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Comparison of methodological approaches in COVID-19 vaccine effectiveness estimation using observational data - *Additional file*

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Statistical analyses

Single time zero with inverse probability weighting

Inverse probability of treatment weighting (IPTW) was used to adjust for confounding and inverse probability of censoring weighting (IPCW) to adjust for informative censoring due to non-random loss to follow-up. At each time point t, for each individual, stabilized IPTWs were calculated as [probability of the observed treatment given time-fixed confounders] / [probability of the observed treatment history from time 0 to t given time-fixed and time-varying confounders]. Time-fixed baseline confounders were sex and educational level. Time-varying confounders were age group, medical risk condition and time since prior infection. The stabilized IPCWs were calculated as [the probability of remaining uncensored given time-fixed covariates] / [probability of remaining uncensored at t given time-fixed and time-varying covariates]. Time-fixed and time-varying covariates were the same as for the IPTWs. The cumulative probabilities and weights at each time point were estimated using pooled logistic regression by the ipw R package (1). This way, the weights were updated every time an individual's treatment (vaccination) status or value of a time-varying confounder changed until treatment or censoring took place (1, 2). Stabilizing weights results in narrower confidence intervals around the effect estimate (2, 3). The final weights were obtained by multiplying the IPTWs and the IPCWs. Extreme weights (>10) were truncated to 10.

Multiple time zeros with inverse probability weighting

Inverse probability weighting was used to adjust for confounding (IPTW) and informative censoring due to loss to follow-up ($IPCW_{LTFU}$) and due to protocol deviation, i.e. vaccination of unvaccinated controls during follow-up ($IPCW_{PD}$). Weights were calculated with the ipw package in R, whereby logistic regression was used for IPTW and pooled logistic regression for both $IPCW_{LTFU}$ and $IPCW_{PD}$. The stabilized IPTWs were determined in the index week of each cohort and were fixed for the follow-up of that cohort (4). The IPTWs were calculated as [crude probability of the observed treatment in the index week] / [probability of the observed treatment in the index week given confounders]. Confounders were measured at the end of the index week and included age group, sex, educational level, medical risk condition and time since prior infection. The stabilized $IPCWs_{PD}$ were estimated per follow-up week of each unvaccinated individual within each cohort, allowing the association between covariates and censoring due to protocol deviation to vary per cohort. To obtain the stabilized $IPCWs_{LTFU}$, the probabilities of remaining uncensored were estimated per follow-up week of each individual. The cumulative probability of remaining uncensored per person per week was then computed per cohort. The stabilized IPCWs were calculated as: [probability of remaining uncensored given time-fixed variables (stabilization factors)] / [probability of remaining uncensored given time-fixed and time-varying variables]. Time-fixed variables included sex and educational level and time-varying variables were age group, medical risk condition and prior infection. The final weights were obtained by multiplying the IPTWs, $IPTWs_{PD}$ and $IPCWs_{LTFU}$. Extreme weights (>10) were truncated to 10.

1. van der Wal WM, Geskus RB. ipw: An R Package for Inverse Probability Weighting. Journal of Statistical Software. 2011;43(13):1 – 23
2. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656-64.
3. Grafféo N, Latouche A, Geskus RB, Chevret S. Modeling time-varying exposure using inverse probability of treatment weights. Biometrical Journal. 2018;60(2):323–32.
4. McConeghy KW, Bardenheier B, Huang AW, White EM, Feifer RA, Blackman C, et al. Infections, Hospitalizations, and Deaths Among US Nursing Home Residents With vs Without a SARS-CoV-2 Vaccine Booster. JAMA Network Open. 2022;5(12):e2245417–e.

Fig. S1 Cumulative incidence curve for the single time zero approaches

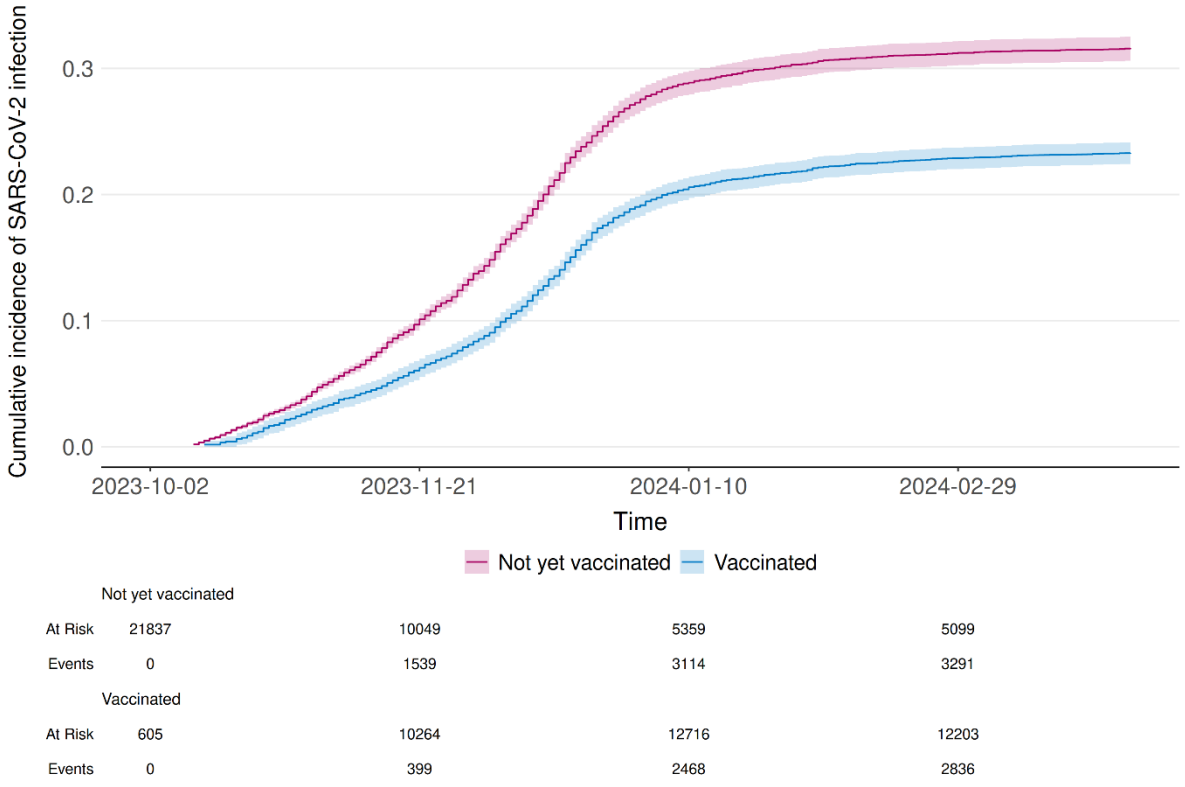


Fig. S2 14-day moving average SARS-CoV-2 incidence per 100,000 participants, by prior infection and age group (single time zero approaches)

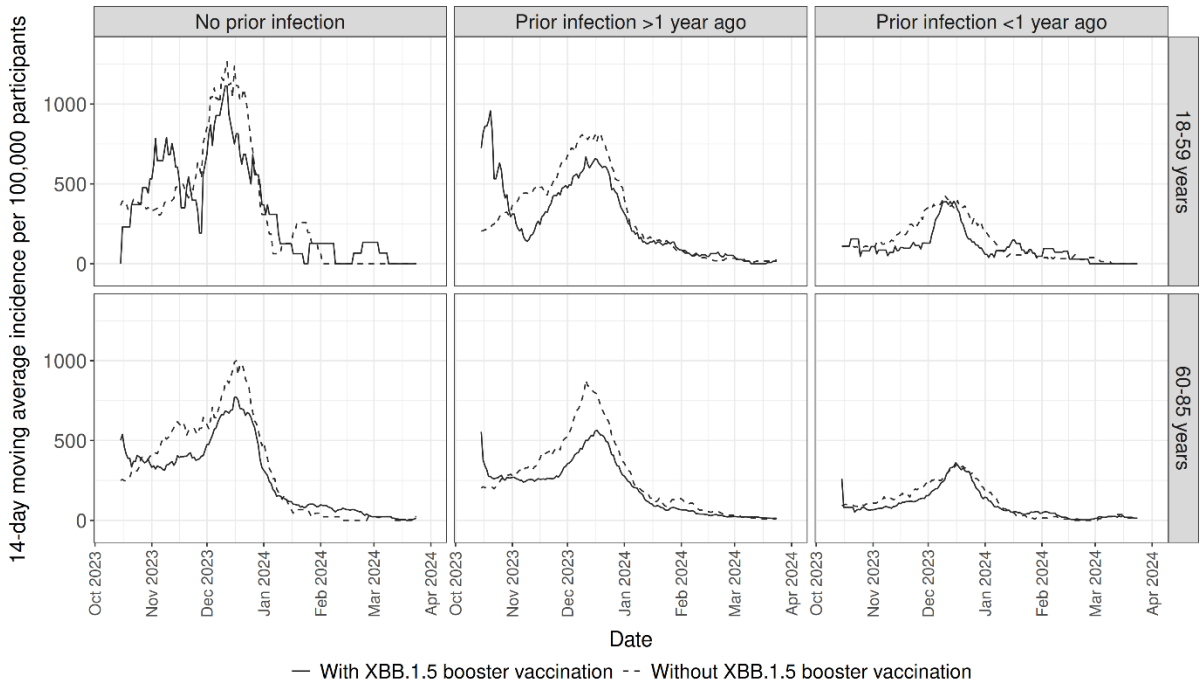


Table S1 Number of person-weeks or participants and SARS-CoV-2 infections

	Person-weeks / persons	Number of infections	Rate (per 1,000 weeks / per 100 persons)	Adjusted[1] vaccine effectiveness (%) (95% CI)
Single time zero with regression adjustment[2]				
Overall				
Without XBB.1.5 booster vaccination	202,961	3318	16.3	Reference
With XBB.1.5 booster vaccination	265,660	2900	10.9	30 (26-34)
By time since XBB.1.5 vaccination				
Without XBB.1.5 booster vaccination	202,961	3318	16.3	Reference
With XBB.1.5 booster vaccination (1-6 weeks)	87,197	1527	17.5	35 (30-39)
With XBB.1.5 booster vaccination (7-12 weeks)	77,754	1122	14.4	24 (18-30)
With XBB.1.5 booster vaccination (13-18 weeks)	67,774	211	3.1	8 (-9-23)
Single time zero with inverse probability weighting[2]				
Overall				
Without XBB.1.5 booster vaccination	225,727	3637	16.1	Reference
With XBB.1.5 booster vaccination	265,660	2900	10.9	28 (24-32)
By time since XBB.1.5 booster vaccination				
Without XBB.1.5 booster vaccination	225,727	3637	16.1	Reference
With XBB.1.5 booster vaccination (1-6 weeks)	87,197	1527	17.5	33 (28-38)
With XBB.1.5 booster vaccination (7-12 weeks)	77,754	1122	14.4	22 (15-28)
With XBB.1.5 booster vaccination (13-18 weeks)	67,774	211	3.1	2 (-18-20)
Multiple time zeros with covariate matching[3]				
Overall				
Without XBB.1.5 booster vaccination	12,904	1844	14.3	Reference
With XBB.1.5 booster vaccination	12,904	1409	10.9	25 (18-30)[4]
By time since XBB.1.5 booster vaccination				
Without XBB.1.5 booster vaccination (1-6 weeks)	12,928	1001	7.7	Reference
With XBB.1.5 booster vaccination (1-6 weeks)	12,928	650	5.0	35 (28-41)[4]
Without XBB.1.5 booster vaccination (7-12 weeks)	6,586	707	10.7	Reference
With XBB.1.5 booster vaccination (7-12 weeks)	6,586	523	7.9	26 (17-34)[4]
Without XBB.1.5 booster vaccination (13-18 weeks)	4,142	97	2.3	Reference
With XBB.1.5 booster vaccination (13-18 weeks)	4,142	89	2.1	8 (-22-32)[4]
Multiple time zeros with inverse probability weighting[2]				
Overall				
Without XBB.1.5 booster vaccination	1,262,490	19,886	15.8	Reference
With XBB.1.5 booster vaccination	255,358	2,744	10.7	27 (24-31)
By time since XBB.1.5 booster vaccination				
Without XBB.1.5 booster vaccination	1,262,490	19,886	15.8	Reference
With XBB.1.5 booster vaccination (1-6 weeks)	72,345	1,288	17.8	33 (29-38)
With XBB.1.5 booster vaccination (7-12 weeks)	78,104	1,182	15.1	24 (18-29)
With XBB.1.5 booster vaccination (13-18 weeks)	68,870	230	3.3	5 (-13-22)

[1] Adjusted for age group, sex, medical risk condition, educational level, and time since prior infection

[2] Person-weeks and rate per 1,000 person-weeks are shown.
[3] Number of persons and rate per 100 persons are shown.
[4] The interquartile range of the VE point estimate based on 50 repetitions was 22.9-25.6 for the overall estimate, 33-36 1-6 weeks after vaccination, 25-29 7-12 weeks after vaccination and -1-17 13-18 weeks after vaccination.

Fig. S3 Love-plots for assessing covariate balance for the single time zero with inverse probability weighted marginal structural model approach

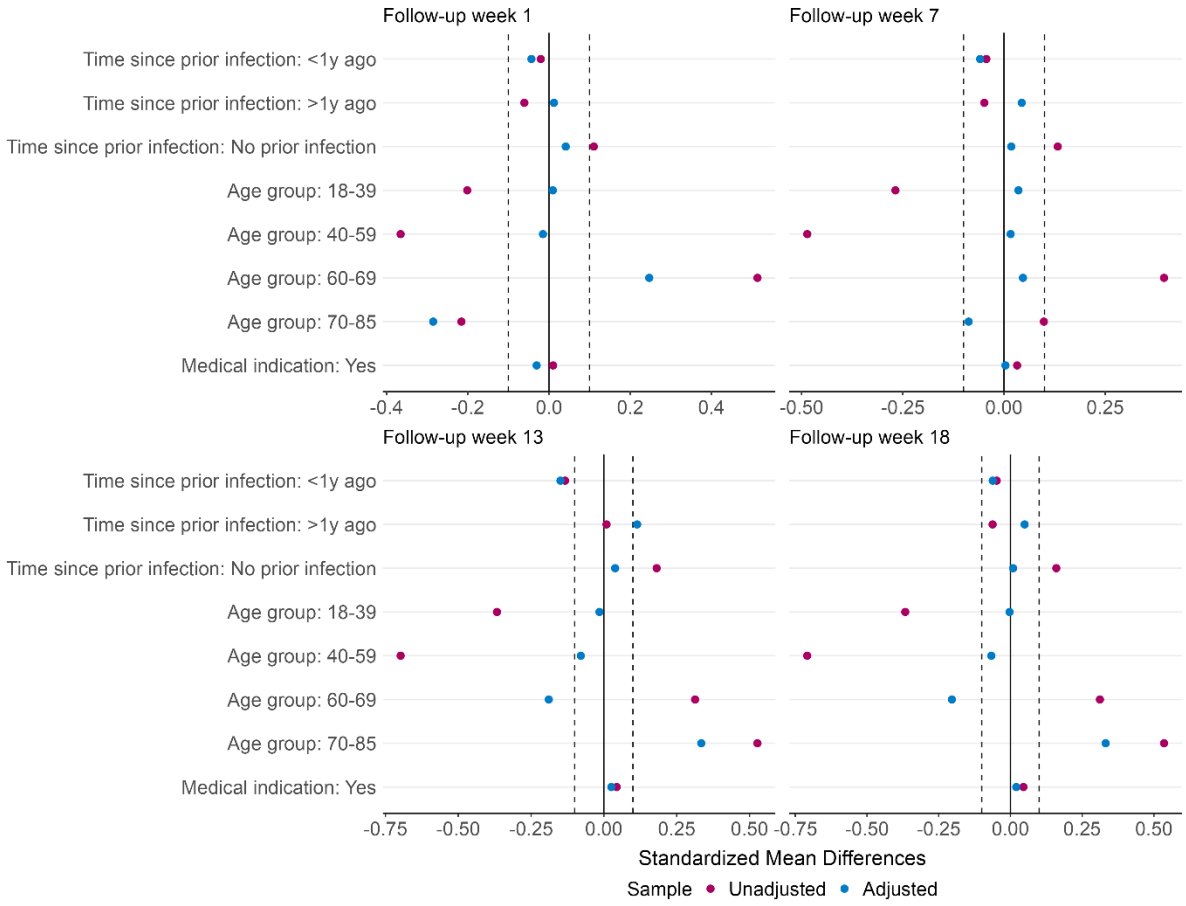
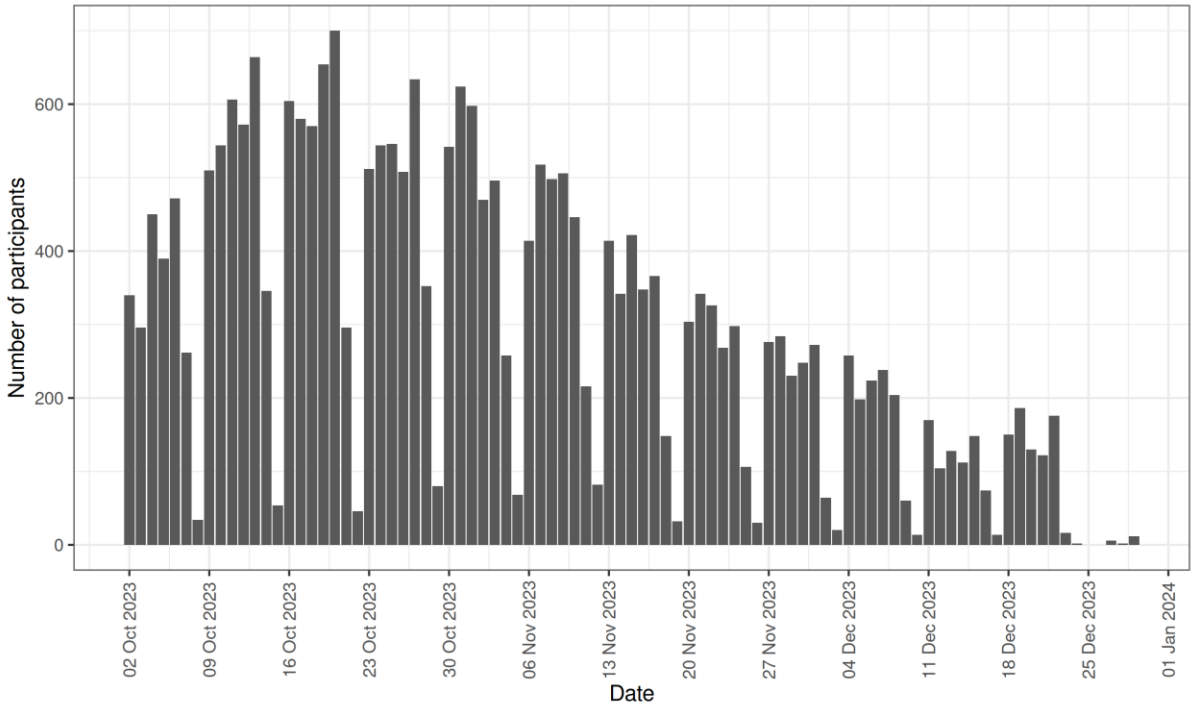
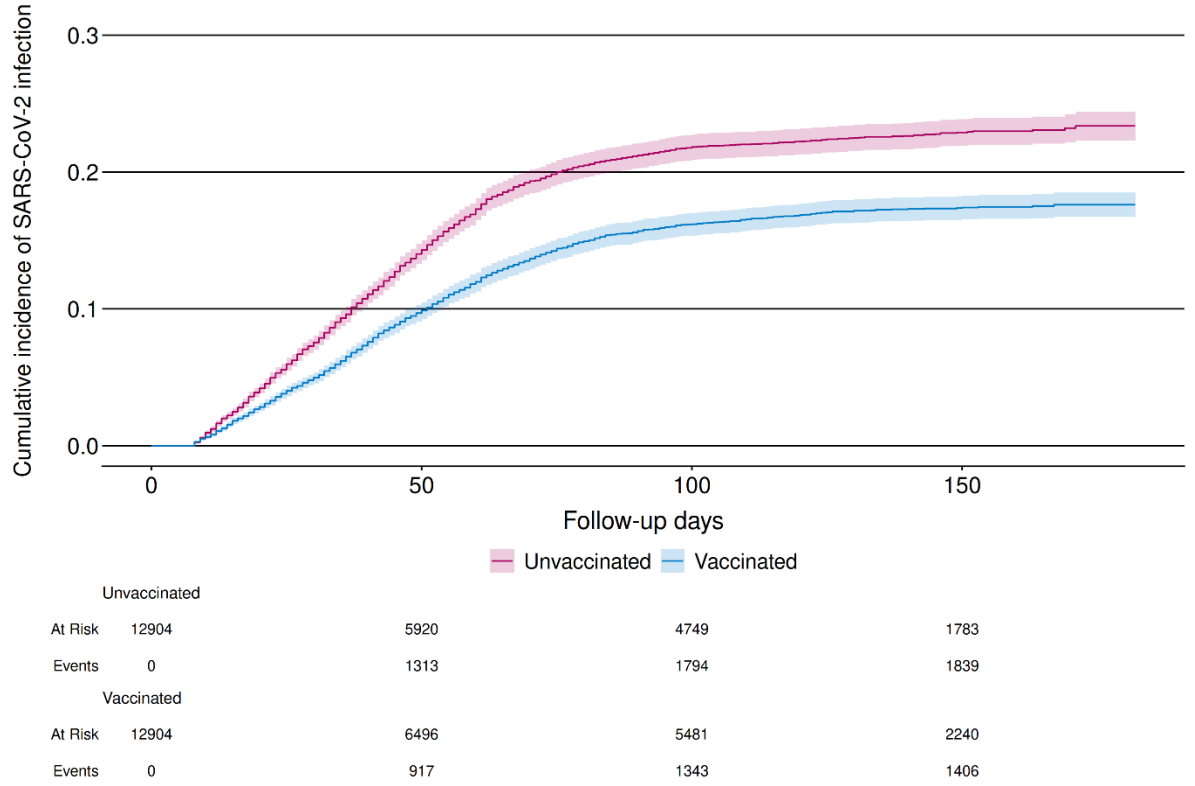


Fig. S4 Number of participants per trial* in the multiple time zeros with covariate matching approach



* Based on the matched population of which the VE estimate was closest to the point estimate. 8 trials, starting on 4, 12, 15 and 18 January 2024, 1 and 20 February 2024 and 3 and 7 March 2024, were excluded from the figure to improve readability. These trials consisted of 4 (4 January 2024) or 2 (all others) participants.

Fig. S5 Cumulative incidence curve for the multiple time zeros with covariate matching approach*



* Based on the matched population of which the VE estimate was closest to the point estimate.

Fig. S6 Love-plots for assessing covariate balance per for the multiple time zeros with inverse probability weighting approach

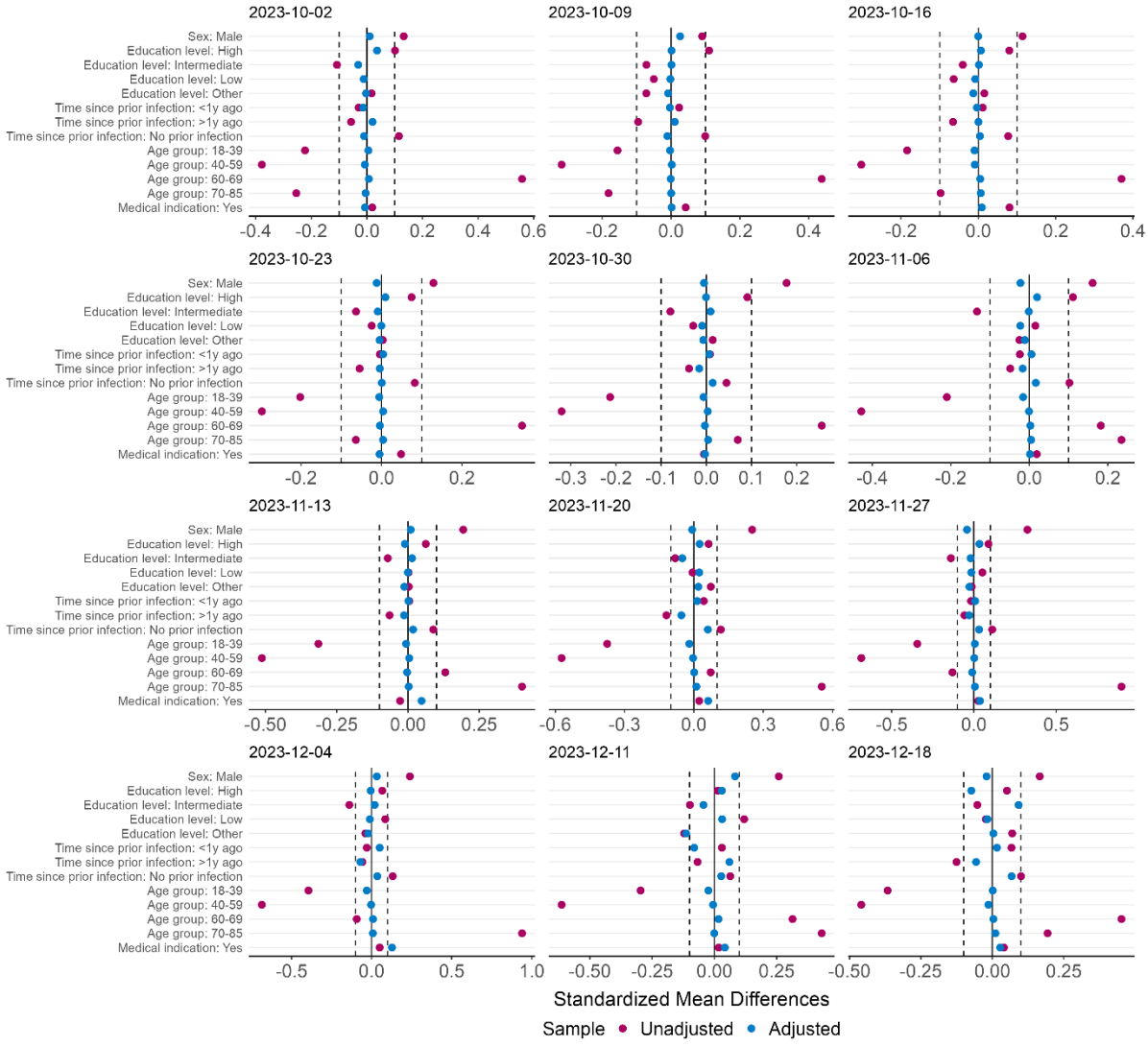
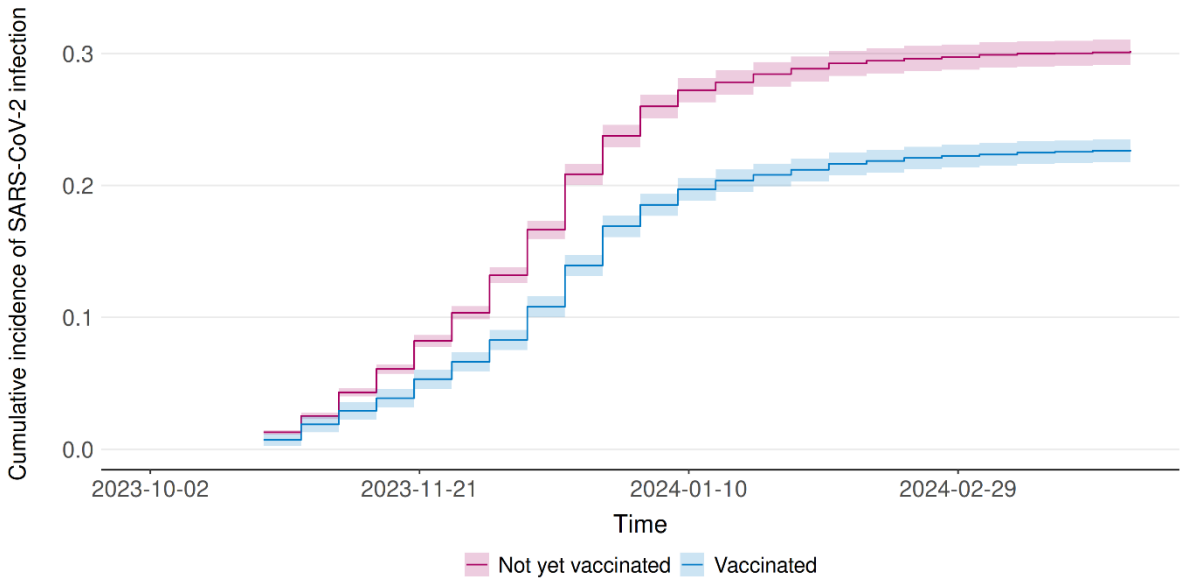


Fig. S7 Cumulative incidence curve for the multiple time zeros with inverse probability weighting approach



Not yet vaccinated				
At Risk	19610	9980	5212	4926
Events	0	1258	2861	3040
Vaccinated				
At Risk	1261	10010	12718	12202
Events	0	295	2273	2673

Fig. S8 Vaccine effectiveness estimates of the sensitivity analysis, in which lost to follow-up date was defined as date of violation of the protocol, overall and by time since vaccination

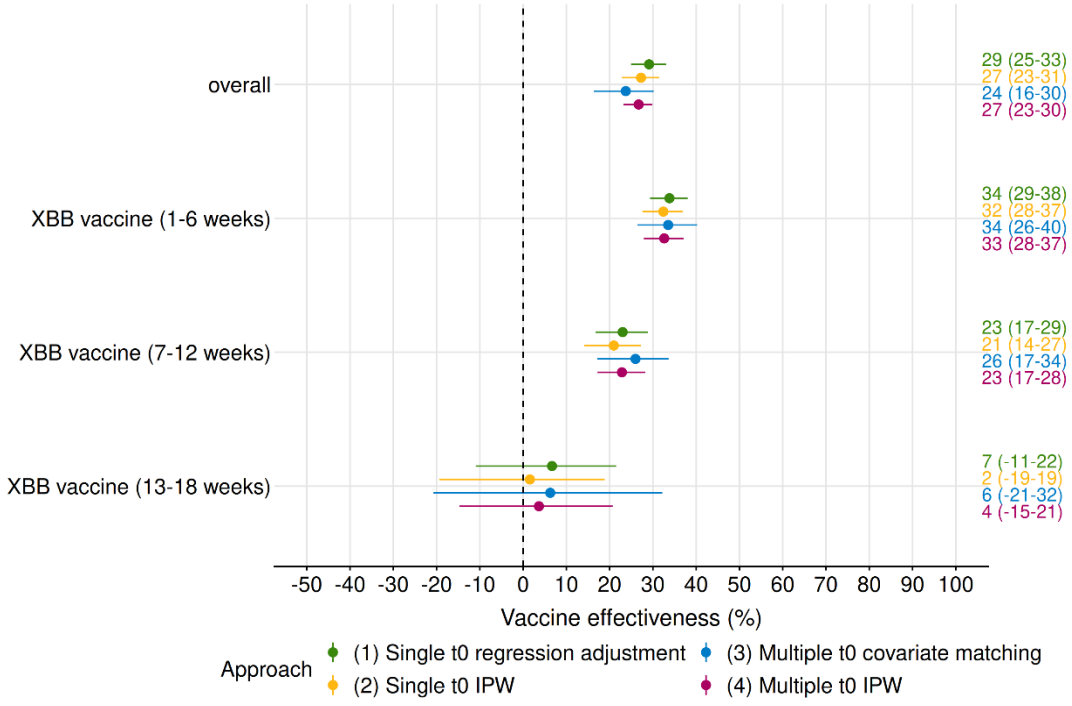


Fig. S9 Vaccine effectiveness estimates of the sensitivity analysis, adjusting for the four most common medical risk conditions, overall and by time since vaccination

