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A multi-country study of dengue vaccination strategies with Dengvaxia and a future vaccine candidate in three dengue-endemic countries: Vietnam, Thailand, and Colombia

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ABSTRACT

Background: The dengue vaccination era began when Dengvaxia (CYD-TDV) became available in 2016. In addition, several second-generation vaccine candidates are currently in phase 3 trials, suggesting that a broader availability of dengue vaccines may be possible in the near future. Advancing on the recent WHO-SAGE recommendations for the safe and effective use of CYD-TDV at the regional level on average, this study investigates the vaccination impacts and cost-effectiveness of CYD-TDV and of a hypothetical new vaccine candidate (NVC) in a country-specific manner for three endemic countries: Vietnam, Thailand, and Colombia.

Methods: The vaccination impacts of CYD-TDV and NVC were derived by fitting the empirical seroprevalence rates of 9 year olds into an individual-based meta-population transmission model, previously used for the WHO-SAGE working group. The disability-adjusted life years were estimated by applying country-specific parametric values. The cost-effectiveness analyses of four intervention strategies in combination with routine and catch-up campaigns were compared for both vaccines to inform decision makers regarding the most suitable immunization program in each of the three countries.

Results and conclusion: Both CYD-TDV and NVC could be cost-effective at the DALY threshold cost of $2000 depending upon vaccination costs. With CYD-TDV, targeting 9 year olds in routine vaccination programs and 10–29 year olds as a one-off catch-up campaign was the most cost-effective strategy in all three countries. With NVC, while the most cost-effective strategy was to vaccinate 9–29 and 9–18 year olds in Vietnam and Thailand respectively, vaccinating younger age cohorts between 1 and 5 years old in Colombia was more cost-effective than other strategies. Given that three countries will soon face decisions regarding whether and how to incorporate CYD-TDV or future dengue vaccines into their budget-constrained national immunization programs, the current study outcomes can be used to help decision makers understand the expected impacts and cost-effectiveness of such vaccines.

1. Introduction

Dengue fever is a major public health concern in many parts of the tropics and subtropics. The global burden of dengue has increased substantially in recent years. A recent study shows that there are approximately 96 million apparent and 294 million inapparent dengue infections occurring annually [1]. The majority of dengue-endemic regions of the world, and therefore the burden of dengue, are in developing countries. Nevertheless dengue control activities are not often considered a priority for public health interventions, partly due to the absence of specific treatment, and the costly nature of vector control activities in a developing-country setting [2,3].

Due to the complexity of the disease which is caused by four related but antigenitically distinct viruses (serotypes), it has been challenging not only to have a full understanding of dengue ecology and immunology [4], but also to develop effective vaccines against it [5]. For example, it is known that infection with one dengue serotype provides life-long immunity only to that specific serotype and temporary cross-protection to other serotypes, but sequential infection with two different serotypes can bring favorable (short-term heterologous protection) or detrimental outcomes due to a high degree of antigenic cross-reactivity [5–8]. In particular, while a patient with a primary dengue infection nor-

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mally experiences mild symptoms, a heterologous secondary infection tends to lead to more severe illness, partly due to the antibody dependent enhancement (ADE) caused by non-protective heterotypic antibodies arising from the primary infection [6,7,9]. Humans who have experienced a secondary, heterologous infection and recovered are believed to be protected against further infections [4].

A first live, attenuated tetravalent vaccine (Dengvaxia, CYD-TDV) became commercially available in 2016 and has already been licensed in some dengue-endemic countries (e.g. Brazil, Mexico, Philippines, and Thailand). There have been several debates regarding the safety signal of CYD-TDV where the main issue is the increased risk of developing severe illness on vaccinated seronegative individuals [10–13]. The Strategic Advisory Group of Experts (SAGE), WHO's independent expert advisory committee, organized a consortium of eight modeling groups to produce WHO/SAGE reports and position papers on the safe and effective use of CYD-TDV [14,15]. The researchers recently published the estimated long-term safety, public health impact, and cost-effectiveness of CYD-TDV based on the outcomes from the modeling groups [16]. The WHO's main aim was to inform general recommendations on the optimal use of CYD-TDV. Critically, these reports raise the importance of having country-specific inputs when considering the introduction of CYD-TDV, given that the use of CYD-TDV is not recommended for populations with low seroprevalence due to potential longer-term risks of severe dengue in vaccinated seronegative individuals [14]. In particular, the authors reported that the cost-effectiveness results should be interpreted as the regional cost-effectiveness of vaccination on average, and not as the cost-effectiveness in a country-specific context. More recently (2017), Sanofi Pasteur officially confirmed that while CYD-TDV provides protective benefit against dengue fever in those who are seropositive, more severe illness could occur following vaccination upon a subsequent dengue infection in those who are seronegative [17]. Based on the preliminary results from the recent analysis of vaccine safety of CYD-TDV, WHO also updated its position that CYD-TDV should be administered only to individuals who have been infected with dengue prior to vaccination, such that why are seropositive prior to vaccination [18].

The main interests of the current study lie in understanding the cost-effectiveness of dengue vaccines in three endemic countries: Vietnam, Thailand, and Colombia. Dengue has been highly prevalent in these countries, causing substantial economic burden [3]. Nonetheless, CYD-TDV has not been introduced into a nationwide vaccination program in any of the countries at the time of this research. The vaccine is licensed in Thailand but is currently being used only in the private sector, and neither Vietnam nor Colombia has licensed the vaccine yet. In addition to CYD-TDV, there are several second-generation vaccine candidates in phase 3 trials, and it is therefore expected that these three countries will soon face decisions on incorporating the current and future vaccine candidates into their budget-constrained national vaccination programs [3,19]. Therefore, having robust estimates of the cost-effectiveness of existing and future dengue vaccines would help facilitate the process of vaccine introduction into national immunization programs. This study presents vaccination impacts and cost-effectiveness analyses (CEA) of dengue vaccines with various vaccination strategies for two different vaccine types: Dengvaxia (CYD-TDV) and a new vaccine candidate (NVC). In the case of NVC, the current study proposes hypothetical vaccine profiles and measures impact outcomes compared with CYD-TDV. Vaccination impacts were derived via a transmission model previously used in the WHO study, and this is the first time that country-specific CEA has been conducted by applying such a model to current and future vaccines.

2. Methods

2.1. Transmission model

Vaccination impact was estimated using a spatially explicit, individual-based meta-population transmission model [9,20] developed by the Oxford/Exeter group for the WHO SAGE working group exercise; the details on model parameters can be found in Flasche et al. [16]. Briefly, human individuals were categorized into susceptible, incubating, infectious or recovered with respect to each serotype, allowing for up to four sequential infections. The human population was arranged in a regular grid of subpopulations with size kept constant, and death rates for both humans and mosquitos were age-dependent. For the current multi-country study, the model was fitted against empirical seroprevalence rates of children at 9 years old by adjusting the human-to-vector and vector-to-human transmission probabilities, as done previously by the Oxford/Exeter group [16]. The seroprevalence rates of 9 year olds in Colombia and 9–12 year olds in Vietnam and Thailand were obtained from two published results and used as the baseline seroprevalence rates in these countries [21,22].

Table 1 summarizes key parameter values and vaccination strategies considered in this study. Vaccine efficacy for CYD-TDV was that reported from the two phase 3 trials (CYD14 and CYD15), and thus vaccine efficacy varied by serotype [23]. Vaccine efficacy for NVC was assumed to be 80% against all four serotypes. In order to understand the long-term safety of CYD-TDV, long-term follow-up analysis has been carried out [23]. One of the findings in the follow-up study was the decrease in the protective effect of

Table 1
Parameter values for transmission model and vaccination strategies.

	CYD-TDV	NVC
Vaccine efficacy[a]	58.4% (serotype1), 47.1% (serotype2),73.6% (serotype3), 83.2%(serotype4)	80% for all serotypes
Efficacy half-life (exponential decay)	3 years for seropositives; 1 year for seronegatives	8 years for all serostatus
Coverage rate	80% (alternatively 50%)	80% (alternatively 50%)
Vaccine doses	3 doses	2 doses
Vaccination strategies	9yo routine 9yo routine & 10–18 catch-up 9yo routine & 10–29 catch-up	9yo routine 9yo routine & 10–18yo catch-up 9yo routine & 10–29yo catch-up 1yo routine & 2–5yo catch-up
Seropositivity rate at 9yo[b]	62.1 (Vietnam), 79.5 (Thailand), 20.5 (Colombia)	
Transmission probabilities (human to vector)	0.5 (Vietnam), 0.425 (Thailand), 0.2951 (Colombia)	
Transmission probabilities (vector to human)	0.51 (Vietnam), 0.43 (Thailand), 0.2953 (Colombia)	

[a] Source for CYD-TDV: [23].
[b] Sources: [21,22].