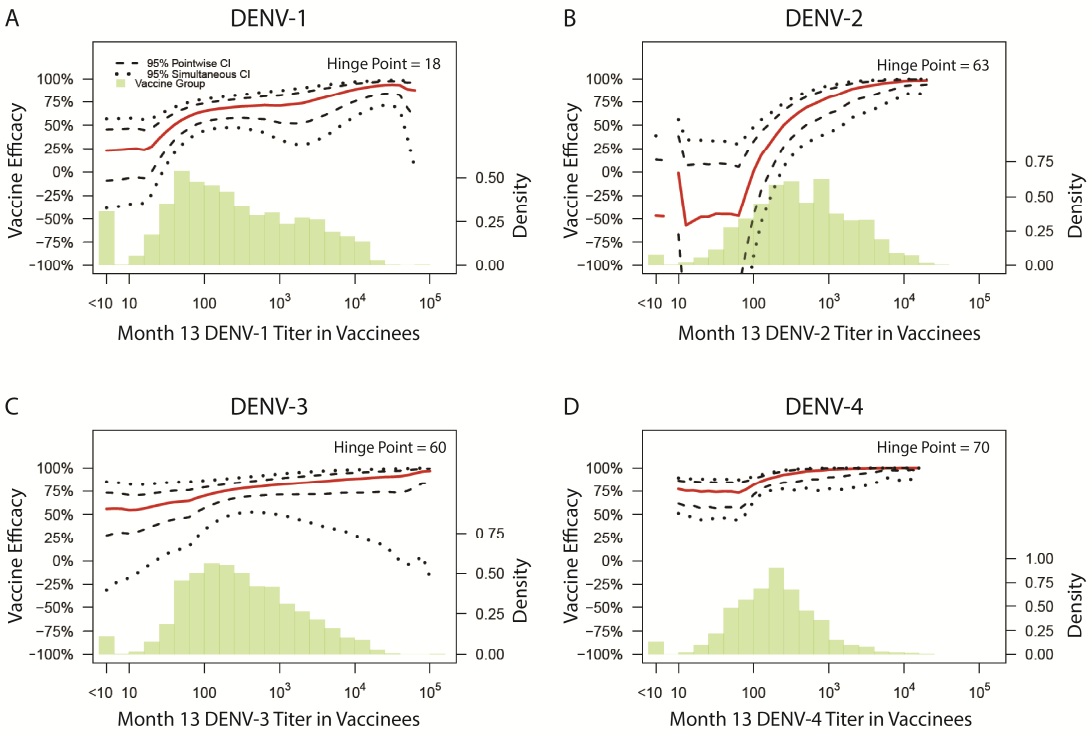
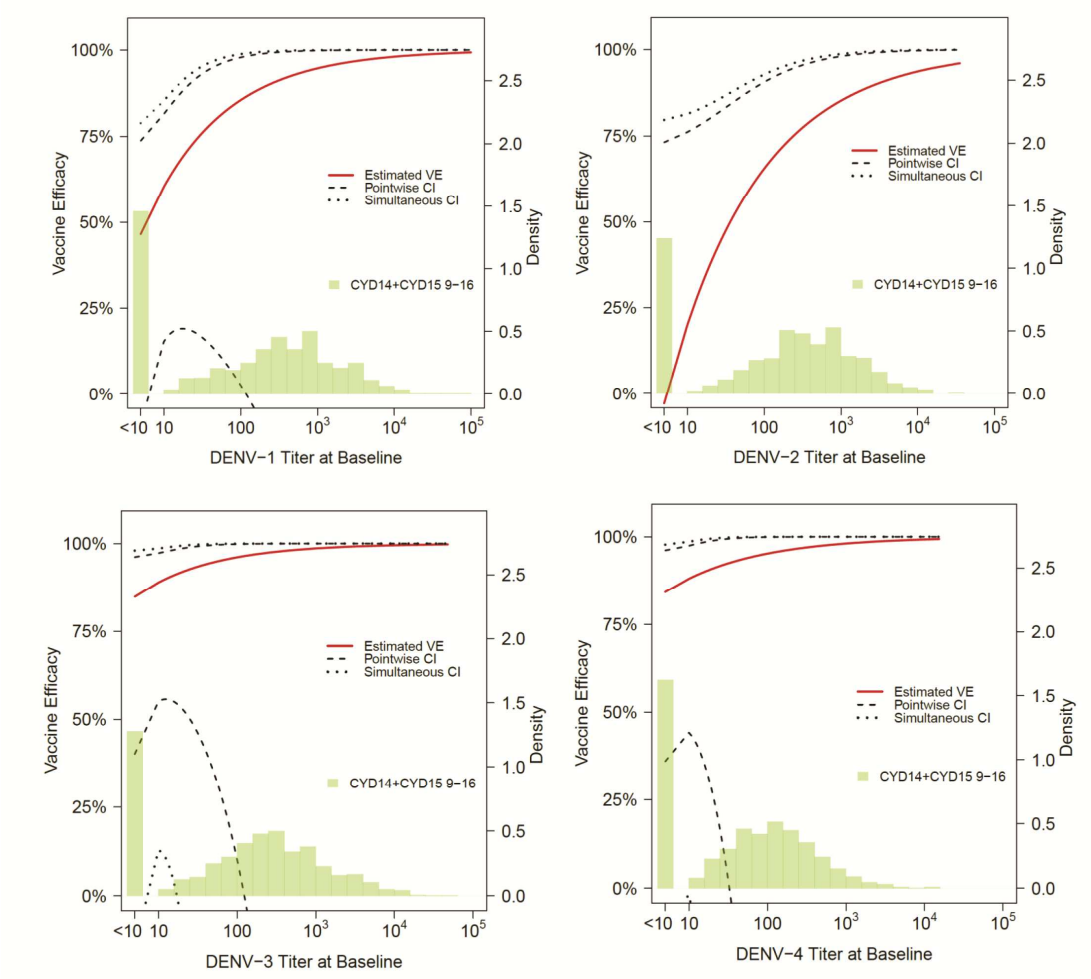
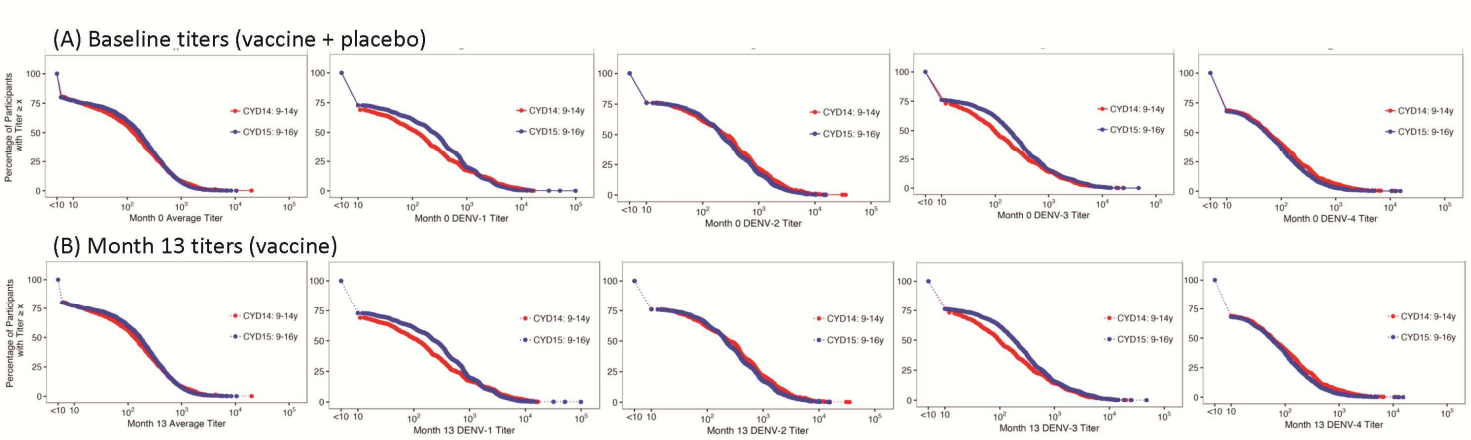
Supplemental Figure S1. For CYD14+CYD15 9−16-year-olds, estimated vaccine efficacy against DENV-v between Month 13 and 25 for each serotype v=1,2,3,4 by vaccinated subgroup defined by Month 13 homologous serotype v titer Sv with pointwise and simultaneous 95% CIs, using the Juraska et al. method (available in the Supplementary Material of [1]) as implemented in [1].



Supplemental Figure S2. For CYD14+CYD15 9−16-year-olds, estimated vaccine efficacy against DENV-v from Month 0 and 25 for each serotype v=1,2,3,4 by subgroup defined by baseline homologous serotype v titer Xv with pointwise and simultaneous 95% CIs, using the Huang, Gilbert, and Janes (2012) logistic regression method[2] as implemented in [1].

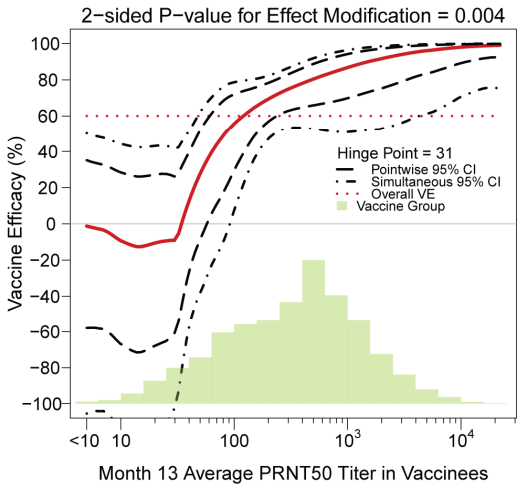


Supplemental Figure S3. Reverse cumulative distribution functions of (A) baseline neutralizing antibody titers ($PRNT_{50}$) in CYD-TDV vaccine and placebo recipients pooled and (B) Month 13 $PRNT_{50}$ in CYD-TDV vaccine recipients receiving all three vaccinations for CYD14 (9−14-year-olds) versus CYD15 (9−16-year-olds).

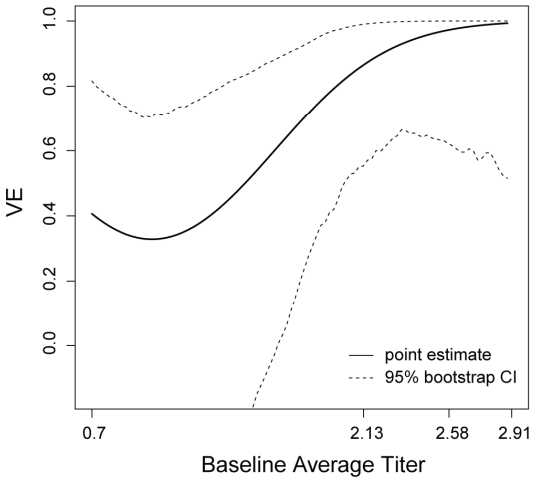


Supplemental Figure S4. (A) Vaccine efficacy against hospitalization with DENV-Any through to the end of the CYD14/15 study follow-up (72 months) by Month 13 average $PRNT_{50}$ titer in CYD-TDV vaccine recipients aged 9 years or older in CYD14 and CYD15 combined. The analysis is based on the Month 13 Hospitalized DENV-Any Case-Cohort with membership defined by having Month 13 average titer measured and either (i) being a case (i.e., experienced an hospitalized DENV-Any event after the Month 13 visit) or (ii) being a control, defined as having a study visit at or after Month 13 and never having a registered hospitalized DENV-Any event. The analysis uses fixed bandwidths in the kernel density estimation. (B) Estimated vaccine efficacy against hospitalization with DENV-Any by Month 13 with 95% confidence intervals as a function of baseline average titer (on the $\log_{10}$ scale), based on quadratic correlate of risk logistic regression models. For further details, see the "Statistical Analysis Plan for Additional Analyses of CYD14 and CYD15 9-16 year-old Study Participants in Preparation for the FDA VRBPAC Meeting March 7, 2019" (January 17, 2019) provided in the supplementary materials.

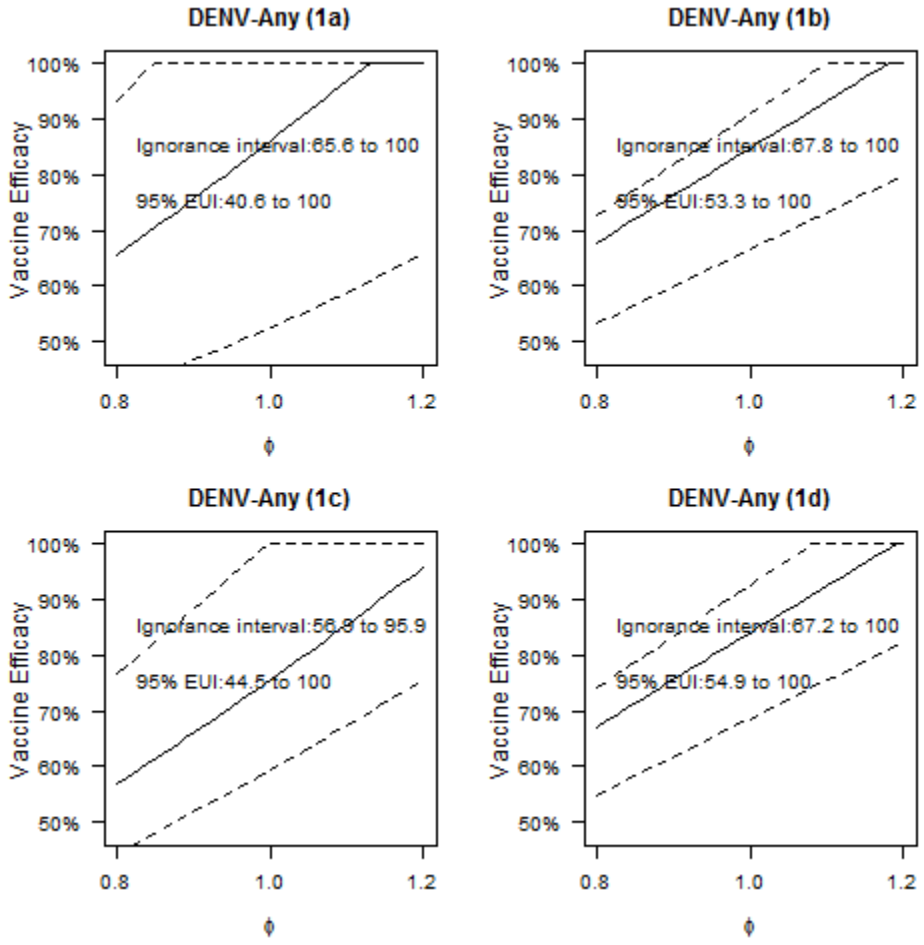
A


2−sided P−value for Effect Modification = 0.004
Vaccine Efficacy (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
Hinge Point = 31
Pointwise 95% CI
Simultaneous 95% CI
Overall VE
Vaccine Group
<10
10
100
10^3
10^4
Month 13 Average PRNT50 Titer in Vaccinees

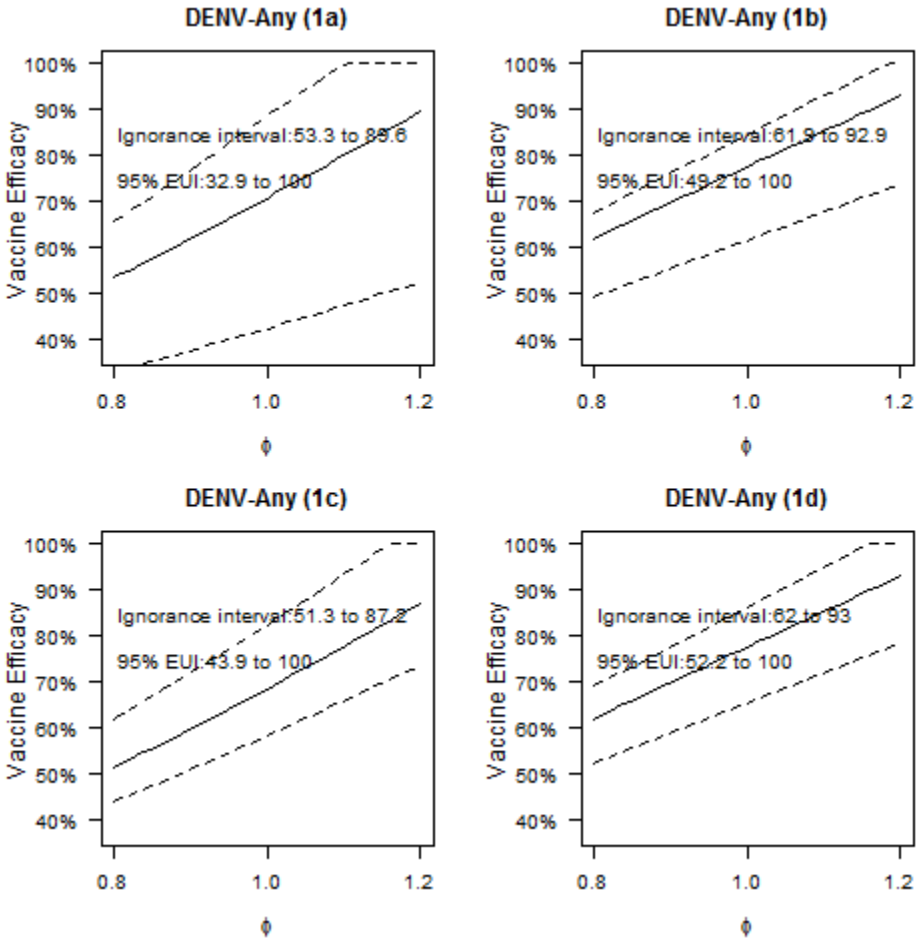
B


VE
0.0
0.2
0.4
0.6
0.8
1.0
point estimate
95% bootstrap CI
0.7
2.13
2.58
2.91
Baseline Average Titer

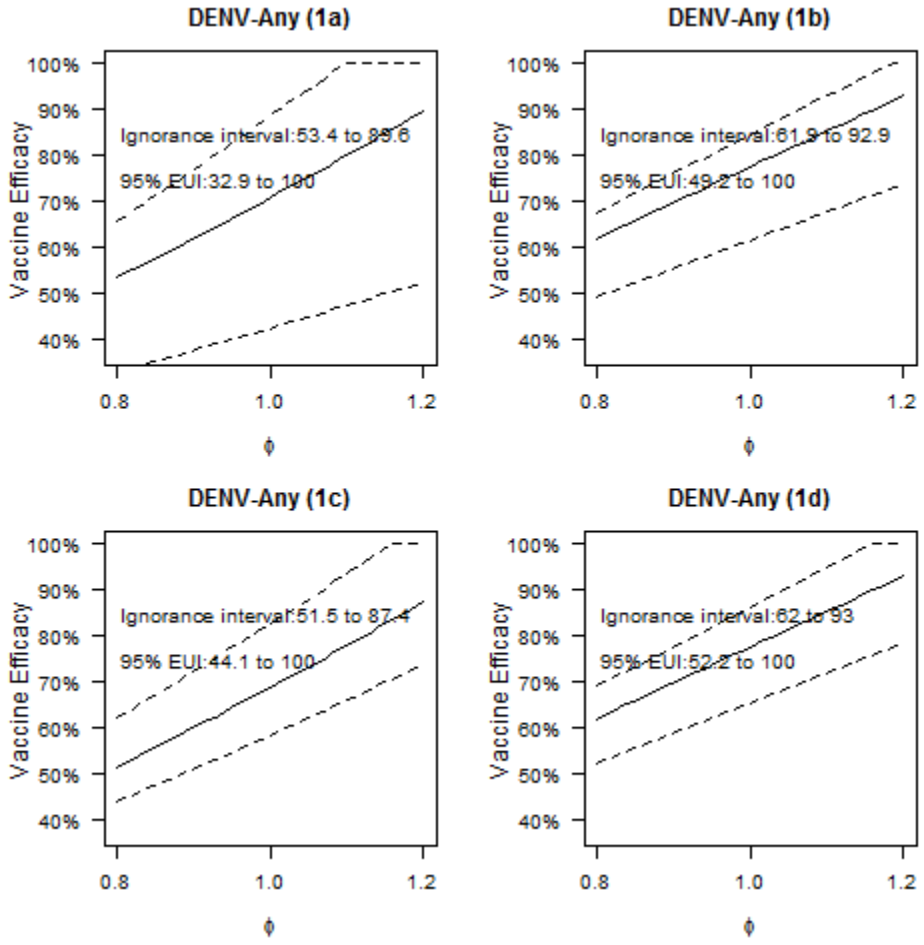
Supplemental Figure S5. Second sensitivity analysis showing estimated vaccine efficacy against DENV-Any from Month 0 to 25 with 95% CIs for the sensitivity parameter ϕ varying between 0.8 and 1.2 and sensitivity parameter ρ = 0.8 for hypothetical CYD14+CYD15 18−45-year-olds (Bridging Population 1). The union of the point estimates is the estimated ignorance interval and the union of the 95% CIs is the estimated uncertainty interval.



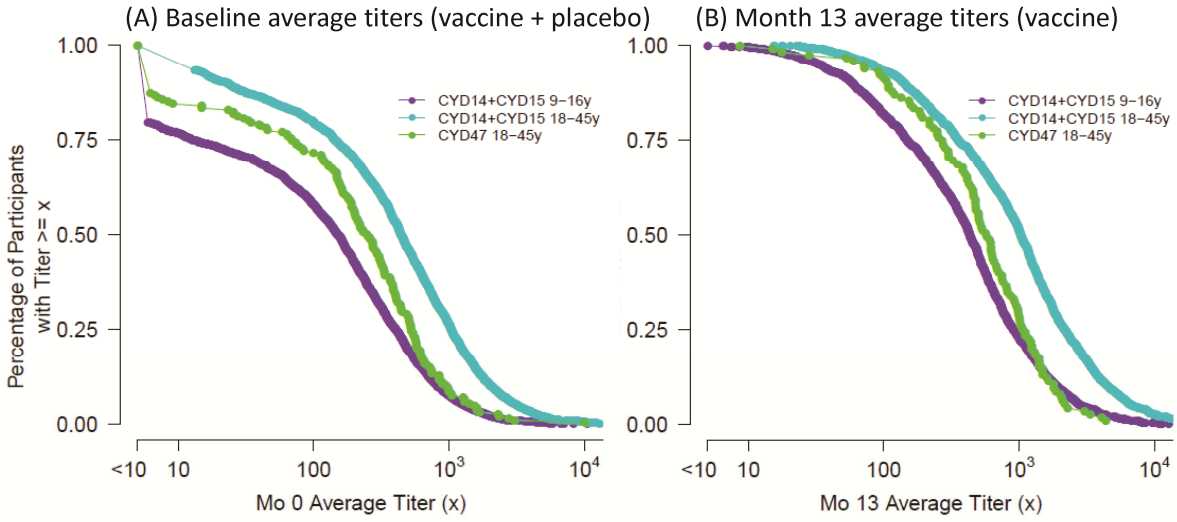
Supplemental Figure S6. First sensitivity analysis showing estimated vaccine efficacy against DENV-Any from Month 0 to 25 with 95% CIs for the sensitivity parameter ϕ varying between 0.8 and 1.2 and sensitivity parameter ρ = 1.0 for hypothetical India 18−45-year-olds (Bridging Population 2). The union of the point estimates is the estimated ignorance interval and the union of the 95% CIs is the estimated uncertainty interval.



Supplemental Figure S7. Second sensitivity analysis showing estimated vaccine efficacy against DENV-Any from Month 0 to 25 with 95% CIs for the sensitivity parameter ϕ varying between 0.8 and 1.2 and sensitivity parameter ρ = 0.8 for hypothetical India 18−45-year-olds (Bridging Population 2). The union of the point estimates is the estimated ignorance interval and the union of the 95% CIs is the estimated uncertainty interval.



Supplemental Figure S8. Reverse cumulative distribution functions of (A) baseline neutralizing antibody average titers in CYD-TDV vaccine and placebo recipients pooled and (B) Month 13 average titers in CYD-TDV vaccine recipients receiving all three vaccinations for CYD14+CYD15 9−16-year-olds, CYD14+CYD15 18−45-year-olds, and CYD47 18−45-year-olds.



Supplemental Table S1. Assumptions for the bridging VE estimation methods*

Assum.	Method	Assumption Statement
Assum-ption 1 (BP 1,2)	1a, 2a	$VE^{18\text{-}45}(t=25,v\|Sv=s) = VE^{14.15.9\text{-}16}(t=25,v\|Sv=s)$ for all s and v=1,2,3,4 $VE^{18\text{-}45}(t=13,v\|Xv=x) = VE^{14.15.9\text{-}16}(t=13,v\|Xv=x)$ for all x and v=1,2,3,4
	1b, 2b	$VE^{18\text{-}45}(t=25,v\|Xv=x) = VE^{14.15.9\text{-}16}(t=25,v\|Xv=x)$ for all x and v=1,2,3,4
	1c	$VE^{18\text{-}45}(t=25\|Savg=s) = VE^{14.15.9\text{-}16}(t=25\|Savg=s)$ for all s $VE^{18\text{-}45}(t=13\|Xavg=x) = VE^{14.15.9\text{-}16}(t=13\|Xavg=x)$ for all x
	1d	$VE^{18\text{-}45}(t=25\|Xavg=x) = VE^{14.15.9\text{-}16}(t=25\|Xavg=x)$ for all x
Assum-ption 2 (BP 1)	1a, 2a	The cdfs of Sv and Xv for the two CYD22 age cohorts (18−45 vs. 9−16) are linked by a mixed binary and continuous location-shift model, and for each of Sv and Xv the odds ratio of positive response $PRNT_{50} > 10$ for 18−45 vs. 9−16− and the location-shift model in positive responders− is the same for CYD14+CYD15 and CYD22.
	1c	Same as for (1a, 2a) for Savg and Xavg instead of Sv and Xv
	1b, 2b, 1d	Same as for (1a, 2a) for Xv only (Sv not involved)
Assum-ption 3 (BP 1,2)	1a, 2a	Conditional on Sv, unvaccinated dengue-v risk from Month 13 to 25 is the same for the two agecohorts. Conditional on Xv, unvaccinated dengue-v risk from Month 0 to 25 is the same for the age cohorts.
	1b, 2b	Same as for (1a, 2a) for Xv only (Sv not involved)
	1c	Same as for (1a, 2a) for Savg and Xavg instead of Sv and Xv
	1d	Same as 1c for Xavg only (Savg not involved)

*BP 1 = Bridging Population 1 (hypothetical CYD14+CYD15 18−45); BP 2 = Bridging Population 2 (India 18−45); Sv=Month 13 serotype v titer; Xv=baseline serotype v titer; Savg=Month 13 average titer; Xavg=baseline average titer; see the Statistical Analysis Plan for complete details.

Supplemental Table S2. Estimated additive-difference vaccine efficacy (VE^d) against DENV-Any from Month 0 to 25 for hypothetical CYD14+CYD15 18−45 year olds (Bridging Population 1) and for India 18−45 year olds (Bridging Population 2), with results from CYD14+CYD15 9−16 year olds for comparison (methods 1a−1d).

Bridging Population	**Estimated Additive-Difference VE (95% Confidence Interval) Against VCD from Month 0 to 25***			
	Method 1a	Method 1b	Method 1c	Method 1d
1. CYD14+CYD15 18-45 year olds	-0.032 (-0.040, -0.022)	-0.031 (-0.044, -0.019)	-0.033 (-0.041, -0.028)	-0.037 (-0.051, -0.025)
2. India 18-45 year olds	-0.036 (-0.043, -0.023)	-0.039 (-0.050, -0.025)	-0.036 (-0.043, -0.030)	-0.041 (-0.053, -0.028)

*Additive difference VE is the cumulative probability of DENV-Any by Month 25 for the vaccine group minus this cumulative probability for the placebo group. Under the assumption that the vaccine does increase the risk of DENV-Any, it has interpretation as the (negative) probability that a vaccine recipient has DENV-Any by Month 25 averted by vaccination (thus -0.039 means that 3.9 DENV-Any cases are averted per 100 vaccinations).

Supplemental Table S3. Estimated additive-difference vaccine efficacy (VE^d) against hospitalized DENV-Any VCD from Month 0 to 72 for hypothetical CYD14+CYD15 18−45 year olds (Bridging Population 1) and for India 18−45 year olds (Bridging Population 2), with results from CYD14+CYD15 9−16 year olds for comparison (methods 1c and 1d).

Bridging Population	**Estimated Additive-Difference VE (95% Confidence Interval) Against Hospitalized VCD from Month 0 to 72***	
	Method 1c	Method 1d
1. CYD14+CYD15 18-45 year olds	-0.010 (-0.013, -0.007)	-0.012 (-0.019, -0.006)
2. India 18-45 year olds	-0.010 (-0.013, -0.008)	-0.013 (-0.021, -0.006)

*Additive difference VE (VE^d) is the cumulative probability of hospitalized DENV-Any by Month 72 for the vaccine group minus this cumulative probability for the placebo group.

Supplemental Table S4. Ignorance intervals for vaccine efficacy (VE) against hospitalized DENV-Any from Month 0 to 72 for hypothetical CYD14+CYD15 18−45 year olds (Bridging Population 1) and for India 18−45 year olds (Bridging Population 2), with results from CYD14+CYD15 9−16 year olds for comparison (methods 1c and 1d).

Bridging Population	**Ignorance Intervals for VE (95% Estimated Uncertainty Intervals) Against Hospitalized VCD from Month 0 to 72**	
	Method 1c	Method 1d
1. CYD14+CYD15 18-45 year olds	45.1 to 74.4 (31.2, 100)	58.8 to 98.2 (35.7, 100)
2. India 18-45 year olds	38.6 to 64.3 (28.9, 88.2)	52.7 to 79.1 (31.4, 98.6)

Supplemental Table S5. Ignorance intervals for additive-difference vaccine efficacy (VE^d) against hospitalized DENV-Any VCD from Month 0 to 72 for hypothetical CYD14+CYD15 18−45 year olds (Bridging Population 1) and for India 18−45 year olds (Bridging Population 2), with results from CYD14+CYD15 9−16 year olds for comparison (methods 1c and 1d).

Bridging Population	**Ignorance Intervals for Additive-Difference VE (95% Estimated Uncertainty Interval) Against Hospitalized VCD from Month 0 to 72**	
	Method 1c	Method 1d
1. CYD14+CYD15 18-45 year olds	-0.010 to -0.006 (-0.013, -0.004)	-0.011 to -0.008 (-0.019, -0.004)
2. India 18-45 year olds	-0.010 to -0.006 (-0.013, -0.005)	-0.013 to -0.009 (-0.020, -0.004)

Supplemental References

1. Moodie Z, Juraska M, Huang Y, Zhuang Y, Fong Y, Carpp LN, Self SG, Chambonneau L, Small R, Jackson N, Noriega F, Gilbert PB. Neutralizing Antibody Correlates Analysis of Tetravalent Dengue Vaccine Efficacy Trials in Asia and Latin America. *J Infect Dis*: Nov 29. doi: 10.1093/infdis/jix1609.

2. Huang Y, Gilbert PB, Janes H. Assessing Treatment-Selection Markers using a Potential Outcomes Framework. *Biometrics* 2012; **68**: 687-696.