Statistical Analysis Plan for bridging VE from the CYD14+CYD15 9–16 year old cohort to a new setting (18–45 year old adults) via the Gilbert and Huang (2016) bridging method

Used for the Gilbert et al. manuscript "Bridging efficacy of a tetravalent dengue vaccine from children/adolescents to adults in high endemic countries based on neutralizing antibody response"

Peter B. Gilbert, Ying Huang

Statistical Center for HIV/AIDS Research and Prevention
Vaccine and Infectious Disease Division
Fred Hutchinson Cancer Research Center

April 5, 2017

1 Introduction

This statistical analysis plan (SAP) uses the same notation used in Gilbert and Huang (2016, *Epidemiological Methods*) (henceforth GH).

There are two objectives of the bridging method, each for a fixed study time t post first vaccination assuming the vaccination schedule used in CYD14 and CYD15:

1) To make inference on $\text{VE}^{d*}(t, v)$ and $\text{VE}^{*}(t, v)$ [additive-difference and multiplicative-reduction vaccine efficacy against DENV-v based on the virologically confirmed dengue (VCD) endpoint between month 0 and month t for each serotype v=1,2,3,4] for a specific hypothetical Phase 3 trial with study time follow-up from 0 to t during a specific calendar period of follow-up in a specific study population.

2) To make inference on $\text{VE}^{d*}(t)$ and $\text{VE}^{*}(t)$ [additive-difference and multiplicative-reduction vaccine efficacy against DENV-Any based on the VCD endpoint between month 0 and month t] for a specific hypothetical Phase 3 trial with study time follow-up from 0 to t during a specific calendar period of follow-up in a specific study population.

For addressing objectives 1) and 2), the time point t is chosen to be 25 months post first vaccination, to match the active surveillance follow-up period for VCD in the CYD14 and CYD15 efficacy trials. The specific hypothetical Phase 3 trial of interest is for 18—45 year olds in a given region where dengue is highly endemic. The focus will be on addressing this objective for 18–45 year olds for the hypothetical setting where the entire CYD14+CYD15 study (all countries included in CYD14/CYD15) had included an 18-45 year old cohort under identical follow-up/ecological conditions and surveillance for VCD as for the 9-16 year olds, which we refer to as Goal 1.

Goal 1 is accomplished by using the CYD22 study as a 'calibration study,' because it measured PRNT_{50} baseline and Month 13 neutralization titers for both 9-16 year olds and 18-45 year olds, which allows estimation of the age-differences in these distributions. Assuming that these age-differences in CYD22 would be the same in CYD14+CYD15 allows using the PRNT_{50} baseline and Month 13 neutralization titers from CYD14+CYD15 9-16 year olds– plus calibrations from CYD22– to estimate these titer distributions in the hypothetical CYD14+CYD15 18-45 year old study.

In addition, the objectives will be addressed for bridging to a country not included in CYD14 or CYD15, assuming that PRNT_{50} neutralization titer data are measured in the 18-45 year old cohort of interest in that country. This approach is applied to India using CYD47 data that measured PRNT_{50} baseline and Month 13 neutralization titer data in 18-45 year olds. This analysis for a country not included in CYD14 or CYD15 can be done using the same methods as for the other objectives, using the empirical baseline and month 13 titers from 18-45 years old in the new country, by conceptualizing the analysis as bridging to the new country for the hypothetical scenario that the background/unvaccinated DENV-Any VCD risk through 25 months and the serotype frequencies in that country are the same as for hypothetical CYD14+CYD15 18-45 year olds.

In general, the bridging formula may also be applied to any assumed scenario about background/unvaccinated DENV-Any VCD risk and/or serotype frequencies in the new country, where these scenarios may be informed by epidemiological data in the new country.

Two statistical approaches based on estimating different vaccine efficacy curves in CYD14 +CYD15 9-16 year olds are used to address the serotype-specific objective 1), which we summarize as follows:

Serotype-Specific VE **Approach 1:** First, apply the GH method to estimate the four serotype-specific VE curves through 25 months as functions of Month 13 homologous titers using the Juraska et al. method with a hinge correlate of risk model that was used in Moodie et al. (2016). Second, estimate the four serotype-specific VE curves through 13 months as functions of baseline homologous titers using the Huang, Gilbert, and Janes (2012) logistic regression method. These estimates are combined to accomplish the bridging objectives.

Serotype-Specific VE **Approach 2:** Apply the GH method to estimate the four serotype-specific VE curves through 25 months as functions of baseline homologous titers using the

Huang, Gilbert, and Janes (2012) logistic regression method. This approach only uses baseline titers, not using Month 13 titers.

In addition, four statistical approaches based on estimating different vaccine efficacy curves in CYD14+CYD15 9-16 year olds are used to address the overall dengue objective 2):

Overall VE **Approach 1:** After applying Serotype-Specific VE Approach 1, aggregate the results to obtain the answer (the results from the serotype-specific analyses yield the overall results).

Overall VE **Approach 2:** After applying Serotype-Specific VE Approach 2, aggregate the results to obtain the answer (the results from the serotype-specific analyses yield the overall results). This approach only uses baseline titers, not using Month 13 titers.

Overall VE **Approach 1 Average Titers:** First, apply the GH method to estimate the overall dengue VE curve through 25 months as a function of Month 13 average titers using the Juraska et al. method that was used in Moodie et al. (2016). Second, estimate the overall dengue VE curve through 13 months as a function of baseline average titers using the Huang, Gilbert, and Janes (2012) logistic regression method. These estimates are combined to accomplish the bridging objectives.

Overall VE **Approach 2 Average Titers:** Apply the GH method estimating the overall dengue VE curve through 25 months as a function of baseline average titers using the Huang, Gilbert, and Janes (2012) logistic regression method. This approach only uses baseline titers, not using Month 13 titers.

The Approach 1 methods make use of baseline and Month 13 titers. In contrast, the Approach 2 methods make no use of Month 13 titer data; they are based on baseline titers.

The rationale for using these two approaches is that they each have advantages and disadvantages, such that it is prudent to do both analyses and compare the answers. An advantage of the Approach 1 methods is that previous correlates analyses reported in Moodie et al. (2016) support that Month 13 titers are more predictive than baseline titers, supporting using methods that use Month 13 titers. In contrast, it is logistically simpler to base bridging on baseline titers because future Phase I bridging studies would not require 13 months of follow-up for measuring post-vaccination titers, and the methods based on baseline average titers do not make any assumptions about counterfactual causal parameters whose estimation is made more complicated by missing data. However, the challenge posed to this approach is that baseline titers were only measured in a 10-15% fraction of VCD cases in CYD14 and CYD15, limiting precision. Thus, using both approaches is complementary, and similar answers across the approaches would lend some support to reliable results.

We elaborate how the different bridging estimation approaches operate conceptually, with

mathematical details provided in subsequent sections.

Serotype-Specific VE Approach 1 is partly based on the v-specific VE curve through $t = 25$ months as a function of Month 13 serotype v titers in CYD14+CYD15 9–16 year olds, denoted by $VE(t = 25, v|S_v(1) = s_1)$. Specifically, DENV-$v$ VE in the new setting through 25 months in participants at-risk for serotype v dengue at Month 13 under both treatment assignments is estimated by averaging the estimate of $VE(t = 25, v|S_v(1) = s_1)$ over the distribution of serotype v Month 13 titers if assigned vaccine in the new setting, with weighting by (i) a specified ratio of the true $\text{VE}(t = 25, v|S_v(1) = s_1)$ curve in the new setting compared to the original setting of CYD14+CYD15 9–16 year olds; and (ii) an estimate of the background/unvaccinated DENV-v risk conditional on serotype v Month 13 titers in the new setting, as in formulas (8)–(11) of the GH Supplementary Material. Serotype-Specific VE Approach 1 is also based on the v-specific VE curve through $t = 13$ months as a function of baseline serotype v titers in CYD14+CYD15 9–16 year olds, denoted by $\text{VE}(t = 13, v|X_v = x)$. Specifically, VE in the new setting through 13 months is estimated by averaging the estimate of $\text{VE}(t = 13, v|X_v = x)$ over the distribution of serotype v baseline titers in the new setting, with weighting by (i) a specified ratio of the true VE curve $\text{VE}(t = 13, v|X = x)$ in the new setting compared to the original setting of CYD14+CYD15 9–16 year olds; and (ii) an estimate of the background/unvaccinated dengue risk conditional on serotype v baseline titers in the new setting, as in formula (3) of GH. These two steps yield estimates of the serotype-specific vaccine efficacies in the new setting, using four separate implementations of the GH transport formula (8)–(11) in the GH Supplemental Material.

Then, Overall VE Approach 1 is accomplished by first estimating the overall additive-difference vaccine efficacy $\text{VE}^{d*}(t)$ as the sum of the four serotype-specific VE estimates obtained from Serotype-Specific VE Approach 1, and then estimating $\text{VE}^{*}(t)$ by plugging in the estimate of $\text{VE}^{d*}(t)$ using the formula listed immediately after equation (3) in GH.

Serotype-Specific VE Approach 2 is accomplished using the simpler transport formula (3) in GH, which does not use VE curves by Month 13 titers but only uses the v-specific VE curve through $t = 25$ months as a function of baseline serotype v titers in CYD14+CYD15 9–16 year olds. Then Overall VE Approach 2 is accomplished by aggregating the results from Serotype-Specific VE Approach 2.

Overall VE Approach 1 Average Titers is accomplished using the identical method as for Serotype-Specific VE Approach 1 (both steps), except that serotype information is not accounted for, and the bridging is based on the overall dengue VE curve through $t = 25$ months as a function of Month 13 average titers in CYD14+CYD15 9–16 year olds, and on the overall VE curve through $t = 13$ months as a function of baseline average titers in CYD14+CYD15 9–16 year olds. Overall VE Approach 2 Average Titers is accomplished using the identical method as for the second step of Serotype-Specific VE Approach 2, except the bridging is based on the overall VE curve through $t = 25$ months as a function of baseline average titers in CYD14+CYD15 9–16 year olds.

Overall VE Approach 1 is valid under the assumption that no trial participant in either

setting has the VCD endpoint with more than one serotype during follow-up month 0 to month t. The Appendix provides mathematical details of how this is the case. This assumption is not exactly true, but is approximately true based on the low rate of multi-serotype VCD endpoints observed in the efficacy trials. Specifically, 14 out of 595 (CYD14), 20 out of 662 (CYD15), and 4 out of 134 (CYD23) of the VCD endpoint cases during the course of the studies had two distinct serotype VCD endpoints during the 25-month active VCD surveillance follow-up period, and no participant had more than two.

The remainder of this SAP is sequenced as follows. Section 2 describes choices that are made on how to implement the transport formula of GH to accomplish each of the approaches listed above. For the approaches that use Month 13 titers We plan to use the formula that assumes early no-harm monotonicity (ENHM) [instead of equal early clinical risk (EECR)], to avoid the assumption of no vaccine efficacy before $\tau = 13$, the month 13 visit when the PRNT_{50} titers are measured, which is false based on the fact that VE in CYD14 and CYD15 was substantial between Month 0 and Month 13. Section 3 expresses the transport formula from GH that is used, and Section 4 comprehensively lists the assumptions needed to consistently estimate the target vaccine efficacy parameters from this transport formula, and discusses the plausibility of these assumptions. The connection between Sections 2 and 4 is that Section 4 details the exact assumptions that are made, whereas Section 2 provides additional background on the assumptions and the set-up for the bridging. Section 5 describes the methods used for estimating the needed vaccine efficacy curves in CYD14 + CYD15 9–16 year olds. Sections 6 describes how the background conditional dengue risks in the new setting through time t and through time τ, respectively, are estimated. Section 7 describes how to estimate the titer distributions in the new setting based on CYD14+CYD15 9-16 year old data combined with data from the CYD22 calibration study. Section 8 summarizes how confidence intervals and estimated uncertainty intervals about the parameters of interest are obtained. Section 9 summarizes the planned output in the statistical analysis report. The Appendix provides mathematical details of how bridging of overall vaccine efficacy can be based on bridging of serotype-specific vaccine efficacy.

2 Four assumptions used to apply the GH transport formula for Goal 1

In this section we describe the four assumptions needed for the Approach 1 methods for Goal 1 to apply the GH transport formula listed in (8)–(15). After this description, we summarize how the simpler Approach 2 methods are implemented using the GH transport formula (3) in the GH paper, which uses a subset of the assumptions used for the Approach 1 methods, and uses a different version of Assumption 1.

2.1 Some notation

Let X_v be baseline PRNT_{50} serotype v titer, for $v = 1, 2, 3, 4$, and let X_{at} be baseline average titers. The average is computed as described in Moodie et al. (2016), as the average of $\log_{10}$-transformed titers with negative values being assigned value $\log_{10}(5)$. It is used as an effect modifier of serotype v vaccine efficacy through 13 months and through 25 months. Let $S_v(1)$ be Month 13 PRNT_{50} serotype v titer if assigned to the vaccine treatment arm, for $v = 1, 2, 3, 4$. It is used as an effect modifier of serotype v vaccine efficacy through 25 months. Let $S(1) = (S_1(1), S_2(1), S_3(1), S_4(1))^T$ and $S_{at}(1)$ be the potential outcome month 13 titers under assignment to vaccine.

2.2 Four assumptions

1. **Assumption 1:** The index assumptions used for the Approach 1 bridging analysis are stated as two assumptions. First,

$$\phi(t = 25, v|S_v(1) = s_1) = 1 \tag{1}$$

for each $v = 1, 2, 3, 4$ and all fixed s_1 in the support of $F_v^*(\cdot)$, the cdf of $S_v(1^*)$ in the new setting: $F_v^*(s_1) \equiv P(S_v(1^*) \leq s_1|T(1^*) > \tau, T(0^*) > \tau)$. Second,

$$\phi(\tau = 13, v|X_v = x) = 1 \tag{2}$$

for each $v = 1, 2, 3, 4$ and all fixed x in the support of $H_v^*(\cdot)$, the cdf of X_v^* in the new setting: $H_v^*(x) \equiv P(X_v^* \leq x|T(1^*) > \tau, T(0^*) > \tau)$.

Then, a second bridging analysis is done that relaxes the above unity assumptions, and conducts a sensitivity analysis by specifying

$$\frac{1}{\Gamma} \leq \phi(t = 25, v|s_1) \leq \Gamma$$

and

$$\frac{1}{\Gamma} \leq \phi(\tau = 13, v|x) \leq \Gamma$$

for each v and s_1 in the support of $F_v^*(\cdot)$ and x in the support of $H^*(\cdot)$ for a fixed constant $\Gamma > 1$ specified.

2. **Assumption 2:** Each cdf $F_v^*(\cdot)$ of $S_v(1^*)$ in the new setting (for $v = 1, 2, 3, 4$), which is 18–45 year olds in hypothetical CYD14+CYD15 in total (all CYD14/CYD15 countries), is estimated using two sets of mixed binary and continuous data model, where the continuous data is assumed to follow location-shift models. To describe the first set, let $F_v^{22.9.16}(\cdot)$ be the distribution of $S_v(1)$ in the CYD22 trial for 9-16 year old

vaccinees, and let $F_v^{22.18.45}(\cdot)$ be the distribution of $S_v(1)$ in the CYD22 trial for 18-45 year old vaccinees. Let c indicate the threshold for negative response. Let

$$F_v^{22.9.16}(s_1) = (1 - p_{v+}^{22.9.16}) + p_{v+}^{22.9.16} F_{v+}^{22.9.16}(s_1)$$
$$F_v^{22.18.45}(s_1) = (1 - p_{v+}^{22.18.45}) + p_{v+}^{22.18.45} F_{v+}^{22.18.45}(s_1),$$

where $p_{v+}^{22.9.16} = P^{22.9.16}(S_v(1) > c), p_{v+}^{22.18.45} = P^{22.18.45}(S_v(1) > c)$ are probabilities of positive responses among 9-16 and 18-45 year olds, respectively, and $F_{v+}^{22.9.16}$ and $F_{v+}^{22.18.45}$ are CDFs among positive responders, for all s_1 and each $v = 1, 2, 3, 4$. We further assume $F_+^{22.18.45}(s_1) = F_+^{22.9.16}(s_1 + \Delta_v)$, where the Δ_v are four fixed constants. Each Δ_v is estimated by the Hodges-Lehman estimator (e.g., through the R function wilcox.test) or by the difference in median among positive responders. The response rates $p_+^{22.9.16}, p_+^{22.18.45}$ are estimated by the empirical proportion of positive responses.

Second, with $F_v^{1415.9.16}(\cdot)$ the distribution of $S_v(1)$ in the CYD14+CYD15 trial for 9-16 year old vaccinees, and $F_v^*(\cdot)$ the distribution of $S_v(1^*)$ for hypothetical CYD14+CYD15 18-45 year old vaccinees, we have

$$F_v^{1415.9.16}(s_1) = (1 - p_{v+}^{1415.9.16}) + p_{v+}^{1415.9.16} F_{v+}^{1415.9.16}(s_1)$$
$$F_v^*(s_1) = (1 - p_{v+}^*) + p_{v+}^* F_{v+}^*(s_1),$$

where $p_{v+}^{1415.9.16} = P^{1415.9.16}(S_v(1) > c), p_{v+}^* = P^*(S_v(1) > c)$ are probability of positive responses among 9-16 and 18-45 respectively, and $F_{v+}^{1415.9.16}$ and F_{v+}^* are cdfs among positive responders, for all s_1 and each $v = 1, 2, 3, 4$. We further assume $F_+^*(s_1) = F_+^{1415.9.16}(s_1 + \Delta_v)$, and a constant odds ratio of positive response between the two countries

$$OR_v = \frac{p_{v+}^{22.18.45}/(1 - p_{v+}^{22.18.45})}{p_{v+}^{22.9.16}/(1 - p_{v+}^{22.9.16})} = \frac{p_{v+}^*/(1 - p_{v+}^*)}{p_{v+}^{1415.9.16}/(1 - p_{v+}^{1415.9.16})}.$$

Under these models $F_v^*(s_1)$ is estimated by first estimating each OR_v and Δ_v from CYD22 data, with estimates $\widehat{OR}_v$ and $\widehat{\Delta}_v$, and then setting

$$\widehat{F}_v^*(s_1) = (1 - \hat{p}_{v+}^*) + \hat{p}_{v+}^* \widehat{F}_{v+}^{1415.9.16}(s_1 + \widehat{\Delta}_v), \tag{3}$$

where $\widehat{F}_{v+}^{1415.9.16}(\cdot)$ is the empirical estimator (NPMLE) of $F_{v+}^{1415.9.16}(\cdot)$ based on positive responders among CYD14+CYD15 9-16 year olds with the constant offset $\widehat{\Delta}_v$ incorporated into the estimator, and

$$\hat{p}_{v+}^* = \frac{\widehat{OR}_v \hat{p}_{v+}^{1415.9.16}/(1 - \hat{p}_{v+}^{1415.9.16})}{1 + \widehat{OR}_v \hat{p}_{v+}^{1415.9.16}/(1 - \hat{p}_{v+}^{1415.9.16})},$$

where $\hat{p}_{v+}^{1415.9.16}$ is the empirically estimated positive response rate among CYD14+CYD15 9-16 year olds.

In addition, each cdf $H_v^*(\cdot)$ of X_v^* (baseline titers) in the new setting is estimated in the exact same fashion as detailed above , except now based on vaccine and placebo recipients pooled, given that baseline titers have the same distribution in the two treatment groups.

3. **Assumption 3:** We assume that after accounting for the month 13 PRNT_{50} data $S(1)$, age group (9–16 vs. 18–45) does not affect background/unvaccinated dengue risk for each serotype. That is, assume

$$mrisk_0^*(t, v|S_v(1^*) = s_1) \;=\; mrisk_0(t, v|S_v(1) = s_1) \tag{4}$$

for each $v = 1, 2, 3, 4$ and all s_1 in the support of $F_v^*(\cdot)$. An important feature of these assumptions is that they are made for each serotype separately.

We also use average-titer versions of these assumptions:

$$mrisk_0^*(t|S_{at}(1^*) = s_1) \;=\; mrisk_0(t|S_{at}(1) = s_1) \tag{5}$$

for all s_1.

4. Similarly, we assume that after accounting for the baseline PRNT_{50} data X_v, age group (9–16 vs. 18–45) does not affect background/unvaccinated dengue risk for each serotype. That is, assume

$$risk_0^*(t, v|X_v^* = x) \;=\; risk_0(t, v|X_v = x) \tag{6}$$

for each $v = 1, 2, 3, 4$ and all x in the support of $H_v^*(\cdot)$.

5. **Assumption 4:** $\text{VE}^{EP}(t = 25, v|s_1, x) = \text{VE}(t = 25, v|s_1, x)$, $F_v^{*EP}(\cdot) = F_v^*(\cdot)$, $H_v^{*EP}(\cdot) = H_v^*(\cdot)$, and $\phi^{EP}(\cdot) = \phi(\cdot)$. It simplifies the GH transport formula (8)–(15) [see equations (9) and (10)].

2.3 How the Assumptions Differ for Approach 2

Approach 2 does not use any of the assumptions involving Month 13 titers. It uses parts of Assumptions 2 and 3 identical to those made for Approach 1, and uses a new version of Assumption 1.

Approach 2 Assumption 1: The bridging assumption function $\phi(t = 25, v|X_v = x)$ satisfies

$$\phi(t = 25, v|X_v = x) = 1 \tag{7}$$

for all fixed x in the support of $H_v^*(\cdot)$, the cdf of X_v^* in the new setting: $H_v^*(x) \equiv P(X_v^* \leq x|T(1^*) > \tau, T(0^*) > \tau)$, for each $v = 1, 2, 3, 4$. This is similar to assumption (2) made for Approach 1 except it is through 25 months of follow-up.

Approach 2 Assumption 2: Use the same model for the distribution of baseline titers $H_v^*(\cdot)$ as used for Approach 1.

Approach 2 Assumption 3: Use assumption (6) for $t = 25$ months, where the assumptions (4) and (5) are not needed.

2.4 Robustness to the key bridging assumptions

For Approach 1, they key assumption (1) could be in question, because it would fail if baseline titers modify VE after accounting for Month 13 titers, as long as the baseline titers have a different distribution in the original and new settings (as is the case for 9–16 vs. 18–45 year olds). Suppose this violation does occur, yet the vaccine efficacy surface $\text{VE}(t = 25, v|S_v(1), X_v)$ that conditions on both Month 13 and baseline titers is the same in the two settings. Also suppose that $H_v^*(\cdot)$ is stochastically larger than $H_v(\cdot)$, which is expected and holds based on the empirical data for 9–16 vs. 18–45 year olds. Under these two conditions, it follows that the bridging assumption function $\phi(t = 25, v|s_1)$ of (1) is bounded below by 1. This is a useful result, because it implies that application of the Approach 1 methods under this assumption violation would under-estimate the vaccine efficacy in 18–45 year olds. This supports that any violations of the key bridging assumption would make the resulting estimates conservative, thus being lower bounds for the expected vaccine efficacy in the new setting.

For Approach 2, the same argument applied swapping the roles of Month 13 and baseline titers implies that under the two conditions (i) $\text{VE}(t = 25, v|S_v(1), X_v)$ is the same in the two settings and (ii) $F_v^*(\cdot)$ is stochastically larger than $F_v(\cdot)$, then the bridging assumption function $\phi(t = 25, v|x)$ of (7) is bounded below by 1. Again this is a useful result, because it implies that application of the Approach 2 methods under this assumption violation would under-estimate the vaccine efficacy in 18–45 year olds, and the results may be interpreted as lower bounds.

3 Transport Formula Under Approach 1

We implement the transport formula of GH based on CYD14 and CYD15 combined for 9–16 year olds, wherein participants are followed for occurrence of the virologically confirmed dengue (VCD) study endpoint with active follow-up through to $t = 25$ months. We will focus on implementing the method for estimating $\text{VE}^{d*}(t = 25)$, $\text{VE}^{*}(t = 25)$, $\text{VE}^{d*}(t = 25, v)$, and $\text{VE}^{*}(t = 25, v)$ defined in Section 1. Estimation of the first key terms $VE^{d*EAS}(t)$ will use month 13 titers $S(1)$ but not baseline titers X; this choice is made given the limited data on baseline titers in VCD cases and the approximate plausibility of the assumptions stated below that allow this choice. The formula uses $\tau = 13$ months as the time for measuring the immune response markers $S(1)$ and $t = \tau_1 = 25$ months as the fixed time point for inference.

The transport formula is as in equations (8)–(11) of the Web Supplement of GH:

$$\text{VE}^{d*}(t) \;=\; \text{VE}^{d*EAS}(t) P(T(0^*) > \tau) - \text{VE}^{d*}(\tau)\, \text{VE}^{d*EP}(t) \tag{8}$$

for $t \in (\tau, \tau_1]$ where

$$\begin{aligned} \mathrm{VE}^{d*EAS}(t) &\equiv P(T(1^*) \le t | T(1^*) > \tau, T(0^*) > \tau) - P(T(0^*) \le t | T(1^*) > \tau, T(0^*) > \tau) \\ \mathrm{VE}^{d*EP}(t) &\equiv P(T(1^*) \le t | T(1^*) > \tau, T(0^*) \le \tau) - P(T(0^*) \le t | T(1^*) > \tau, T(0^*) \le \tau). \end{aligned}$$

Algebra then yields, for $t \in (\tau, \tau_1]$,

$$\begin{aligned} \mathrm{VE}^{d*EAS}(t) &= -\int\int \sum_{v=1}^{4} \phi(t, v|s_1, x)\, \mathrm{VE}(t, v|s_1, x) \\ &\quad \times mrisk_0^*(t, v|s_1, x) dv dF^*(s_1|x) dH^*(x), \qquad (9) \\ \mathrm{VE}^{d*EP}(t) &= -\int\int \sum_{v=1}^{4} \phi^{EP}(t, v|s_1, x)\, \mathrm{VE}^{EP}(t, v|s_1, x) \\ &\quad \times mrisk_0^{*EP}(t, v|s_1, x) dF^{*EP}(s_1|x) dH^{*EP}(x), \qquad (10) \\ \mathrm{VE}^{d*}(\tau) &\equiv -\int \sum_{v=1}^{4} \phi(\tau, v|x)\, \mathrm{VE}(\tau, v|x) risk_0^*(\tau, v|x) dH^*(x). \qquad (11) \end{aligned}$$

Under the simplifying assumptions 5 listed in the Introduction [$\mathrm{VE}^{EP}(t = 25, v|s_1, x) = \mathrm{VE}(t = 25, v|s_1, x)$; $F^{*EP}(\cdot) = F^*(\cdot)$, $H^{*EP}(\cdot) = H^*(\cdot)$, and $\phi^{EP}(\cdot) = \phi(\cdot)$], this formula is applied with (10) replaced with

$$\mathrm{VE}^{d*EP}(t) = -\int\int \sum_{v=1}^{4} \phi(t, v|s_1, x)\, \mathrm{VE}(t, v|s_1, x) dF^*(s_1|x) dH^*(x), \qquad (12)$$

which uses the fact that $mrisk_0^{*EP}(t, v|s_1, x) = 1$. In this transport formula the terms $P(T(0^*) > \tau)$, (9), (11), and (12) need to be estimated. The version of the transport formula we apply removes the X in the $\mathrm{VE}^{d*EAS}(t)$ and $\mathrm{VE}^{d*EP}(t)$ pieces, and keeps it in the $\mathrm{VE}^{d*}(\tau)$ piece, resulting in

$$\begin{aligned} \mathrm{VE}^{d*EAS}(t) &= -\int \sum_{v=1}^{4} \phi(t, v|s_1)\, \mathrm{VE}(t, v|s_1) \\ &\quad \times mrisk_0^*(t, v|s_1) dF^*(s_1), \qquad (13) \\ \mathrm{VE}^{d*EP}(t) &= -\int \sum_{v=1}^{4} \phi(t, v|s_1)\, \mathrm{VE}(t, v|s_1) dF^*(s_1), \qquad (14) \\ \mathrm{VE}^{d*}(\tau) &\equiv -\sum_{v=1}^{4} \phi(\tau, v|x)\, \mathrm{VE}(\tau, v|x) risk_0^*(\tau, v|x) dH_v^*(x). \qquad (15) \end{aligned}$$

Thus, (8), (13), (14), and (15) constitute the transport formulas we use for additive-difference VE. Lastly, $\mathrm{VE}(t, v)$ is estimated by plugging in the estimate of $\mathrm{VE}^d(t, v)$ into the formula listed immediately after equation (3) in Gilbert and Huang (2016) that links the

multiplicative-reduction and additive difference parameters:

$$\text{VE}^*(t,v) = -VE^{d*}(t,v)/risk_0^*(t=25,v). \tag{16}$$

The approaches based on average titers use the same formula except there is a single failure type (DENV-Any).

It can be shown that the simplifying assumption $\text{VE}^{EP}(t=25,v|s_1,x) = \text{VE}(t=25,v|s_1,x)$ is equivalent to a conditional independence assumption

$$I(T(1) \leq t) \perp\!\!\!\perp I(T(0) \leq \tau)|S(1), T(0) \leq t, T(1) > \tau.$$

In words, this assumption states for that for placebo recipients experiencing DENV-Any earlier or later over t months, this fact of timing does not affect whether the individual would have DENV-Any by t if vaccinated, all conditional on immune response $S(1)$. The fact that DENV-Any is a rare event provides some support for this assumption.

4 Elaboration of Assumptions for Applying the Transport Formula for Approach 1

The following assumptions are needed for the transport formula (12), (13), and (15) to provide consistent estimation of the four vaccine efficacy target parameters for the new setting. These assumptions are consistent with those discussed and listed in the previous section.

A. **Assumptions for the 9–16 year old population of CYD14/CYD15:**

A.1 (listed in Section 2.1 of GH) Standard assumptions in a randomized trial: SUTVA (no-interference between units and only one version of treatment), ignorable treatment assignment (a randomized trial), random censoring for each treatment group, whether S and X are observed depends only on the observed data (missing at random), and the data for each participant are independent copies across the n study participants.

A.2 No-early-harm for each v: $P(I(T_v(1) > \tau) = I(T_v(0) > \tau)) = 1$

A.3 $\text{VE}(t,v|S_v(1) = s_1)$ is consistently estimated for each v.

A.4 $\text{VE}(\tau,v|X_v = x)$ is consistently estimated for each v.

A.5 No participant has two or more VCD endpoints of distinct serotypes during the follow-up period 0 to t.

A.1 is reasonable because CYD14 and CYD15 were randomized with geographically dispersed sites, and the sampling of neutralization titers was in control of the investigators such that missing at random holds. A.2 states that the vaccine does not increase the rate of serotype v specific VCD compared to placebo. A.2 is well-defended by the observed data given that each VE(v) in 9–16 year olds was inferred to be much higher than 0, with the lower 95% confidence limit above 0. Achieving consistent estimation as stated in A.3 was the main topic of Moodie et al. (2016). Consistent estimation of VE(τ, v) in A.4 is more straightforward to achieve, given that the parameter is identified from the standard assumptions A.1 in a randomized trial. A.5 is approximately true as discussed in Section 1.

B. **Assumptions for the new Phase I/II trial/hypothetical Phase 3 trial in the new setting:**

B.1 Standard assumptions in a randomized trial (parallel to A.1)

B.2 $F_v^*(\cdot)$ and $H_v^*(\cdot)$ are consistently estimated for each v

B.3 No-early-harm*: $P(I(T_v(1^*) > \tau) = I(T_v(0^*) > \tau)) = 1$ for each v

B.4 No participant has two or more VCD endpoints of distinct serotypes during the follow-up period 0 to t.

B.1 and B.3 are well-defended. B.2 is reasonable because the existence of the CYD22 calibrating study provides a rationale way to alter the observed titer distributions in CYD14+CYD15 9-16 yeare olds based on how the age difference (18-45 vs. 9-16) altered them in CYD22. This assumption that the observed age differences in Viet Nam (CYD22) carries over to all other countries in CYD14+CYD15 is not testable, however, such that a sensitivity analysis is warranted, as described further below. B.4 is approximately true following the same arguments that A.5 is approximately true.

C. **Assumptions combined over the original trial (CYD14+CYD15 9–16 year olds and the new setting):**

C.1 VE($t, v|s_1$) is the same in 9–16 year olds as in 18–45 year olds

C.2 $\phi(t, v|S_v(1) = s_1) = 1$. Equivalently, for each v, the neutralization titer variable $S_v(1)$ selected for the transport formula includes all modifiers of VE(t, v) and $S_v(1^*)$ includes all modifiers of $mrisk_0^*(t, v)$ (among modifiers that have a different distribution in the two settings).

C.3 $\phi(\tau, v|X_v = x) = 1$. Equivalently, for each v, the neutralization titer variable X_v selected for the transport formula includes all modifiers of VE(τ, v) and X_v^* includes all modifiers of $risk_0^*(\tau, v)$ (among modifiers that have a different distribution in the two settings).

D. **Assumptions about background VCD risk in the new setting, relative to in the original setting:**

D.1 $mrisk_0^*(t, v|s_1)$ is consistently estimated

D.2 $risk_0^*(\tau, v|x)$ is consistently estimated

As developed below, the following assumptions are helpful for making D.1 and D.2 hold:

D.3 Define

$$w_{Inc}(t) \equiv \frac{risk_0^*(t)}{risk_0(t)}.$$

Assume

$$\Omega_{Inc}^l \leq w_{Inc}(t) \leq \Omega_{Inc}^u$$

for fixed constants $\Omega_{Inc}^l \leq 1$ and $\Omega_{Inc}^u \geq 1$.

D.4 Define

$$w_V(t, v) \equiv \frac{risk_0^*(t, v)}{risk_0^*(t)} / \frac{risk_0(t, v)}{risk_0(t)}.$$

Assume

$$\Omega_V^l \leq w_V(t, v) \leq \Omega_V^u$$

for fixed constants $\Omega_V^l \leq 1$ and $\Omega_V^u \geq 1$.

D.5 Define

$$w_{Inc}(\tau|X = x) \equiv \frac{risk_0^*(\tau|X = x)}{risk_0(\tau|X = x)}.$$

Assume

$$\Omega_{Inc}^l \leq w_{Inc}(\tau|X = x) \leq \Omega_{Inc}^u$$

for the same fixed constants $\Omega_{Inc}^l \leq 1$ and $\Omega_{Inc}^u \geq 1$ specified in D.3.

D.6 Define

$$w_V(\tau, v|X_v = x) \equiv \frac{risk_0^*(\tau, v|X_v^* = x)}{risk_0^*(\tau|X_v^* = x)} / \frac{risk_0(\tau, v|X_v = x)}{risk_0(\tau|X_v = x)}.$$

Assume

$$\Omega_V^l \leq w_V(\tau, v|X_v = x) \leq \Omega_V^u$$

for the same fixed constants $\Omega_V^l \leq 1$ and $\Omega_V^u \geq 1$ specified in D.4.

Specifying D.3 requires subject matter experts to specify the lower and upper bounds for how much greater the cumulative VCD rate may be in the new setting compared to the original setting. If the same country and the same follow-up period is used for the original and new settings, then specifying $\Omega^u_{Inc} = 1$ may be reasonable, which expresses the assumption that the background VCD rate is expected to be at least as high in 9–16 year olds as in adults. A sensitivity analysis would repeat the analysis varying Ω^l_{Inc} and Ω^u_{Inc}.

D.4 specifies bounds for the ratio of the relative frequencies of the serotypes exposing and causing VCD in the original and new settings. The special case of the narrowest interval $\Omega^l_V = \Omega^u_V = 1$ may approximately hold for bridging to 18–45 year olds from 9–16 year olds within the same country and in the same follow-up period.

The following additional simplifying assumptions allow application of the GH transport formula without accounting for baseline titers X.

E. **Additional simplifying assumptions:**

E.1 $\phi(t, v|s_1, x) = \phi(t, v|s_1)$

E.2 $\text{VE}(t, v|s_1, x) = \text{VE}(t, v|s_1)$

E.3 $mrisk^*_0(t, v|s_1, x) = mrisk^*_0(t, v|s_1)$

E.4 $w_V(t, v|x) = w_V(t, v)$ (related to E.3)

E.5 $mrisk^*_0(t, v|s_1) = w_{Inc}(t)w_V(t, v)mrisk_0(t, v|F^{-1}_v(F^*_v(s_1)))$ where $F^{-1}_v(\cdot)$ is the inverse of $F_v(\cdot)$.

The additional assumptions E.1–E.6 are assumed in the assumption statements C.1–C.3 and D.1; otherwise those assumptions would also condition on X.

Assumptions E.2 and E.3 are reasonable under a Markov type assumption– that after accounting for Month 13 neutralization titers, one does not also need neutralization titers measured 13 months earlier to predict VE or background dengue risk. These Markov type assumptions may not exactly hold, but they are expected to be approximately true, and there are not enough data on baseline titers in VCD cases in CYD14 and CYD15 to permit adequately precise estimation of $\text{VE}(t, v|s_1, x)$ and $mrisk^*_0(t, v|s_1, x)$ including baseline titers. Essentially, the fact that baseline titers from CYD14 and CYD15 were only available from 10–15% of VCD cases implies that the only viable transport formula is implemented without accounting for baseline titers X.

5 Estimation of $\text{VE}(t, v|S_v(1) = s_1)$ and $\text{VE}(\tau, v|X_v = x)$ based on CYD14 + CYD15 9–16 year olds

5.1 Estimation of $\text{VE}(t, v|S_v(1) = s_1)$

The vaccine efficacy curve $\text{VE}(t = 25, v|S_v(1) = s_1)$ for each serotype v is estimated using the Juraska et al. method that was used in the primary analysis of Moodie et al. (2016). Juraska and Gilbert (2016, *Technical Report*) describes this method that was included in the Supplementary Material of Moodie et al. (2016).

The Approach 1 methods base bridging on the estimated serotype-specific VE curves $\text{VE}(t = 25, v|s_1)$ in the submitted correlates manuscript Moodie et al. (2016), for 9—16 year olds pooling over CYD14 and CYD15. Both the estimated average titer VE curve for DENV-Any, and the four separately estimated serotype-specific titer specific VE curves for $DENV - v$, (for $v = 1, 2, 3, 4$) are considered. We detail key assumptions made in this method:

- To simplify estimation of $\text{VE}(t = 25, v|s_1, x)$, a variety of assumptions could be considered. We select the assumption that was used in the main analysis of the Moodie et al. correlates manuscript– the Juraska et al. method– which made the following assumption:

$$risk_0(t = 25, v|S_v(1), S_v(0), X) = risk_0(t = 25, v|S_v(0), X). \tag{17}$$

  where X is gender, age, and country. This assumption identifies the LHS from the RHS. The supplement of Moodie et al. (2016) includes the Juraska and Gilbert (2016) technical report that shows how to estimate $risk_0(t = 25, v|S_v(1))$ based on this assumption.

  In addition to making assumption (17), it is also helpful to make the two assumptions

$$\begin{aligned} \text{VE}(t, v|S(1), X) &= \text{VE}(t, v|S(1)) \\ &= \text{VE}(t, v|S_v(1)). \end{aligned}$$

  The first equality states that after accounting for month 13 vaccine-induced titers $S(1)$ baseline titers X contain no additional information about serotype v specific dengue risk, and the second equality states that only serotype v titers are needed to predict serotype v dengue risk.

  The combination of these assumptions allows applying the Juraska method to estimate the LHS by estimating the RHS.

  Similarly, for estimating $\text{VE}(\tau, v|X)$, we assume

$$\text{VE}(\tau, v|X) = \text{VE}(\tau, v|X_v),$$

which states that only serotype v baseline titers are needed to predict serotype v dengue risk over the first $\tau = 13$ months of follow-up (i.e., baseline serotype titers of mismatched serotypes are not needed).

- Whatever method is used to estimate the VE curve based on CYD14 and CYD15 combined 9–16 year olds, any assumptions made in the estimation of $\text{VE}(t = 25, v|s_1, x)$ must also be made for estimation of $mrisk_0^*(t = 25, v|s_1, x)$ [for self-consistency; e.g., see the assumption the Juraska et al. method makes noted above in equation (17)].

An important fact about these VE curves $\text{VE}(t = 25, v|s_1)$ is that for each v they condition on both $T(1) > \tau$ and $T(0) > \tau$ in the notation of GH. To understand this, for fixed v $T(1)$ in this formula is the time from enrollment until DENV-v VCD if assigned vaccine, such that $T(1) > \tau$ means that only vaccine recipients not experiencing DENV-v VCD during the first 13 months are included in the analysis. Similarly $T(0)$ in this formula is the time from enrollment until DENV-v VCD if assigned placebo, such that $T(0) > \tau$ means that only vaccine recipients who would not have experienced DENV-v VCD during the first 13 months had they been assigned placebo, are included in the analysis. Note that for the analysis of DENV-v, occurrence of a VCD endpoint of a non-v serotype during the first 13 months is not taken into account; this is consistent with the approach taken in Moodie et al. (2016) and reflects the knowledge that individuals experiencing VCD of one serotype are still at risk for VCD with the other serotypes. For the alternate analysis that ignores serotypes and bases the bridging formula on the overall VE curve $\text{VE}(t = 25|s_1)$ for the DENV-Any endpoint and average titers, the event $T(1) > \tau$ and $T(0) > \tau$ indicates no occurrence of DENV-Any over the first 13 months under either treatment assignment. Again this is consistent with the analyses conducted in Moodie et al. (2016).

Bridging is also based on the estimated serotype-specific VE curves $\text{VE}(\tau = 13, v|x)$ in the supplemental materials of the submitted correlates manuscript, for 9—16 year olds pooling over CYD14 and CYD15. Again the assumption is made that the serotype-specific VE curves for 9–16 year olds are the same as those for 18–45 year olds. (These two major elements of the bridging analysis are summarized in Section 1.)

5.2 Estimation of $\text{VE}(\tau, v|x)$

Note that for the parameter $\text{VE}(\tau, v|x)$, the conditioning event is $X_v = x$, such that when assessing serotype v risk we only allow the matched serotype titers to affect the risk. The term

$$\begin{aligned} \text{VE}(\tau, v|x) &\equiv 1 - \frac{risk_1(\tau, v|x)}{risk_0(\tau, v|x)} \\ &= 1 - \frac{P(T(1) \leq \tau, V(1) = v|x)}{P(T(0) \leq \tau, V(0) = v|x)} \end{aligned}$$

can be estimated by fitting a logistic regression model that regresses the risk of infection by serotype v by time τ on x_v, vaccination status, and their interaction.

6 Estimation of background dengue VCD risks in the new setting $mrisk_0^*(t, v|S_v(1^*) = s_1)$ and $risk_0^*(t, v|X_v = x)$

6.1 Estimation of $mrisk_0^*(t, v|S_v(1^*) = s_1)$ for a country included in CYD14 or CYD15 and bridging to adults with the same follow-up period as in CYD14/CYD15

In this section we consider estimation of $mrisk_0^*(t, v|s_1)$ for the problem of bridging to 18–45 year old adults to all (i.e., Goal 1) or one of the countries included in CYD14 or CYD15, assuming the same time period of follow-up for VCD that occurred in the actual CYD14 and CYD15 trials. In the following section we consider bridging to a new country not included in CYD14/CYD15, with application to Goal 2 (bridging to India 18-45).

We use a variant of the approach specified in equation (5) of GH, where we assume

$$mrisk_0^*(t, v|s_1) = \frac{risk_0^*(t, v)}{risk_0(t, v)} w_{Sv}(s_1) mrisk_0(t, v|g_v(s_1)) \tag{18}$$

for some specified paired functions $w_{Sv}(s_1)$ and $g_v(s_1)$ chosen to ensure both constraints $risk_0^*(t, v) = \int mrisk_0^*(t, v|s_1) dF_v^*(s_1)$ and $risk_0(t, v) =$
$\int mrisk_0(t, v|s_1) dF_v(s_1)$ for each $v = 1, 2, 3, 4$, which with (18), require

$$risk_0(t, v) = \int w_{Sv}(s_1) mrisk_0(t, v|g(s_1)) dF_v^*(s_1). \tag{19}$$

Note that $risk_0(t, v)$ for this particular setting refers to the risk in the EAS stratum (i.e., with $T(0) > \tau$, $T(1) > \tau$).

The idea of this approach is to shift the problem from estimation of $mrisk_0^*(t, v|s_1)$, which is relatively hard, to the simpler problems of estimation of $risk_0^*(t, v)/risk_0(t, v)$ and $mrisk_0(t, v|s_1)$. To estimate the former term, we factor it into two ratios reflecting (i) different background overall conditional disease cumulative incidences,

$$w_{Inc}(t) \equiv \frac{risk_0^*(t)}{risk_0(t)},$$

and (ii) different distributions of circulating and VCD causing dengue serotypes V,

$$w_V(t, v) \equiv \frac{risk_0^*(t, v)}{risk_0^*(t)} / \frac{risk_0(t, v)}{risk_0(t)}.$$

The numerator of $w_V(t,v)$ measures the relative fraction of the circulating dengue serotypes potentially infecting and causing VCD with serotype v, while the denominator measures this relative fraction in the original setting. Under the constraint (19)

$$mrisk_0^*(t,v|s_1) = w_{Inc}(t)w_V(t,v)w_{Sv}(s_1)mrisk_0(t,v|g_v(s_1)). \tag{20}$$

We specify each (w_{Sv}, g_v) in a way that satisfies the constraint (19). We do this by making an equipercentile assumption $g_v(s_1) = F_v^{-1}(F_v^*(s_1))$ and $w_{Sv}(s_1) = 1$ where $F_v^{-1}(\cdot)$ is the inverse of $F_v(\cdot)$. Direct calculation shows that the constraint holds under this approach. Thus, the assumption used is

$$mrisk_0^*(t,v|s_1) = w_{Inc}(t)w_V(t,v)mrisk_0(t,v|F_v^{-1}(F_v^*(s_1))), \tag{21}$$

which is assumption E.6.

To implement the approach, we need to estimate $mrisk_0(t,v|s_1)$ and both terms $w_{Inc}(t)$ and $w_V(t,v)$.

The term $mrisk_0(t,v|s_1)$ is estimated as part of the process for estimating the VE curve as addressed earlier in Section 6.1.

For estimating $w_{Inc}(t)$ and $w_V(t,v)$, a different approach is needed for bridging to hypothetical CYD14+CYD15 18-45 year olds in total as compared to bridging to aspecific CYD14/CYD15 country. We first consider bridging to the total set of countries (i.e., Goal 1); we also summarize the latter because it may be relevant in future analyses, for example projecting efficacy for 18–45 year olds in Puerto Rico. For Goal 1, the numerators and denominators are for the same set of countries/region, such that the only differences in the numerators vs. denominators are in the age group 9-16 vs. 18-45. Because of this, we expect the background VCD rate to be at least as high in 9–16 year olds as in adults; thus we specify $w_{Inc}(t) \leq 1 = \Omega_{Inc}^u$ in assumption D.3. If there were adequate epidemiological VCD surveillance data in adults, then $w_{Inc}(t)$ could be estimated by estimating the numerator from the CYD14/CVYD15 trial data, and estimating the numerator from the epidemiological surveillance data. At present, the available surveillance data in adults does not seem adequate to implement this task with adequate precision. Therefore, we rely on the assumption that adults generally experience the same amount of dengue exposure as 9–16 year olds, such that we expect $w_{Inc}(t)$ to only be slightly less than 1.

For $w_V(t,v)$, under assumption D.4 above (that the circulating serotypes expose adults and 9–16 year olds with the same relative frequencies), we simply specify $\Omega_V^l = \Omega_V^u = 1$ such that $w_V(t,v) = 1$. Plausibility of this assumption relies on bridging to the adult population for the same region (set of countries) during the same period of follow-up as the 9–16 year olds in the randomized trial, which is indeed our set-up for Goal 1.

Second we consider estimation of $w_{Inc}(t)$ and $w_V(t,v)$ for bridging to hypothetical CYD14/ CYD15 18-45 year olds for a specific CYD14/CYD15 country. The first approach described above does not completely work, because the denominators are estimated using

all CYD14+CYD15 9-16 year olds, yet the numerators are for a specific country only. As such, the numerators vs. denominators differ in both region and age cohort. To isolate the age factor and hence proceed similar to the first approach, we let $risk_0^{sc}(t)$ be the background risk for the specific country in CYD14 and CYD15 being bridged to, and write

$$\begin{aligned} w_{Inc}(t) &\equiv \frac{risk_0^*(t)}{risk_0(t)} \\ &= \frac{risk_0^*(t)}{risk_0^{sc}(t)} \times \frac{risk_0^{sc}(t)}{risk_0(t)} \end{aligned} \tag{22}$$

and

$$w_V(t,v) \equiv \frac{risk_0^*(t,v)}{risk_0^*(t)} / \frac{risk_0^{sc}(t,v)}{risk_0^{sc}(t)} \times \frac{risk_0^{sc}(t,v)}{risk_0^{sc}(t)} / \frac{risk_0(t,v)}{risk_0(t)}. \tag{23}$$

The first terms in the above products are both for the same country, such that we now apply the same assumptions as above to these first terms, i.e.,

$$\Omega_{Inc}^l \leq \frac{risk_0^*(t)}{risk_0^{sc}(t)} \leq \Omega_{Inc}^u = 1$$

and

$$1 = \Omega_V^l \leq \frac{risk_0^*(t,v)}{risk_0^*(t)} / \frac{risk_0^{sc}(t,v)}{risk_0^{sc}(t)} \leq \Omega_V^u = 1.$$

Estimation proceeds as under the first approach except now the second terms in each of (22) and (23) need to be estimated based on the CYD14+CYD15 9-16 year old data. These terms are straightforward to estimate, as all needed terms $risk_0^{sc}(t)$, $risk_0(t)$, $risk_0^{sc}(t,v)$, $risk_0^{sc}(t)$, and $risk_0(t,v)$ can be directly empirically estimated.

The term $risk_0^*(t,v|X_v = x)$ is estimated in a parallel fashion as

$$risk_0^*(t,v|X_v = x) = w_{Inc}(t|X_v = x) w_V(t,v|X_v = x) risk_0(t,v|X_v = x).$$

6.2 Estimation of $mrisk_0^*(t,v|S_v(1^*) = s_1)$ and $risk_0^*(t,v|X_v = x)$for a country not included in CYD14 nor CYD15, with application to Goal 2

When the problem is to bridge to a new country not included in CYD14/CYD15, then the simplifying assumption E.5 is not reasonable. One way to estimate it would be based on molecular epidemiology data for estimating the relative background VCD causing serotype frequencies in the new setting,

$$f_v^* \equiv \frac{risk_0^*(t,v)}{risk_0^*(t)},$$

for each serotype $v = 1, 2, 3, 4$, with $f_1^* + f_2^* + f_3^* + f_4^* = 1$. If adequate molecular epidemiological data are not available, then one could implement the transport formula specifying different values for $(f_1^*, f_2^*, f_3^*, f_4^*)$. The interpretation of the answer would be in terms of "what would VE be during a time period with a certain specified distribution of circulating serotypes."

Assumption D.3 may be used for a new country, where now the assumption $\Omega_{Inc}^u = 1$ may no longer be reasonable, and a wider range $[\Omega_{Inc}^l, \Omega_{Inc}^u]$ may need to be specified.

If subject matter experts find that it is very difficult to specify reasonable bounds Ω_{Inc}^l and Ω_{Inc}^u, then an alternative approach may explicitly use national surveillance data in the new country. In particular, $w_{Inc}(t)$ may be estimated by the estimated expansion ratio (ER) (e.g., Sarti et al., 2015; Nealon et al., 2016), which reflects the rate of VCD case detection under a country's national surveillance program versus the rate of VCD case detection under surveillance as done in CYD14 and CYD15. Given that the expansion ratio probably does not capture all differences between background VCD risk in the original and new settings, for such an application we implement the transport formula using

$$\Omega_{Inc}^l ER \leq w_{Inc}(t) \leq \Omega_{Inc}^u ER,$$

where again Ω_{Inc}^l and Ω_{Inc}^u are specified by subject matter experts.

An alternative approach does not use ERs, given the limited precision of ER estimates, and instead would use the national surveillance data for estimating how confirmed dengue incidence varies among the different age groups (9–16 in CYD14/CYD15 vs. 18-45 year olds). In particular, under the assumption that the ratio of confirmed dengue incidences in the two age groups measured via the national surveillance system, $R(t)$, equals the ratio if active surveillance as per CYD14/CYD15 had been used, then $w_{Inc}(t)$ would be estimated based on the equation

$$w_{Inc}(t) = R(t).$$

Parallel approaches may be used to estimate $risk_0^*(t, v|X_v = x)$.

For Goal 2, none of these approaches seem adequate, given limited epidemiological data in India. Therefore, we implement the method simply assuming background/unvaccinated VCD risk is the same in the two settings, i.e., $mrisk_0^*(t, v|s_1) = mrisk_0(t, v|s_1)$ and $risk_0^*(t, v|x) = risk_0(t, v|x)$ for all v, s_1, and x. Thus the Goal 2 bridging is really for a hypothetical "as if" scenario that background/unvaccinated dengue risk in India were the same as for CYD14+CYD15 9–16 year olds.

6.3 Estimation of $P(T(0^*) > \tau)$

Based on the above, an estimate of $risk_0^*(\tau, v|X_v^* = x)$ is obtained for each $v = 1, 2, 3, 4$ and each x in the support of $H_v^*(\cdot)$. Based on the equation

$$P(T(0^*) > \tau) = 1 - \sum_{v=1}^{4} risk_0^*(\tau, v|X_v^* = x) dH_v^*(x),$$

$P(T(0^*) > \tau)$ is estimated simply by plugging in the estimates for $risk_0^*(\tau, v|X_v^* = x)$ and $H_v^*(x)$ summing over all observed data points $X_v^* = x$.

7 Estimation of the cdfs $F_v^*(\cdot)$ and $H_v^*(\cdot)$

This procedure is described in points 2 and 4 in Section 2.

8 Obtaining Confidence Intervals and Estimated Uncertainty Intervals

Confidence intervals about all of the vaccine efficacy target parameters are obtained under the methods that set $\phi(t = 25, v|s_1) = \phi(\tau = 13, v|x) = w_{Inc}(t = 25) = w_V(t = 25, v) = w_{Inc}(\tau = 13|x) = w_V(\tau = 13, v|x) = 1$. They are obtained by a bootstrap, where all estimated terms are re-estimated based on with-replacement sampled data sets.

A sensitivity analysis is conducted by specifying $\phi \equiv \phi(t = 25, v|s_1) = \phi(\tau = 13, v|x)$ equal to a fixed constant varying over a specified range and $\rho \equiv w_{Inc}(t = 25) = w_{Inc}(t = 25|x) = w_{Inc}(\tau = 13|x)$ equal to a fixed constant varying over a specified range, and a confidence interval is computed for each fixed value pair (ϕ, ρ). A Wald 95% estimated uncertainty interval (EUI) is computed by noting the most extreme confidence interval limits for all pairs (ϕ, ρ) varying over the specified plausible region. The EUI is computed using the method of Imbens and Manski (2004) and Vansteelandt et al. (2006), as described in formulas (40) and (41) of Richardson et al. (2014).

9 Planned Data Analysis Output

The following summarizes the results that are obtained.

We conduct two bridging analyses, one for inference for hypothetical CYD14+CYD15 18-45 year olds (all countries included– Goal 1) as if this age cohort had been studied in

CYD14/CYD15, and one for 18–45 year olds in India. In each case, the objective is estimation with 95% confidence intervals or estimated uncertainty intervals for the parameters $\text{VE}^{d*}(t = 25, v)$, $\text{VE}^{d*}(t = 25)$, $\text{VE}^{*}(t = 25, v)$, $\text{VE}^{*}(t = 25)$ for $v = 1, 2, 3, 4$.

We first apply the method described in the SAP using the assumptions defined in Section 4, with the following choices for the sensitivity parameters:

[C.4, C.5] Specify $\phi(t = 25, v|s_1) = 1$ and $\phi(\tau = 13, v|x) = 1$

[D.3–D.6] Specify $w_{Inc}(t = 25) = 1$, $w_{Inc}(t = 25|x) = 1$, $w_V(t = 25, v) = 1$, $w_{Inc}(\tau = 13|x) = 1$, $w_V(\tau = 13, v|x) = 1$

This analysis is the "index analysis" for which point estimates and 95% confidence intervals are reported. Together with these primary outputs, estimates of terms needed in the transport formula would be described graphically, including the estimated vaccine efficacy curves from CYD14 + CYD15 9–16 year olds (both the curves varying over month 13 titers and varying over baseline titers), the distributions of baseline and Month 13 neutralization titers in CYD22 and CYD47 as they compare to the corresponding distributions in CYD14 + CYD15 9–16 year olds, and estimates of the conditional background VCD risks in the new setting being targeted. Next, this index analysis includes use of the alternative method, mentioned in Section 1, that only uses baseline titers for estimating $\text{VE}^{d*}(t = 25, v)$, $\text{VE}^{d*}(t = 25)$, $\text{VE}^{*}(t = 25, v)$, $\text{VE}^{*}(t = 25)$, under which [C.2, C.3] and [D.3–D.6] simplify to:

[C.2, C.3] Specify $\phi(\tau = 13, v|x) = 1$

[D.3–D.6] Specify $w_{Inc}(\tau = 13|x) = 1$, $w_V(\tau = 13, v|x) = 1$

The second set of analyses conducts sensitivity analysis, keeping $w_V(t = 25, v) = 1$ and $w_V(\tau = 13, v) = 1$ but allowing the other sensitivity parameters to vary. As described above in Section 10, we specify $\phi \equiv \phi(t = 25, v|s_1) = \phi(\tau = 13, v|x)$ equal to a fixed constant varying over the range 0.8 to 1.2 and specify $\rho \equiv w_{Inc}(t = 25) = w_{Inc}(t = 25|x) = w_{Inc}(\tau = 13|x)$ equal to the fixed constant 0.8 or 1.0, and a 95% confidence interval is computed for each fixed value pair (ϕ, ρ). A 95% estimated uncertainty interval is computed by noting the most extreme confidence interval limits for all pairs (ϕ, ρ) varying over the specified plausible region.

10 Appendix: Approach to estimating the four vaccine efficacy target parameters

This Appendix elaborates mathematical details of the material in Section 1. As summarized in Section 1, bridging is based on estimation of the marginal additive-difference VE curves for each serotype. Let T_v denote the first VCD event time for serotype v. We construct the marginal VE curve based on T_v conditional on serotype-specific titer $S_v(1)$ for each $v = 1, 2, 3, 4$. That is, we define

$$mrisk_{v,z}(t|s_{v1}) = P(T_v(z) \leq t | T_v(1) > \tau, T_v(0) > \tau, S_v(1) = s_{v1}),$$
$$\text{VE}_v(t|S_{v1}) = 1 - mrisk_{v,1}(t|s_{v1})/mrisk_{v,0}(t|s_{v1}).$$

This approach requires estimation of each $\text{VE}_v(t|S_{v1} = s_{v1})$ over a range of fixed s_{v1} values in the support of $F_v^*(\cdot)$. As stated in Section 1, an advantage of this approach is that once the problem of bridging serotype-specific vaccine efficacy is solved, bridging overall vaccine efficacy is also solved.

We can estimate $\text{VE}_v^{d*}(t) = P(T_v(1^*) \leq t) - P(T_v(0^*) \leq t)$ using the transport formula as in GH for each of $v = 1, 2, 3, 4$ separately. Then we can estimate $\sum_{v=1}^4 \text{VE}_v^{d*}(t) = \sum_{v=1}^4 P(T_v(1^*) \leq t) - \sum_{v=1}^4 P(T_v(0^*) \leq t)$.

Note that our goal is estimation of

$$\text{VE}^{d*}(t) = P(min_{v\in\{1,2,3,4\}}(T_v(1^*)) \leq t) - P(min_{v\in\{1,2,3,4\}}\}(T_v(0^*)) \leq t)$$

and

$$\text{VE}^*(t) = 1 - \frac{P(min_{v\in\{1,2,3,4\}}(T_v(1^*)) \leq t)}{P(min_{v\in\{1,2,3,4\}}\}(T_v(0^*)) \leq t)}.$$

Here

$$\begin{aligned}
& P(min_{v\in\{1,2,3,4\}}(T_v(z^*)) \leq t) \\
= \; & P(T_1(z^*) \leq t \text{ or } T_2(z^*) \leq t \text{ or } T_3(z^*) \leq t \text{ or } T_4(z^*) \leq t) \\
= \; & \sum_{i=1}^4 P(T_i(z^*) \leq t) + \\
& \left\{ - \sum_{i=1}^3 \sum_{j=i+1}^4 P(T_i(z^*) \leq t, T_j(z^*) \leq t) \right. \\
+ \; & \sum_{i=1}^2 \sum_{j=i+1}^3 \sum_{k=j+1}^4 P(T_i(z^*) \leq t, T_j(z^*) \leq t, T_k(z^*) \leq t) \\
- \; & \left. P(T_1(z^*) \leq t, T_2(z^*) \leq t, T_3(z^*) \leq t, T_4(z^*) \leq t) \right\},
\end{aligned}$$

which approximately equals $\sum_{v=1}^4 P(T_v(z^*) \leq t)$ only if the term inside $\{.\}$ equals zero, e.g. if it is very rare for a participant to experience the VCD endpoint with more than one dengue

serotype before $t = 25$. This assumption is approximately true, given that 14 out of 595 (CYD14), 20 out of 662 (CYD15), and 4 out of 134 (CYD23) of the VCD endpoint cases during the course of the studies had two (out of four) serotypes measured in their blood, and no one had more than two.

11 References

1. Gilbert PB, Huang Y (2016). Predicting overall vaccine efficacy in a new setting by recalibrating baseline covariate and intermediate response endpoint effect modifiers of Type-Specific vaccine efficacy. Epidemiological Methods.

2. Huang Y, Gilbert PB, Janes H (2012). Assessing treatment selection markers using a potential outcomes framework. Biometrics 68:687-696.

3. Imbens GW, Manski CF (2004). Confidence intervals for partially identified parameters. Econometrica. 72(6):1845-57.

4. Juraska M, Gilbert PB (2016). Nonparametric smoothing method for assessing effect modification by a post-randomization biomarker with application to vaccine efficacy trials. Fred Hutchinson Cancer Research Center Technical Report, February, 2016.

5. Moodie Z, Juraska M, Huang Y, Zhuang Y, Fong Y, Self SG, Chambonneau L, Small R, Jackson N, Noriega F, Gilbert PB (2016). Neutralizing antibody correlates analysis of tetravalent dengue vaccine efficacy trials in Asia and Latin America. Submitted.

6. Nealon J, Taurel AF, Capeding MR, Tran NH, Hadinegoro SR, Chotpitayasunondh T, Chong CK, Wartel TA, Beucher S, Frago C, Moureau A (2016). Symptomatic Dengue Disease in Five Southeast Asian Countries: Epidemiological Evidence from a Dengue Vaccine Trial. PLoS Negl Trop Dis. 17;10(8):e0004918.

7. Richardson A, Hudgens MG, Gilbert PB, Fine JP (2014). Nonparametric bounds and sensitivity analysis of treatment effects. Statistical science: a review journal of the Institute of Mathematical Statistics. 29(4):596.

8. Sarti E, L'Azou M, Mercado M, Kuri P, Siqueira JB, Solis E, Noriega F, Ochiai RL (2016). A comparative study on active and passive epidemiological surveillance for dengue in five countries of Latin America. International Journal of Infectious Diseases. 31;44:44-49.

9. Vansteelandt S, Goetghebeur E, Kenward MG, Molenberghs G (2006). Ignorance and uncertainty regions as inferential tools in a sensitivity analysis. Statistica Sinica. 1:953-79.