THE IMPACT OF THE NEWLY LICENSED DENGUE VACCINE IN ENDEMIC COUNTRIES

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INTRODUCTION

Since April 2016, a dengue vaccine is available being produced by Sanofi Pasteur, Dengvaxia, and recommended by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on immunisation to be used in regions with high endemicity, as defined by the prevalence of dengue antibodies of more than 50% in the targeted age group 9-45 years [1]. Analysis of year 3 results of phase III trials of Dengvaxia suggest high rates of protection of vaccinated partial dengue immunes but high rates of hospitalizations during breakthrough dengue infections of persons who were vaccinated when seronegative, with Dengvaxia raising dengue infection-enhancing antibodies (ADE) [2,3].

Here, we discuss the risks behind Dengvaxia recommendation [4], after analyzing an age structured dengue model [5], using the publicly available vaccine trial data [1].

OBJECTIVES AND METHODOLOGY

Using mathematical models, we investigate the impact of the newly licensed dengue vaccine in endemic countries [5]. An age structured model was developed to explore the clinical outcome of two vaccination strategies: 1) vaccinate all individuals, ages 9-45 years and 2) vaccinate only persons, ages 9-45 years, who are dengue seropositive.

Modelling the efficacy of the Sanofi Pasteur dengue vaccine

Efficacy for confirmed dengue cases (years 1-2):

Using the available dengue vaccine trials data in the Asian-Pacific region (CYD14) as reported in [6] and the Latin American countries (CYD15) as reported in [7], the overall vaccine efficacy for virologically confirmed dengue cases was estimated, via the Bayesian approach, obtaining a probability $p(k|I_v, I_c)$ for the vaccine efficacy k with infected individuals I_v in the vaccine group and I_c in the control group.

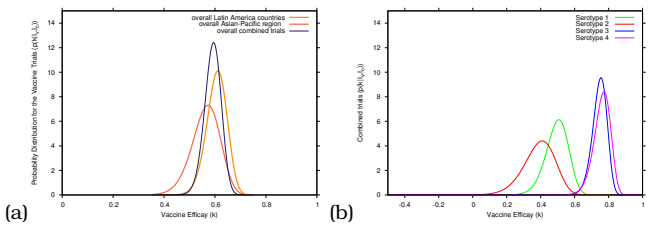
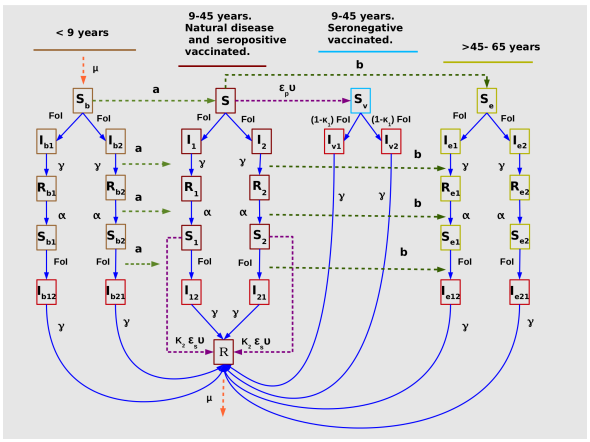


Fig. 1: The Bayesian estimate of the combined vaccine efficacy trials is $k = 59.2\%$ with a 95%-CI of $[52.4; 65.0]$ (see Fig. 1 (a), dark blue curve). For the serotype specific vaccine efficacy we observe that any possible common efficacy for all serotypes is statistically excluded (see Fig. 1 (b)).

Mathematical modelling of future vaccine impact

An age structured model was developed based on the WHO's recommendation for vaccine implementation in endemic countries. Only individuals $9 - 45$ years of age are vaccinated. We define seropositive individuals to be those that have been already exposed and infected with at least one dengue virus in life and seronegative individuals those that have never been infected with any dengue virus.



Efficacy for hospitalized dengue cases (age groups, years 1-4):

Similar to the analysis performed above, we now use the publicly available data for the annual incidence of dengue case hospitalizations for the CYD14 trial, presented as relative risk in the WHO report [see table 8 in ref. 6], to estimate the vaccine efficacy for dengue case hospitalizations.

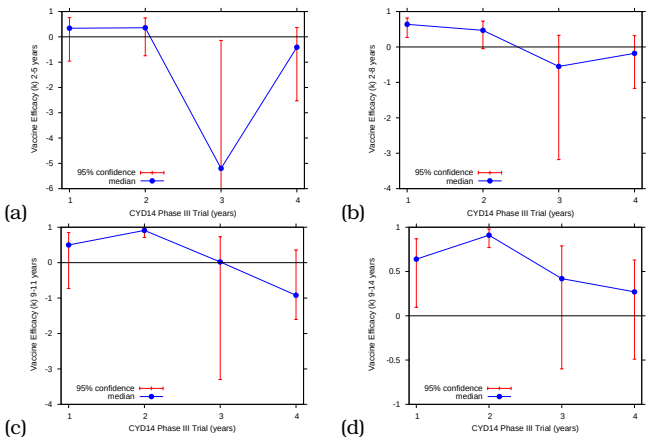


Fig. 2: Vaccine efficacy (VE) is not a static measure. In a) children between $2 - 5$ years of age. In b) aggregated data for children UNDER 9 years of age ($2 - 8$ years old). In c) children between $9 - 11$ years old and in d) aggregated data for children OLDER 9 years of age ($9 - 14$ years old). During year 3, the Bayesian estimate of the vaccine efficacy for hospitalized cases in children under 9 years of age (Figure 2 (b)) is $k = -53.6\%$ with a 95%-CI of $(-279.8; 38.2)$, whereas for children between $2 - 5$ years of age (Figure 2 (a), the Bayesian estimate of the vaccine efficacy for hospitalized cases is $k = -530.6\%$ with a 95%-CI of $(-631.6; -40.1)$. Here, any positive vaccine efficacy is statistically rejected. During year 4, a negative vaccine efficacy was also estimated for individuals between $9 - 11$ years old ($k = -92.4\%$ and a 95%-CI of $[-160.3; 36.8]$). For more information, see [10], where a clear correlation between age and serostatus is shown.

Efficacy for hospitalized dengue cases (by age, by serostatus, years 1-6):

We now use the publicly available data for the annual incidence of dengue case hospitalizations for the CYD14/15/57 trials, presented as relative risk in [9], to estimate the vaccine efficacy for dengue case hospitalizations by age and individual serostatus.

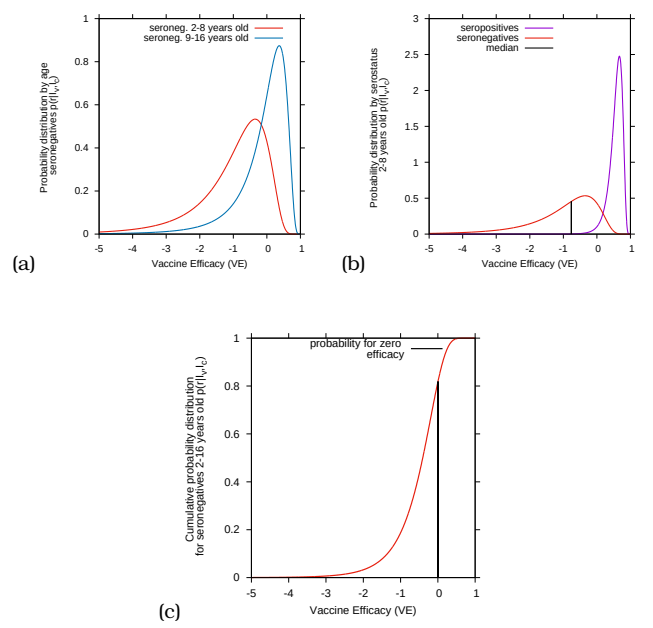


Fig. 3: The comparison between VE distributions by serostatus, for seronegatives and seropositives sharing the same age, shows a significant difference among those individuals, (Fig. 3 a), with little overlap observed. However, regardless of age differences, a large overlap between the VE distributions of seronegatives of 2-8 and 9-16 years of age (Fig 3 b) is observed, suggesting that serostatus is determining the efficacy of this vaccine and not age. As for the cumulative distribution for all seronegative individuals, 2-16 years, enrolled in the vaccine trials (Fig. 3 c), we observe 82% probability of negative VE but only 18% probability of positive VE, indicating that the individual immune status prior to vaccination needs to be considered.

RESULTS

Dengvaxia implementation WITHOUT immunological screening:

In this scenario, both seropositive and seronegative individuals are eligible to receive the vaccine without prior immunological screening. 4% of population $9 - 45$ years old is vaccinated per year, according to Sanofi's first expectations [13].

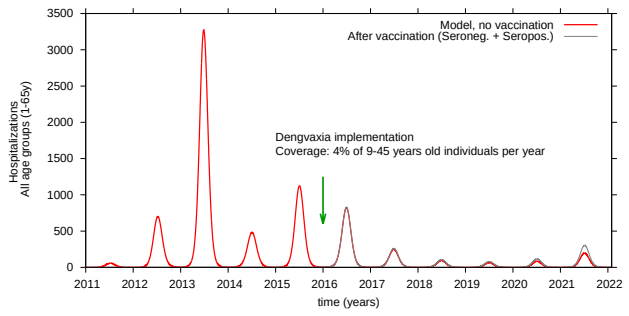


Fig. 4: Hospitalizations increase on average by 25% in 5 years.

Dengvaxia implementation AFTER prior immunological screening:

In this scenario, Dengvaxia is administrated only to seropositive individuals after population screening.

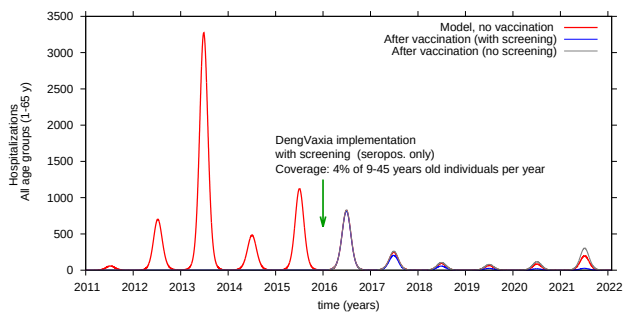


Fig. 5: Here, we observe an overall reduction of hospitalization of more than 40% in 5 years, when 4% of seroposive invidividuals, between $9 - 45$ years, are vaccinated per year.

CONCLUSIONS

Analysis of recent publicly available data on age and serostatus confirmed statistically a vaccine induced risk in seronegative individuals. Although the disease extinction is not reachable with this vaccine, by restricting vaccination to only seropositive individuals, a significant impact of reducing hospitalization is observed. Our results show that to achieve significant reduction in disease burden and hospitalization, the vaccination program is most effective if it includes only individuals that have been already exposed to at least one dengue virus. Immunological screening of the population prior to vaccination is advised [4,5] and vaccination strategies must be planned based on epidemiological disease dynamics for each specific endemic region [10].

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