Supplementary appendix

Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines

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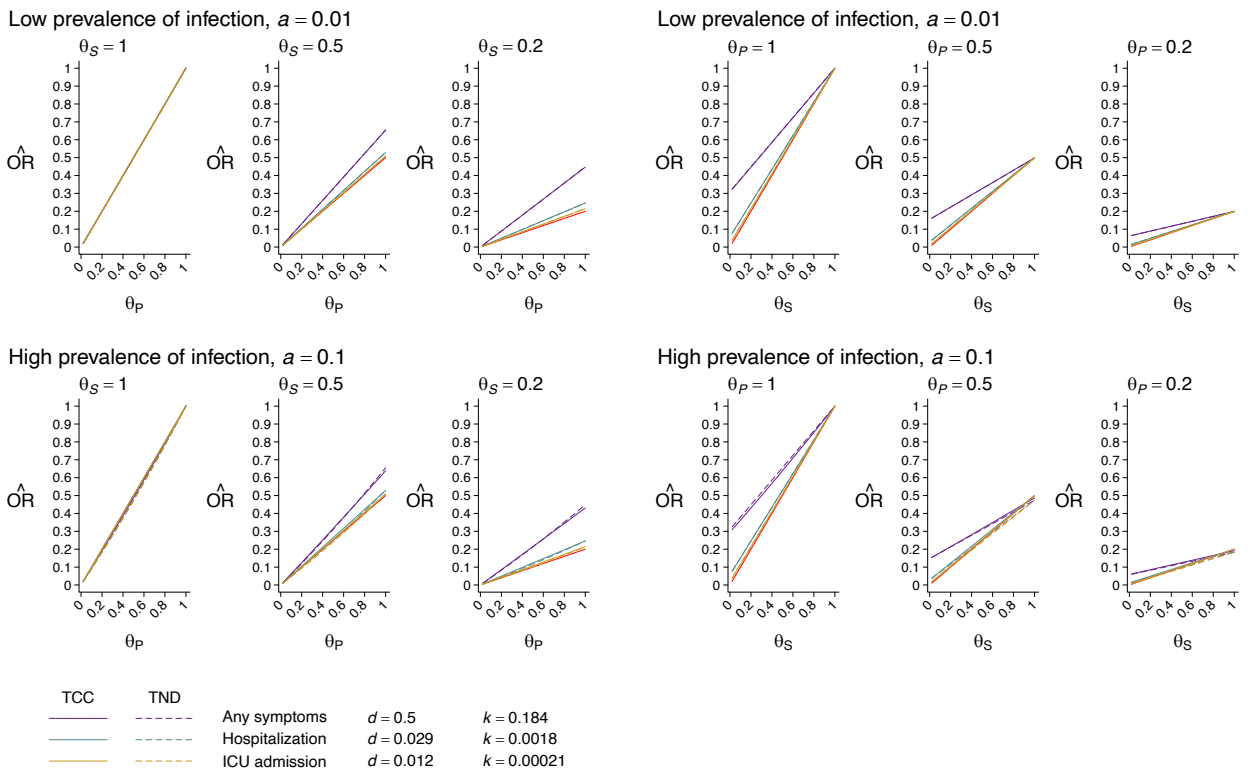
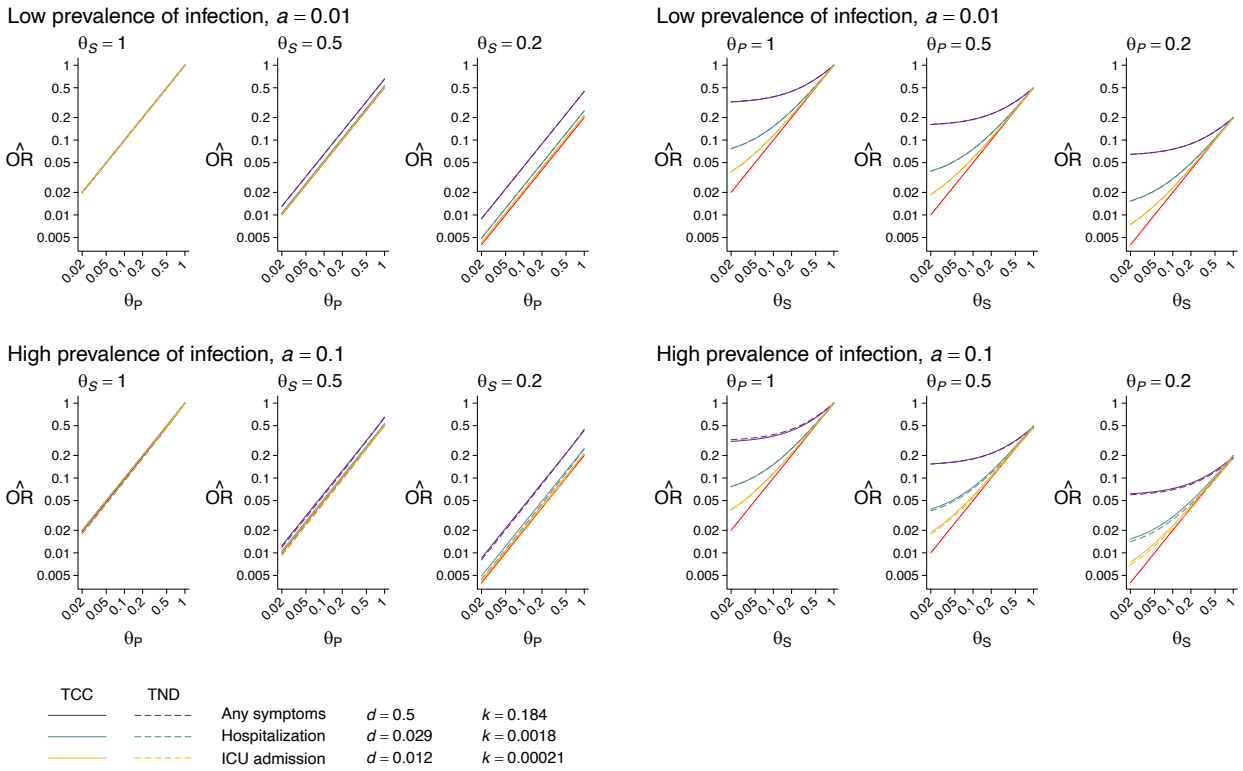
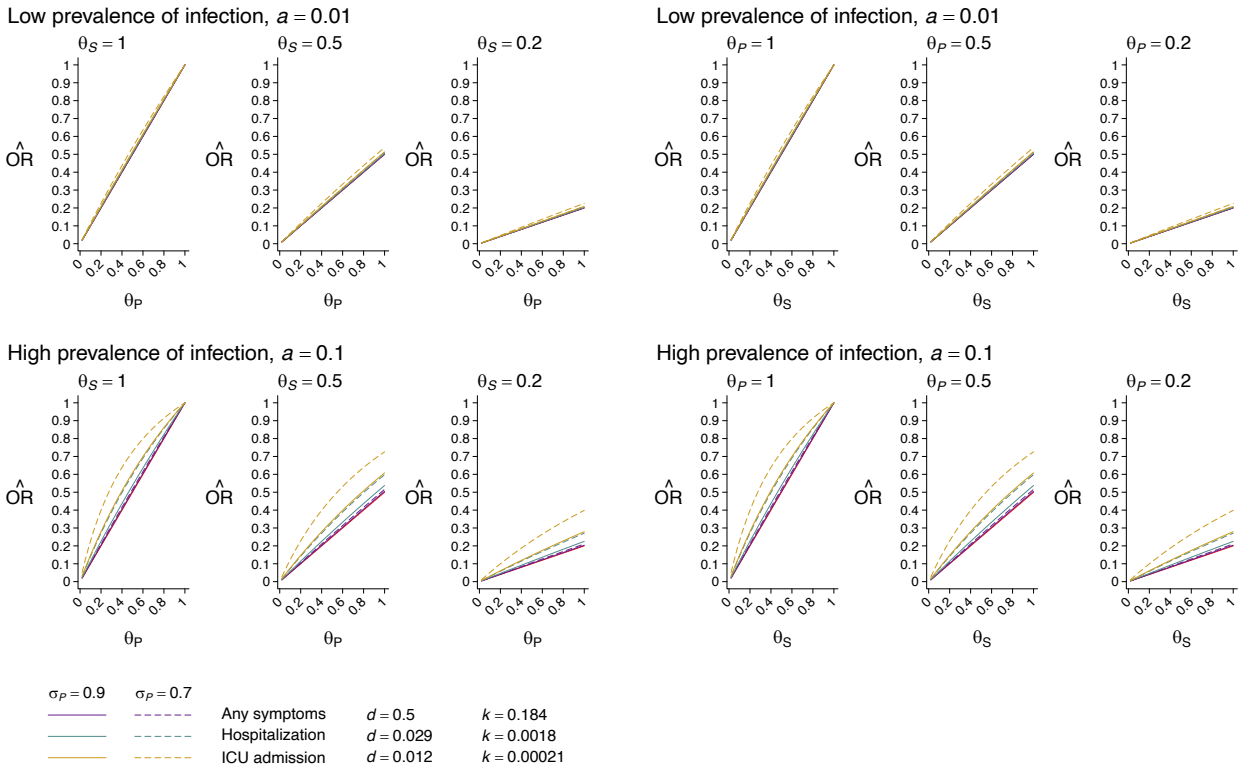


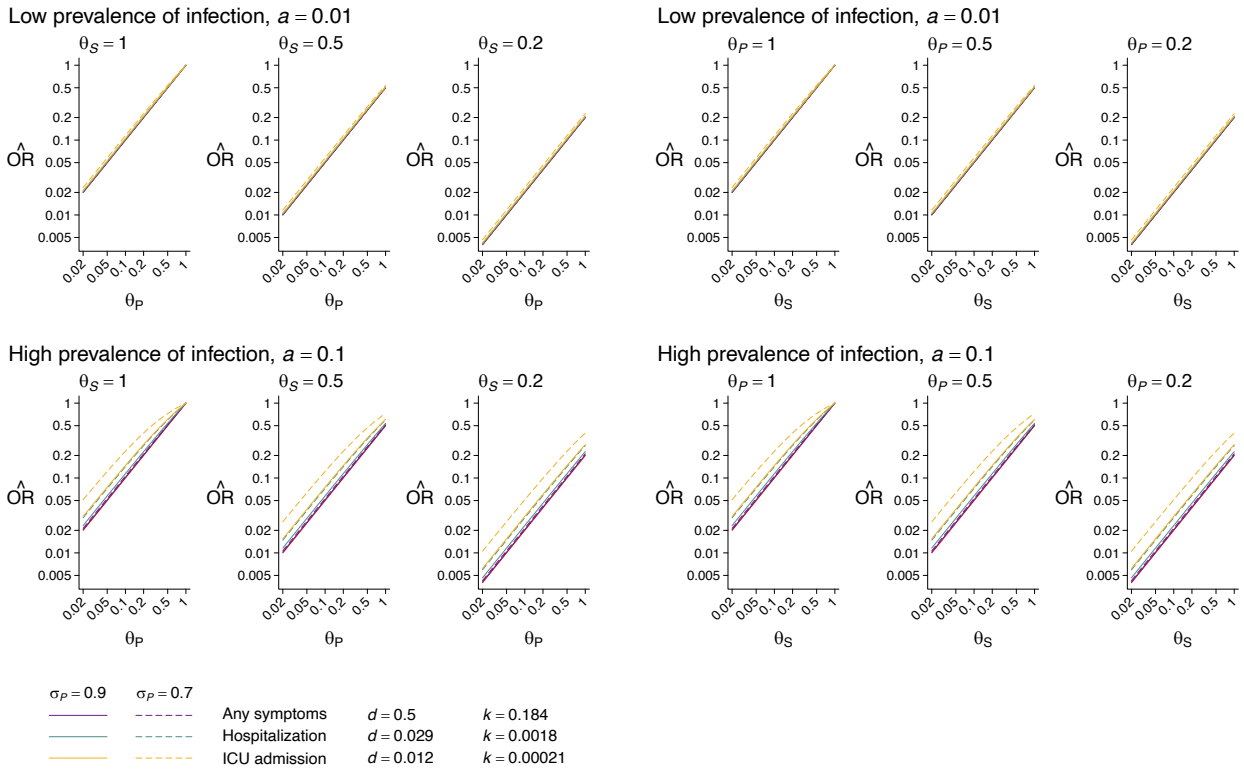
eFigure 1: True and estimated vaccine effectiveness under the traditional case–control and test-negative design. We illustrate expected estimates of the odds ratio of vaccination given case versus control status under the TCC (solid lines) and TND (dashed lines) with differing prevalence of infection (top row, $a = 0.01$; bottom row, $a = 0.1$). Panels on the left and right illustrate effect measures with varying values of θ_P (for fixed values of θ_S) and θ_S (for fixed values of θ_P), respectively. Colors correspond to values of d and k for differing endpoints based on the estimates laid out in **Table 1**. Red diagonal lines across each panel illustrate the true effect. The same data are plotted on log-scale axes in **eFigure 2**.



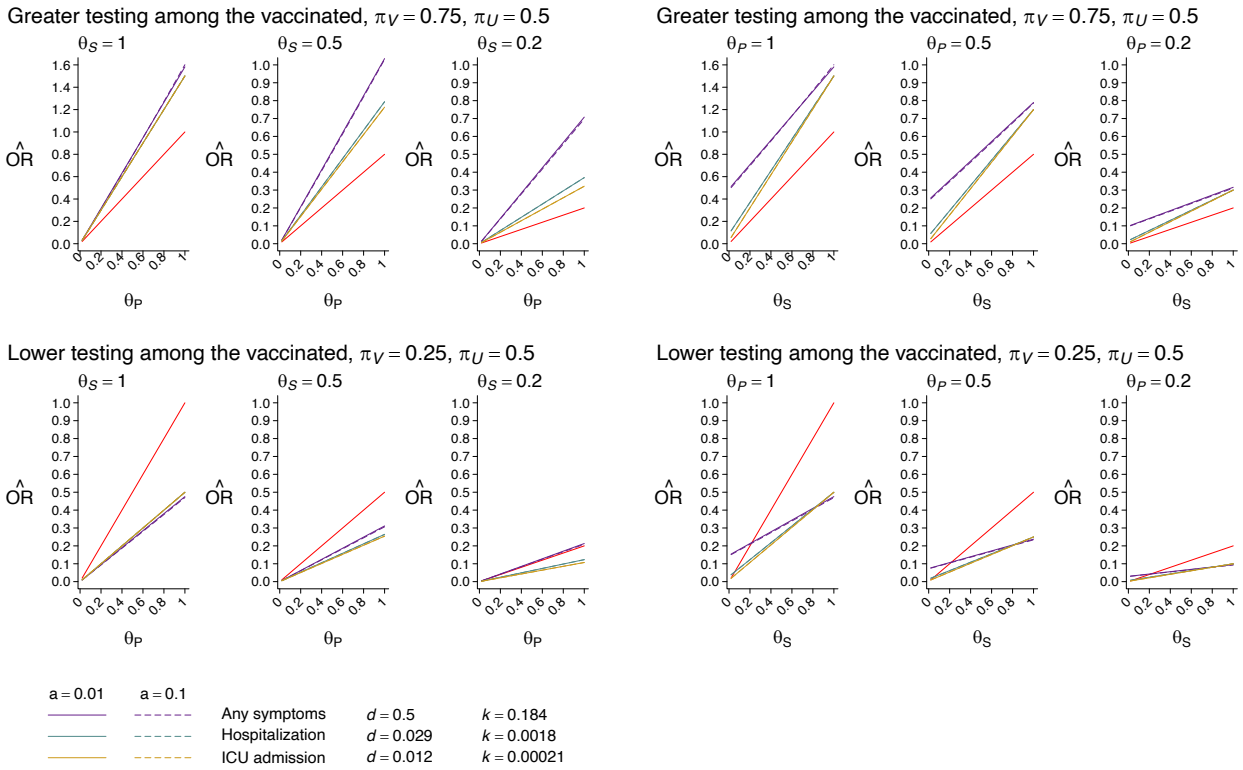
eFigure 2: True and estimated vaccine effectiveness under the traditional case–control and test-negative design. We illustrate expected estimates of the odds ratio of vaccination given case versus control status under the traditional case–control (solid lines) and test-negative design (dashed lines) with differing prevalence of infection (top row, $a = 0.01$; bottom row, $a = 0.1$). Panels on the left and right illustrate effect measures with varying values of θ_P (for fixed values of θ_S) and θ_S (for fixed values of θ_P), respectively. Colors correspond to values of d and k for differing endpoints based on the estimates laid out in **Table 1**. Red diagonal lines across each panel illustrate the true effect.



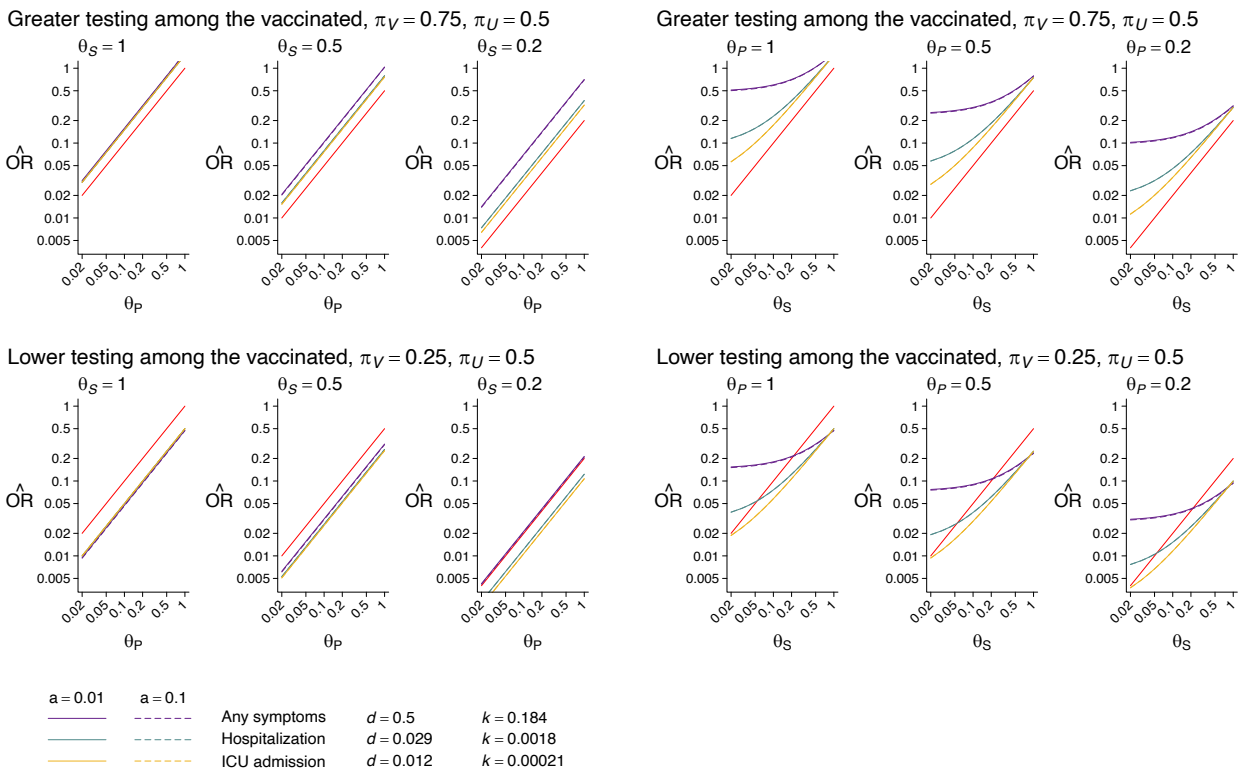
eFigure 3: Estimated vaccine effectiveness under the test-negative design with discrimination of non-etiologic SARS-CoV-2 detection. We illustrate expected estimates of the odds ratio of vaccination given case versus control (test-negative) status assuming $\sigma_S = 0$, under conditions with differing sensitivity for SARS-CoV-2 detection among COVID-19 cases ($\sigma_P = 0.9$, solid lines; $\sigma_P = 0.7$, dashed lines), considering differing prevalence of infection (top row, $a = 0.01$; bottom row, $a = 0.1$). Panels on the left and right illustrate effect measures with varying values of θ_P (for fixed values of θ_S) and θ_S (for fixed values of θ_P), respectively. Colors correspond to values of d and k for differing endpoints based on the estimates laid out in **Table 1**. Red diagonal lines across each panel illustrate the true effect. The same data are plotted on log-scale axes in **eFigure 4**.



eFigure 4: Estimated vaccine effectiveness under the test-negative design with discrimination of non-etiologic SARS-CoV-2 detection. We illustrate expected estimates of the odds ratio of vaccination given case versus control (test-negative) status assuming $\sigma_S = 0$, under conditions with differing sensitivity for SARS-CoV-2 detection among COVID-19 cases ($\sigma_P = 0.9$, solid lines; $\sigma_P = 0.7$, dashed lines), considering differing prevalence of infection (top row, $a = 0.01$; bottom row, $a = 0.1$). Panels on the left and right illustrate effect measures with varying values of θ_P (for fixed values of θ_S) and θ_S (for fixed values of θ_P), respectively. Colors correspond to values of d and k for differing endpoints based on the estimates laid out in **Table 1**. Red diagonal lines across each panel illustrate the true effect.



eFigure 5: Estimated vaccine effectiveness under the traditional case–control design with differential testing, given symptoms, among vaccinated and unvaccinated persons. We illustrate expected estimates of the odds ratio of vaccination given case versus control status, considering differing likelihood of testing among vaccinated and unvaccinated individuals, given the same clinical presentation (top row, greater testing among the vaccinated; bottom row, lower testing among the vaccinated). Panels on the left and right illustrate effect measures with varying values of θ_P (for fixed values of θ_S) and θ_S (for fixed values of θ_P), respectively. Colors correspond to values of d and k for differing endpoints based on the estimates laid out in **Table 1**; solid and dashed lines correspond to low ($a = 0.01$) and high ($a = 0.1$) infection prevalence scenarios, respectively. Red diagonal lines across each panel illustrate the true effect. The same data are plotted on log-scale axes in **eFigure 6**.



eFigure 6: Estimated vaccine effectiveness under the traditional case–control design with differential testing, given symptoms, among vaccinated and unvaccinated persons. We illustrate expected estimates of the odds ratio of vaccination given case versus control status, considering differing likelihood of testing among vaccinated and unvaccinated individuals, given the same clinical presentation (top row, greater testing among the vaccinated; bottom row, lower testing among the vaccinated). Panels on the left and right illustrate effect measures with varying values of θ_P (for fixed values of θ_S) and θ_S (for fixed values of θ_P), respectively. Colors correspond to values of d and k for differing endpoints based on the estimates laid out in **Table 1**; solid and dashed lines correspond to low ($a = 0.01$) and high ($a = 0.1$) infection prevalence scenarios, respectively. Red diagonal lines across each panel illustrate the true effect.

eTable 1: Contingency tables for TCC and TND studies with differing assay sensitivity for SARS-CoV-2 shedding and COVID-19.

Exposure	Outcome		
	Test-positive case (symptomatic)	Community control (asymptomatic)	Test-negative control (symptomatic)
Vaccinated	$v\theta_S a[\theta_P d\sigma_P + (1-\theta_P d)k\sigma_S]$	$v(1-k)(1-\theta_S\theta_P ad)$	$(1-v)[k(1-\theta_S a\sigma_S) + (1-k)\theta_S\theta_P ad(1-\sigma_P)]$
Unvaccinated	$(1-v)a[d\sigma_P + (1-d)k\sigma_S]$	$(1-v)(1-k)(1-ad)$	$(1-v)[k(1-a\sigma_S) + (1-k)ad(1-\sigma_P)]$