Evaluation of extended efficacy of Dengvaxia vaccine against symptomatic and subclinical dengue infection

Supplementary Information

Figure S1

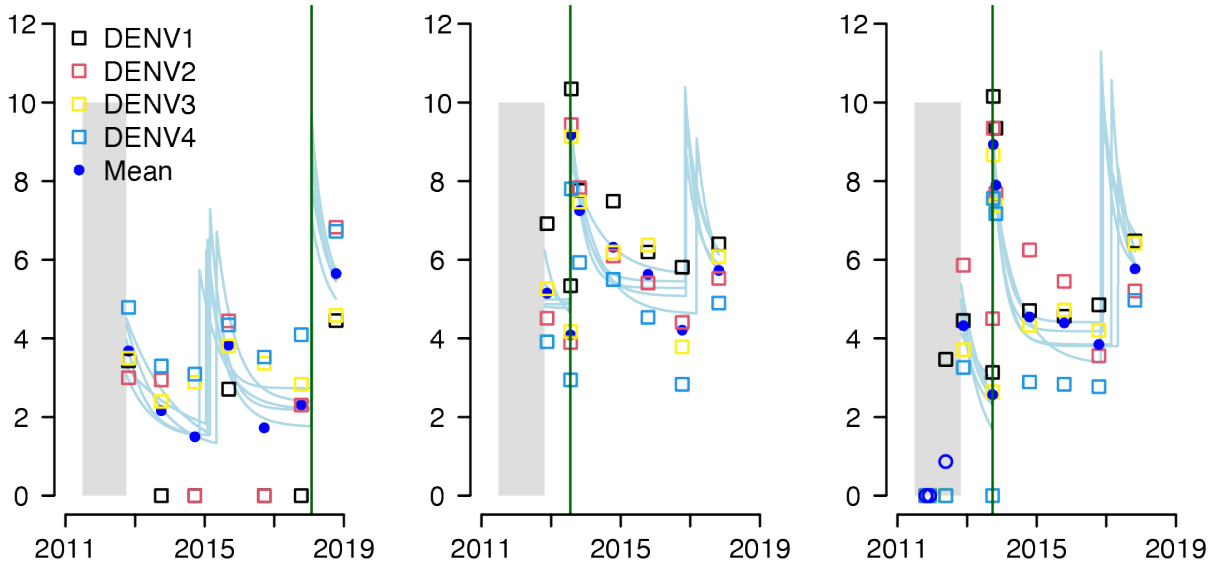

Figure S1. Example antibody responses during follow-up with serotype data. (A)-(C) Measured (dots) and modelled (lines) antibody titers for three individuals (same three individuals as Figure 1). Individuals **(A)** and **(C)** were vaccine recipients and **(B)** received a placebo. The dark green lines represent symptomatic infection events.

Figure S2

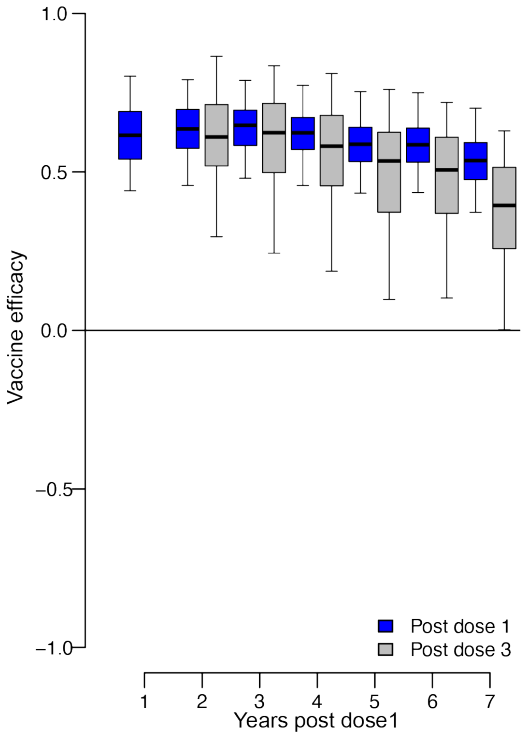

Figure S2. Vaccine efficacy to symptomatic infection comparing post dose 1 to post dose 3 in baseline seropositive individuals. Symptomatic infections were detected in all individuals in the first year post the first vaccine dose by Sanofi Pasteur, irrespective of whether they were recruited into the ancillary study. This allows us to compare the cumulative vaccine efficacy when it is calculated from the time of the first dose (blue) with when it is calculated from the third dose (grey). The boxplots represent the mean, the interquartile range and 2.5 and 97.5 percentiles of the estimated vaccine efficacy.

Figure S3

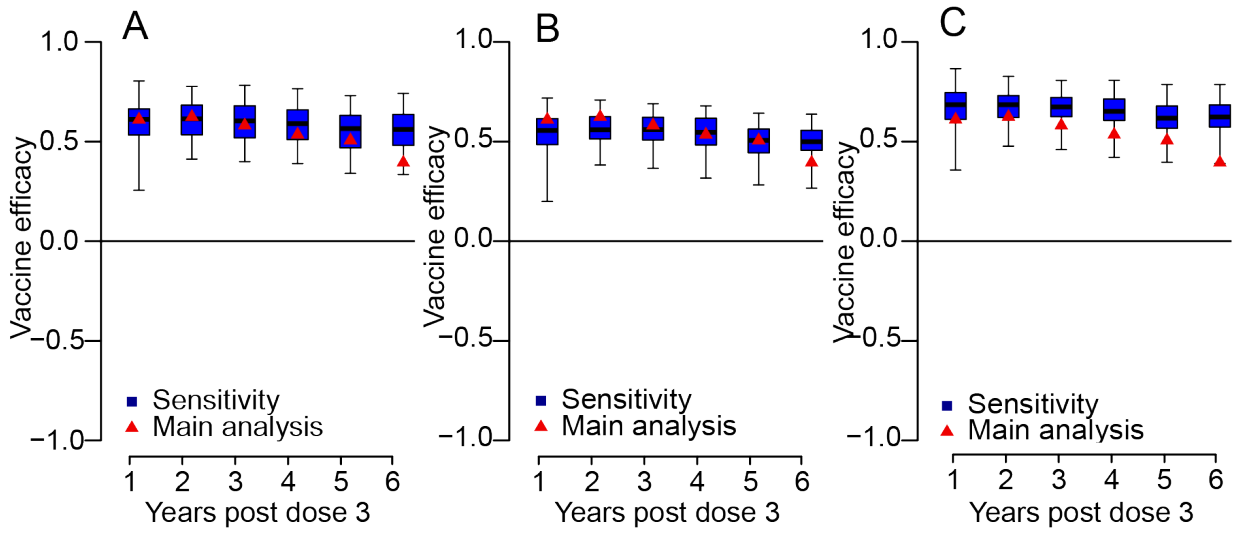

Figure S3. Sensitivity analysis of baseline serostatus on vaccine efficacy in seropositive individuals. (A) Sensitivity analysis where there is no temporary protection from an additional infection in the 365 days following an infection event. **(B)** Sensitivity analysis when no adjustment is made for baseline serostatus (i.e, the status at post dose 3 is used). **(C)** Sensitivity analysis where 80% of vaccinated individuals with indeterminate baseline status as per the NS1 assay are assumed to have been seronegative prior to the first vaccine dose. In each panel, the boxplots represent the mean, the interquartile range and 2.5 and 97.5 percentiles of the estimated vaccine efficacy.

Figure S4

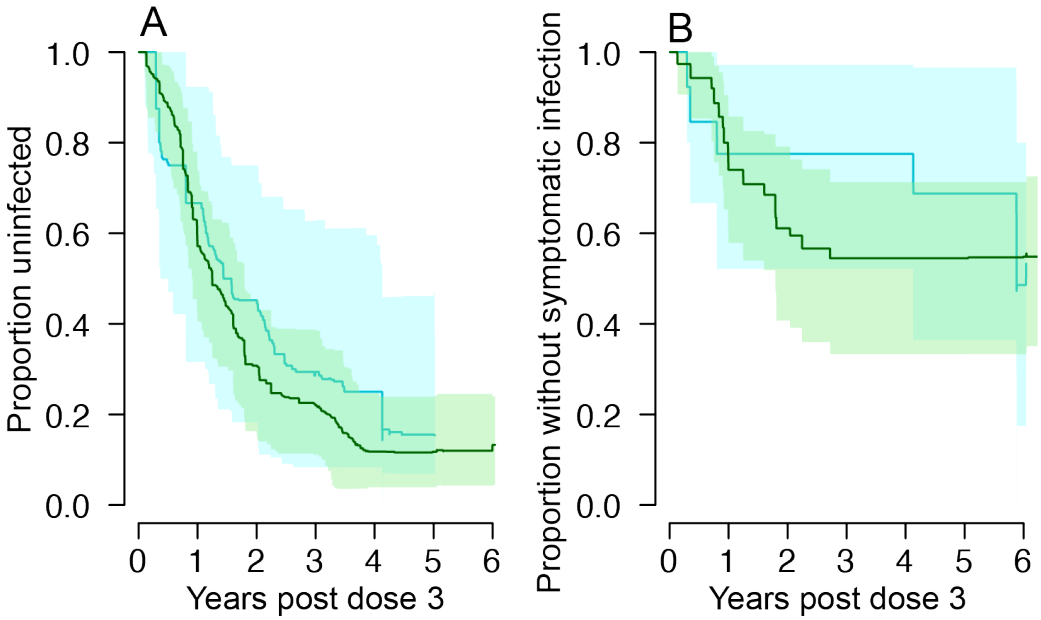

Figure S4. Time to event in seronegative individuals (A) Survival from any infection for individuals seronegative at baseline comparing vaccine recipients (green) with placebo recipients (blue). **(B)** Survival from symptomatic infection for individuals seronegative at baseline comparing vaccine recipients (green) with placebo recipients (blue). In each panel, both the mean and 95% confidence intervals are presented.

Table S1

	Placebo (N=194)	**Vaccine** (N=417)	**Overall** (N=611)
Mean age at enrollment (range)	8.3 (2-14)	8.4 (2-14)	8.3 (2-14)
No. <5 years at enrollment (%)	40 (21%)	70 (17%)	110 (18%)
No. 5-9 years at enrollment (%)	74 (38%)	175 (42%)	249 (41%)
No. >9 years at enrollment (%)	80 (41%)	172 (41%)	252 (41%)
No. female (%)	101 (52%)	216 (52%)	317 (52%)
No. recruited prior to first dose (%)	32 (16%)	80 (19%)	112 (18%)
No. recruited after third dose (%)	162 (84%)	337 (81%)	499 (82%)
Baseline serostatus			
No. seronegative (%)	13 (7%)	36 (9%)	49 (8%)
No. seropositive (%)	181 (93%)	381 (91%)	562 (92%)

Table S1. Study participant characteristics.

Table S2

	Placebo (N=194)	**Vaccine** (N=417)	**Overall** (N=611)
Baseline serostatus using NS1 (Vaccine recipients only, N=417)			
No. seronegative (%)	-	36/417 (9%)	-
No. seropositive (%)	-	324/417 (77%)	-
No. indeterminate (%)	-	57/417 (14%)	-
Baseline serostatus using post dose 3 titers (placebo recipients only, N=194)			
No. seronegative (%)	11/194 (6%)	-	-
No. seropositive (%)	183/194 (94%)	-	-
Baseline serostatus among individuals with pre-dose 1 samples (N=112)			
Serostatus based on pre-dose 1 neutralization titers (N=112):			
No. seronegative (%)	4/32 (13%)	7/80 (9%)	11/112 (10%)
No. seropositive (%)	28/32 (87%)	73/80 (91%)	101/112 (90%)
Serostatus based on post-dose 3 NS1 test (vaccine recipients only, N=80)			
No. seronegative (%)	-	7/80 (9%)	-
No. seropositive (%)	-	68/80 (85%)	-
No. indeterminate (%)	-	5/80 (6%)	-
Serostatus based on post-dose 3 neutralization titers (placebo recipients only, N=32)			
No. seronegative (%)	2/32 (6%)	-	-
No. seropositive (%)	30/32 (94%)	-	-

Table S2. Baseline serostatus as measured through neutralization titers and NS1 assay.

Table S3

	Placebo	Vaccine	Total
Prior to dose 3			
- DENV1	19	13	32
- DENV2	3	7	10
- DENV3	4	6	10
- DENV4	1	0	1
Total symptomatic	27	26	53
Of which hospitalized	2	0	2
Post dose 3			
- DENV1	4	8	12
- DENV2	15	28	43
- DENV3	4	12	16
- DENV4	4	2	6
Serotype unknown	5	5	10
Total symptomatic	32	55	87
Of which hospitalized	2	7	9
By baseline serostatus			
Total hospitalized:			
- Seropositive	4	5	9
- Seronegative	0	2	2
Total symptomatic			
- Seropositive	53	62	115
- Seronegative	6	19	25

Table S3. Number of symptomatic cases by vaccine and placebo group.

Table S4

Parameter	Estimate (95% CrI)
Vaccine response	
Rise in short-lived antibodies (sero -ve) (${\gamma^{V,neg}}_m$)	3.41 (2.95-3.88)
Rise in short-lived antibodies (sero +ve) (${\gamma^{V,pos}}_m$)	1.94 (1.68-2.24)
Rise in long-lived antibodies (sero -ve) (${\omega^{V,neg}}_m$)	0.90 (0.55-1.27)
Decay in short-lived antibodies (sero -ve) (${\delta^{V,neg}}_m$)	0.0055 (0.0040-0.0071) /day
Decay in short-lived antibodies (sero +ve) (${\delta^{V,pos}}_m$)	0.0019 (0.0016-0.0024) /day
Natural infection response	
Rise in short-lived antibodies (placebo) (${\gamma^{I,plac}}_m$)	3.76 (3.44-4.07)
Rise in short-lived antibodies (vaccine sero +ve) (${\gamma^{I,posV}}_m$)	4.23 (3.85-4.60)
Rise in short-lived antibodies (vaccine sero -ve) (${\gamma^{I,negV}}_m$)	5.23 (4.74-5.70)
Rise in long-lived antibodies (placebo) (${\omega^{I,plac}}_m$)	1.34 (1.07-1.62)
Rise in long-lived antibodies (vaccine sero -ve) (${\omega^{I,negV}}_m$)	1.98 (1.45-2.59)
Rise in long-lived antibodies (vaccine sero +ve) (${\omega^{I,posV}}_m$)	1.89 (1.44-2.37)
Decay in short-lived antibodies (all) (${\delta^{I}}_m$)	0.0069 (0.0062-0.0076) /day
Applicable to all titers	
Variance in short-lived rise in titers (γ_V)	0.69 (1.53-0.89)
Variance in long-lived rise in titers (ω_v)	1.22 (0.84-1.75)
Variance in decay in titers (δ_v)	6e-6 (5e-6 - 9e-6)
Assay error (log-titers) (σ)	0.44 (0.43-0.46)
Force of infection parameters	
Force of infection in 2012 (λ)	0.45 (0.38-0.55)
Relative force of infection in 2011 (vs 2012) ($\beta_{\|2011\|}$)	0.93 (0.16-2.55)
Relative force of infection in 2013 (vs 2012) ($\beta_{\|2013\|}$)	1.51 (0.88-2.46)
Relative force of infection in 2014 (vs 2012) ($\beta_{\|2014\|}$)	1.28 (0.78-2.02)
Relative force of infection in 2015 (vs 2012) ($\beta_{\|2015\|}$)	0.93 (0.55-1.50)
Relative force of infection in 2016 (vs 2012) ($\beta_{\|2016\|}$)	0.54 (0.30-0.90)
Relative force of infection in 2017 (vs 2012) ($\beta_{\|2017\|}$)	0.66 (0.38-1.09)
Relative force of infection in 2018 (vs 2012) ($\beta_{\|2018\|}$)	0.37 (0.19-0.66)
Relative force of infection in 2019 (vs 2012) ($\beta_{\|2019\|}$)	0.94 (0.50-1.61)

Table S4. Parameter estimates

Table S5

Serotype	Strain	Origin	Year
DENV1	16007	Thailand	1964
DENV2	16681	Thailand	1964
DENV3	16562	Philippines	1964
DENV4	C0036/06	Thailand	2006

Table S5. Reference viruses used in assay.