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Optimizing age of cytomegalovirus screening and vaccination to avert congenital disease in the US

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ABSTRACT

Cytomegalovirus (CMV) infection is the leading cause of congential cognitive deficit, visual impairment and hearing loss in the US. Clinical trials are underway to evaluate the efficacy of CMV vaccine candidates in seronegative females. The optimal age of such vaccination depends on the interplay among age-specific transmission dynamics, vaccine efficacy and vaccine waning. We developed an age-structured model of CMV transmission dynamics in the US and estimated age-specific transmission rates of CMV based on age-stratified CMV prevalence, congenital infections per birth, breastfeeding patterns and demographic data. We found that the optimal age of vaccination depended on the duration of vaccine protection. For most scenarios, the optimal age of vaccination was between 19 and 21 years of age. However, for a rapidly waning vaccine, the optimal age of vaccination can shift to infants under 1 year. This shift arises when the duration of vaccine efficacy is too brief to offer appreciable protection during the child-bearing years. In this case, it becomes more effective to achieve indirect protection by reducing transmission from infants, the transmissibility from whom was estimated to be an order of magnitude higher than other age classes. Knowledge of vaccine waning is paramount to optimizing CMV vaccination and is thus a key parameter for longitudinal clinical evaluation.

1. Introduction

Human cytomegalovirus (CMV) infects more than half of the population worldwide [1]. Congenital CMV infection is the primary cause of birth defects in the United States [2], responsible annually for an estimated 4470, 2382 and 895 new childhood cases of hearing loss, cognitive deficit and visual impairment, respectively [3]. The Institute of Medicine ranks the development of a CMV vaccine as a high priority given the morbidity and mortality that it could avert [4]. While there are currently no drugs or vaccines licensed for CMV, several candidate vaccines are under evaluation in clinical trials [5–7]. The chances of congenital infection and subsequent disease are more than 20 times higher if the mother develops a primary infection during pregnancy, compared to women who are infected but have recovered from the primary infection phase [8]. Consequently, the vaccine development efforts have been focused on preventing congenital infection in seronegative women.

The optimal timing of vaccination is determined by a balance between two factors: (i) the increase of seroprevalence with age and (ii) the potential waning of vaccine protection over time. Because CMV infection is lifelong [9], seroprevalence increases with age. Therefore, fewer females are seronegative later in life, making it possible to achieve a higher coverage of vaccination in infants than in older females. In contrast, if the vaccine protection wanes with time, vaccinating too early in life could mean that the protection will have waned by the time that women reach child-bearing ages. To evaluate how the balance of these two factors interact to determine the optimal age for CMV screening and vaccination, we developed a dynamic transmission model for CMV, calibrated to age-specific seroprevalence in the US. We assessed a range of scenarios that varied with regard to screening coverage, vaccine efficacy and duration of vaccine protection. For most cases, we found that the optimal age for vaccination was 19–21 years. However, if vaccine efficacy wanes so quickly that it cannot offer sufficient duration of protection during the childbearing years, it can become more effective to protect mothers from infection by vaccination of the highly transmissible infant age class.

2. Methods

We developed an age-structured model of CMV transmission dynamics composed of a system of differential equations

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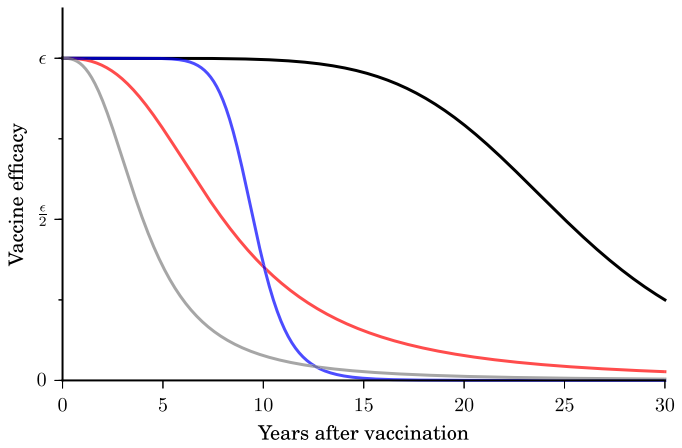

Fig. 1. Vaccine efficacy with respect to time after vaccination. The vaccine efficacy depends on the duration of vaccine protection. Here the durations of protection have the same functional sigmoidal form (Supplement), but different half-life (HL) and quarter-life (QL), defined as the number of years over which the efficacy drops to a half and to a quarter of the initial efficacy (ε), respectively. We defined a short protection as a HL of 4 years and a QL of 6 years (gray), an intermediate protection with gradual decline as a HL of 8 years and a QL of 12 years (red), an intermediate protection with steep decline as a HL of 9.5 years and a QL of 10.5 years (blue), and a long protection as a HL of 25 years and a QL of 30 years (black). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

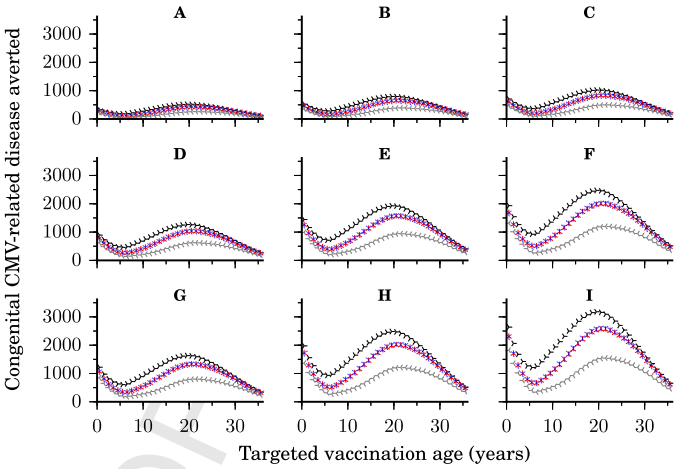

Fig. 2. Cumulative cases of congential CMV-related disease averted with respect to the target age of vaccination. The scenarios vary with respect to screening coverage (20%: **A**, **B** and **C**; 60%: **D**, **E** and **F**; 90%: **G**, **H** and **I**), initial vaccine efficacy (50%: **A**, **D** and **G**; 75%: **B**, **E** and **H**; 95%: **C**, **F** and **I**), as well as the duration of vaccine protection (as depicted in Fig. 1): short (gray), intermediate with gradual descent (red), intermediate with steep descent (blue) and long (black). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

(Supplement). We stratified the modeled population by infection status, distinguishing among individuals who are susceptible, have a primary infection, or have a non-primary infection. Individuals acquire primary infection by contact with infectious individuals, or by vertical transmission, either congenitally or perinatally, from their mothers [10]. Upon recovery from a primary infection, individuals remain in a non-primary infection for the remainder of their life [11,12]. Individuals with primary infections are more transmissible than those with non-primary infections, because viral shedding is higher during primary infections [13]. Likewise, mothers with a primary infection have a higher probability of transmitting CMV congenitally [8]. Similarly, young children are more transmissible and have a higher risk of infection than adults [14–16].

Age-specific transmission and other key parameters were fitted to the US demographic dynamics (population size by age [17,18], births by maternal age [19–21], deaths by age [22] and immigration by age [23]), CMV seroprevalence [24–27], breastfeeding patterns [28–35], and to the estimated fraction of congenital infections per birth in the US [3]. Details of the fitting procedure are provided in the Supplement.

To evaluate vaccination, we further compartmentalized the population by sex and varied the age at which women were screened for CMV seropositivity. Women that tested seronegative within the target age group were vaccinated, and thus obtained a protection against primary infection that depended on the initial vaccine efficacy and the rate at which protection waned.

We evaluated 1260 scenarios of vaccination that varied according to three values of vaccine efficacy: low (50%), intermediate (75%) and high (95%); four types of duration of protection: short, intermediate with steep decline, intermediate with gradual decline, and long (defined in Fig. 1); three coverages of screening within the targeted age group: low (20%), intermediate (60%) and high (90%); and 36 possible age targets for vaccination (0–35 years old in annual increments). The outcome measure compared was the cumulative number of congenital CMV-related disabilities averted by vaccination over a period of 20 years starting in 2025.

3. Results

Calibrating the model to the US demographics and CMV seroprevalence, we estimated the odds of transmission of infants compared to adults (9.6), the odds of transmission of non-primary infections compared to primary infections (0.0024), as well as the probability of vertical transmission to the infant by breastfeeding (0.14), among other parameters (Supplement Table S2). The calibrated model was then extended to evaluate the optimal age of vaccination for 1260 scenarios of vaccine profile.

For each scenario, we calculated the cumulative cases of disease averted (Fig. 2). We found that the number of cases averted as a function of the age of vaccination exhibited two local maxima: the first was at under 1 year of age, and the second was between 19 and 21 years. Faster waning reduced the difference between the local maxima, indicating that protection from a rapidly waning vaccine would not span most of the childbearing ages.

The overall optimal age of vaccination was determined as the global maximum of cases averted (Table 1). We found that the optimal age of vaccination ranged from 19 to 21 years for most scenarios. However, for the scenarios with relatively short protection combined with intermediate or high screening coverage, it was optimal to vaccinate infants younger than 1 year old. As expected,

Table 1
Optimal age of screening and vaccination for CMV.

Efficacy	Coverage	Duration of protection			
		Short	Gradual	Steep	Long
50%	20%	21	20	20	19
50%	60%	21	20	20	19
50%	90%	0	20	20	19
75%	20%	21	20	20	19
75%	60%	0	20	20	19
75%	90%	0	20	20	19
95%	20%	21	20	20	19
95%	60%	0	20	20	19
95%	90%	0	20	20	19

The optimal age depends on the initial efficacy of the vaccine, the screening coverage and the duration of protection. Duration of protection was parameterized as short, intermediate with a gradual decline (gradual), intermediate with a steep decline (steep), and long as depicted in Fig. 1.

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