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Country- and age-specific optimal allocation of dengue vaccines

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HIGHLIGHTS

- We model dengue transmission and incorporate age-specific distribution of dengue burden.
- We identify optimal dengue vaccine allocations that minimize dengue hemorrhagic fever cases.
- We showed that optimal vaccine allocation strategies vary with the demographic burden of dengue.

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ABSTRACT

Several dengue vaccines are under development, and some are expected to become available imminently. Concomitant with the anticipated release of these vaccines, vaccine allocation strategies for dengue-endemic countries in Southeast Asia and Latin America are currently under development. We developed a model of dengue transmission that incorporates the age-specific distributions of dengue burden corresponding to those in Thailand and Brazil, respectively, to determine vaccine allocations that minimize the incidence of dengue hemorrhagic fever, taking into account limited availability of vaccine doses in the initial phase of production. We showed that optimal vaccine allocation strategies vary significantly with the demographic burden of dengue hemorrhagic fever. Consequently, the strategy that is optimal for one country may be sub-optimal for another country. More specifically, we showed that, during the first years following introduction of a dengue vaccine, it is optimal to target children for dengue mass vaccination in Thailand, whereas young adults should be targeted in Brazil.

1. Introduction

Dengue is a mosquito-borne *Flavivirus* disease and a growing public health problem in many tropical and sub-tropical countries (Beatty et al., 2011), with around 2.5 billion people worldwide at risk of infection (Suaya et al., 2009; Halstead, 2007). It is estimated that 50 to 100 million cases of dengue and 12,000 deaths occur annually (Suaya et al., 2009). Dengue is primarily transmitted by the mosquito vector *Aedes aegypti*, but *Aedes albopictus* and *Aedes polynesiensis* may also act as vectors (Halstead, 2007). The disease is caused by a virus organized in four distinct, but closely related and co-circulating, serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 (Halstead, 2007). Infection with a serotype appears to provide life-long immunity against reinfection with that serotype, but not against the others (Murrell et al., 2011). The severity of the disease varies from asymptomatic infections to life-threatening dengue hemorrhagic fever (DHF). DHF is a potentially fatal complication of dengue due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment (Halstead, 2007). DHF is the leading cause of viral hemorrhagic fever worldwide with more than 500,000 cases annually (Srikiatkhachorn et al., 2010; Whitehorn and Farrar, 2010). Importantly, severe disease, including DHF, is much more likely among individuals who have already recovered from a primary infection and are experiencing a secondary infection with a different serotype (Murrell et al., 2011).

Epidemics of dengue fever were first reported in Southeast Asia in the 19th century (Chareonsook et al., 1999). The four dengue serotypes have long been endemic in many Southeast Asian countries, including Thailand, which is one of the world's most affected countries (Chareonsook et al., 1999; Nagao and Koelle, 2008). Starting as early as the 1960s, Thailand was implementing vector control programs through insecticide use and health education (Nagao and Koelle, 2008). In contrast to Thailand, dengue was reintroduced in Brazil in 1989 after an absence of over 20 years (Rodriguez-Barraquer et al., 2011). Three serotypes, DENV-1,2, and 3, are currently endemic throughout Brazil with the four serotype emerging (Rodriguez-Barraquer et al., 2011). Despite government efforts to promote surveillance and vectors control,

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dengue is continuing to spread in Brazil (Rodriguez-Barraquer et al., 2011; Siqueira et al., 2005; Luz et al., 2011).

Vaccine development has been challenging by the need for vaccines conferring strong protection against all four serotypes to avoid the elevated risk of severe disease associated with secondary infections (Schmitz et al., 2011). However, several vaccine candidates are currently under development that target the four dengue serotypes (Murrell et al., 2011; Schmitz et al., 2011). A Sanofi Pasteur vaccine, which is currently undergoing phase 3 trials (Sabchareon et al., 2012), is projected to become available by 2015–2020 (Amarasinghe and Mahoney, 2011; Watson, 2011). It has been suggested that during the first years of roll-out, vaccination campaigns should focus on the routine vaccination of infants and catch-up mass vaccination for the remainder of the population (Amarasinghe and Mahoney, 2011; Watson, 2011; Amarasinghe et al., 2010). However, logistical and supply limitations are likely to make the vaccine scarce during the first years following its release (Watson, 2011). Thus, we determine the optimality of vaccine allocation strategies that most effectively minimize the incidence of dengue hemorrhagic fever.

The demographic burden of dengue differs geographically (Halstead, 2006). For example, DHF is predominant among adults in Latin American countries such as, and most notably, Brazil where the dengue burden is high and continues to increase (Rodriguez-Barraquer et al., 2011; San Martín et al., 2010; Shepard et al., 2011). By contrast, children are disproportionately affected by DHF in Southeast Asia, such as Thailand, burdened with the largest endemic prevalence (Halstead, 2006; Nisalak et al., 2003; Shekhar and Huat, 1992; Endy et al., 2002). As a consequence of the heavy dengue burden in Thailand and Brazil, these countries are likely to be among the first to introduce dengue vaccination (Amarasinghe and Mahoney, 2011; Lee et al., 2011).

Several mathematical models have been developed to investigate issues related to dengue transmission dynamics, such as seasonality, infection-induced immunity, antibody-dependent enhancement of disease (Johansson et al., 2011; Andraud et al., 2012), vector control (Luz et al., 2011), and vaccination (Chao et al., 2012). To our knowledge, ours is the first model to address the problem of optimal allocation of dengue vaccine during the early stage of vaccine availability. We extended a previous dengue transmission model (Luz et al., 2011; Durham et al., 2013) to account for human demography, four dengue serotypes, and the different epidemiological profiles for DHF corresponding to Brazil and Thailand. Our dengue transmission model consists of a system of ordinary differential equations describing the rates at which humans and mosquitoes transition between different infection and immunity states (Luz et al., 2011). We used the dengue transmission model to identify the optimal vaccine allocation strategies for minimizing the overall number of DHF cases during the initial phase of a dengue vaccine roll-out. We found that optimal vaccine allocation strategies vary significantly with the profile of the age-specific dengue burden and with vaccine availability. Consequently, a mass vaccination strategy that is optimal in one country is not necessarily optimal in another. Specifically, we found that it is optimal to target children in Thailand and to target young adults in Brazil, when initial vaccine supplies are limited.

2. Methods

We constructed a deterministic, compartmental model capturing features known to affect the transmission dynamics of dengue: host–vector interactions; immunological interactions between the 4 dengue serotypes; population age structure; and age-specific levels of transmission. We assumed that all infants are born protected against dengue infection through maternal immunity (Murphy, 2011). As maternal immunity wanes, individuals become susceptible to the four dengue serotypes. Infection with a serotype provides lifelong immunity against that specific serotype. We account for antibody-dependent enhancement by assuming that the probability of developing dengue hemorrhagic fever (DHF) after secondary/tertiary/quaternary infection is greater than that of primary infection. Each individual can develop up to four dengue infections during their lifetime. We assumed that vaccine recipients would have reduced susceptibility and infectiousness.

We calibrated our model to an endemic dengue incidence of 5% annually, which is consistent with epidemiological data from Thailand and Brazil under the assumption that approximately 80% of dengue infections are asymptomatic, also consistent with clinical data (Shepard et al., 2011; Nisalak et al., 2003; Endy et al., 2002). We compared two epidemiological profiles for the demographic burden of dengue. The first profile was representative of empirical epidemiological profile of DHF incidence in Thailand, where children are disproportionately infected (Nisalak et al., 2003; Sriprom et al., 2003; Cummings et al., 2009). The second profile was representative of empirical epidemiological profiles of DHF incidence in Brazil, where DHF is more common among adults (San Martín et al., 2010; Guzmán et al., 2002). To generate the different DHF epidemiological profiles, we parameterized an age-dependent probability of mosquito-to-human transmission. This probability was chosen because it is the main factor influencing the age-dependent DHF incidence in our model. We varied these probabilities to capture the patterns of empirical DHF incidence (Fig. S2).

We optimized the age-targeted vaccination programs. Given that some vaccines are used inefficiently on recovered and immune individuals, we additionally optimize a vaccine program where individuals are vaccinated according to their infection history (never infected *versus* infected at least once). Information on individuals' infection history can be obtained using commercially available serological tests such as immunoglobulin M and immunoglobulin G enzyme-linked immunosorbent assay (ELISA Peeling et al., 2010). Although such a policy may be impractical (Peeling et al., 2010), it gives an upper bound on the effectiveness of vaccination programs.

Given a number T_{vac} of daily vaccine doses, we used an optimization routine (Boggs and Tolle, 2000; Nocedal and Wright, 2006) to identify the age-specific allocation of vaccine doses that minimizes the incidence of DHF. We assumed that there were only enough doses to vaccinate 10% of the population (older than six months old) annually. Such a constraint in vaccine availability is likely to be observed during the first years of a dengue vaccine roll-out due to high demand from dengue endemic countries and limited production capacity of pharmaceutical companies (Watson, 2011). We also assumed that, in addition to age-targeted vaccination, routine vaccination of infants (at six months old) was independently carried out at a rate ν_{vac}. We assumed that infants younger than six months old are protected against dengue infection through maternal antibodies (Murphy, 2011). Full model description is given in the Supplementary Materials.

To calculate the degree of vaccine coverage necessary to sustain herd immunity, we assumed a fraction ν_{vac} of infants receive the vaccine and calculated the equilibrium level of dengue infections while varying ν_{vac} from 0 to 1. We defined herd immunity as occurring when dengue incidence was lower than 1% of the pre-vaccination incidence.

Given that different values of the age-dependent probability of mosquito-to-human transmission could generate similar DHF profiles, we performed an uncertainty analysis to test the