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Mathematical modelling highlights the crucial role of early childhood immunization in preventing congenital CMV in countries with high CMV seroprevalence

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ABSTRACT

Background: Congenital cytomegalovirus infection (cCMVi) is a major global health problem and a leading cause of childhood hearing, visual, and intellectual disability. Development of an effective vaccine against CMV is a high priority, and there is optimism that one will be achieved soon. Previous mathematical modelling to predict the impact of CMV vaccination in low CMV seroprevalence, high-income populations indicate that vaccinating infants could be a highly efficient strategy to prevent cCMVi, even with only a modestly effective vaccine (i.e., <50% protective against primary infection). However, whether vaccinating infants is optimal in high CMV seroprevalence settings, where rates of cCMVi are correspondingly higher, is unclear.

Methods: We adjusted our existing agent-based stochastic model to study CMV vaccine efficacy in high seroprevalence settings (reaching 90%) with Brazil as a test case.

Results: Our results suggest that vaccinating 12-year-old girls and women of childbearing age would have limited ability to reduce cCMVi rates in Brazil, even with a vaccine conferring complete life-long protection against CMV infection. In contrast, vaccinating infants was predicted to provide substantial long-term reductions in the number of cCMVi cases in Brazil, even if it only induced protection equivalent to natural immunity against CMV reinfection and reactivation. Further, our model predicted that if two-thirds of Brazilian infants were vaccinated, a modestly effective vaccine would reduce the number of cCMVi cases by up to 76%.

Conclusion: Together with results from other studies, this analysis underscores that infancy is likely the optimal target age for CMV vaccination to prevent cCMVi in all populations, regardless of the CMV seroprevalence. Furthermore, our findings predict large reductions in disease due to cCMVi worldwide through attainable vaccination scenarios.

1. Introduction

Cytomegalovirus (CMV) infects the majority of humans during their lifetimes, but most of these initial infections are asymptomatic. However, CMV infection that occurs in utero (congenital CMV infection, cCMVi) is a major cause of childhood deafness and other neurodevelopmental disability [1]. CMV is transmitted horizontally to children through breastfeeding and to adults or children through exposure to saliva or urine by an infected individual [2]. Infants and toddlers are efficient transmitters because they persistently shed virus at extremely high levels in saliva and urine over months up to years [3], and because these fluids are poorly contained at that age. After acquiring CMV, the initial phase of viral replication and shedding is eventually controlled and the infection becomes latent, persisting for life. The

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immune response to CMV is incomplete, resulting in periodic reactivation and viral replication during chronic infection, as well as reinfection with different CMV strains. Importantly, CMV may be transmitted vertically from mother to fetus following maternal primary or non-primary infection during pregnancy. Non-primary maternal CMV infection, which represents reactivation of an earlier infection or reinfection with a new viral strain, accounts for more cases of cCMVi than primary CMV maternal infection during pregnancy. Furthermore, at the population level, the greater the proportion of women that were infected prior to becoming pregnant, the higher the rate of cCMVi [4,5].

Because CMV is the most common congenital infection and cCMVi impacts 1 in every 150 live-born infants (0.7%) globally [6], much effort has been put into the development of a CMV vaccine. Clinical trials of CMV vaccine candidates against primary infection of women of child-bearing age have so far demonstrated efficacy of <50% and no vaccine has yet been approved for clinical use [7,8]. Other CMV vaccine trials are being conducted and hold promise [9], but numerous important questions plague the field, including the level of vaccine efficacy required, the optimal target group for vaccination, and the impact of CMV seroprevalence rates on the vaccine's ability to reduce the burden of cCMVi, which is an important outcome [10].

Mathematical modelling enables the prediction of different vaccination strategy outcomes decades post-introduction, guiding and extending insights from costly and operationally challenging clinical trials and post-marketing studies [11,12]. Using mathematical modelling, our group and others have found that vaccinating at an early age represents an optimal strategy to decrease cCMVi cases overall [11,13]. Specifically, our group recently developed a stochastic mathematical model to investigate the impact of a CMV vaccine in high-income, low seroprevalence populations [11]. This model considered vaccine implementation in multiple age groups and with variable vaccine coverage and estimated that the greatest reductions in cCMVi prevalence 50 years after vaccination roll-out would be achieved by vaccinating 2-month-old children. However, given that this model was parameterized to data from low seroprevalence countries (~50% adult seropositivity), it is unclear how generalizable these results are to populations with much higher seroprevalence. To study this question, we extended our model to describe CMV transmission dynamics in Brazil, a country with almost 100% CMV seroprevalence by age 12 in certain regions [14]. Our results indicate that despite important differences in CMV transmission between high and low seroprevalence populations, immunization of infants still resulted in the highest overall reductions in cCMVi cases. This study therefore motivates the continued development of CMV vaccines suitable for use in young children as an effective strategy for reducing the burden of disease from cCMVi.

2. Methods

2.1. Agent based mathematical model of within-host and population-level CMV infection dynamics

Following previous work [11], we constructed an agent-based stochastic model of CMV transmission that follows the dynamics of each individual in a synthetic population of about 15,000 people based on a variety of data from Brazil. In our model, the general population includes men, women without children, and children aged ≥5 years, while households are modelled as units that include mother with her child (ren) (Supplementary Fig. 2). When a woman gives birth, a new household is created, if she was previously in general population, or the newborn is added to her existing household; children leave the household at 5-years-old and enter the general population. If a household has no children, the mother returns to the general population. Births occur according to age-specific fertility rates. Due to a lack of sex specific contact intensity data for people older than 50, after individuals turn 50, they are removed from the population.

CMV transmission occurs in two ways (Fig. 1A). First, through population-level contacts that are defined by age- and sex- specific contact intensities estimated from a synthetic contact matrix in Brazil [15] that we scaled to reflect for daily contact frequences; second from within household interactions. The synthetic Brazilian matrix originally lacked sex-specificity. Thus, we incorporated sex-specific patterns in contacts by combining the Brazilian contact matrix with a contact survey in Peru [16], a country with similar demographic structure to Brazil. The second CMV transmission pathway (i.e., household interactions) primarily describes mother-child transmission events that occur through breastfeeding and diaper use, both of which increase the risk of exposure to CMV.

Infection dynamics are represented as a continuous process. Individuals may experience either a primary CMV infection or reinfection with a separate strain of CMV during which their infectiousness peaks at

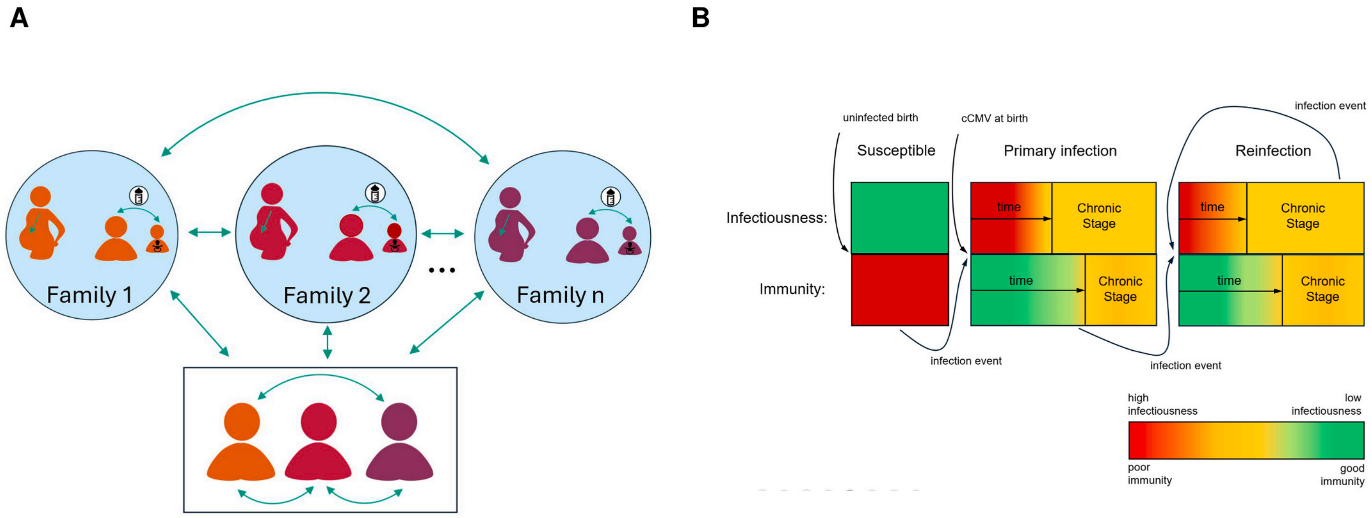

Fig. 1. Stochastic agent based mathematical model of CMV infection dynamics. (A) The model describes population transmission dynamics based on individual characteristics and contacts, including close interactions between individuals such a breastfeeding and diaper changing. Individuals interact according to age- and sex-dependent contact rates. (B) During primary infection, individuals are highly infectious with strong immunity against reinfection. Both infectiousness and immunity wane over time to chronic levels. During chronic infection, previously infected individuals are susceptible to reinfection, which takes a similar course to that of primary infection but with decreased infectiousness and increased immunity. Reinfections can happen repeatedly. Viral reactivations are modelled as a constant rate of infectiousness during the chronic stage of the disease. Taken from Byrne et al. [11] with permission.

the beginning of an infection before decreasing exponentially to the chronic rate of infectivity. Uninfected individuals are categorized as being susceptible (no immunity) to primary CMV infections (Fig. 1B). If a transmission event occurs, previously naïve individuals enter the primary infection stage with high infectiousness and immunity, with both values waning over time to the chronic level. Reinfection is assumed to be less transmissible than primary infection; mathematically this translates to scaling infectiousness by a constant factor $R \in (0,1)$. Accordingly, the probability of vertical transmission is higher for primary infections than for non-primary infections. Individuals are assumed to maintain partial immunity from previous infections, though reinfections can occur repeatedly.

The model is parametrized to account for *child infectiousness* (i.e., the maximum infectivity of young children), *adult infectiousness* (i.e., a decreased rate of viral shedding for adults), and *chronic infectiousness* (i.e., long-term constant shedding rate). Additional parameters include a *breastfeeding factor*, which increases the probability of transmission between mothers and their breastfed infants, and a *diaper factor*, which increases mother-child risk of transmission before children are toilet trained. Input parameters related to immunity consist of an *immune waning rate,* which defines how quickly protection against reinfection decreases, and a *minimum immune protection* constant, which sets the minimum of partial immunity after the infection. These parameters were estimated from various data sources using Approximate Bayesian Computation (ABC) via the Lenormand algorithm [17,18]; please see the Supplementary Information for a complete description of data and the estimation procedure.

We use τ-leaping to simulate the model. For this, the expected rates of possible events (e.g., infections, births) are calculated according to event probabilities ($rate \times \Delta t$) at each time step Δt (here, we used $\Delta t = 1/12$ of a year). The number of new events is then sampled from a binomial or a multinomial distribution. To construct each binomial distribution, representing e.g., mother gives birth, congenital infection at birth, introduction of potty training, breastfeeding cut-off, we repeat a True/False trial across many individuals and count the number of “Trues” drawn. The multinomial distribution representing e.g., infection with potential multiple sources such as population and family-level contacts, like mother-child/child-mother transmissions, is constructed by assigning probabilities to several possible outcomes, sampling, and counting how many events fall into each outcome. The state space is then updated according to the new events that occurred within Δt and this process is continued for 50 years post-vaccine introduction.

To consider different seroprevalence scenarios (see next section), we accounted for variations in population structure across geographical regions (i.e., North Brazil and South Brazil) while keeping the overall birthrate constant.

2.2. Model parameter estimation in high seroprevalence Brazil

Adapting the model to Brazil required re-estimating parameter values for age-specific CMV seroprevalence, birth, breastfeeding, and toilet training rates. For this, we extracted seroprevalence data from several studies [14,19–21]. Published seroprevalence data varied substantially (Supplementary Fig. 1A), likely due in part to differences in socio-economic status between North and South Brazil. Lanzieri et al. [19] analyzed data from Caieiras in Sao Paulo state (South Brazil), where CMV seroprevalence reached 100% around age 35 years. Yamamoto et al. [14] reported 96% of pregnant women ≥12 years of age in Ribeirao Preto in Sao Paulo state (South Brazil) were infected with CMV. In Manaus, Amazonas in North Brazil seroprevalence was estimated to be lower −70% in individuals ages 18–34 years, 64% in individuals ages 35–49 years, and 68% in individuals >50 years of age [20]. In another region of North Brazil, Costa et al. [21] reported CMV seroprevalence of 77% in pregnant women >18 years of age (for a full description of the CMV seroprevalence data, please see the Supplementary Information). Due to these differences, we therefore categorized three regions, defined according to CMV seroprevalence: (1) North Brazil, (2) All-of-Brazil (average values across the country), and (3) South Brazil. It is important to note that North Brazil is considered to have relatively lower seroprevalence, whereas South Brazil has relatively higher seroprevalence, which reflects the variations in transmission dynamics within the country.

To ensure our model predictions represented the observed ranges in each region, we performed sensitivity analyses to the range of possible intervals for key model outputs (see Seroprevalence section in the Supplementary Information). We assumed the cCMVi rate to be constant across the three regions, though this has been found to vary by region [22–26] (Supplementary Table 2). For this study we used the observed cCMVi rate of 1% from Yamamoto et al. [22] Breastfeeding is a major mode of mother-to-child CMV transmission, and is reported to be practiced more often and for longer in Brazil than in lower seroprevalence regions [27,28]. On the other hand, toilet training, which is expected to reduce exposure to CMV in urine, tends to be introduced earlier in Brazil, at age 1 year [29]. To update CMV seroprevalence and the rates of birth, breastfeeding, and toilet training in our model, we used the Lenormand algorithm (Supplementary Fig. 1B and 1C) used in the previous model [17,18]. Further discussion of the data and the model fitting process can be found in the Supplementary Information, and the input data values are shown in Supplementary Table 1.

2.3. Modelling vaccination coverage and population targets

To estimate vaccine efficacy, we modelled a vaccine providing equivalent protection to post-CMV infection immunity (“natural immunity vaccine”) and compared it to a vaccine conferring long-life protection (“ideal vaccine”). An ideal vaccine is modelled as conferring sterilizing immunity to susceptible individuals; thus, vaccinated individuals move to a vaccinated-uninfected state within which they have zero infectivity while maintaining complete immune protection. Seropositive individuals who are infected at the time of the vaccination instead move to the vaccinated-infected class. Their infectivity dynamics follow the same course of infection as infected-non-vaccinated individuals, however their (future) immune protection is modulated according to the e.g., vaccine-induced waning rate and the long-term protection floor value. We also used our model to predict the efficacy of the natural immunity vaccine with boosters, as was done previously [11]. In the booster scenario, we simulated booster doses administered at 2 and 12 years of age among children who received a first dose at 2 months.

Vaccine efficacy was quantified as the decrease in cCMVi cases 50 years after vaccine implementation:

$$\text{Efficacy} = 100\% - \frac{median(freq_{cCMV})}{cCMV_i} \times 100\%, \qquad (1)$$

where $cCMV_i$ denotes the prevalence of cCMVi cases with no vaccination for each considered i scenario ($i =$ North Brazil, All-of-Brazil, South Brazil), and $\text{median}(freq_{cCMV})$ represents the predicted median frequency of cCMVi cases 50 years after vaccination roll-out, specific to the simulated vaccinated population and vaccine coverage.

2.4. Effect of reduced reactivation events on vaccine efficacy

As individuals in the chronic stage of infection have a low level of infectivity, spontaneous viral reactivations can cause viral shedding events. To investigate the impact of a natural immunity vaccine capable of reducing the frequency of CMV reactivation among infected individuals, we decreased the parameter of chronic infectivity by 25%, 50% and 75%. The duration of each decrease was modelled to last 1-, 5-, and 10-years after vaccination.

To quantify the sensitivity of vaccine-induced reductions in reactivation on the rate of cCMVi, we used the vaccine efficacy ($\text{Efficacy}_{\text{RV}}$)

(Eq. (1)) for each age group and level of vaccine coverage and calculated the additional decrease in cCMVi cases (for more information, please refer to the Supplementary Information) by subtracting the efficacy of the standard natural immunity vaccine ($\text{Efficacy}_{\text{V}}$):

$$VE = \text{Efficacy}_{\text{RV}} - \text{Efficacy}_{\text{V}}. \qquad (2)$$

3. Results

3.1. Successful model prediction of cCMVi rate and CMV seroprevalence in Brazil

After fitting to available data, our model predicted cCMVi prevalence to be 0.55%, 0.95%, and 0.99% in North Brazil (lower seroprevalence), All-of-Brazil (country average), and South Brazil (higher seroprevalence), respectively versus the observed 1% from Yamamoto et al. [22] (Fig. 2A, C, and E). Model predictions also successfully recapitulated CMV seroprevalence in each of the regions, with slight under estimations in North Brazil (Fig. 2B, D, and F).

3.2. The proportions of cCMVi cases caused by reinfection versus primary infection, but not reactivation, during pregnancy is positively correlated with seroprevalence

After calibrating our model with respect to rates of cCMVi and CMV seroprevalence in Brazil (Fig. 2), we determined how each maternal infection type (primary, reinfection or chronic) was predicted to contribute to the number of pre-vaccination cCMVi cases and their relationship to CMV seroprevalence. As expected, our model predicted that South Brazil, where seroprevalence is highest, had most cCMVi cases being caused by reinfections during pregnancy (Fig. 3C, Supplementary Table 8). In contrast, in All-of-Brazil and North Brazil regions, as CMV seroprevalence decreases, a larger proportion of cCMVi cases were driven by primary infection during pregnancy compared to reinfections (Fig. 3A and Fig. 3B). In all regions, most primary infections and reinfections were acquired through contact with young children.

Of note, our model predicted little effect of CMV seroprevalence on the contribution of chronic stage reactivation events to cCMVi cases. Indeed, despite the fact that 89% of women are in the chronic stage in South Brazil (representing the highest seroprevalence among the three regions examined), 31.3% of cCMVi cases were predicted to arise due to the chronic stage, versus similar magnitudes of 38.5% and 36.7% in All-of-Brazil (country-wide average seroprevalence) and North Brazil (lower seroprevalence), respectively (Fig. 3, Supplementary Tables 6 and 7). The fact that the number of cCMVi cases caused by maternal chronic infections is not strictly dependent on the seroprevalence therefore suggests that the impact of a vaccine preventing cCMVi cases due to viral reactivation during pregnancy would not depend on seroprevalence.

3.3. Infant vaccination effectively reduces the number of cCMVi cases in Brazil

To gain a more complete understanding of how key factors, such as vaccine characteristics, age at vaccination, and vaccine coverage affect rates of cCMVi in the high CMV seroprevalence setting of Brazil, we studied both an “ideal vaccine” that confers complete life-long protection against CMV infection and a “natural immunity” vaccine equivalent to post-infection immunity (see Methods). In different simulations of our model, each vaccine was administered to either 2-month-olds, or 2-, 12- or 25-year-olds with 1/3, 2/3 or full (100%) vaccine coverage, and the impact of cCMVi cases was measured 50 years after implementing each scenario (Fig. 4). Overall, our results suggest that vaccine efficacy is dependent on CMV seroprevalence, except in the scenario of vaccinating infants, in which large reductions in cCMVi cases occurred regardless of vaccine efficacy. For example, we found vaccine efficacy to decrease faster with age in regions with high seroprevalence (i.e., South Brazil and All-of-Brazil) compared to North Brazil where seroprevalence was lowest, especially when vaccinating older individuals. In particular, the natural immunity vaccine was predicted to have no benefit in South Brazil if administered to individuals 12 and 25 years old (Fig. 4B, Supplementary Table 5). On the contrary, the same vaccine was found to reduce 52% of cCMVi cases if administered to 100% of 12 years old in North Brazil (Fig. 4B, Supplementary Table 3).

Strikingly, assuming 50 years have passed since vaccine implementation, our model predicted a 50% reduction in cCMVi cases in the highest seroprevalence scenario (South Brazil) when vaccinating smaller fractions of 2-month-olds using the natural immunity vaccine (Fig. 4B, Supplementary Table 5). Moreover, by vaccinating 2-month-olds at 100% coverage with a natural immunity vaccine, cCMVi cases were predicted to be reduced by around 90% in all three regions (Fig. 4B). Our results also suggest that a natural immunity vaccine with booster strategy is marginally more effective only when coverage is low (i.e., 1/3). In this case, a natural immunity vaccine with boosters was predicted to reduce cCMVi cases by 47% versus 39% for a vaccine with no boosters in All-of-Brazil (Supplementary Table 4).

We next probed the major contributors of cCMVi cases upon implementing each vaccination strategy in All-of-Brazil (which is representative of the average scenario). For both the ideal and natural immunity vaccines, our model's predictions showed that most cCMVi cases were a result of the mother being in the chronic stage of infection for the duration of her pregnancy (Fig. 5, Supplementary Figs. 6 and 7). The contribution of the chronic stage to new cCMVi cases was particularly

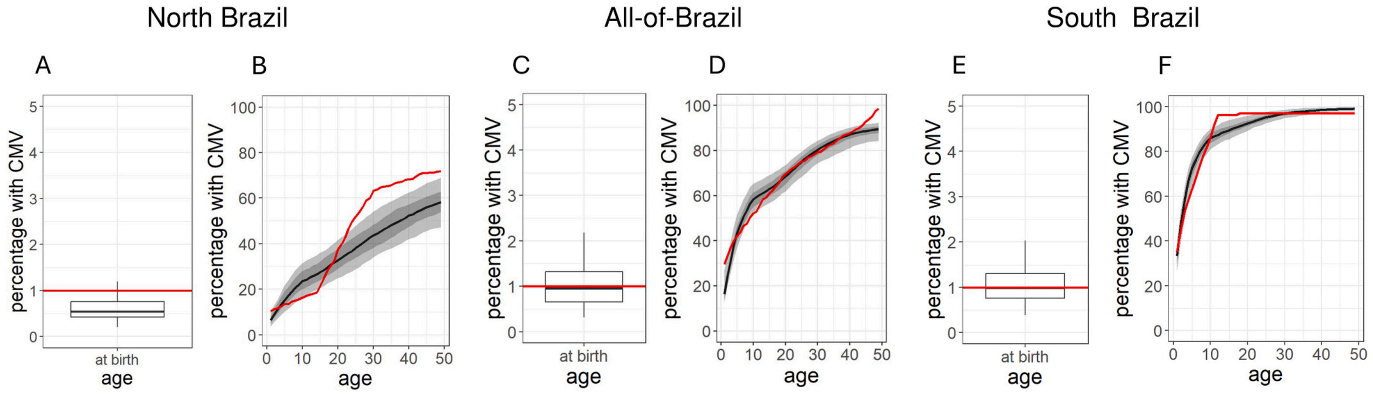

Fig. 2. Successful prediction of cCMVi rates and CMV seroprevalence in Brazil. The model predicted cCMVi at birth (panels A, C, and E) and seroprevalence with age (panels B, D, and F) compared to data from different regions in Brazil. Red solid lines, published data [14,19–21]; black solid lines, median model predictions; grey shaded regions, standard deviations of model predictions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

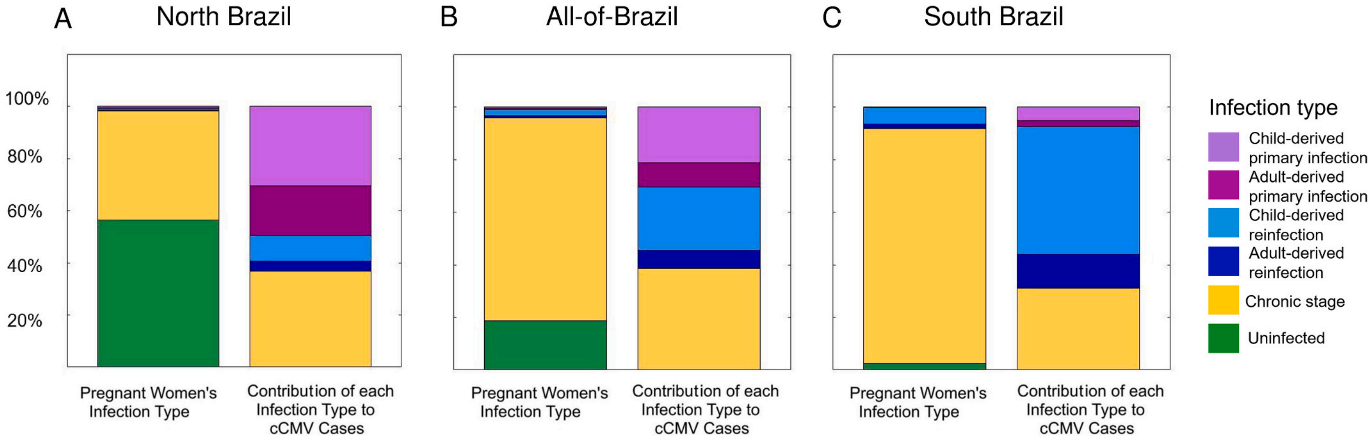

Fig. 3. Predicted women's infection type and contribution of each infection type to cCMVi cases in the absence of vaccination. Pregnant women's infection type and contributions of infection types to cCMVi cases in (A) North Brazil, (B) All-of-Brazil, and (C) South Brazil. As seroprevalence increases, more cCMVi cases are caused by child- and adult-derived reinfections (pregnant women acquiring a reinfection from contact with children or adults, respectively) and fewer from primary infections. Our model did not predict an association between seroprevalence and the relative contribution of chronic infection (viral reactivation) during pregnancy to cCMVi cases.

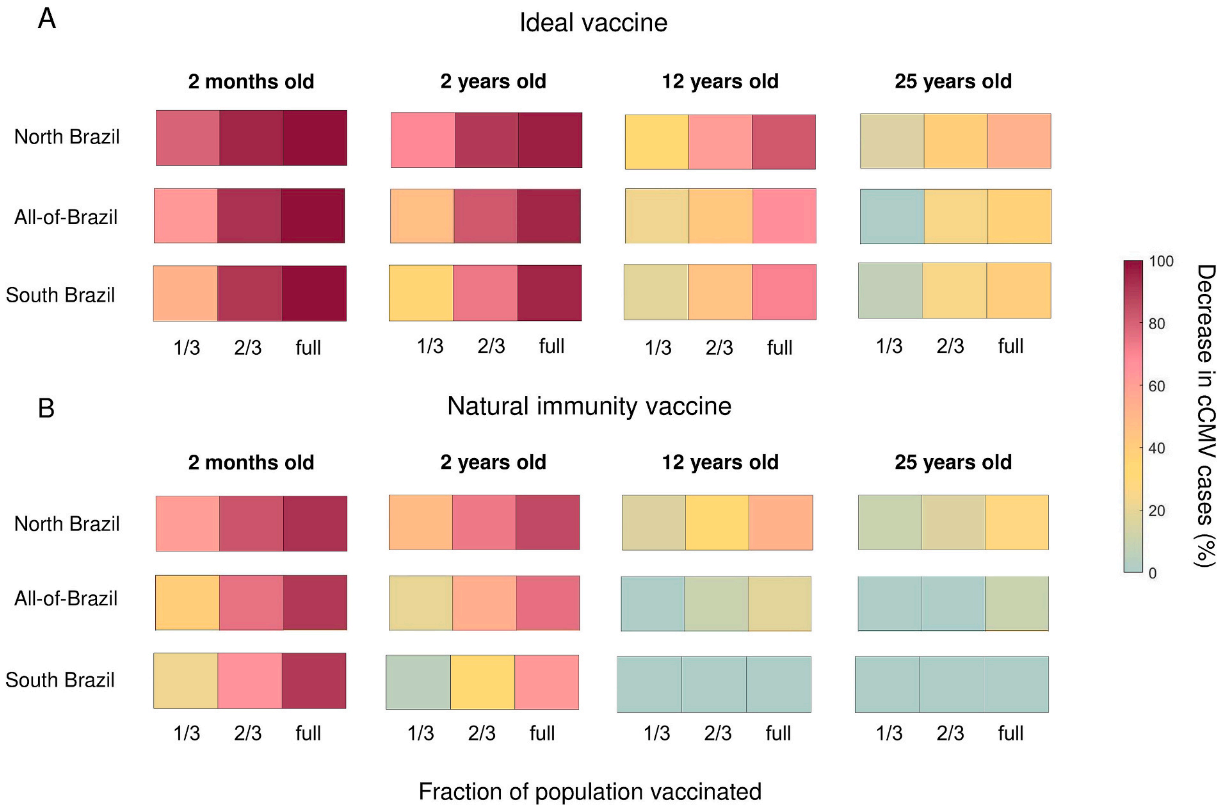

Fig. 4. Decrease in cCMVi cases 50 years after vaccine implementation in North Brazil, All-of-Brazil and South Brazil. (A) cCMVi reported as prevalence at birth in Brazil after the introduction of an ideal vaccine providing long-life protection. (B) cCMVi reported as prevalence at birth in Brazil after the introduction of a hypothetical natural immunity vaccine that provides similar protection as post-infection immunity. For each vaccine, the age group vaccinated, and the vaccine coverage are indicated. In all scenarios, the greatest reduction was obtained by vaccinating 2-month-old infants (maximal reductions in cCMVi cases of up to 99% for an ideal vaccine, and 92% for a natural immunity vaccine at full coverage).

prominent at higher levels of vaccine coverage. For example, our model predicted that 50 years after the introduction of an ideal vaccine to all 2-month-olds, 2-year-olds and 12-year-olds, 100% of cCMVi cases would come from chronic infections in mothers (Fig. 5A). For a natural immunity vaccine, most cases of cCMVi were also predicted to originate from mothers being in the chronic stage infection. However, in the natural immunity vaccine scenario, we also observed high contributions to cCMVi cases by pregnant mothers reinfected through interactions with children and adults (Fig. 5B).

3.4. *Analysis of cCMVi dynamics by maternal infection type and vaccination status reveals heterogenous patterns following vaccination*

After analysing the contribution of different infection stages in

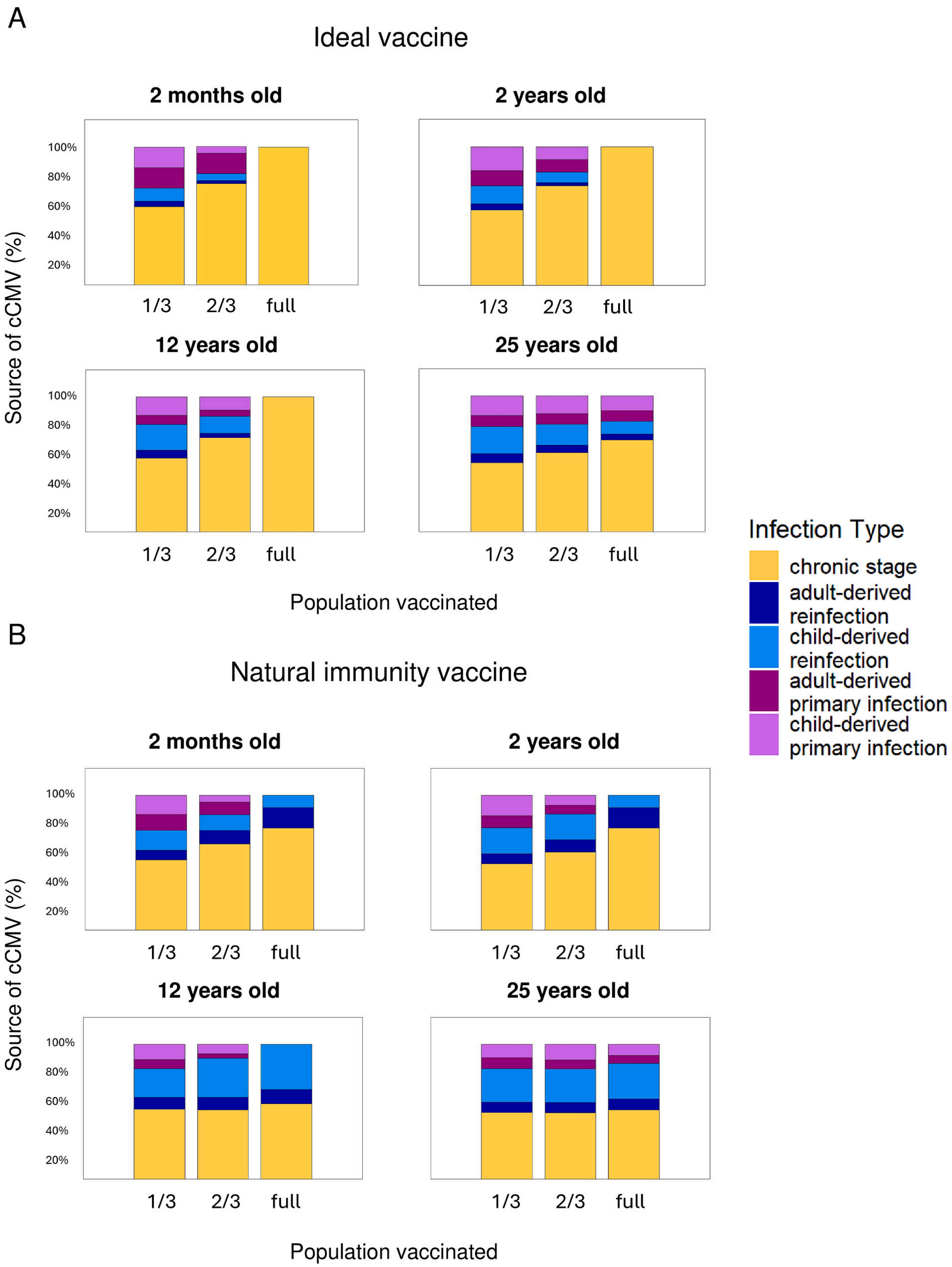

Fig. 5. Contribution of different infection stages in pregnant mothers to cCMVi cases 50 years after vaccine implementation in All-of-Brazil. Sources of cCMVi cases 50 years post-vaccine introduction for (A) an ideal vaccine and (B) a natural immunity vaccine. For each vaccine, the age group vaccinated, and the vaccine coverage are indicated. In all scenarios, 50 years after vaccine implementation under full coverage, most cCMVi cases were predicted to originate from the chronic infection stage, i.e., viral reactivation during pregnancy (yellow bars). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pregnant women to cCMVi cases at the end of simulation (50 years post-vaccine implementation), we also examined the dynamics of cCMVi cases over time after stratification by maternal infection type. Compared to the baseline rate of cCMVi, the occurrence of cCMVi due to child and adult-derived reinfections was increased in the North Brazil scenario if vaccinating adolescents and adults (Supplementary Fig. 8). Similar trends were found in the higher seroprevalence All-of-Brazil setting. Here, our model predicted an increase in cCMVi cases caused by reinfections in pregnant women vaccinated at 12 years of age compared to the baseline, non-vaccine scenario (Supplementary Fig. 9). However, unlike in North-of-Brazil, the higher seroprevalence in All-of-Brazil abrogates the reinfection effect for 25-year-olds. Finally, in the South Brazil setting (which has an approximately 90% seroprevalence by the age of 12), immunization with a natural immunity vaccine was only found to have an impact when administered in early life (i.e., 2-months-old or 2-years-old). As in the All-of-Brazil scenario, this is because almost all individuals have already acquired CMV by adolescence (Supplementary Fig. 10). Early vaccination reduces the overall number of primary infections in children. Our results show that if vaccinating the entire population of 2 months old, the number of adult-derived primary infections in mothers decreases drastically around 20 years after vaccine implementation. At this point, the full population of adults (including mothers) is vaccinated, thus retaining at least partial immunity against infection, while there is the additional benefit of vaccination reducing the child-to-adult transmission. Together, these act to significantly reduce the risk of all infection types.

We subsequently analyzed the dynamics of cCMVi cases in vaccinated versus unvaccinated mothers in the All-of-Brazil scenario. Approximately 25 years after introducing the vaccine, vaccinating the entire population at either 2 months or 2 years of age provided comparable benefits when considering unvaccinated mothers, presumably through indirect protection (Supplementary Fig. 11); other contributory factors include the decrease in the number of unvaccinated mothers over time as girls and women age in the population. In contrast, the percentage of cCMVi cases from vaccinated mothers when vaccinating 2-year-olds versus 2-month-olds was found to increase throughout the 50 years post-vaccination period. Vaccinating at 12 years of age eliminated cCMVi cases from unvaccinated mothers after 30 years, but the number of cCMVi cases among vaccinated mothers is highest in this case. Further, if vaccinating at 25 years of age, unvaccinated mothers contributed to approximately 40% of cCMVi cases (0.34% cCMVi from unvaccinated vs. 0.54% from vaccinated mothers), similar to the observed outcomes when vaccinating 2/3 of the population of 12-year-olds.

3.5. *Vaccine-induced reductions of viral reactivation confer nominally better vaccine efficacy*

Reactivation of latent virus during the chronic stage of infection in pregnant women was frequently identified as the primary cause of cCMVi cases in all modelled scenarios. Thus, we performed a sensitivity analysis to explore the potential benefits of a vaccine that, in addition to providing protection against infection/reinfection, also reduces reactivation events among infected individuals. To model this, we simulated the impact of a vaccine that provides infection protection equivalent of natural immunity and decreases the rate of reactivation during the chronic stage by 25%, 50% and 75% for 1, 5, and 10 years after vaccination (see Methods).

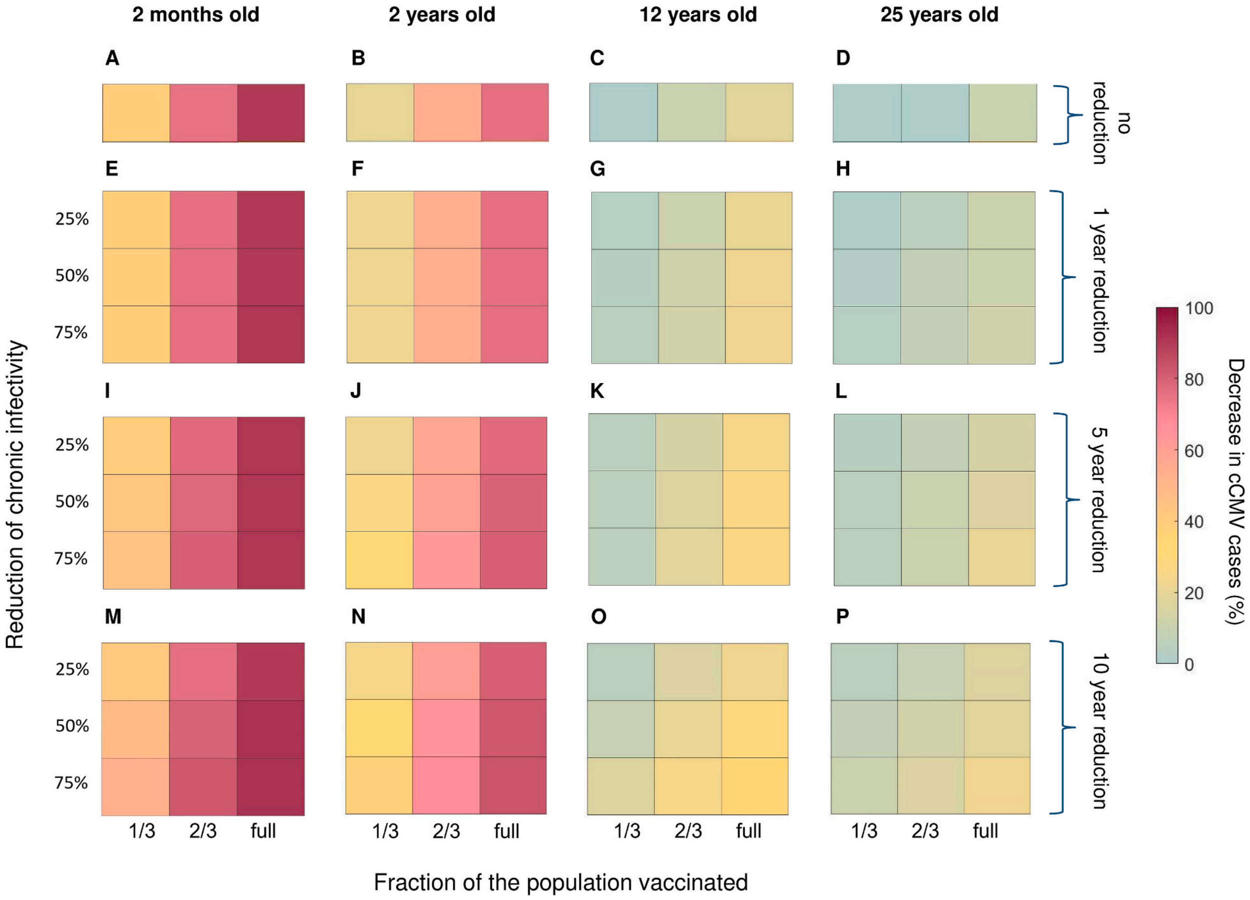

Fig. 6. Nominal impact on cCMVi cases of a natural immunity vaccine that reduces viral reactivation during chronic infection. Heat maps show the decrease of cCMVi cases (50 years after vaccine roll-out) in the All-of-Brazil scenario for a natural immunity vaccine that reduces reactivation for 1 year (E–H), 5 years (I–L), and 10 years (M–P) compared to natural immunity vaccine with no reduction (A–D).

A 1-year reduction in reactivation following vaccination did not impact vaccine efficacy, and our model predicted a further decrease in cCMVi cases of less than 5 percentage points (Supplementary Tables 12–13 and Fig. 6E–H). For reductions in reactivation lasting 5 or 10 years, our model predicted a moderate additional decrease in cCMVi cases of up to 12 percentage points with a 5-year reduction (Fig. 6I–L and Supplementary Tables 14–15) and 18 percentage points with a 10-year reduction (Fig. 6M–P and Supplementary Tables 16–17). Full results can be found in Supplementary Tables 12–17.

4. Discussion

Previous CMV vaccine candidates have demonstrated limited efficacy in clinical trials as they were at most 50% effective against primary infections [8], and none has been approved. Although cCMVi is the most common congenital infection, it occurs too rarely to be feasible as the primary endpoint in vaccine trials [30]. As a more common outcome, and a prerequisite for congenital infection, prevention of primary infection in women of childbearing age is currently of high interest [8]. However, there are currently no widely accepted laboratory or clinical methods to directly assess vaccine efficacy against CMV reinfection and reactivation [31]. Other outcomes, such as reducing CMV transmission to pregnant women, and transmission from the pregnant woman to her fetus, may also be important characteristics of a successful vaccine, even without conferring high protection against primary infection. Given these complexities, CMV vaccine development would benefit from predictive models that assess vaccine characteristics and deploy scenarios beyond traditional clinical trials. As such, we employed mathematical modelling to explore these questions and thus accelerate vaccine development.

Our previous mathematical model of CMV vaccination in high income, low seroprevalence populations indicated that vaccinating infants even with only a modestly protective vaccine substantially reduced the rate of cCMVi [11]. To study how higher CMV seroprevalence might alter the impact of CMV vaccination, we adapted this agent-based stochastic mathematical model to parameters in Brazil. Given that published estimates of CMV seroprevalence differ by region, we studied three assumptions of seroprevalence: North Brazil (lower seroprevalence), South Brazil (higher seroprevalence) and All-of-Brazil (country average). Our results in the North Brazil region align with those in our previous study in low seroprevalence populations [11], which indicates that seroprevalence is the major factor impacting vaccine efficacy. However, vaccinating older groups in higher seroprevalence settings (South Brazil, All-of-Brazil scenarios) was found to be less effective in prevention of cCMVi than in lower seroprevalence (North Brazil) settings, with virtually no reductions in cCMVi cases when vaccine was administered to 25-year-olds (All-of-Brazil) or even 12-year-olds (South Brazil). Thus, aiming to immunize young children or infants against CMV appears even more important in high seroprevalence populations.

The relative benefits of vaccinating younger groups appear to be due to the reduction of CMV transmission from infants and children to pregnant women. Compared to older children and adults, young children with primary infection tend to shed CMV in saliva and urine at higher levels and for longer [32,33]. Furthermore, pregnant women may be more likely to come into close contact with the saliva and urine of young children (through drooling, diaper changing, etc.) compared to older children or adults. These factors result in young children being highly efficient transmitters of CMV [34,35]. Our model predicted minor benefits of boosting children, who were first vaccinated with the natural immunity vaccine at 2 months old and then boosted at 2 and 12 years of age, but only when coverage was low. This result is related in part to the already large decreases in cCMVi cases with high to complete infant vaccination coverage without a booster. Further reductions from boosting 2- and 12-year-olds did not significantly reduce cCMVi rates likely because they are much less infectious than infants for the reasons described above.

As expected, our model predicted that the proportion of cCMVi cases due to maternal reinfection versus primary infection during pregnancy increased with population seroprevalence. However, surprisingly, the proportion of cCMVi cases caused by reactivation of maternal infection (chronic infection) was not tightly linked with CMV seroprevalence prior to vaccination (Fig. 3). In all three regions, our model predicted that nearly the entire proportion of cCMVi cases were due to chronic infection after the introduction of the vaccine. However, this may be due to a significant decrease in the total number of cases magnifying the contribution of chronic infections (Supplementary Tables 9–11).

Theoretically, late vaccination (i.e., of 12- and 25-year-olds) could leave future mothers unprotected relative to vaccinating children. Thus, they would be more likely to acquire a primary infection and, at childbearing age, be subsequently more likely to be reinfected by unvaccinated infected children. This is due to the higher rate of viral shedding in infected children. Although reinfections increase in women vaccinated at age 12 in the All-of-Brazil scenario (Supplementary Fig. 9), the background seroprevalence cancels out this effect for 25-year-olds. This is consistent with the fact that most women are already infected by the time they receive the vaccine, so immunization provides a short-term boost to immunity, without a marked reduction to the chronic rate of infectiousness. We also observed a modest reduction in primary infections during pregnancy in infection-naïve women. As vertical transmission is higher during primary infections than reinfections, this causes a very modest drop in cCMVi caused by primary infections, without influencing cCMVi caused by reinfections. Similarly, early-life vaccination reduces childhood infections in South Brazil (Supplementary Fig. 10) but leads to more primary infections later in life by shifting susceptibility to later ages. Thus, there are more mothers who experience primary infection transmitted through children, particularly if the population is only partially vaccinated, and it is more likely for children to be infected and then transmit the infection to pregnant women and other adults. This predicted pattern highlights the potential risk of early-in-life and partial vaccination, as shifting susceptibility to older ages could increase the number of primary infections during pregnancy, as observed with Rubella [36]. However, such an increase has not been observed with Varicella [37–39]; instead, a shift in primary infections from younger to older children has been detected, but an increase has not occurred among adolescents and adults. Despite this potential increase in maternal primary CMV infections in some partially vaccinated scenarios, the total number of cCMVi cases remained lower than in non-vaccination scenario, indicating that this increase was compensated by reductions in other infection types.

Because some scenarios showed more cCMVi cases in vaccinated mothers (Supplementary Fig. 11), we additionally examined the number of births in each maternal group (Supplementary Fig. 12) and the relative cCMVi burden (Supplementary Fig. 13). This analysis showed that part of the observed pattern can be explained by the increasing proportion of births occurring in vaccinated mothers over time (Supplementary Fig. 12). After accounting for all births, the relative cCMVi burden was generally higher in unvaccinated mothers and lower in vaccinated mothers, especially for early vaccination strategies (Supplementary Fig. 13), whereas differences were weaker under later vaccination strategies, for which the cCMVi case:birth ratio remained close to 1 after normalization (Supplementary Fig. 13).

Previous mathematical models developed to study the impact of various CMV vaccines have included many of the parameters used here, such as the role of CMV reinfection and use of boosters [19,40–43] and the effects of the vaccine on the reactivation in latently infected individuals [44]. However, none mechanistically modelled the potential benefits of vaccine-induced reductions in CMV reactivation separately during chronic infection under different assumptions about both vaccine strength and duration of protection against reactivation. To study this, we predicted the effects of a natural immunity vaccine that decreases the rate of chronic infectiousness by 25%, 50%, and 75%, with these reductions lasting 1, 5 and 10 years. As expected, the most impactful were reductions lasting 10 years; the greatest benefits of reduction of CMV reactivation were observed at lower vaccine coverage levels (i.e., 1/3 of the population) when vaccinating 2-month-olds and 2-year-olds, while vaccine coverage did not seem to affect the results when vaccinating older groups. The former prediction is likely because there is already a strong decrease in cCMVi cases (up to 92% 50 years after the vaccine introduction) for high vaccine coverage in the youngest group, so decreasing the occurrence of reactivations would have only minor benefits. Latter may follow from the fact that targeting older groups has a direct impact on cCMVi cases regardless of vaccine coverage, as those age groups contain future mothers/pregnant women. While a reduction lasting 10 years provided some benefits, reducing the incidences of viral reactivations for 1 year did not affect the overall number of cCMVi cases in any of the vaccinated groups. From this sensitivity analysis, we can conclude that a vaccine reducing viral reactivations would provide some benefits; however, the primary focus should remain on preventing/delaying/modifying CMV infection in infants to reduce their infectiousness.

Our model has limitations. Model inputs were obtained from a limited number of studies conducted across various regions, each with varying degrees of representativeness. This reflects the relative paucity of evidence from lower resource settings. Moreover, results may not be generalizable to all settings with high CMV seroprevalence which different socioeconomic realities. Brazil was not among the countries with a contact matrix reported in the POLYMOD study [45,46] used in our previous model, and the synthetic contact matrix [15] we employed (see Methods and Supplementary Information) lacked sex-specificity. To resolve this limitation, we integrated sex-specific contact rates from Peru [16], assuming it to have a comparable population structure and social dynamics. This could affect our model's predictions of the contribution of a woman's infection status during pregnancy to cCMVi cases, for example. Due to the sparse and the partially missing sex-specificity data in the contact survey from Peru, after individuals turn 50, they are removed from the population. However, unlike women of child-bearing age, older adults generally do not engage in the behaviours most strongly associated with CMV transmission risk to the same extent. Thus, we believe this is a reasonable modelling assumption. Limitations of available contact matrices also influenced our generated population structure, which does not fully align with that of the current Brazilian population despite being generated based on the current Brazilian birth rate in 2021 [17]. In our model, the proportion of newborns and children is slightly higher than that of adults, which may modestly influence the number of new disease transmission cases, as children are more contagious. Since we tested different seroprevalence scenarios from different Brazil regions, we accepted these modest differences, as presumably population structure differs between tested regions. Indeed, urban population structures tend to differ from rural ones, as shown in Prem et al. [15]. For example, in rural settings in Colombia (a country with an overall similar population structure to Brazil), population structure remains constant from birth until around age of 25, after which the number of people decreases with age, whereas it increases till the age of 30 in urban settings. Lastly, our understanding of the chronic stage and reactivation remains limited, and the reductions of 25%, 50% and 75%, while instructive, were selected for convenience. This highlights the need for further research into the role of reactivation and its impact on CMV transmission dynamics.

Preventing CMV transmission and thus reducing cCMVi cases will provide worldwide benefits. It is critical to study the effects of vaccination in a country like Brazil due to its high CMV seroprevalence, higher mixed-aged contacts, and prolonged breastfeeding habits which lead to high CMV transmission. Our findings emphasize the importance of implementing CMV vaccination in the youngest age groups, including children and infants, particularly in regions with high CMV seroprevalence. Further, our results indicate that a CMV vaccine does not need to provide lifelong protection against infection to effectively reduce cCMVi cases in high seroprevalence settings. Indeed, even a vaccine with protection equal to post-infection immunity (i.e., <50% protective) was predicted to result in significant benefits to the whole population. However, certain conditions must be met, including high (at least 2/3) coverage of the target populations. Given the similarity of our model's predictions to the low seroprevalence scenario [11], it seems likely that infants and younger children are optimal targets for CMV vaccination, irrespective of a country's seroprevalence. Hence, results of this study provide an optimistic outlook for a substantial reduction in the burden of cCMVi cases if a vaccine conferring even modest protection is administered to infants. Future CMV vaccine trials should evaluate safety and efficacy in infants and measure the impact of vaccination on transmission as well as on acquisition of infection.

CRediT authorship contribution statement

Sonia Gazeau: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Catherine Byrne:** Writing – review & editing, Validation, Software, Methodology, Investigation. **Daniel Coombs:** Writing – review & editing, Validation, Investigation. **Colin Kunzweiler:** Writing – review & editing, Validation, Data curation, Conceptualization. **Renato Calabro Calheiros:** Writing – review & editing, Validation, Conceptualization. **John Diaz-Decaro:** Writing – review & editing, Validation, Conceptualization. **Soren Gantt:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Morgan Craig:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Code availability

The computational code to create the synthetic Brazilian population and simulate the vaccine scenarios is available on GitHub at https://github.com/Craig-Lab/Mathematical-modeling-of-CMV-in-Brazil.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128788.

Data availability

Data will be made available on request.

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