vaccine that received a weaker recommendation during childhood and/or represented an additional injection, with or without the requirement for additional medical contacts, would likely be substantially lower [70,71]. The rapid development and implementation process of COVID-19 vaccines, as well as their efficacy and safety profiles, continue to influence vaccine confidence and uptake in complex ways potentially affecting introduction of new vaccines [72,73].

Information is lacking regarding the potential demand for a CMV vaccine in LMIC. Despite the apparent high global burden of cCMV disease (see other Sections), there has been far less clinical research, screening, or advocacy related to cCMV. Furthermore, it is possible that a CMV vaccine could be viewed as a low priority compared with other infections associated with higher mortality. Historically, deployment of vaccines in LMIC lags significantly behind HIC, for example with those to prevent rotavirus, and, most recently, COVID-19. Furthermore, even for those routine childhood vaccines included in the WHO EPI, there are substantial challenges to achieving target immunization rates [74,75]. This highlights the need for additional investments into increasing immunization coverage generally as well as the introduction of new vaccines in LMIC.

The importance of a CMV vaccine was emphasized in 2000 by the US National Institute of Medicine, citing the health and economic burden of cCMV [76]. The US federal government has also shown a commitment to CMV vaccine development by contributing to other guidance documents, funding, infrastructure, and counsel for industry partners [50,51,77]. In contrast, the Canadian government ranked CMV among the lowest priorities for vaccine development in 2015, without elaboration of the criteria or ranking process [78]. Whether priority statements from other governments/health systems are available, or the perceived importance of a CMV vaccine elsewhere is not readily apparent.

Because of the available data on the disease burden, economic costs, and active engagement by numerous advocacy groups, it is expected that the demand for a CMV vaccine will be high in HIC. The efforts by the advocacy groups have led to mandating cCMV education and/or hearing targeted screening programs in several US states. In addition, the state of Minnesota in the US and Ontario and Saskatchewan provinces in Canada have established universal newborn CMV screening programs (see Table 3).

Reliable information about disease burden and the potential demand for a CMV vaccine is not available for LMIC settings except for Brazil. Although studies have shown high prevalence of cCMV in LMIC, studies providing detailed disease burden data have not been conducted and the advocacy groups have not been actively engaged in LMIC.

4. Existing guidance on preferences/preferred product attributes for vaccines against CMV

As described above, the disease burden from cCMV likely has a disproportionately greater impact in LMICs. Estimates of the overall burden of cCMV indicate that most cCMV infections occur in infants born to women with preexisting seropositivity to CMV (non-primary maternal infections). However, at present, a PPC (Preferred Product Characteristics) or TPP (Target Product Profile) have not been developed by WHO or other global priority-setting bodies, and studies to provide reliable data on the disease burden in LMIC have not been conducted (Table 4).

5. Vaccine development

5.1. Probability of technical and regulatory success (PTRS):

5.1.1. Controlled human infection model (CHIM)

Although there is no formal CHIM available, the solid organ transplant (SOT) setting where the date of inoculation of virus is likely the date of transplant in seronegative individuals receiving

Table 3
Overview of non-commercial stakeholders engaged, their interest and potential demand.

Stakeholders engaged	Summary of position/interest
National CMV Foundation (US)	• Extensive discussion of the importance of vaccine development [79], advocacy for increased funding for vaccine development, provide research funding for projects that include CMV vaccinology/immunology, and encouraging state legislatures for mandating education and newborn CMV screening efforts [80].
Canada CMV Foundation	• "A national charity committed to eradicating congenital CMV infection"; • Funding relevant and innovative research–supporting vaccine development, and distributing scientific grants to improve screening and treatment options [81].
CMV Action (UK)	• Support and advocate for families affected by CMV. • Educate professionals, parents, and public about prevention of CMV. • Support the development and implementation of research into CMV. • Estimated annual cost of cCMV [82,83].
StopCMV (Chile)	• Education and Advocacy [84].
FAMILIAS CMV (Spain)	• Give visibility to CMV infection during pregnancy, thus preventing new cases from occurring. • Promote information on preventive measures and carry out serologies for pregnant women [85].
Spolu proti CMV (Slovakia, Czeck Republic, Poland))	• Provides "support for science and research in the field of treatment and vaccine development."[86]
Association CMV; Chanter Marcher Vivre (France)	• No specific mention of vaccine development, but strong focus on prevention and education [87].
Association for Congenital Toxoplasmosis and Cytomegalovirus infections (Japan)	• Promotes education and prevention [88].
Israeli Association for CMV Pregnancy	• The association's vision: "All women of childbearing age in Israel will know how to prevent CMV virus infection."[89]
AntiCito Onlus (Italy)	• Support families affected by CMV. • CMV awareness [90].
CMV Australia	• Support families affected by CMV. • Raise awareness. • Collaborate with Australian research on CMV [91].
European Congenital Cytomegalovirus Initiative	• Biannual international congress on cCMV, including sessions dedicated to vaccines [92].
International Congenital CMV Conference and International CMV Workshop	• Biannual international cCMV meeting, including sessions dedicated to all aspects of vaccine development [93].
Congenital Cytomegalovirus Public Health and Policy Conference	• Biannual international conference: The goal of the conference is to present the latest research on diagnosis and treatment, raise awareness, delineate prevention efforts, provide information about early intervention options, and disseminate family support resources in an effort to reduce the number of babies born with CMV and connect families affected by CMV with the resources they need to improve their quality of life [94].
International Herpesvirus workshop	• Annual international scientific meeting that includes a focus on CMV vaccine development [95].
National Center for Hearing Assessment and Management and Utah State University	• Serves as the Early Hearing Detection and Intervention, National Technical Resource Center (EHDI NTRC) funded by [96] the [97] United States Department of Health and Human Services [98].
Baylor College of Medicine National Congenital CMV Disease Registry (US)	• Their mission is to provide continuous research on the biology, epidemiology, clinical manifestations, methods to diagnose, treatment and prevention of congenital CMV disease as well as to raise public awareness of the life-long impact it may have. Also strives to improve the quality of life of children with cCMV through prevention of disease by providing community resources and a parent support worldwide network [99].
Institute of Medicine (US)	• Concluded that CMV vaccine development was a Level I (highest/most favorable) priority [76].
Centers for Disease Control and Prevention (US)	Specific activities include: Research • Evaluating the various laboratory tests for newborn screening for CMV; • Determining the most effective screening approaches to identify babies with cCMV; • Characterizing the impact of the disease in various populations; and • Assessing the long-term outcomes of children with cCMV. Education • Updating the CDC website [100] regularly to include the latest information about cCMV; • Developing and disseminating [101] – including fact sheets, graphics and videos – to educate pregnant women, parents, and healthcare providers about cCMV; and • Promoting June as National CMV Awareness Month [102], and work with partners to ensure that messages about cCMV reach healthcare providers, pregnant women, and parents of children born with cCMV [103].

(continued on next page)

Table 3 (*continued*)

Stakeholders engaged	Summary of position/interest
National Vaccine Advisory Committee (US)	• A CMV vaccine to prevent congenital infections, neurologic damage, and deafness should remain a high priority, as recommended by the Institute of Medicine. To accomplish this goal, the strong support of government agencies will be required [77].
Office of Vaccines Research and Review, FDA (US)	"Developing a vaccine to prevent CMV disease is recognized as a high public health priority." Report describes how FDA has developed platforms to support the development of a CMV vaccine [50,51]: • PCR assay • Neutralization assay • Immortalized cell lines for use in CMV assays
Office of Vaccines Research and Review, FDA (US)	• Reports from a meeting convened by the FDA of stakeholders: "On January 10–11, 2012, representatives from government, industry, academia, patient advocacy groups, and professional societies met to identify and begin to address challenges to CMV vaccine development. This manuscript summarizes available data, considerations, and proposals for future research and clinical trials discussed by meeting participants." [50,51]
US State governments	• Numerous US States require education and/or newborn screening for congenital CMV infection. Minnesota recently adopted universal newborn screening. • Does not directly address vaccination but shows interest and investment in the problem of cCMV, and therefore indicates potential support for CMV vaccination. • Summarized in [104].
Government of Ontario, Canada	• Universal newborn screening program since 2019 • Does not directly address vaccination, but shows interest and investment in the problem of cCMV, and therefore indicates potential support for CMV vaccination [105].

Table 4
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs.

Product attribute	Minimal characteristic, if described	Preferential characteristic	Publishing entity
Indication	Prevention and/or modification of sequelae associated with cCMV	• Prevention of cCMV infection	[76]
Target population(s)	Women of childbearing age	• Immunization of male and female adolescents • Routine immunization at 12–18 months (boys and girls) • Women prior to pregnancy	[76]
Outcome measure(s) and target efficacy	Not determined	• Minimal efficacy standards have not been defined • The IOM report assumed 70 % efficacy [76]	[76]
Safety profile	Not defined	Safety and reactogenicity comparable to existing routine vaccines	[106]
Number of doses and schedule	Not determined	TBD	
Route of administration	Not determined	• All of the vaccine candidates currently in testing are Injectable (intramuscular)	[106]
Duration of protection	Through reproductive age	• Duration of protection should extend through reproductive age	[106]
Co-administration with other vaccine		• Should not interfere with other vaccines when co-administered	[106]
Product stability and storage		• Vaccines and diluents that can be stored for extended periods at temperatures above + 8 °C • Vaccines with data and licensing allowing for higher temperature storage.	[106]
Vaccine presentation		• Meet WHO generic preferred product profile for vaccine presentation to minimize number of steps and potential for error during preparation and administration	[106]

the organ from seropositive donors, has provided useful information. To date, such studies in SOT remain the only studies in humans that have identified a correlate of protection from CMV disease. In addition, in CMV seropositive SOT recipients, reactivation of recipient CMV and reinfection with donor virus can lead to symptomatic infection [107]. However, the relevance of data from studies of the impact of candidate vaccines on CMV infection and associated disease in SOT recipients to modifications of the natural history of cCMV is unclear.

5.2. CMV infections in solid organ transplant (SOT) patients

Natural history studies show that CMV appears in the blood (viremia) of SOT patients in the first weeks after transplant and increasing levels can be associated with serious end-organ disease in lungs, liver, gastrointestinal tract or retina [108]. These adverse outcomes can be routinely prevented by treating SOT recipients with ganciclovir (or its prodrug valganciclovir) in one of two ways, prophylaxis or preemptive therapy [108].

Clinical management of these patients with CMV infection relies on monitoring viral load level that triggers initiation and the duration of treatment [108]. These viral load parameters are sufficiently robust to be accepted by regulators to define the primary endpoint in phase 2 and phase 3 randomized clinical trials of antiviral drugs [109]. Protocols utilizing preemptive therapy have allowed experimental CMV vaccines given pretransplant to be compared with placebo for their capacity to alter these post-transplant measures of viral load using a pharmacodynamic study design.

In a double-blind, randomized trial, Griffiths and colleagues gave placebo or a vaccine consisting of glycoprotein B (gB) plus MF59 adjuvant to seronegative or seropositive patients awaiting transplantation of a kidney or a liver at a single clinical site [110]. The vaccine induced high levels of antibody against gB and boosted the gB titers of those who were already seropositive. When the patients proceeded to transplantation, the parameters of viral load were reduced in vaccine recipients [110]. A correlate of protection against CMV viremia was the titer of antibodies that individuals made against gB [110]. Importantly, the protection was not mediated by antibodies with neutralizing activity [110,111]. However, once the vaccine recipients proceeded to transplant, those who had received vaccine produced neutralizing antibodies more rapidly than did those who received placebo [112]. This suggests that vaccine primes the human immune system and that challenge with an infected organ boosts that response.

5.3. Women of childbearing age

A phase 2 double-blind, randomized, placebo-controlled study of gB/MF59 vaccine in seronegative postpartum women reported that the vaccine provided approximately 50 % protection against acquiring primary infection [62,113]. However, the vaccine efficacy waned during the first 15 months of the study [62]. The same vaccine given to teenagers failed to provide protection from primary infection compared to placebo [114]. Studies of the immune correlates of protection conferred by this vaccine in adult women showed that antibodies able to mediate virion phagocytosis correlated with protection [115]. In this study of only vaccine recipients, there was reduced viral load in the saliva of vaccinees and evidence that protection was better against strains that had the gB genotype 1 background found in the Towne vaccine [116]. In studies of serum samples from both the adult and adolescent vaccine recipients, IgG bound preferentially to gB presented at a cell surface rather than the soluble form used in the vaccine [117].

In summary, the gB/MF59 studies in women show similarities in the immunogenicity of this vaccine with findings from SOT recipients given the same vaccine. Neutralization of cell-free virus may not correlate with protection suggesting that assays of other functional antibody activities may identify correlates of protection induced by vaccines against this virus. The parameters that are thought be needed for the development of an effective CMV vaccine are shown Table 5.1.

Estimates of overall burden of cCMV worldwide indicate that vast majority of cCMV infections that occur in maternal populations with high CMV seroprevalence likely follow nonprimary maternal infections and that the majority of infants with cCMV who develop sequelae are born to women with non-primary CMV infections [119,126,128]. It is unclear whether candidate vaccines that induce responses similar to those following natural infection provide protection against both infection and outcome of cCMV in infants born to women from populations with high CMV seroprevalence.

5.4. Overview of the vaccine candidates in the clinical pipeline:

The current CMV vaccine candidates that are in various stages of testing are shown in Fig. 1. Multivalent candidate vaccines for CMV that are being evaluated include those targeting envelope glycoproteins of the virus, glycoprotein B and the pentameric glycoprotein complex (gH,gL,Ul128,Ul130-131), as well as candidate vaccines that express glycoprotein B together with nonenvelope virion proteins (ppUL83/pp65) together with the nonstructural protein (ppUL123/IE-1) in some formulations (see Table 5.2). Most vaccine development programs have focused on vaccine formulations that induce antiviral antibodies, specifically antibodies that neutralize cell free virus. However, the two controlled trials in which CMV hyperimmune globulin containing virus neutralizing antibodies administered to pregnant women failed to demonstrate a significant impact on the rate of cCMV or outcomes in infants with cCMV as compared to placebo [133,134]. Multivalent vaccines that induce CD4/CD8 + T lymphocyte responses by inclusion of dominant CD8 + T lymphocyte targets such as ppUL83 and ppUL123 have been shown to also induce robust CD8 + T lymphocyte responses. However, the importance in CMV specific CD8+ (or CD4 +) T lymphocyte responses in modification of the natural history of cCMV remains unclear. Lastly, a candidate vaccine consisting of intact virus with restricted replication has also entered clinical trials and has been shown to induce antiviral antibodies and a spectrum of T lymphocyte responses.

In Table 5.2, candidate vaccines that have been developed to alter the natural history of CMV infections in pregnancy are listed. The target populations to receive a CMV vaccine could include all infants (similar to rubella vaccine), adolescent females, seronegative and possibly seropositive women, and women in the postpartum period (with the aim of preventing cCMV in future offspring). Importantly, these candidate vaccines represent only a subset of the current CMV vaccines under development, many of which have been designed and formulated to modify CMV infections in patients undergoing solid organ or hematopoietic cell transplantation. Whether these vaccines could be deployed in women of childbearing age will be determined in future clinical trials.

6. Health impact of a vaccine on burden of disease and transmission

The impact of future vaccines and hygiene interventions has been addressed by several recent modeling studies [61,113,141–144]. In view of the large uncertainties with respect to the quantitative contributions of different transmission routes, these studies include a broad range of modelling assumptions (Table 7). Also, given uncertainties with respect to target populations for future vaccines and vaccination schedules, the models differ considerably with respect to presumed target groups, vaccination coverages, and vaccine effectiveness.

6.1. Summary of knowledge and research gaps in modeling health impact on disease burden and transmission

- Model-based vaccine evaluations are not available for LMICs. In view of the significant differences in the epidemiology of cCMV between HIC and LMIC, this is an important research gap that needs to be addressed.
- Rates of intrauterine transmission and attributed burden from primary and non-primary infections are not well defined, and likely vary depending on maternal seroprevalence and exposure to young children.

Table 5.1
Overview of parameters that inform scientific feasibility of developing an effective vaccine for LMIC public market use.

Parameter	Issues and Evidence
Diagnosis/case ascertainment	• Available diagnostic methodologies are robust, validated and widely available. • Newborn screening required for case ascertainment as 90 % congenitally infected infants exhibit no clinical findings [118–120].
Biomarkers/Correlates of risk/protection – Maternal infection	• Risk factors for maternal infection (both primary and nonprimary infection) include young age, exposure to young children, and sexually transmitted infections (STIs). • Immune correlate(s) of protection: Only limited definitive data are available. • Specific antibody activities and outcomes reported but rigorous validation as correlates of protection not available [12,31,37,117,121].
Sero-epidemiological data	• Multiple natural history studies have shown that CMV immunity prior to conception provides substantial protection from intrauterine transmission. In regions of the world with high maternal CMV seroprevalence, cCMV prevalence and outcome following cCMV are similar to those in populations with much lower maternal prevalence of CMV infection, suggesting that a single CMV vaccine may not be effective in all populations. • Overall, a consensus about the importance of immunity acquired following natural infection in prevention and/or modification of congenital infections is lacking [12,122–131]

Clinical Endpoints	Potential endpoints include:
	• Prevention of primary infection and/or reinfection in children or women of childbearing age. It is not clear whether different vaccine candidates are needed to achieve these goals.
	• It may be necessary to:
	  • Control of infection (viremia, viral shedding, infectiousness).
	  • Intrauterine transmission
	  • Prevention of sequelae that occur in children with cCMV

Controlled human infection model (CHIM)	Not available
Opportunity for innovative clinical trial designs	• Clinical trials in populations at increased risk for acquisition of CMV infections and seroconversions during pregnancy. • Limited number of studies in populations with high CMV seroprevalence [12,132].
Regulatory approach(es) including potential accelerated approval strategies	• Identification of informative surrogates for prevention of intrauterine transmission and/or CMV related sequelae in infected children, especially those born to women with non-primary infection, could accelerate clinical trials and speed approval. • Early approvals are most likely in North America and Europe.
Potential for combination with other vaccines	• Possible, but will be dependent on durability of protective immunity provided by candidate vaccines.
Feasibility of meeting presentation and stability requirements	• Dependent on individual vaccine candidates.
Vaccine platform	• Vaccine platforms are likely amenable for large scale production. Strain variability will not limit selection of vaccine platforms (see Table 5.2). The platforms could potentially include mRNA, subunit, and replication incompetent virus.
Large scale manufacturing capacity/interest	• Likely required if vaccines are introduced into populations with greatest disease burden.

- Data on duration of CMV shedding in young children is based on small studies. Although some models rely heavily on the assumption that duration of infectiousness is much longer in children with primary infection than in adults, only limited evidence is available currently.
- In general, CMV has a complex and poorly understood epidemiology, and the quantitative contributions of different transmission routes to overall transmission are at present subject to considerable uncertainty. This may render all modeling exercises and in particular assessments of the impact of vaccination on reduction of cCMV somewhat speculative.
- Most modeling studies assume that cCMV causes the main burden of disease. However, a long-term impact of latent CMV infection has been linked to immunosenescence in older individuals since it diminishes the abundance of naive and early memory T-cells [147–150]. This could potentially have a profound impact on the health and effectiveness of vaccination in older persons. However, this document focuses on cCMV, and the effects of CMV infection in other populations are not taken into account in transmission models.

7. Social and/or economic impact of a vaccine

The potential economic impact of a CMV vaccine resulting from the prevention of cCMV has been assessed in several modeling studies that employed varying assumptions about disease burden and vaccine efficacy (Table 8). A 2021 review article discussed these studies as well as estimates of the economic burden of cCMV in general [45]. The burden of cCMV, although substantial, is difficult to estimate precisely, hindering the assessment of models of the potential benefits of vaccination. Neither the social impacts of cCMV on families nor the economic impacts of a CMV vaccine on high-risk individuals/populations have not been systematically assessed.

7.1. Summary of knowledge and research gaps in modeling studies that measure anticipated socio-economic impact of the vaccine

- Data on the overall economic impact of cCMV on families and societies, including parental time use, are lacking.
- A number of modeling studies that examined potential benefits (economic and other) of a CMV vaccine used assumptions about cCMV disease burden that do not appear fully consistent with published data. In addition to these limitations and biases, data for representative cohorts of children with cCMV are limited [45].
- Furthermore, models have compared economic benefits of a CMV vaccine administered to different target population groups. One of the modeling study examined adolescent females as the target group [151].

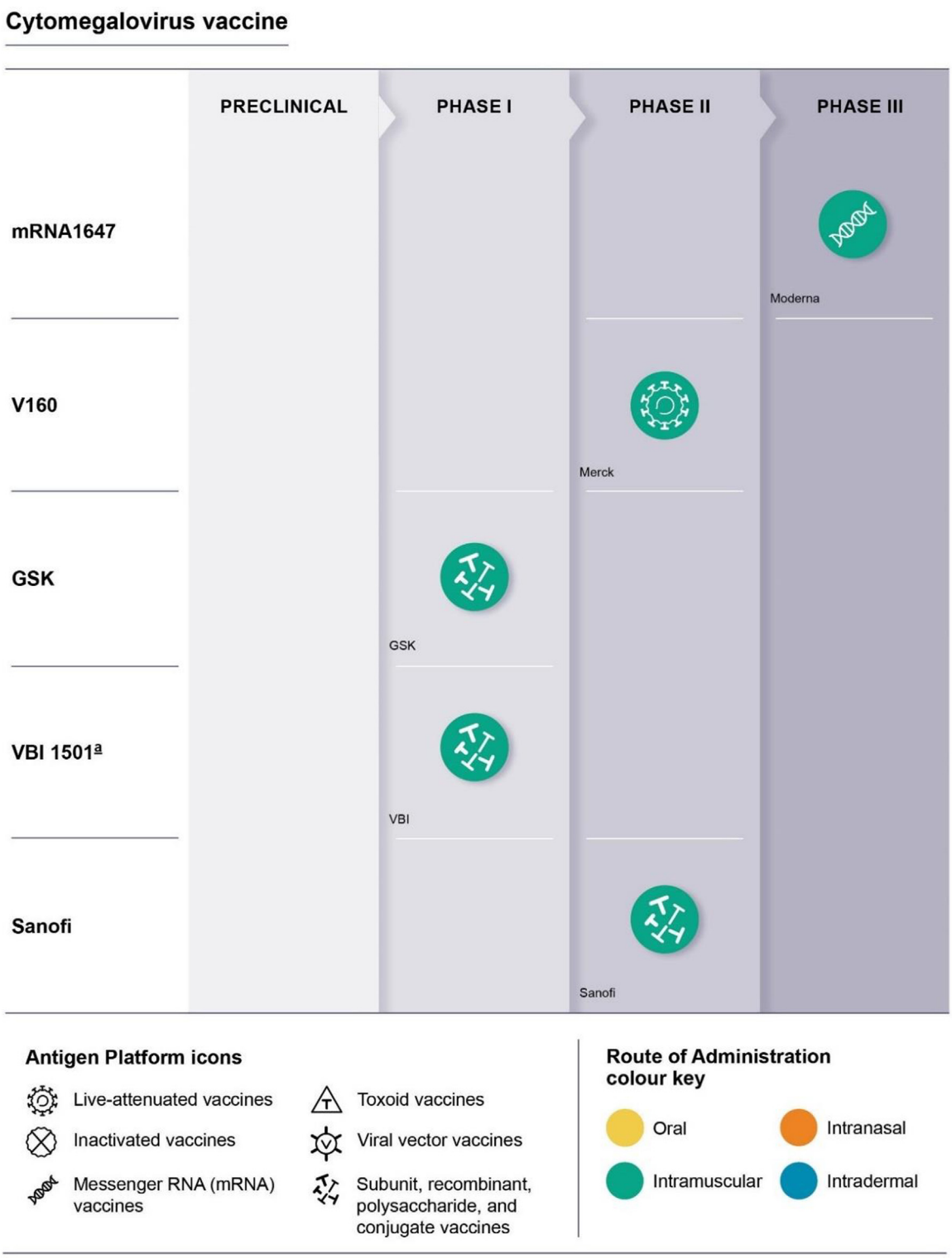

Fig. 1. Overview of vaccine candidates in the clinical pipeline.

8. Policy considerations and financing

A WHO policy recommendation for the use of CMV vaccine is a prerequisite for WHO Prequalification, and for financing by Gavi, the Vaccine Alliance. A WHO policy recommendation would be developed based on a review of evidence by the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization covering the established Evidence-to-Recommendations (EtR) criteria of public health problem, benefits and harms, equity, feasibility, acceptability, resource use, and values and preferences (Table 9) [155]. These criteria generally align with those used by Regional Immunization Technical Advisory Groups (RITAGs) for regional-level vaccination recommendations and National Immunization Technical Advisory

Table 5.2
Overview of vaccine candidates in clinical trials.

Candidate	Antigen/Platform	Developer	Phase	Route of administration/ no. doses[1]	Presentation/ Stability	Clinical Trials Ref.[2]
mRNA1647	gB/Pentamer (gH/gL/UL128/UL130/ UL131a); mRNA	Moderna	II/III	IM (days 1,57, 169))	Lyophilized/saline reconstituted	[135]
V160	Replication defective CMV; Adjuvanted	Merck	II	IM (0,2,6 months)	Adjuvanted formulation at 4 °C	[136,137]
GSK	gB/Pentamer (gH/gL/UL128/UL130/ UL131a); Adjuvanted	GSK	I	IM (0,2,6 months)	Adjuvanted recombinant protein	[138]
VBI 1501[a]	gB/VLP (virus like particles)	VBI	I	IM (days 0, 58, 168)	Alum adjuvanted VLP	[139]
Gb	gB; Adjuvanted	Sanofi	II	IM (0,1,6 months)	Oil:water emulsion adjuvanted recombinant protein	[140]

1) IM, intramuscularly.
2) Clinical trials registered in: https://clinicaltrials.gov/.

Groups (NITAGs) in individual countries for national-level vaccine use recommendations. It is expected that the recommendations of these expert advisory groups would inform the ultimate policy decisions made by countries' ministries of health and national public health agencies about whether and how to introduce a new vaccine against CMV, including what level of funding to commit to such efforts.

National-level recommendations will likely depend on the country's epidemiological context, existing vaccination schedule/ delivery platforms for potential target populations (e.g., infants, adolescents, and/or women of childbearing age), cost-effectiveness and affordability considerations relative to other potential vaccine and non-vaccine health sector investments. Given the prevalence of cCMV globally across both HIC and LMIC markets, there is dual-market potential for CMV vaccines to be of interest to both self-procuring countries and countries receiving external donor support for vaccine procurement.

In HICs, vaccine licensure would likely follow established pathways of national or regional regulatory authorities (e.g., U.S. Food and Drug Administration (FDA); European Medicines Agency (EMA)), with recommendations for vaccine use formulated by NITAGs (e.g., Advisory Committee on Immunization Practices (ACIP) in the U.S., National Advisory Committee on Immunization (NACI) in Canada, Joint Committee on Vaccines and Immunization (JCVI) in the UK, Standing Committee on Vaccination (STIKO) in Germany) and established as policy by national public health agencies and national health insurance schemes, depending on the country context. The financing of a CMV vaccine in high-income countries would likely follow that of other vaccines recommended for similar age groups, with public purchasing for some or all recommended populations and/or provision through private health care systems with payment from public or private health insurance, depending on the country.

Although the absolute burden of cCMV is larger in LMICs, introduction of a CMV vaccine in such settings may depend heavily on whether financial support is available from Gavi. Should a CMV vaccine become available, it is expected that Gavi would evaluate it through its Vaccine Investment Strategy (VIS), which is delivered on a 5-year cycle. The VIS process is centered on a robust and transparent mechanism for evaluation of vaccine products based on a number of criteria, which include elements such as health and economic impact, contribution of equity and social protection, feasibility and implementation costs. It is assumed that Gavi will apply similar criteria to inform its future Vaccine Investment Strategy (VIS) as have been applied in the most recent VIS (VIS 2018) for vaccines for endemic disease prevention through planned, preventive immunization for the period 2021–2025 (Table 9) [156]. If a CMV vaccine meets the criteria of the Gavi VIS evaluation framework and is approved by Gavi's Board for financial support, a CMV vaccine introduction program would be important in providing access to the vaccine to Gavi-eligible LMICs through Gavi's market shaping and co-financing policies. WHO Prequalification would be an important signifier of vaccine quality and safety to permit procurement by UNICEF with funding from Gavi for Gavi-eligible countries, as well as for non-Gavi-eligible middle-income countries who may procure via UNICEF or self-procure. Middle-income countries that are ineligible or would graduate from Gavi support by the time that a CMV vaccine becomes available would be required to self-finance vaccine purchase, potentially at a price higher than that made available to Gavi-eligible countries, which may be an impediment to introduction as has been observed for other new vaccines.

Many of the evidence considerations in the WHO SAGE and Gavi VIS are likely to apply to country-level decision making. For this reason, generation of the data and evidence that will be needed for both policymaking (whether at the national or global level) and Gavi financing can accelerate the pathway to vaccine introduction and use in countries and target populations with the greatest need.

Some additional principles that may impact policy and vaccine introduction decision-making include [157]:

- Integration of CMV vaccine within existing delivery platforms appropriate to the selected target age group for optimal cost-effectiveness and feasibility of implementation.
- National decision-making bodies frequently require evidence of vaccine safety and effectiveness in similar populations before considering their use in the public sector, even for vaccines already licensed locally, or in other countries.
- For some countries the possibility of government uptake of a vaccine will be greatly enhanced if it is manufactured locally, particularly for countries with national policies of self-reliance in vaccine production.
- If a CMV vaccine can be combined (co-formulated) with another vaccine that has a compatible delivery strategy and schedule, this will significantly impact its feasibility of delivery and cost-effectiveness [157].

Table 9 outlines some of the criteria that are likely to be important for policy and financing decision making, based on the WHO SAGE EtR framework, Gavi's VIS criteria and WHO's "Principles and considerations for adding a vaccine to national immunization program". Available evidence for each WHO SAGE criterion is

Table 7
Overview of modeling studies that measure health impact on disease burden and transmission.

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/interpretation
What is the critical vaccination coverage for eradication of CMV from the population? [113]	Age-dependent transmission model with no infection feedback loop. Model is fitted to age-specific serological data.	Simple model with constant infection pressure or with age-dependent but infection-independent infection pressure. No sensitivity analyses available. Type I mortality is assumed. No model documentation available.	Population: United Kingdom. Main assumptions: Permanent immunity after primary infection, i.e. reinfection and reactivation are not included. Vaccination at birth, 80–100 % efficacy, lifelong immunity. Herd effects not included.	Vaccination impact estimated by comparing the number of CMV infections at 16–40 yr before and after vaccination. Results suggest that the critical vaccination coverage for a perfect vaccine is in the range 59 %-62 %, owing to low transmissibility. Results depend critically on assumption of no reinfection and no reactivation.
What are optimal ages for a two-dose vaccination scheme to reduce the incidence of cCMV? [141]	Age-dependent transmission model with infection feedback loop and reactivation but no re-infection. Model is fitted to age-specific serological data.	Dynamic transmission model. The model includes ad hoc formulations of human contact patterns based on CMV age-specific seroprevalence data, and assumes that reactivation occurs on average after 20 years. Vaccination coverage is assumed to be high (90 %). Data is not available. No code is available but model description is available.	Population: Brazil. Main assumptions: No re-infection but occasional reactivation. Various levels of vaccine efficacy (10 %, 30 %, 50 %, 70 %), 90 % coverage, and 2, 10, 20 years or lifelong immunity.	Modeled numbers of cCMV infections with and without vaccination. If immunity lasts lifelong, the best strategy is to vaccinate infants. With waning immunity, vaccination at age 10–11 years is more effective; if duration < 10 years, immunizing infants leads to more cCMV cases. Optimal schedule is doses at both 2–6 months and 10–11 years. Unclear to what extent the results depend on assumed contact patterns, long time to reactivation (20 years), and absence of reinfection. Time to achieve certain cCMV reductions not described.
What is the impact of vaccination on incidence of cCMV and prospects for elimination in countries with moderate to high baseline seroprevalence? [142]	Age-dependent transmission model with infection feedback loop, reactivation and reinfection. Model is fitted to age-specific serological data.	Dynamic transmission model. A distinction is made between primary infection and reinfection/reactivation. Human contact patterns are included. Broad range of vaccine efficacies, coverages, and durations of immunity are considered. Model description is provided but source code is not. The model is formulated using a realistic age-structured model.	Population: United States/Brazil. Key assumptions include a low proportion of cCMV infections due to primary maternal infections, i.e. most are due to reinfection or reactivation. Assumed high infectiousness and contact rates among children ages < 5 years. Duration of vaccine protection varied from 0 to 50 years.	Modeled reductions in the annual number of cCMV infections, overall and by type of infection. In the long run the optimal vaccination strategy is infant vaccination in both countries, potentially resulting in elimination. Increased cCMV was not observed in any scenario, except for a relative increase in proportion attributed to primary maternal infections in Brazil. In the short term the optimal vaccination strategy is less clear.
What is the impact of adolescent vaccination on incidence of cCMV? [143]	Age-dependent transmission model with infection feedback loop, reactivation and reinfection. Model is fitted to age-specific serological data.	Dynamic transmission model. The model includes infectious classes for primary infection, reactivation, re-infection, and reinfection and reactivation. Estimates of the force of infection are based on US serological data, and contact patterns are based on estimated human contact rates. The model uses a realistic age-structured model. No details are provided on model structure or fitting procedure.	Population: United States. A distinction is made between scenarios with vaccination of females only versus males and females, and seronegative only versus seronegative and seropositive individuals. No increase in cCMV observed after vaccination with vaccines providing temporary immunity.	Modeled reductions of cCMV by adolescent vaccination, either females only or both sexes. This is proposed as an alternative to optimal infant vaccination. Estimated age-dependent force of infection, duration of infectiousness, number and relative decreases in cCMV infections in 10, 20, 50, and 100 years post-vaccination.
What is the optimal age for screening and vaccination to reduce the incidence of cCMV-related disability? [144]	Age-dependent transmission model with infection feedback loop, and infectious primary infection. No re-infection or reactivation but individuals remain lifelong infectious after a primary infection. Primary infection can be contracted vertically or horizontally. Calibration to US seroprevalence data.	Dynamic transmission model; distinguishes between susceptible, primarily and latently infected classes. Assumes higher contact rates among newborns and other age groups, decreasing by age until 7 years-old, and remaining constant after that. The model is formulated in terms of differential equations using a realistic age-structured model.	Population: United States. Focus is on screening and vaccination of susceptible individuals to identify and vaccinate CMV-susceptible women, in order to prevent cases of cCMV-related disability. Broad ranges are considered of vaccination ages (0–35 years), screening coverages (20 %, 60 % and 90 %), vaccine coverages (20 %-90 %), vaccine efficacies (50 %-95 %),	Impact of vaccination estimated using cumulative number of cCMV-related disability prevented over a period of 20 years for various vaccination scenarios. Provides an estimate of the probability of intrauterine transmission by breastfeeding (0.14). For most scenarios, the optimal age of vaccination was between 19 and 21 years of age.

(*continued on next page*)

Table 7 (*continued*)

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		Vaccination only works in seronegative persons. No code is available but a fairly complete model description is available in the paper (supplementary material).	and durations of immunity.	
What is the impact of different vaccination strategies in comparison to hygiene interventions in reducing the incidence of cCMV? [61]	Age-dependent transmission model with infection feedback loop, reactivation and reinfection. Model is fitted to age- and sex-specific serological data.	Dynamic transmission model with two infectious classes, after primary infection and after reinfection or reactivation. Estimates of human contact patterns are included. Broad range of vaccination coverages are considered. The model is formulated using a realistic age-structured (RAS) model. Data and model code are available.	Population: The Netherlands. Parameters are estimated from cross-sectional serological data and a birth cohort study [145]. Various vaccination strategies, including infants in the first year of life, adolescent boys and girls at the age of 10 years, adolescent girls at the age of 10 years, or women of reproductive age are considered.	Estimated reduction in cCMV cases in 10, 25 and 50 years following universal vaccination of females with a vaccine preventing primary infection, reinfection, and reactivation. Reduction range of 3–8 %, but ~ 70 % with vaccination during pregnancy, preventing ~ 50 thousand DALYs. Burden of disease estimates using DALYs were based on uncertain earlier estimates [25]. Evidence on the effectiveness of hygiene interventions for the prevention of cCMV is limited.
What is the impact of modestly protective cytomegalovirus vaccination of young children for preventing congenital infection? [146]	Stochastic microsimulation model to describe infection dynamics of CMV in a population of approximately 10,000 individuals. Age and sex-specific data fitted to US seroprevalence data.	Individuals can progress through susceptible, primary infection, or reinfection stages, with varying levels of infectiousness and immunity at each stage. Infectiousness and immunity are boosted following each infection event and wane over time. Includes contact patterns, and vertical transmission can occur especially due contact between mother and infant during breastfeeding or diaper changing. Simulated vaccination with similar level of immunity induced by natural infection.	Population: United States. Vaccination at 2 months, or 2, 12 or 25 years of age, and assumed either 33 %, 67 % or 100 % vaccine uptake; with or without booster doses at 2 or 12 years of age. Assumed vertical transmission due to primary maternal infection of 33.4 %, and estimated 9.4 % following reinfection, and 0.4 % following reactivation.	Post-infection immunity reduces infectiousness and risk of (re)infection. Predicts ~ 50 % women remain in the chronic stage of infection and ~ 2 % of uninfected women experience a primary infection during pregnancy; with 85 % of maternal infections transmitted by children. Estimates 49 % of cCMV due to primary maternal infection, and 51 % of cCMV due to non-primary maternal infection (39 % reinfection, and 61 % chronic infection). For sterilizing vaccine-induced immunity, vaccination at 2 months led to ~ 70 % to 99 % decline in cCMV over 50 years for 33 % to 100 % vaccine coverage, respectively. Impact decreases with increasing age of vaccination. With a vaccine that provides the equivalent of post-infection immunity, vaccinated children will still have breakthrough infections, but duration of viral shedding is reduced, which could effectively reduce the prevalence of cCMV.

described in previous sections of this VVP, as referenced in Table 9. Quantitative estimates for the metrics used in the Gavi VIS are not yet available.

9. Access and Implementation Feasibility

Possibility of Implementation within existing delivery systems

- As described in previous sections, the birth prevalence of cCMV varies depending on country of residence, maternal seroprevalence, and other population characteristics (race, ethnicity, and socioeconomic status). The cCMV disease burden has been shown to be higher in urban disadvantaged population in HIC and in LMIC [4,7,9,13].
- Consideration should be given to different target populations in different countries based on risk-assessment and existing country-specific immunization schedules [50,56].
- While the ideal target population is yet to be determined, (infants vs young children vs adolescents vs women of reproductive age and seropositive vs seronegative recipients), the possibility of implementation of a CMV vaccine within existing delivery systems would be **moderate-high** and will vary

Table 8
Overview of modeling studies that measure anticipated socio-economic impact of the vaccine.

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/ interpretation
Cost-effectiveness of CMV vaccination strategy of pre-adolescent females at age 11 years [151]	Cost-effectiveness analysis	Decision-tree model to assess clinical and economic impacts of universal vaccination of adolescent females against CMV compared with no vaccination. Cost estimates included productivity losses from premature mortality and permanent disability. Costs and outcomes discounted at 3 % per year. Static model, no indirect effects of vaccination on infections. Included sensitivity analysis to determine threshold vaccine efficacy; and one-way sensitivity analysis for all probability variables, costs and utilities documented in supplementary files.	Population: United States. Hypothetical cohort of 100,000 11-year-old girls who had not been previously vaccinated against CMV. Vaccine strategy assumes 100 % coverage is needed to provide protection against primary CMV infection during pregnancy (likely 3 doses). Prior exposure reduced risk of cCMV by 95 %, and all infants born to women without primary, re-infection or reactivation were assumed to be without cCMV sequelae. Vaccine efficacy range 80–99 %, with costs equivalent to HPV. Lifetime direct and indirect costs for hearing loss ($417,062), vision loss ($593,988), and intellectual disability ($1,099,529) in 2010 USD. Adverse events from vaccination assumed to be short-lived and no reduction in QALYs. Loss of utility of 0.14 for hearing loss, 0.41 for intellectual disability, and 0.19 for vision loss	• Net health benefits between strategies of vaccinating and not vaccinating were calculated as quality adjusted life years (QALYs). • In almost all scenarios, vaccination was both less costly and resulted in greater health benefits than no vaccination, unless efficacy $\leq$ 60 %. • CMV vaccination strategy over not vaccinating – cost savings of 32.3 million dollars with a net gain of 1823 lifetime QALYs for the infants born to mothers in the cohort. • Many of the model assumptions appear inconsistent with published evidence. For example, the authors posited deaths among infants with asymptomatic cCMV. The assumed prevalence of cCMV, 1.1 %, was more than twice the actual U.S. prevalence. The assumed share of symptomatic infections, 4.5 %, was less than half the actual fraction. For further information on the study assumptions about frequencies of outcomes and costs, see [45]. • Inclusion of productivity losses from a human capital perspective is not consistent with the perspective of many policy makers. If only direct medical costs were assessed, results would have likely shown decreased benefits from vaccination.
Cost-effectiveness of two vaccination strategies of adolescent girls at age 14 years – routine vaccination of all females and serologic screening followed by targeted vaccination of seronegative females [152]	Cost-effectiveness analysis compared targeted vaccination to a practice of hygiene counseling to prevent CMV seroconversions during pregnancy and compared routine vaccination to targeted vaccination strategies.	Cost-effectiveness assessed from payer (French national health insurance) perspective considering only medical costs. Costs and outcomes discounted at 3 % per year. Markov decision-tree model to assess vaccination: S1 - hygiene counseling and no vaccination. S2 - routine vaccination of females aged 14 years. S3 - screening and vaccination of seronegatives Static model with no indirect vaccine effects. Included one-way and two-way probabilistic sensitivity analyses using 10,000 simulations.	Population: France. Hypothetical cohort of 390,000 females aged 14 years. Base-case assumptions included 20 % seroprevalence, 0.035 % seroconversion rate per week during pregnancy, 41 % vertical transmission risk, and 50 % vaccine efficacy in maternal seroconversion with no effect on fetal transmission among those who seroconvert. Vaccine coverage (all 3 doses) of 100 % in S2 and 80 % in S3; 100 % screening coverage in S3. Symptomatic cCMV in 13 % of cases. Intellectual disability in 18 % of symptomatic and 7 % of asymptomatic cases. Hearing loss in 41 % of symptomatic cases and 11 % of asymptomatic cases. Vision loss in 21 % of symptomatic and 1 % of asymptomatic cases. Loss of utility of 0.09–0.14 for hearing loss, 0.41 for intellectual disability if symptomatic, and 0.19 for vision loss if symptomatic. Lifetime direct medical costs: €143,882 for hearing loss, €487,675 for vision loss, €228,854 for intellectual disability.	• Model estimates quality-adjusted life-years (QALYs) of babies born to hypothetical cohorts; discounted costs; incremental cost-effectiveness ratio (ICER) of S2 compared to S3 and of S3 compared to S1. • Key findings: 1. Universal screening and targeted vaccination is cost-effective relative to no vaccination (2700–13,300 Euros/QALY). 2. Universal vaccination is always more effective than targeted vaccination. Universal vaccination is likely cost-effective relative to S3 (<94,000 Euros/QALY), and if vaccine cost is <€44 it is less costly. • The study did not assess the cost-effectiveness of universal vaccination of 14-year-olds relative to no vaccination. • As the analysis did not include the indirect benefits of vaccination on reducing community transmission of CMV, the estimates of effectiveness and cost-effectiveness may be too conservative. Several of the assumptions can be questioned. For example, the prevalence of intellectual disability may have been understated in symptomatic cCMV and overstated in asymptomatic cCMV. • The frequency, severity, and cost of vision loss due to cCMV appear overstated. For example, a German study estimated 9 % prevalence of mild vision impairment (chorioretinitis). • Two sources were cited for the estimated cost of vision loss. One, a German study by Walter et al. [153], estimated lifetime cost of roughly €1200 per child with visual impairment due to cCMV, which is 1/40th of what N'Diaye et al. [152] assumed.

(*continued on next page*)

Table 8 (*continued*)

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/ interpretation
				The other reference is a study of US elderly individuals with blindness caused by glaucoma that reported an annual cost of roughly $10,000. That estimate is not relevant to children with eye problems due to cCMV [154].

Table 9
Overview of expectations of evidence that are likely to be required to support a global / regional / national policy recommendation, or financing.

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
WHO SAGE POLICY EVIDENCE TO RECOMMENDATION CRITERIA [Related criteria for the Gavi Vaccine Investment Strategy in brackets]		

PROBLEM
Is the problem a public health priority?
[Gavi VIS criteria:
Alternative interventions**]**
	Evidence requirements:
	• Burden of disease (including economic burden), preferably within the target population for which vaccine recommendations are intended
	  • Epidemiological features of the disease
	  • Clinical characteristics of the disease
	• Other options for disease control and prevention
	For Gavi VIS:
	• Optimal use of current and future alternative interventions (prevention and treatment)
	Assumptions for policy/ financing decisions:
	• Stakeholders consider CMV to be a public health priority.
	• Evidence is sufficient across country settings to determine if CMV constitutes a public health priority in those settings.
		Policy guidance available:
		• Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation.
		Evidence available for evidence requirements and assumptions:
		• Burden of disease: see VVP Section 1
		• Other options for disease control and prevention: see VVP Section 1
		• Stakeholders consider CMV to be a public health priority: see VVP Section 3
		• Evidence is sufficient across country settings to determine if CMV constitutes a public health priority in those settings: see VVP Section 1

BENEFITS & HARMS OF VACCINATION • Are the desirable anticipated effects of the intervention [CMV vaccine] large? • Are the undesirable anticipated effects of the intervention [CMV vaccine] small? • Balance between benefits and harms • What is the overall quality of this evidence for the critical outcomes? **[Gavi VIS criteria:** • Health Impact • Other Impact**]**	***Evidence requirements:*** • How large are the beneficial effects of the intervention on individual (vaccine efficacy/effectiveness) and population level (herd immunity)? • Is the baseline benefit similar across subgroups (age, gender, pregnancy, lactation, healthcare workers, immunostatus, disability, race, and SES, and other groups such as refugees and asylum seekers)? Should there be separate recommendations for subgroups based on benefit or disease severity levels? • Are there deleterious effects of the intervention, either on the individual ((serious) adverse events following immunization) or on the population level (age-shift of disease, serotype replacement, etc.)? • Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendations for subgroups based on harms? • Please provide GRADE (safety and effectiveness) tables with respective rating of the intervention. • For Gavi VIS: • Total future deaths averted in the 2020–2035 period, and per 100,000 vaccinated • Total future cases averted in the 2020–2035 period, and per 100,000 vaccinated • Total under-five deaths averted in the 2020–2035 period, and per 100,000 vaccinated • Total DALYs averted in the 2020–2035 period, and per 100,000 vaccinated ***Assumptions for policy/ financing decisions:*** • CMV vaccine will demonstrate positive benefit-risk balance for the target population • Evidence will be of sufficient quality to assess benefit-risk balance • Evidence that CMV vaccine will benefit both seronegative and seropositive women and in populations with high seroprevalence	***Policy guidance available:*** • Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation. (https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers) ***Evidence available for evidence requirements and assumptions:*** • Desirable effects of CMV vaccine candidates: see VVP Sections 5 and 6 • Undesirable effects of CMV vaccine candidates: see VVP Section 5
VALUES & PREFERENCES • How certain is the relative importance of the desirable and undesirable outcomes?	***Evidence requirements:*** • Information on the relative importance the target population attributes to the desirable and the undesirable outcomes related to the intervention as well as the comparison.	***Policy guidance available:*** • Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation.

Table 9 (*continued*)

Parameter for policy/financing consideration	Assumptions	Guidance/reports available

• Values and preferences of the target population: Are the desirable effects large relative to the undesirable effects?	• Evidence on target population values & preferences related to intervention as well as the comparative health outcomes.
	  • Is there uncertainty or variability in the preference target groups attribute to the harms and benefit outcomes?
	  • Are the benefits, harms and costs of the intervention valued differently by disadvantaged populations compared to the privileged populations?
	  • All critical outcomes relevant measured?
	  • If target group doesn't value the intervention or attributes little to the harms and benefits outcomes- are advocacy measures needed?
	Assumptions for policy/ financing decisions:
	• CMV vaccine and delivery modality will be demonstrated to be compatible with values and preferences of the target population [or tailored demand generation measures can increase vaccine uptake in the target population]
		Evidence available for evidence requirements and assumptions:
		• Target population is not yet defined; for considerations of potential target population values and preferences, see: VVP Section 2

RESOURCE USE
• Are the resources required small?
• Cost-effectiveness
[Gavi VIS criteria:
• Value for Money
• Economic impact
• Operational cost
• Vaccine cost
• Additional implementation costs]
	Evidence requirements:
	• Data on intervention costs as well as programmatic costs (e.g., employing/training of health care workers, supply chain expenses)
	• Opportunity cost: is this intervention and its effects worth withdrawing or not allocating resources from other interventions?
	• Cost-effectiveness data of the intervention in the target population
	• For Gavi VIS:
	  • Vaccine procurement cost per death averted
	  • Vaccine procurement cost per case averted
	  • Vaccine procurement cost per DALY averted
	  • Direct medical costs averted
	  • Indirect costs averted
	  • Total procurement cost to Gavi and countries, 2020–2035
	  • Incremental in-country operational costs per vaccinated person
	  • Additional costs for introduction
	Assumptions for policy/ financing decisions:
	• CMV vaccine and delivery costs will be affordable for national immunization programs
	• CMV vaccination of the target population will be considered cost-effective relative to country-specific willingness-to-pay thresholds when evaluated from perspectives and against alternatives that are relevant to immunization policy makers
		Policy guidance available:
		• Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation.
		Evidence available for evidence requirements and assumptions:
		• Empirical cost of vaccine and delivery modality not yet defined; for modeling evidence on cost-effectiveness of hypothetical vaccines and delivery strategies, see: VVP Section 7

EQUITY
• What would be the impact on health inequities
[Gavi VIS criteria:
• Equity and social protection impact]
	Evidence requirements:
	• Is the condition more common in certain disadvantaged groups, or is its severity greater in people from specific groups or with a particular disability?
	• Is there a risk that discrimination could impact outcomes?
	• Are there significant differences resulting in varying levels of access to intervention or coverage levels?
	• For Gavi VIS:
	  • Disproportionate impact of disease on vulnerable groups
	  • Special benefits of vaccination for women and girls
	Assumptions for policy/ financing decisions:
	CMV vaccination programs will not worsen health inequities and may improve health inequities
	The disease burden from cCMV is significantly greater in disadvantaged groups and LMIC population
		Policy guidance available:
		• Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation.
		Evidence available for evidence requirements and assumptions:
		• Condition prevalence and severity in disadvantaged groups: see VVP Section 1
		• Risk of discrimination and differences in levels of access/coverage: evidence not yet available as target population and delivery modality for CMV vaccine not yet defined

ACCEPTABILITY • Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)? • Which option is acceptable to target group? **[Gavi VIS criteria:** • Implementation feasibility**]**	***Evidence requirements:*** • Assessment whether intervention would be acceptable to stakeholders (ethically, programmatically, financially, etc.) • Assessment whether intervention would be acceptable to target group (ethically, religious, related to opportunity costs, financially, etc.) • For Gavi VIS: • Acceptability in target population ***Assumptions for policy/ financing decisions:*** CMV vaccination assessed to be acceptable to stakeholders and the target population	***Policy guidance available:*** • Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation. ***Evidence available for evidence requirements and assumptions:*** • Acceptability to key stakeholders: see VVP Section 3 • Acceptability to target population: target population is not yet defined; for acceptability to potential target populations, see: VVP Sections 3 and 9

(*continued on next page*)

Table 9 (*continued*)

Parameter for policy/financing consideration	Assumptions	Guidance/reports available

FEASIBILITY
• Is the intervention feasible to implement?
[Gavi VIS criteria:
• Implementation feasibility**]**
	Evidence requirements:
	• Feasibility: Is this intervention accessible, acceptable to target groups and providers and affordable to disadvantaged as well as advantaged populations?
	• Providers: Are programmatic issues considered (e.g., costs related to health care workers' training and employment, logistics/cold chain)?
	• Target population: Opportunity costs (e.g., additional visits to health care clinic), community demand, etc.
	• For Gavi VIS:
	  • Ease of supply chain integration
	  • Need for healthcare worker behaviour change
	  • Feasibility of vaccination time point
	  • Acceptability in target population
	  • Long-term financial implications
	Assumptions for policy/ financing decisions:
	• CMV vaccination is feasible to implement in the specific country setting from the perspective of the national immunization program, health care providers, and the target population
		Policy guidance available:
		• Not CMV-specific; general WHO SAGE EtR criteria are expected to apply for WHO policy recommendation.
		Evidence available for evidence requirements and assumptions:
		• Feasibility evidence: see VVP Section 9

GAVI VACCINE INVESTMENT STRATEGY CRITERIA [not corresponding to WHO SAGE criteria]		
Gavi comparative advantage	• Degree of vaccine market challenges • Potential for Gavi support to catalyze additional investment	
Global health security impact	• Epidemic potential of disease • Impact of vaccination on antimicrobial resistance (AMR)	

between LMIC's and HIC's (e.g. inclusion in WHO EPI in LMIC and ongoing childhood immunization programs in HIC with additional doses included for adolescents and women planning pregnancy offered as part of routine care).

- No CMV vaccine is currently approved. Multiple candidate CMV vaccines are currently in clinical trials and are outlined in Table 5.2. While a gB/Pentamer vaccine developed by Moderna, in phase III, is evaluating the efficacy, safety and immunogenicity in seropositive and seronegative women, 16–40 years [158], most other candidate vaccines are in phase I/II of development.

Commercial attractiveness

- Commercial attractiveness will likely be high in HIC based on the disease burden estimates and ongoing cCMV awareness programs. Although the disease burden of cCMV is higher in LMIC [7,125], commercial attractiveness for a cCMV vaccine would onlybe low-moderate. However, with increasing awareness of cCMV disease burden and financing by Gavi, the Vaccine Alliance in LMIC, the commercial attractiveness would be moderate-high.

Clarity of licensure and policy decision pathway

- No CMV vaccine is currently approved in HIC or LMIC with multiple vaccine candidates in various stages of testing.
- Licensure process for a CMV vaccine would vary significantly between HIC and LMIC. In HIC, vaccine approval and licensure would follow vaccine recommendation by regulatory authorities as outlined. In LMIC, the pathway for vaccine approval would vary between countries but heavily depend on financial support from Gavi.

Expected financing mechanism

- Public or private health insurance for HIC.
- Gavi-eligible LMIC through a CMV vaccine introduction program.
- Middle-income countries ineligible for Gavi support may be required to self-finance the purchase of vaccine.

Ease of uptake

- Knowledge of cCMV among pregnant women and women of childbearing age, one of the potential target population, has shown to be low in studies from several HIC [65,159,160].
- Awareness of cCMV is high among healthcare professionals in many countries, but knowledge about prevention is lower. Further, most obstetric providers do not counsel about cCMV and prevention measures [161–163].
- The above mentioned studies demonstrate that education improves knowledge and practices among the target populations and healthcare providers about cCMV. Thus, a variety of modalities are needed for the education of providers and potential vaccinees.

10. Conclusion

Human CMV infection is common throughout the world but exhibits significant geographic variability [2]. CMV seroprevalence serves as a marker for the size of the population virus reservoir and reflects transmission dynamics as well as variations in the environment, host, behavioral, social, and cultural characteristics associated with the risk of infection. Infection can be acquired at any age, but in most regions worldwide, primary infection is acquired during infancy and childhood. CMV seroprevalence is higher in LMICs and in individuals from lower socioeconomic groups/regions at any given age. Although CMV infections in healthy individuals rarely causes mononucleosis-like illness, infants with intrauterine CMV infection and immunocompromised individuals such as allograft recipients and those with HIV/AIDS can experience significant morbidity and mortality [1,4,5,9,13,23].

CMV is likely the most common infection transmitted from mothers to their children in utero (cCMV) and a leading cause of birth defects and developmental disabilities worldwide, including

sensorineural hearing loss (SNHL), microcephaly, motor disabilities, vision loss, and cognitive deficits. Congenital CMV infection affects an average of 6.7/1000 live births, but this prevalence is population-dependent [10]. In contrast to other congenital infections such as rubella and toxoplasmosis, the prevalence of cCMV increases with CMV seroprevalence rates in the population. The prevalence of cCMV also varies based on characteristics of the sub-populations within a country or region. Most infants (85–90 %) with cCMV have no clinical abnormalities at birth (asymptomatic infection) and about 10 % to 15 % of these children develop SNHL, which can be present at birth or occur later during childhood. CMV-related hearing thresholds may also continue to worsen throughout childhood. Of the infected children with abnormal clinical findings at birth (symptomatic cCMV), 40–60 % of those with moderate to severe symptomatic infection will have permanent sequelae such as SNHL, cognitive deficits, cerebral palsy, and chorioretinitis. In addition, CMV has been identified as an important cause of fetal death and still-births.

Therefore, the significant cCMV disease burden in both HICs and LMICs demonstrate the need for developing a vaccine to prevent or reduce disabilities in children. The US National Institute of Medicine expressed the importance of a CMV vaccine to prevent cCMV disease [76]. The US federal government has also shown a commitment to CMV vaccine development by contributing to other guidance documents, funding, infrastructure, and counsel for industry partners [50,51,77]. In addition, considerable interest has been generated by advocacy groups and commercial entities in developing a CMV vaccine.

Although knowledge and awareness about CMV risk in women remain low in HICs, studies have shown that educational strategies do improve the practice of risk reduction behaviors [134,159–164]. However, information on CMV awareness in LMIC is lacking and whether CMV risk reduction education would be acceptable and/or effective in women in LMICs is not known. Understanding the impact and economic burden of cCMV in LMICs is also limited. These issues will impact vaccine uptake, and additional information is needed for both HICs and LMICs. Unique challenges to CMV vaccine development are that immune correlates of protection from acquiring CMV infection have not been clearly defined, and the majority of infected infants in the world are born to women who were CMV seropositive before pregnancy.

Several candidate vaccines to prevent CMV infection during pregnancy are in various stages of clinical trials. Although these trials were initially designed to prevent primary CMV infection, ongoing studies examine the effectiveness of vaccine candidates to prevent non-primary infection. One vaccine candidate is in phase III trials, two vaccine candidates are in phase II trials, and two more are in phase I testing. Therefore, it is possible that one or more vaccine candidates will receive approval from regulatory agencies in the next 5 to 10 years. Although several models with different assumptions have been produced for the efficacy and uptake of CMV vaccines, data for the LMIC setting are lacking.

11. Data statement

The CMV Vaccine Value Profile was developed using the data in published reports and appropriate references were cited in the manuscript. This VVP does not contain original data that has not been published.

12. Author agreement

The authors declare that this is original work which has not been published before, and that all authors have agreed to the submitted paper.

14. Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Data availability

Only the data that is available in publications was used in the manuscript

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Suresh B. Boppana reports a relationship with Merck, Moderna, and GSK that includes: consulting or advisory and funding grants. William J. Britt reports a relationship with Moderna, Sanofi Pasteur, and Hoopika that includes: consulting or advisory role. Soren Gantt reports a relationship with Merck, Moderna, GSK, Curveo, VBI Vaccines, Meridian Biosciences, and Altona Diagnostics that includes: consulting or advisory and funding grants. Marisa M. Mussi-Pinhata reports a relationship with Sanofi Pasteur and Moderna that includes: consulting or advisory role. Paul D. Griffiths reports a relationship with Biotest, Evrys, GSK, Hookia, and Takeda that includes: consulting or advisory. William Rawlinson reports a relationship with Moderna Inc that includes: consulting or advisory role. Paul D. Griffiths has patent #United Kingdom Patent Application No. 2020135.6 “Human CMV Vaccine” Assigned to University College London issued to Paul D. Griffiths.

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Appendix A. Supplementary material

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