Supplementary Appendix

Let S denote the time when the participant receives the first dose of a vaccine, and T denote the time when the participant develops symptomatic COVID-19; both times are measured in months from the start of the study. We specify that the hazard function of T is related to S through the Cox regression model

$$\lambda(t|S) = \lambda_0(t)e^{\eta(t-S)I(S<t)}, \tag{1}$$

where $\lambda_0(\cdot)$ is an arbitrary baseline hazard function, $\eta(\cdot)$ is the log hazard ratio characterizing the time-varying effect of vaccination, and $I(\cdot)$ is the indicator function. Under this formulation, the baseline hazard function varies over the calendar time, and the effect of vaccine on the risk of disease depends on the time elapsed since vaccination. We define the vaccine efficacy (VE) on the hazard rate at month t as $\text{VE}_{\text{HR}}(t) = 1 - e^{\eta(t)}$.

To make a comprehensive comparison of the sensitivity to waning VE between the proposed and standard approaches, we simulated the following four clinical trials, each of which was replicated 1,000 times.

Trial 1. We assumed that 40,000 participants entered the trial at a constant rate over four months and were randomly assigned to vaccine or placebo at a 1:1 ratio. Crossover occurred at month $6 + G$ of the trial, where G follows the exponential distribution with mean 1. We censored all participants at crossover in order to avoid bias due to behavioral confounding. We generated the event time T from model (1) with

$$\log \lambda_0(t) = -6.5 + 0.4t - (t-6)_+$$

and

$$\eta(t) = -3.0t + 3.0(t-1)_+ + 0.4(t-2)_+,$$

such that the true VE_{HR} increases from 0 at month 0 to a peak of 95% at month 1, stays constant for one month, and then decreases gradually to 70% at month 7.

Trial 2. We used the same design as in the first trial but set

$$\log \lambda_0(t) = -3.8 - 0.5t + 1.4(t-5)_+.$$

In this way, the incidence rate first decreases and then increases, and the nadir coincides with the period of the strongest VE.

Trial 3. We randomly assigned 40,000 participants to the vaccine or placebo group at a 1:1 ratio in the beginning of the trial and followed them for 7 months. We generated the event time T from model (1) with $\log \lambda_0(t) = -5$. We assumed that the true VE_{HR} increases from 0 at month 0 to a peak of 95% at month 1, stays constant for one month, then gradually decreases, and eventually reaches a plateau at month 6. Specifically, we set

$$\eta(t) = -3.0t + 3.0(t-1)_+ + 0.4(t-2)_+ - 0.4(t-6)_+.$$

Trial 4. We used the designed of the third trial but assumed that the true VE_{HR} to reach a plateau at month 4.5, i.e., in model (1),

$$\eta(t) = -3.0t + 3.0(t-1)_+ + 0.4(t-2)_+ - 0.4(t-4.5)_+.$$

For each simulated dataset, we fit model (1) by setting $\eta(t)$ to be piecewise linear with change points placed at 1, 3, and 5 months, i.e.,

$$\eta(t) = \gamma_0 t + \gamma_1(t-1)_+ + \gamma_2(t-3)_+ + \gamma_3(t-5)_+,$$

where $\gamma_0, \ldots, \gamma_3$ are unknown parameters, and $t_+ = t$ if $t > 0$ and 0 otherwise. We estimated $\text{VE}_{\text{HR}}(t)$ using the maximum partial likelihood estimators of $\gamma_0, \ldots, \gamma_3$. We also fit the proportional hazards model and estimated VE_{const} over 0-2, 2-4, or 4-6 months since full vaccination.