Article

The impact of serotype cross-protection on vaccine trials: DENVax as a case study

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1   **Abstract:** There is a growing public health need for effective preventive interventions against dengue,
2   and a safe, effective and affordable dengue vaccine against the four serotypes would be a significant
3   achievement for disease prevention and control. Two tetravalent dengue vaccines, Dengvaxia (Sanofi
4   Pasteur) and DENVax (Takeda Pharmaceutical Company), have now completed phase 3 clinical
5   trials. While Dengvaxia resulted in serious adverse events and is restricted to individuals with prior
6   dengue infections, DENVax has shown, at first glance, some encouraging results. Using the available
7   data for the TAK 003 trial, we estimate, via the Bayesian approach, vaccine efficacy (VE) of the
8   post-vaccination surveillance periods. Although better measurement over long time was expected
9   for the second part of the post-vaccination surveillance, variation in serotype-specific efficacy needs
10   careful consideration. Besides observing that individual serostatus prior to vaccination is determinant
11   of DENVax vaccine efficacy, we also compare the VE estimations for 12 and 18 months and we observe
12   that the efficacy is decreasing over time. The comparison of efficacies over time is informative and
13   very important, bring up the discussion of the role of temporary cross-immunity in dengue vaccine
14   trials and the impact of serostatus prior to vaccination in the context of dengue fever epidemiology.

15   **Keywords:** Dengue; Dengue vaccine trials; vaccine efficacy; cross-protection; serotypes; serostatus;
16   Bayesian approach

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17   **1. Introduction**

18   Dengue fever is a viral mosquito-borne infection, a major international public health concern, with
19   approximately 3 billion people at risk of acquiring the infection. Caused by four antigenically related
20   but distinct serotypes (DENV-1 to DENV-4), it is estimated that 390 million dengue infections occur
21   every year, of which 96 million manifest symptoms with any level of disease severity [1]. Antibodies
22   generated by exposure to any one type cross-react with other types, providing short duration cross
23   protective immunity. Subsequent infections by any other of the 3 heterotypic serotypes increases
24   the risk of developing severe dengue due to an immunological process called antibody-dependent
25   enhancement (ADE) [2–5]. Treatment of uncomplicated dengue cases is only supportive, and severe
26   dengue cases require hospitalization. There is a compelling public health need for an effective
27   preventive intervention against dengue. A safe, effective and affordable dengue vaccine against
28   the four serotypes would be a significant achievement for disease prevention and control.

29   Two tetravalent dengue vaccines have now completed phase 3 clinical trials, and a third vaccine is
30   currently in a phase 3 trial [6–11]. The first product, Dengvaxia, is a chimeric yellow fever tetravalent
31   dengue vaccine developed by Sanofi Pasteur and when given to seronegative children resulted in a
32   significantly higher rate of hospitalized severe dengue cases compared with age-matched seronegative

controls [6–8]. The risks behind giving this vaccine have been discussed [12,13]. An age structured mathematical model was developed, based on Sanofi's recommendation, and its analysis has shown a significant increase on the number of hospitalizations in a population when this vaccine was administered without population screening [14], i.e. given to both seropositive and seronegative individuals as previously suggested in [15]. Reviews in 2016-2017 identified individual serostatus prior to vaccination as determinants of Dengvaxia efficacy and adverse events [16,17], anticipating Sanofi Pasteur's retest of the entire phase 3 serum collection announced in November 2017 [18,19]. Dengvaxia is licensed in more than 20 countries, although mass vaccination programs, initiated in the Philippines [20] and in the South of Brazil, are now suspended.

Based upon recent licensing statements (in 2019) by the E.U. and the US Food and Drug Administration (FDA), Dengvaxia administration is restricted to individuals with prior dengue infections. An issue that must be addressed is the availability of a screening test that will accurately identify dengue seropositives. This is a technical challenge, since ELISA IgG tests vary in specificity and sensitivity [21].

The second product, DENVax (TAK 003), a tetravalent chimeric vaccine developed by Takeda Pharmaceutical Company, consists of a live attenuated dengue 2 virus (DENV-2) that provides the genetic backbone for DENV 1, 3 and 4. A DENVax phase 3 trial consisting of fever-based surveillance of vaccine efficacy (VE) followed by a period of hospitalization surveillance has been completed. Case surveillance over the first 12 months after vaccination of Latin American and Asian children yielded initial encouraging results [9]. Vaccine efficacy against virologically confirmed dengue disease and hospitalization was higher and more balanced than efficacies reported for Dengvaxia [8]. DENVax achieved a 74.9% and 82.2% [9] compared with Dengvaxia's 52.5% and 81.9% efficacies in seronegative and seropositive children, respectively [8].

Vaccine efficacy data have now been extended to 18 months of surveillance [10] indicating that, similarly to Dengvaxia, individual serostatus prior to vaccination is determinant of vaccine efficacy. Vaccine efficacy estimations for 12 and 18 months show that DENVax efficacy is decreasing over time and therefore, long-term surveillance consisting of prudent and careful observation of vaccine phase 3 recipients is required [20].

In this manuscript, DENVax vaccine efficacy for virologically confirmed dengue cases are estimated via a Bayesian approach. Vaccine efficacy measurements over time, six months apart, are compared and the variations observed in serotype-specific efficacies brings up the discussion of the role of temporary cross-immunity on dengue vaccine trials and the impact of serostatus prior to vaccination in the context of dengue fever epidemiology.

2. Results

Using the publicly available DENVax phase 3 trial data [9,10], vaccine efficacy for virologically confirmed dengue cases are estimated via a Bayesian approach to obtain the probability $p(k|I_v, I_c)$ for the vaccine efficacy k with infected individuals I_v in the vaccine group and infected individuals I_c in the control group. The statistical description of the vaccine trial data was in good agreement with the published 12 and 18 month surveillance results as shown in Table 1 and Table 2 respectively. For detailed calculations, see Section 4.

Vaccine efficacy by serotype and serostatus estimations are shown in Table 1 part A, using data for the first 12 months surveillance period [9]. As expected, vaccine efficacy againt serotype 2, the serotype that provides the genetic "backbone" for Takeda's DENVax was very high, independent of the individual serostatus prior to vaccination: with estimated 96.2% and 100% versus 96.5% and 100% as reported in [9] for seropositives and seronegatives respectively. Note that in the seronegative vaccinated group, no dengue 2 cases were observed, but in the seropositive group there were. Vaccine efficacy against serotype 1 was observed to be slightly smaller in seronegative (estimated 79.8% as reported in [9]) than in seropositive individuals (estimated 65.9% versus 67.2% reported in [9]).There was a negative vaccine efficacy estimated for serotype 3 in seronegative individuals (−31.2% versus −38.7%

Table 1. Compilation of vaccine efficacies estimation for Takeda's DENVax vaccine phase 3 trial post-vaccination surveillance period part 1 (12 months) [9]. Section A shows the vaccine efficacies by serostatus and serotype, and Section B shows the overall vaccine efficacy by serotype. Highlighting problems observed for serotypes 3 (blue) and 4 (grey) are indicated.

Part 1 efficacy data of the TAK-003 phase 3 trial [15]									
section A						section B			
Dengue Serotype	Seropositive at baseline (82.2%)			Seronegative at baseline (74.9%)			Overall (seropositive and seronegative) vaccine efficacy		
	Vaccinated (n= 9167)	Control (n=4589)	Estimated vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n=3531)	Control (n=1726)	Estimated Vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n= 12700)	Control (n=6316)	Estimated vaccine efficacy and 95% Confidence Interval [17]
	Dengue cases	Dengue cases		Dengue cases	Dengue cases		Dengue cases	Dengue cases	
ALL	41	110	81.4% [73.6%, 87.1%]	20	39	74.8% [57.4%, 85.4%]	61	149	79.7% [72.8%, 85.1%]
DEN1	7	17	78.9% [51.8%, 91.4%]	9	13	65.9% [22.2%, 85.8%]	16	30	73.2% [52.2%, 85.4%]
DEN2	3	42	96.2% [89.9%, 98.8%]	0	22	100%	3	64	97.5% [93.6%, 99.3%]
DEN3	28	47	70.0% [52.6%, 81.4%]	11	4	-31.2% [-353.2.7%, 53.8%]	39	51	61.9% [42.4%, 75.8%]
DEN4	3	4	**61.9% [-63.2%, 91.9%]**	0	0	inconclusive	3	4	**61.9% [-62.4%, 91.9%]**

82 as reported in [9]) against an intermediate vaccine efficacy in seropositives (estimated 70% versus 71.3%
83 reported in [9]), shown in Table 1 Section part A, in light blue color. Results for serotype 4 were shown
84 to be statistically insignificant for seropositives (estimated 61.9% with 95%CI $[-63.2\%-91.9\%)$ and
85 completly "inconclusive" for seronegatives, as no cases were observed in any of the groups, vaccinated
86 or control (see Fig. 2a)).

87   Table 1 Section B presents, in yellow, the overall vaccine efficacy (not by serostatus, but by
88 serotype only), with high efficacy for serotype 2 (estimated 97.5% versus 97.7% as reported in [9]) and
89 intermediate efficacies for serotypes 1 (estimated 73.2% versus 73.7% as reported in [9]) and serotype 3
90 (estimated 61.9% versus 62.6% as reported in [9]). Results for serotype 4 were statically insignificant
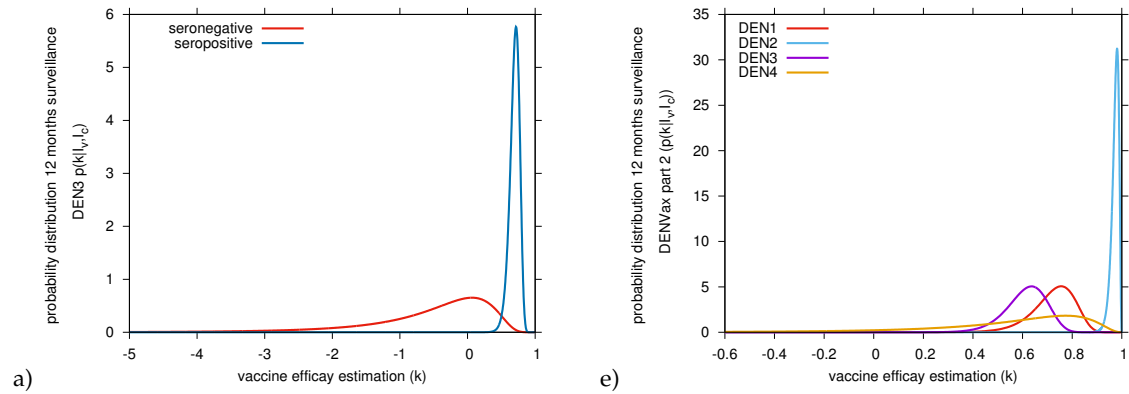91 due to small numbers (see Fig. 2b)).

Figure 1. Bayesian estimate of DENVax vaccine efficacies (VE) against virologically confirmed dengue for the first 12 months surveillance (part 1). In a) DEN3 serotype specific vaccine efficacy by serostatus. Red and blue curves show the estimates for the seronegative and seropositive individuals respectively. In b) serotype-specific VE estimations. Data from Table 1, as reported in [9], are used to estimate the distribution by dengue serotype for individuals aged 4–16 years old. High vaccine efficacy for dengue serotype 2 and intermediate to low vaccine efficacy for the other serotypes are observed.

92   Table 2 is also divided in "Section A", presenting our estimations obtained by serotype and
93 serostatus and in "Section B", showing the results stratified by serotype only.
94   A slight decrease in vaccine efficacies was observed for the second surveillance period, with the
95 overall vaccine efficacy estimated to be of 72.5% and the 95%-CI [65.6%, 78.1%], instead of $k = 79.7\%$
96 and the 95%-CI [72.8%, 85.1%] estimated for the first surveillance period. Overall vaccine efficacy for

Table 2. Compilation of vaccine efficacies estimation for Takeda's DENVax vaccine phase 3 trial post-vaccination surveillance period part 2 (18 months) [10]. Section A shows the vaccine efficacies by serostatus and serotype, and Section B shows the overall vaccine efficacy by serotype. Highlighting problems observed for serotypes 3 (blue) and 4 (grey) are indicated.

	Part 2 efficacy data of the TAK-003 phase 3 trial [16]								
	section A						section B		
	Seropositive at baseline (82.2%)			Seronegative at baseline (74.9%)			Overall (seropositive and seronegative) vaccine efficacy		
Dengue Serotype	Vaccinated (n= 9167)	Control (n=4589)	Estimated vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n=3531)	Control (n=1726)	Estimated Vaccine efficacy and 95% Confidence Interval [17]	Vaccinated (n= 12700)	Control (n=6316)	Estimated vaccine efficacy and 95% Confidence Interval [17]
	Dengue cases	Dengue cases		Dengue cases	Dengue cases		Dengue cases	Dengue cases	
ALL	75	150	75.8% [67.2%, 81.0%]	39	56	66.1% [48.9%, 77.3%]	114	206	72.5% [65.6%, 78.1%]
DEN1	21	37	71.2% [51.8%, 83.3%]	17	25	66.7% [39.2%, 82.1%]	38	62	69.4% [54.6%, 79.7%]
DEN2	7	54	93.2% [91.1%, 97.1%]	1	26	97.7% [90.7%, 99.7%]	8	80	94.6% [90.3%, 97.7%]
DEN3	43	54	60.3% [40.6%, 73.2%]	20	6	**-59.9% [-328.5%, 31.1%]**	63	60	47.7% [25.4%, 63.1%]
DEN4	4	5	**59.5% [-47.2%, 89.4%]**	1	0	inconclusive	5	5	**50.1% [-72.5%, 85.4%]**

specific dengue serotype 2 was estimated to be high, $k = 94.6\%$ [90.3%, 97.7%], whereas vaccine efficacy for dengue serotype 1, $k = 69.4\%$ [54.6%, 79.7%] and dengue serotype 3, $k = 47.7\%$ [25.4%, 63.1%], were estimated to be much lower than the estimations obtained for the first 12 months of surveillance. Results for serotype 4 were still statistically insignificant, $k = 50.1\%$ [−72.5%, 85.4%], including negative vaccine efficacy. Figure 1a) shows the Bayesian estimates of DENVax serotype-specific vaccine efficacy (see Fig. 2).

Regarding the estimations obtained by serotype and serostatus, shown in Table 2 Section A, vaccine efficacy estimation was kept very high against DENV serotype 2, with $k = 93.2\%$ and $k = 97.7\%$ for seropositive and seronegative respectively. Vaccine efficacy against serotype 1 was observed to be slightly lower for seronegative, with $k = 66.7\%$ [39.2%, 82.1%], than in seropositive individuals, with $k = 71.2\%$ [51.8%, 83.3%]. Of concern, as shown in Table 2 section A, blue color, negative vaccine efficacy, $k = −59.9\%$ [−328.5%, 31.1%], was estimated for vaccinated seronegative individuals who were infected with serotype 3, as opposed to an intermediate efficacy, $k = 60.3\%$ [40.6%, 73.2%] for seropositives. Similarly to the other serotypes, DENV 3 efficacy declined over the following 6 months of surveillance data (see Fig. 1b).
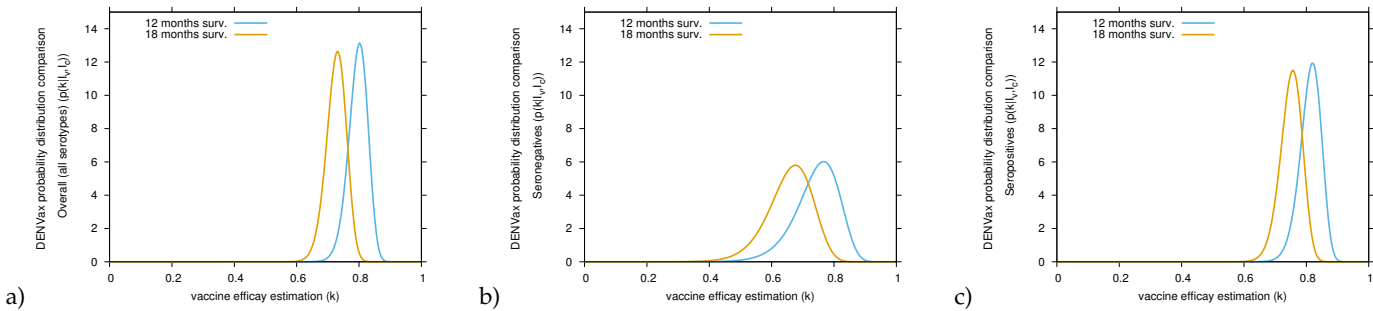

Figure 2. Bayesian estimates comparison of DENVax vaccine efficacies (VE) against virologically confirmed dengue cases. Yellow and light blue curves show the estimates for the first 12 months (part 1) and the 18 months (part 2) surveillance respectivelly. In a) overall VE estimations for all serotypes, in b) VE estimation for seronegative individuals and in c) VE estimations for seropositive individuals. Data from Tables 1 and 2, as reported in [9,10], are used to estimate the distribution by dengue serotype and serostatus for individuals aged 4–16 years old. Vacine efficacy is decreasing over time.

It is important to note that these results obtained within 12-18 months post-vaccination periods are still within the well established period of cross-protective immunity against clinical disease that

114 follows a first dengue infection [22,23]. And this trend suggests that early DENVax protective efficacy
115 may be attributed to cross-protection and therefore may continue to decline over time. Vaccine efficacy
116 estimations for serotype 4 were kept statistically insignificant during the 18 months of surveillance. The
117 small number of cases contained a suggestion of negative vaccine efficacy for vaccinated seropositive
118 children. The possibility exists that efficacy against DENV 4 may follow the pattern of serotype 3 as
119 case numbers increase.

120   Curiously, for both trials combined, the Asian-Pacific and the Latin American, Sanofi Pasteur's
121 Dengvaxia produced higher vaccine efficacies against serotypes 3 and 4 (over 70%, see Fig. 2 a)) than
122 to serotypes 1 and 2 (around 40%) [24] while the pattern of Takeda DENVax efficacy has been the
123 opposite, high overall vaccine efficacies for serotypes 1 and 2 and moderate to low vaccine efficacy for
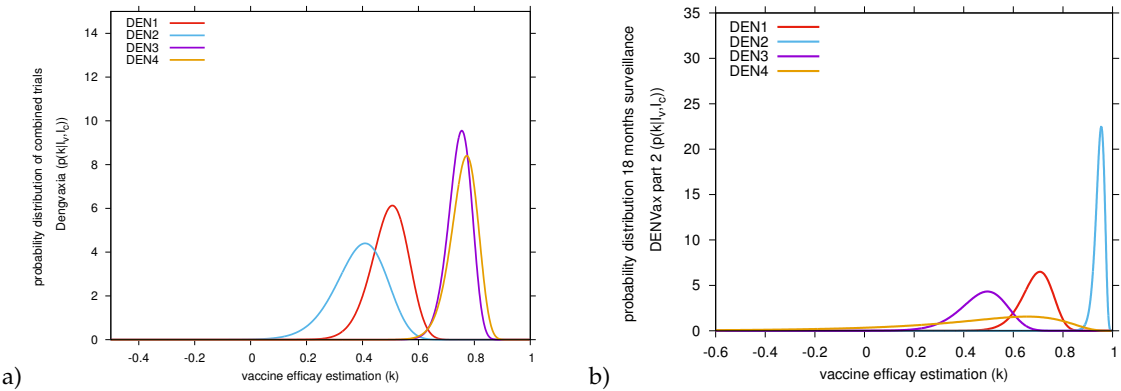124 serotypes 3 and 4 (see Fig. 2 b)).

Figure 3. Bayesian estimate of vaccine efficacies (VE) against virologically confirmed dengue. In a) serotype-specific VE for Dengvaxia, Sanofi Pasteur. Data reported in [8] were used for VE estimation by dengue serotype for individuals aged 9 years and older. In b) serotype-specific VE for DENVax, Takeda. Data from Table 2, as reported in [10], are used for VE estimation by dengue serotype for individuals aged 4–16 years old.

3. Discussion

126   DENVax vaccine efficacy against virologically confirmed dengue disease and hospitalization
127 were shown to be higher than efficacies reported for the Sanofi Pasteur tetravalent dengue vaccine,
128 Dengvaxia, with a more balanced efficacy in seronegatives and seropositives. Takeda's DENVax
129 vaccine efficacy for participants who were seronegative at baseline was estimated to be of 74.9% and
130 82.2% for those who were seropositive at baseline (see Table 1, Section B), whereas Sanofi Pasteur's
131 Dengvaxia has shown a 52.5% and 81.9% vaccine efficacy in seronegative and seropositive individuals,
132 respectivelly, as reported in [8].

133   Using the new DENVax phase 3 trial data, vaccine efficacy measurements over time, six months
134 apart, are compared and the variations observed in serotype-specific efficacies are discussed. Of
135 concern, negative vaccine efficacy was estimated for vaccinated seronegative individuals who were
136 infected with serotype 3, as opposed to an intermediate efficacy for seropositives. The possibility exists
137 that efficacy against DENV 4 may follow the pattern of serotype 3 as case numbers increase.

138   Variations in serotype-specific efficacies of DENVax are concerning when it is recalled that for
139 Dengvaxia high rates of hospitalization of vaccinated young children, mis-interpreted as vaccine
140 failure, were resolved long after the vaccine was widely licensed and administered in millions of
141 children. Initial low vaccine efficacy was shown to include vaccine adverse events, a significant
142 incidence of hospitalization for severe dengue in vaccinated compared with unvaccinated seronegative
143 children.

144   Besides observing that individual serostatus prior to vaccination is determinant of DENVax
145 vaccine efficacy, we also compare the VE estimations for 12 and 18 months and we observe that

the efficacy is decreasing over time. The comparison of efficacies over time is informative and very important since it brings up the discussion of the role of temporary cross-immunity on dengue vaccine trials and the impact of serostatus prior to vaccination in the context of dengue fever epidemiology.

With respect to DENVax we urge the vaccine community to adopt the stance of "watch and wait." It is too soon to understand the behavior of this vaccine in individuals of differing immunological serostatus or age. Long-term surveillance consisting of prudent and careful observation of vaccine phase 3 recipients is required.

Careful design of vaccine policies are urgently needed and recommendations concerning the use of dengue vaccines should consider a better measurement of vaccine efficacy over time and safety through enhanced phase 4 surveillance.

4. Materials and Methods

Vaccine trials can be modeled using a previously investigated simple epidemiological process, the linear infection model [25], which can be solved analytically in all aspects, and thus serve as a test model for many further aspects, like parameter estimation, model comparison, or analytics of approximation schemes. [26–28].

In this section we describe the methodology used to estimate DENVax vaccine efficacy via a Bayesian approach, using the data from Takeda's dengue vaccine trial in Latin America and Asia [9,10].

4.1. Linear infection model

The basic assumptions for modelling a vaccine trial are exactly the ones described by the linear infection model, which has the following reaction scheme

$$S + I^* \quad \xrightarrow{\beta} \quad I + I^* \tag{1}$$

for infected I and susceptibles $S = N - I$, with population size N, and infection rate β as the only possible transition. The underlying model hypothesis is that infection can be aquired from outside the considered trial population of size N by meeting a constant number of infected individuals I^* from a much larger background population. The master equation for the probability $p(I, t)$ is

$$\frac{\mathrm{d}}{\mathrm{d}t} p(I, t) = \frac{\beta}{N} I^* \cdot (N - (I - 1)) p(I - 1, t) - \frac{\beta}{N} I^* \cdot (N - I) p(I, t) \tag{2}$$

which can be solved using the characteristic function

$$\langle e^{i\kappa I} \rangle := \sum_{I=0}^{N} e^{i\kappa I} \cdot p(I, t) =: g(\kappa, t) \tag{3}$$

with $\beta^* := (\beta/N) I^*$ as the external infection level, and initial condition $p(I, t_0) = \delta_{I, I_0}$, as described in more detail in [26]. The solution of the master equation is given by

$$p(I, t) = \binom{N - I_0}{I - I_0} \left(e^{-\beta^*(t - t_0)} \right)^{N - I} \left(1 - e^{-\beta^*(t - t_0)} \right)^{I - I_0} \quad .$$

Due to the special initial conditions of having exactly I_0 infected at time t_0 this solution is at the same time the transition probability $p(I, t | I_0, t_0)$, needed to construct the likelihood function for parameter estimation of data vector $\underline{I} = (I_0, I_1, ..., I_n)$. See [26] for further discussion on this point.

4.2. Modelling vaccine trials with the linear infection model

For modelling a vaccine trial we have the special case of one data point each for the processes of the "control group" and the "vaccine group". For the control group we have the scheme

$$S_c + I^* \xrightarrow{\beta} I_c + I^* \tag{4}$$

and with initially N_c participants in the control group, we have after a time interval $T := t - t_0$ (here $T = 12$ respectively 18 months for the DENVax vaccine trial [9,10]) the solution of the process given by the probability of having I_c disease cases in the control group

$$p(I_c, T) = \binom{N_c}{I_c} \left(e^{-\beta^* T} \right)^{N_c - I_c} \left(1 - e^{-\beta^* T} \right)^{I_c}$$

with parameter $\theta_\beta := e^{-\beta^* T}$ incorporating the effects of external infection levels over the time period T. The parameter θ_β is also the probability not to become infected over the considered time interval. For parameter estimation purposes, the solution of the master equation $p(I_c, T)$ is also the likelihood of the single model parameter θ_β of the control group process, hence $p(I_c, T) =: L(\theta_\beta) = p(I_c|\theta_\beta)$, with the last notation as used in the Bayesian statistical framework [25–27].

For the vaccine group we have the same epidemiological process, but with (hopefully) reduced infectivity $c \cdot \beta$ instead of β, or with vaccine efficacy $k := 1 - c$,

$$S_v + I^* \xrightarrow{(1-k)\beta} I_v + I^* \tag{5}$$

and solution for N_v participants in the vaccine group to find I_v infected still (in spite of the vaccination effort)

$$p(I_v, T) = \binom{N_v}{I_v} \left(e^{-(1-k)\beta^* T} \right)^{N_v - I_v} \left(1 - e^{-(1-k)\beta^* T} \right)^{I_v}$$

now with parameter $\theta_k := e^{-(1-k)\beta^* T} = \left(e^{-\beta^* T} \right)^{1-k} = \theta_\beta^{1-k}$. The master equation solution is now again to be interpreted as a likelihood function $p(I_v, T) := L(\theta_k) = p(I_v|\theta_k)$ or in terms of the already estimated θ_β we have as well $p(I_v, T) = p(I_v|k, \theta_\beta)$. Hence we have to estimate the parameter of external infection level θ_β from the data of the control group, and then estimate the vaccine efficacy k from the information of the vaccine group. Via the Bayesian approach we obtain explicitly a probability for the vaccine efficacy based on the empirical data from the vaccine trial, $p(k|I_v, I_c)$, where insecurity of the intermediate parameter of external infection level θ_β is taken into account by marginalizing over this parameter.

Previously we have given from the linear infection model the statistical description of the vaccine trial data via the Bayesian approach in very good agreement with the results in [9,10].

5. Bayesian analysis

From the above mentioned likelihood functions we can immediately calculate posterior distributions for the parameters given the data, once the priors for the parameters are chosen. For details especially concerning the linear infection model see [25], and then also [26,27].

In detail, from the likelihood function of θ_β for the control group of the vaccine trial $L(\theta_\beta) = p(I_c|\theta_\beta)$ which has the form of a beta-distribution, we can obtain the posterior distribution $p(\theta_\beta|I_c)$ by using for the prior a conjugate form of a beta-distribution with parameters a and b as

$$p(\theta_\beta|I_c) = \frac{p(I_c|\theta_\beta)}{p(I_c)} \, p(\theta_\beta) \tag{6}$$

with a normalization constant, also called "evidence" in the context of model comparison [27] and further references cited there, $p(I_c) = \int p(I_c|\theta_\beta) \cdot p(\theta_\beta) \, d\theta_\beta$. Then the prior can be given as

$$p(\theta_\beta) = \frac{\Gamma(a+b)}{\Gamma(a) \cdot \Gamma(b)} \, \theta_\beta^{a-1} \cdot (1-\theta_\beta)^{b-1} \tag{7}$$

with parameters a and b to be chosen to be much smaller than the respective exponents in the likelihood function. We chose $a = b = 0.5$ giving a dish shaped distribution with lowest values around $\theta_\beta = 0.5$, hence in no way resembling any one-humped distribution as expected for the posterior. After some calculations, see [25] for any details, we obtain the posterior distribution, the probability density to find the background infection level conditioned on the control group outcome data, as

$$p(\theta_\beta|I_c) = \frac{\Gamma(a+k_2+b+k_3)}{\Gamma(a+k_2) \cdot \Gamma(b+k_3)} \, \theta_\beta^{a+k_2-1} \cdot (1-\theta_\beta)^{b+k_3-1} \tag{8}$$

with $k_2 = N_c - I_c$ and $k_3 = I_c$ as data dependent parameters. Note that another constant k_1 is used in likelihood maximization and cancels out in the Bayesian approach [28].

To calculate the finally sought quantity $p(k|I_v, I_c)$ we also need to obtain from the likelihood $L(k) = p(I_v|k, \theta_\beta)$ for the vaccine group the Bayesian posterior $p(k|I_v, \theta_\beta)$ with

$$p(k|I_v, \theta_\beta) = p(\theta_k|I_v) \cdot \frac{d\theta_k}{dk} \tag{9}$$

with $\theta_k = \theta_\beta^{1-k}$ as defined above. Again after some calculations using the conjugate prior

$$p(\theta_k) = \frac{\Gamma(a_v+b_v)}{\Gamma(a_v) \cdot \Gamma(b_v)} \, \theta_k^{a_v-1} \cdot (1-\theta_k)^{b_v-1} \tag{10}$$

being as uninformed as possible by choosing $a_v = b_v = 0.5$ again, we obtain the result

$$p(k|I_v, \theta_\beta) = \frac{\Gamma(a_v+k_{v2}+b_v+k_{v3})}{\Gamma(a_v+k_{v2}) \cdot \Gamma(b_v+k_{v3})} \, \theta_k^{a_v+k_{v2}-1} \cdot (1-\theta_k)^{b_v+k_{v3}-1} \cdot \left(\ln\left(\frac{1}{\theta_\beta}\right) \cdot \theta_\beta^{1-k} \right) \tag{11}$$

with $k_{v2} = N_v - I_v$ and $k_{v3} = I_v$ as defined above.

But to calculate the finally sought $p(k|I_v, I_c)$, using the previously calculated posteriors $p(\theta_\beta|I_c)$ and $p(k|I_v, \theta_\beta)$, we need to integrate over the parameter θ_β whose insecurity has not been taken into account by our considerations up to now. Hence we calculate $p(k|I_v, I_c)$ as the marginal probability distribution of the joint probability distribution $p(k, \theta_\beta|I_v, I_c) = p(k|I_v, \theta_\beta) \cdot p(\theta_\beta|I_c)$, namely

$$p(k|I_v, I_c) = \int_0^1 p(k|I_v, \theta_\beta) \cdot p(\theta_\beta|I_c) \, d\theta_\beta \tag{12}$$

with the final result plotted in Fig. 2, and its cumulative distribution function $P(k|I_v, I_c)$ in order to read off the confidence intervals around the median as best estimator in the Bayesian approach.

From the data which generates Fig. 2a) for example (the others follow accordingly), we obtain from the median of the marginalized posterior $P(k_{0.5}|I_v, I_c) = 0.5$ the Bayesian estimate of the vaccine efficacy $k_{0.5} = 81.4\%$ for overall seropositives and the 95%-confidence interval from the 0.025 and 0.975 quantiles, hence $P(k_{0.025}|I_v, I_c) = 0.025$ for the lower bound $k_{0.025} = 73.6\%$ and $P(k_{0.975}|I_v, I_c) = 0.975$ for the upper bound $k_{0.975} = 87.1\%$. This is in good agreement with the values given in [9] (with xx % (95%-CI: xx - xx)), given the somehow arbitrary Bayesian priors with their parameters a, b, a_v and b_v.

In total we have given from the linear infection model the statistical description of the vaccine trial data via the Bayesian approach in very good agreement with the results in [9,10] and in addition

211 the graphical representation of the posteriors and the figures 1,2 and 3, indicating where the bulks of
212 the probabilities are concentrated.

References

1. Bhatt, S. et al.. The global distribution and burden of dengue. *Nature* **2013**, *496*, 504-507.

2. Halstead, S. B. Antibody-dependent Enhancement of Infection: A Mechanism for Indirect Virus Entry into Cells. In *Cellular Receptors for Animal Viruses*; ISBN 0-87969-429-7, Chapter 25; Cold Spring Harbor Laboratory Press, 1994; pp. 493-516.

3. Dejnirattisai, W. et al. (2010). Cross-Reacting Antibodies Enhance Dengue Virus Infection in Humans. *Science* **2010**, *328*, 745–748.

4. [10] Scott B. Halstead. Dengue antibody-dependent enhancement: knowns and unknowns. *Microbiol Spectrum* **2014**, *2 (6)*, AID-0022-2014.

5. [11] Leah C. Katzelnick et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science* **2017**, *358 (6365)*, 929-932.

6. Capeding, M.R., et al.. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia:a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* **2014**, *384*, 1358–1365.

7. Villar, L., et al.. Efficacy of a tetravalent dengue vaccine in children in Latin America. *New Engl. J. Med.* **2015**, *372*, 113–123.

8. Hadinegoro, S.R., et al.. Efficacy and long term safety of a dengue vaccine in regions of endemic disease. *New Engl. J. Med.* **2015**, *373*, 1995-1206.

9. Biswal, Shibadas and Reynales, Humberto and Saez-Llorens et al. Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. *New Engl. J. Med.* **2019**, *381*, 2009-2019.

10. [16] Biswal S, Borja-Tabora C, Martinez Vargas L, et al.. Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: a randomised, placebo-controlled, phase 3 trial. *The Lancet* **2020**, *395 (10234)*, 1423-1433.

11. Esper G Kallas et al.. Safety and immunogenicity of the tetravalent, live-attenuated dengue vaccine Butantan-DV in adults in Brazil: a two-step, double-blind, randomised placebo-controlled phase 2 trial. *The Lancet Infectious Diseases* **2020**, *20 (7)*, 839-850.

12. Aguiar M., Stollenwerk N., Halstead S.B. The risks behind Dengvaxia recommendation. *Lancet Infect. Dis.* **2016**, *16*, 882–883.

13. Scott B. Halstead and Philip K Russell. Protective and Immunological Behavior of Yellow Fever Dengue Chimeric Vaccine. *Vaccine* **2016**, *34 (14)*, 1643–647.

14. Maíra Aguiar, Nico Stollenwerk and Scott B. Halstead. The impact of the newly licensed dengue vaccine in endemic countries. *PLoS Neglected Tropical Diseases* **2016**, *10 (12)*, e0005179.

15. World Health Organization Strategic Advisory Group of Experts (SAGE) on Immunization. (2016). Background paper on Dengue Vaccines prepared by the SAGE working group on dengue vaccines and the WHO secretariat. Retrieved from
    $http://www.who.int/immunization/sage/meetings/2016/april/1\_Background\_Paper\_Dengue\_Vaccines\_2016\_03\_17.pdf?ua = 1$

16. Aguiar, M. and Stollenwerk, N. Dengvaxia efficacy dependency on serostatus: a closer look at more recent data. *Clinical Infectious Diseases* **2018**, *66 (4)*, 641-642.

17. Aguiar, M. and Stollenwerk, N. Dengvaxia: age as surrogate for serostatus. *The Lancet Infectious Diseases* **2018**, *18 (3)*, 245.

18. Sanofi updates information on dengue vaccine. Press Release from November 29, 2017. Retrieved from

$https$: $//www.sanofipasteur.com/$ − $/media/Project/One$ − $Sanofi$ − $Web/Websites/Global/Sanofi$ − $Pasteur$ − $COM/Home/en/media$ −

$room/docs/PR_20171130_SanofiUpdatesInfoOnDengueVaccine_EN.pdf$

19. World Health Organization. (2018). Revised SAGE recommendation on use of dengue vaccine. Retrieved from

$https$: $//www.who.int/immunization/diseases/dengue/revised\_SAGE\_recommendations\_dengue\_vaccines\_apr2018/en/$

20. Scott B. Halstead et al.. Ethics of a partially effective dengue vaccine: Lessons from the Philippines. *Vaccine* **2020**, *38*, 5572–5576.

21. Aguiar, M. Dengue vaccination: a more ethical approach is needed. *The Lancet* **2018**, *391 (10132)*, 1769-1770.

22. Sabin A.B. Research on dengue during World War II. *Am. J. Trop. Med. Hyg.* **1952**, *1*, 30-50.

23. Anderson K.B., Gibbons R.V, Cummings D.A., et al. A Shorter Time Interval Between First and Second Dengue Infections Is Associated With Protection From Clinical Illness in a School-based Cohort in Thailand. *J. Infect. Dis.* **2013**, *209 (3)*, 360-368.

24. Maíra Aguiar, Luís Mateus and Nico Stollenwerk. The currently best estimate for worldwide dengue vaccine efficacy. *AIP Conference Proceedings* **2016**, *1738*, 390014.

25. N. Stollenwerk and V. Jansen. In *Population Biology and Criticality: From critical birth–death processes to self-organized criticality in mutation pathogen systems*. Imperial College Press, World Scientific, London, 2011.

26. N. Stollenwerk, M. Aguiar, S. Ballesteros, J. Boto, B. Kooi and L. Mateus. Dynamic noise, chaos and parameter estimation in population biology. *Roy. Soc. Interface Focus* **2012**, *2*, 156-169.

27. L. Mateus, N. Stollenwerk and J. C. Zambrini. Stochastic Models in Population Biology: From Dynamic Noise to Bayesian Description and Model Comparison for Given Data Sets. *Int. Journal. Computer Math.* **2013**, *90*, 2161-2173.

28. L. Mateus, D. Masoero, F. Rocha, M. Aguiar, U. Skwara, P. Ghaffari, J. C. Zambrini and N. Stollenwerk. Epidemiological models in semiclassical approximation: an analytically solvable model as test case. In *Proceedings of the 14th International Conference on Computational and Mathematical Methods in Science and Engineering, CMMSE 2014, Cadiz, Spain, ISBN 978-84-616-9216-3.*