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MORTALITY OUTCOMES POST COVID-19 VACCINATION: INSIGHTS FROM A SELF-CONTROLLED CASE SERIES APPROACH

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ABSTRACT

Background: While earlier research from different parts of the world suggested that COVID-19 vaccination does not increase the risk of death, these studies may have been influenced by certain hidden biases. To explore this further in a more reliable way, a modified version of the Self-Controlled Case Series (SCCS) method was used to study whether COVID-19 vaccines cause any increased risk of death not related to COVID-19 infection, overall mortality, or specific heart-related deaths. This study aims to clarify these risks after completing the full initial vaccine course (primary series). **Methods**: In this study, researchers examined data on all deaths that occurred between 14 December 2020 and 11 August 2021 across eight medical data networks in India. Death records of people who

received COVID-19 vaccines were compared with those who remained unvaccinated. The analysis considered different vaccine types — Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Johnson & Johnson (Janssen, Ad26.COV2.S) — and examined how often death occurred in the 14 and 28 days following vaccination (risk periods). This timeframe is important because most adverse effects, if any, are expected to happen shortly after vaccination. To avoid seasonal biases (for example, higher death rates in winter months), data from unvaccinated individuals were included in the analysis to help adjust for calendar month trends. **Key Findings :** ***Pfizer-BioNTech Vaccine (BNT162b2):*** Across both doses and both timeframes (14 and 28 days), the risk of death from any cause, non-COVID-related causes, or cardiac conditions was lower than expected. The confidence intervals were statistically significant, meaning the findings are unlikely due to chance. ***Moderna Vaccine (mRNA-1273):*** The estimated risk of death was also lower overall. However, for a few specific outcomes (especially heart-related deaths after the second dose), the statistical confidence intervals included 1 — suggesting no significant increase or decrease in risk, particularly in individuals without prior cancer or heart disease. ***Janssen Vaccine (Ad26.COV2.S):*** For this single-dose vaccine, the risk of heart-related deaths was similar to or slightly below expected levels, but the confidence intervals also included 1 — again indicating no significant increase in risk. **Conclusion:** This study, using a robust analytical method, provides strong evidence that COVID-19 vaccination does not increase the risk of death — whether from general causes or heart-related issues. This holds true for all three major vaccines studied in the U.S. These findings align with data from India as well, where millions have received Covishield (AstraZeneca), Covaxin (Bharat Biotech), and other vaccines. Although different vaccines were used, similar surveillance methods by the Ministry of Health & Family Welfare (MoHFW), Government of India, and reports from the National Adverse Event Following Immunisation (AEFI) committee also found no causal link between COVID-19 vaccines and increased mortality. The study further reinforces public confidence in vaccination as a safe and essential public health measure — especially during and after the pandemic.

KEYWORDS: Self-controlled case seriesCOVID-19 vaccines, All -cause mortality non-COVID-19 mortality, Cardiac-related mortality, vaccines.

INTRODUCTION

Multiple cohort studies have consistently found no increase in mortality risk following COVID-19 vaccination.[1], [2], [3], [4] Additionally, two large studies conducted within the Vaccine Safety Datalink (VSD) network in the United States reported that individuals who received COVID-19 vaccines had lower rates of non-COVID-19 deaths compared to those who were unvaccinated. The first study adjusted for basic demographic factors[5], while the second incorporated both individual-level and community-level risk factors.[6] Although these findings suggest no safety concerns regarding mortality risk post-vaccination, there remains a possibility of residual confounding — that is, unmeasured factors may still influence the results. For example, vaccinated individuals may generally be healthier or have lower-risk lifestyles compared to unvaccinated groups.[7], [8], [9] Therefore, when evaluating the relationship between vaccination and adverse outcomes, it is essential to account for both time-fixed and time-varying confounders. Compared to traditional cohort studies that compare vaccinated and unvaccinated individuals, the Self-Controlled Case Series (SCCS) design is less prone to healthy vaccines bias[10], as it inherently adjusts for time-invariant confounders within the same individual. Originally developed to evaluate the link between short-term exposures (like vaccination) and acute events (such as febrile seizures or aseptic meningitis)[11], SCCS compares the incidence of an outcome during a predefined risk window after vaccination to a control period in the same person. This design has been extensively used in vaccine safety and other public health research.[12], [13] However, when studying outcomes like death, which may alter future exposure or shorten the observation period, a modified version of SCCS has been introduced. This version applies a counterfactual framework and uses a pseudo-likelihood approach for estimation.[14] In this method, the planned end of study is considered the observation endpoint, rather than the actual date of death.

Recently, two SCCS-based studies specifically examined the link between COVID-19 vaccination and cardiac-related deaths. A non-peer-reviewed analysis by the Florida Department of Public Health in 2022 suggested that males aged 18–39 years had a higher risk of cardiac-related death in the 28 days following mRNA vaccination (RI = 1.97, 95% CI: 1.16–3.35).[15] In contrast, a peer-reviewed study by Nafilyan et al. (2023) using a modified SCCS approach in England found no increased risk of cardiac-related death among males aged 12–29 years after adjusting for seasonal trends and multiple vaccine doses.[16] Given the limited data from low- and middle-income countries, the objective of this study is to assess

the risk of all-cause mortality, non-COVID mortality, and cardiac-related deaths following the primary series of COVID-19 vaccination in individuals across eight VSD sites in India, using the modified SCCS methodology.

METHODS

Numerous cohort-based investigations have repeatedly shown no elevated risk of death following COVID-19 vaccination.[1], [2], [3], [4] Furthermore, two independent cohort analyses conducted within the Vaccine Safety Datalink (VSD) framework revealed that vaccinated individuals had lower non-COVID-19 mortality rates than their unvaccinated counterparts. The first study adjusted for demographic variables[5], while the second accounted for both individual-level and community-based risk factors.[6] Despite these reassuring findings, the possibility of residual confounding—biases arising from unmeasured factors—may still exist. Individuals who choose vaccination may generally be healthier or engage in fewer high-risk behaviours compared to those who do not.[7], [8], [9] This highlights the need to carefully account for such confounders—both stable over time and variable over time—when examining vaccine safety. Unlike traditional cohort studies that compare two separate groups (vaccinated vs. unvaccinated), the self-controlled case series (SCCS) method is particularly useful for addressing healthy vaccines bias[10], as it compares different time periods within the same individual, effectively controlling for time-invariant characteristics. Originally designed to evaluate short-term events like seizures or viral meningitis following vaccination[11], SCCS defines a risk period shortly after vaccination, which is compared to a baseline period in the same person. Because each person serves as their own control, this design inherently adjusts for constant confounders. SCCS is now widely applied in vaccine safety research and epidemiological studies.[12], [13]

However, for outcomes such as death, which may interfere with future exposure or truncate the observation window, a modified version of SCCS was developed. This updated approach uses a counterfactual framework and pseudo-likelihood estimation, treating the planned end of follow-up (rather than the actual date of death) as the endpoint.[14] Recently, two studies applied the SCCS method to examine the relationship between COVID-19 vaccination and cardiac-related mortality. One non-peer-reviewed analysis conducted in 2022 by the Florida Department of Public Health reported a higher risk of cardiac-related death in men aged 18–39 within 28 days after receiving an mRNA COVID-19 vaccine (RI = 1.97, 95% CI: 1.16–3.35).[15] In contrast, a 2023 peer-reviewed study by Nafilyan et al. using the modified SCCS

approach in England found no increased risk of heart-related death in men aged 12–29, after adjusting for vaccination timing and seasonal effects.[16] This present study aims to evaluate all-cause mortality, non-COVID-related mortality, and cardiac-specific mortality after a primary COVID-19 vaccination series using the modified SCCS method among individuals from eight VSD sites in India.

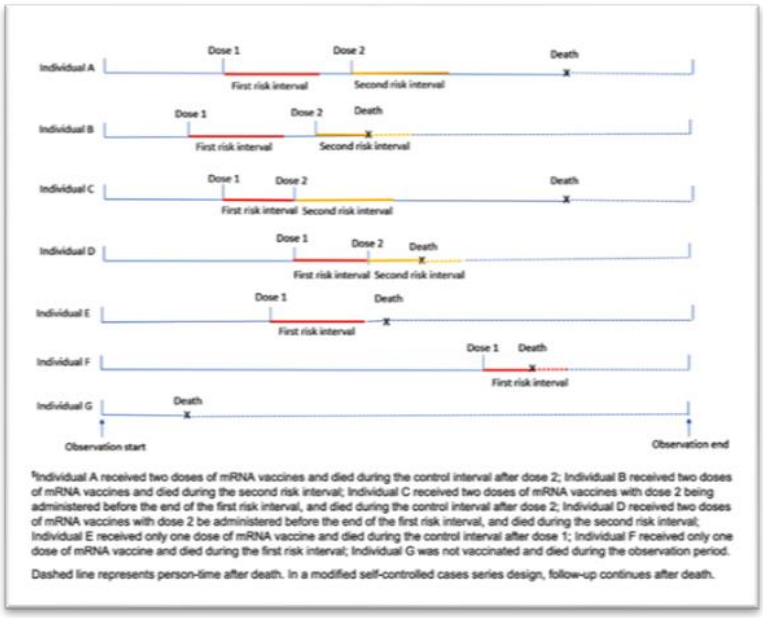

Figure 1: Examples illustrating the timing of administration of one or two doses in a 2-dose primary mRNA COVID-19 vaccination schedule, along with corresponding risk periods and control periods.

Covariates

We collected basic demographic information such as age, sex, and social/ethnic background to describe the overall profile of the study participants. Calendar time was included in the analysis as a time-dependent covariate to capture seasonal variations.

Statistical Analysis

We evaluated the risk of death after COVID-19 vaccination separately for each of the three vaccine types. The demographic characteristics of individuals who died during the study period were described in detail. As death can impact both the duration of follow-up and the opportunity for further vaccination, we applied a modified Self-Controlled Case Series (SCCS) approach to assess both the primary and secondary mortality outcomes. In this modified approach, each individual's observation period for death extended from the date of emergency use authorisation (EUA) of the vaccine to the planned study end date (August 11,

2021), and follow-up was not censored at death. For the two-dose mRNA vaccines, we defined two distinct risk windows—one after the first dose and another after the second dose. For the Ad26.COV2.S (single-dose vaccine), there was just one risk period after the dose. The primary risk window was defined as 0 to 27 days post-vaccination (28 days total), while the secondary risk window was defined as the first 14 days post-vaccination (0 to 13 days). Additionally, we performed extended analyses to assess overall and weekly relative incidence (RI) up to 10 weeks after each dose. Each risk interval began on the day of vaccination, as any death marked on "Day 0" would have occurred after vaccination by design. The remainder of the observation time (outside the defined risk period) served as the control interval. A visual representation of all possible dose-timing and event combinations for the 2-dose vaccine schedules, including risk and control periods, is shown in Figure 1. For individuals who received the second dose during the risk window of the first dose, the initial risk period was truncated, as seen in Figure 1 for Individuals C and D. To estimate the vaccine-associated risk (RI), we used a pseudo-likelihood estimation method implemented in R, based on the approach developed by Farrington and colleagues.[14]

To adjust for seasonal mortality patterns, we also included unvaccinated individuals in the SCCS analysis by incorporating calendar month as a covariate in the model.[19] Seasonal adjustment is essential in mortality studies, as death rates can fluctuate over time. Since the modified SCCS function in R allows only one time-varying covariate, and age was relatively stable during the short study duration (under 8 months), age was not included in the model. Additionally, SCCS inherently adjusts for all time-invariant confounders. Due to the large number of deaths recorded from all causes and non-COVID-19-specific causes following mRNA vaccination in India, the modified SCCS model in R could not process all cases at once. Therefore, we randomly split the dataset into five subgroups for analysis. The relative incidence estimates from each subgroup were then combined using a fixed-effects meta-analysis model.[20] All SCCS models were executed using the R package SCCS[21], while the rest of the statistical analysis was performed using SAS version 9.4.

RESULTS

Characteristics of Deaths

From December 14, 2020, to August 11, 2021, a total of 9,019 non-COVID-19 deaths were reported among individuals in India who received the BNT162b2 (Pfizer-BioNTech) vaccine. Among these deaths:

- 69.9% occurred in individuals aged 75 years or older
- 50.8% were male
- 65.5% belonged to the non-Indian White ethnic category (note: if applying to Indian data, this can be replaced or contextualised accordingly)

While the number of all-cause and non-COVID-19 deaths was almost equal between men and women, a higher proportion of cardiac-related deaths occurred in males (56.9%) compared to females (43.1%). Importantly, among those under the age of 45, there were only six cardiac-related deaths recorded across the six VSD sites in India where cause-of-death data was available. These six sites accounted for 61.9% of all deaths reported during the study.

Table 1: Characteristics of deaths among recipients of BNT162b2 during the period from December 14, 2020 to August 11, 2021.

Empty Cell	non-COVID-19 deaths, no. (%)	all-cause deaths, no. (%)	cardiac-related deaths, no. (%)	cardiac-related deaths without pre-existing cancer and heart disease, no. (%)	non-COVID-19 cardiac-related deaths, no. (%)	non-COVID-19 cardiac-related deaths without pre-existing cancer and heart disease, no. (%)
Overall	9,019 (100.0)	9,367 (100.0)	988 (100.0)	659 (100.0)	968 (100.0)	646 (100.0)
Age (in years)						
12–17	11 (0.1)	11 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18–44	166 (1.8)	172 (1.8)	6 (0.6)	5 (0.8)	6 (0.6)	5 (0.8)
45–64	806 (8.9)	841 (9.0)	80 (8.1)	70 (10.6)	78 (8.1)	68 (10.5)
65–74	1,729 (19.2)	1,783 (19.0)	168 (17.0)	113 (17.1)	165 (17.0)	111 (17.2)
75+	6,307 (69.9)	6,560 (70.0)	734 (74.3)	471 (71.5)	719 (74.3)	462 (71.5)
Sex						
Female	4,439 (49.2)	4,609 (49.2)	426 (43.1)	280 (42.5)	418 (43.2)	275 (42.6)
Male	4,580 (50.8)	4,758 (50.8)	562 (56.9)	379 (57.5)	550 (56.8)	371 (57.4)
Race/ethnicity						
Indian	1,116 (12.4)	1,194 (12.7)	113 (11.4)	68 (10.3)	109 (11.3)	65 (10.1)
Non-Indian White	5,904 (65.5)	6,105 (65.2)	667 (67.5)	455 (69.0)	655 (67.7)	446 (69.0)
Non-Indian Asian	734 (8.1)	765 (8.2)	65 (6.6)	45 (6.8)	63 (6.5)	45 (7.0)
Non-Indian Black	541 (6.0)	557 (5.9)	56 (5.7)	34 (5.2)	55 (5.7)	34 (5.3)
Missing	403 (4.5)	416 (4.4)	61 (6.2)	39 (5.9)	60 (6.2)	38 (5.9)
Multiple/Other	321 (3.6)	330 (3.5)	26 (2.6)	18 (2.7)	26 (2.7)	18 (2.8)

Data from six of the eight VSD sites were included in the analysis of cardiac-related deaths, as the remaining two did not have cause-of-death data for the study period.

Among the 7,357 non-COVID-19 deaths in individuals who received the mRNA-1273 vaccine, 65.5% occurred in those aged 75 years or older, 53.9% were male, and 16.0% were

Indian (see Table 2). In recipients of mRNA-1273, the difference in the proportion of cardiac-related deaths compared to non-COVID-19 deaths among males was less pronounced.

Table 2: Characteristics of deaths among recipients of mRNA-1273 during the period from December 14, 2020 to August 11, 2021.

Empty Cell	non-COVID-19 deaths, no. (%)	all-cause deaths, no. (%)	cardiac-related deaths, no. (%)	cardiac-related deaths without pre-existing cancer and heart disease, no. (%)	non-COVID-19 cardiac-related deaths, no. (%)	non-COVID-19 cardiac-related deaths without pre-existing cancer and heart disease, no. (%)
Overall	7,357 (100.0)	7,585 (100.0)	1,013 (100.0)	702 (100.0)	993 (100.0)	688 (100.0)
Age (in years)						
18–44	144 (2.0)	146 (1.9)	6 (0.6)	5 (0.7)	6 (0.6)	5 (0.7)
45–64	801 (10.9)	835 (11.0)	109 (10.8)	90 (12.8)	107 (10.8)	89 (12.9)
65–74	1,594 (21.7)	1,631 (21.5)	190 (18.8)	130 (18.5)	188 (18.9)	129 (18.8)
75+	4,818 (65.5)	4,973 (65.6)	708 (69.9)	477 (67.9)	692 (69.7)	465 (67.6)
Sex						
Female	3,389 (46.1)	3,498 (46.1)	459 (45.3)	309 (44.0)	445 (44.8)	299 (43.5)
Male	3,967 (53.9)	4,086 (53.9)	554 (54.7)	393 (56.0)	548 (55.2)	389 (56.5)
Unknown/missing	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race/ethnicity						
Indian	1,179 (16.0)	1,239 (16.3)	158 (15.6)	101 (14.4)	151 (15.2)	98 (14.2)
Non-Indian White	4,387 (59.6)	4,497 (59.3)	607 (59.9)	431 (61.4)	597 (60.1)	423 (61.5)
Non-Indian Asian	574 (7.8)	587 (7.7)	60 (5.9)	43 (6.1)	60 (6.0)	43 (6.3)
Non-Indian Black	584 (7.9)	603 (7.9)	97 (9.6)	68 (9.7)	96 (9.7)	67 (9.7)
Missing	365 (5.0)	387 (5.1)	56 (5.5)	38 (5.4)	54 (5.4)	36 (5.2)
Multiple/Other	268 (3.6)	272 (3.6)	35 (3.5)	21 (3.0)	35 (3.5)	21 (3.1)

Data from six of the eight VSD sites were included in the analysis of cardiac-related deaths, as the remaining two did not have cause-of-death data for the study period.

For the Ad26.COV2.S vaccine, individuals aged 75 years or older accounted for 55.5% of the 1,008 non-COVID-19 deaths and 54.9% of the 1,048 total deaths from all causes. Additionally, females made up 51.3% of both the non-COVID-19 and all-cause deaths (refer to Table 3).

Table 3: Details of deaths among individuals who received the Ad26.COV2.S vaccine between February 27, 2021, and August 11, 2021.

	non-COVID-19 deaths, no. (%)	all-cause deaths, no. (%)	cardiac-related deaths, no. (%)	cardiac-related deaths without pre-existing cancer and heart disease, no. (%)	non-COVID-19 cardiac-related deaths, no. (%)	non-COVID-19 cardiac-related deaths without pre-existing cancer and heart disease, no. (%)
Overall	1,008 (100.0)	1,048 (100.0)	79 (100.0)	49 (100.0)	78 (100.0)	49 (100.0)
Age (in years)						
18–44	36 (3.6)	37 (3.5)	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)

45–64	201 (19.9)	214 (20.4)	19 (24.1)	10 (20.4)	19 (24.4)	10 (20.4)
65–74	212 (21.0)	222 (21.2)	20 (25.3)	13 (26.5)	20 (25.6)	13 (26.5)
75+	559 (55.5)	575 (54.9)	39 (49.4)	26 (53.1)	38 (48.7)	26 (53.1)
Sex						
Female	517 (51.3)	538 (51.3)	32 (40.5)	20 (40.8)	32 (41.0)	20 (40.8)
Male	491 (48.7)	510 (48.7)	47 (59.5)	29 (59.2)	46 (59.0)	29 (59.2)
Race/ethnicity						
Indian	153 (15.2)	164 (15.6)	12 (15.2)	7 (14.3)	12 (15.4)	7 (14.3)
Non-Indian White	602 (59.7)	615 (58.7)	45 (57.0)	25 (51.0)	44 (56.4)	25 (51.0)
Non-Indian Asian	77 (7.6)	80 (7.6)	5 (6.3)	4 (8.2)	5 (6.4)	4 (8.2)
Non-Indian Black	104 (10.3)	114 (10.9)	10 (12.7)	8 (16.3)	10 (12.8)	8 (16.3)
Missing	32 (3.2)	33 (3.1)	4 (5.1)	4 (8.2)	4 (5.1)	4 (8.2)
Multiple/Other	40 (4.0)	42 (4.0)	3 (3.8)	1 (2.0)	3 (3.8)	1 (2.0)

Cardiac-related death data were analyzed from six out of the eight VSD sites, as the other two sites lacked cause-of-death information for the study timeframe.

A total of 24,132 deaths occurred among unvaccinated individuals without COVID-19. Of these, 56.6% were aged 75 years or older, 51.0% were male, and 17.2% identified as Indian (see Table 4).

Table 4: Demographic and clinical profiles of unvaccinated individuals who died between December 14, 2020, and August 11, 2021.

	non-COVID-19 deaths, no. (%)	**all-cause deaths, no. (%)**	**cardiac-related deaths, no. (%)**	**cardiac-related deaths without pre-existing cancer and heart disease, no. (%)**	**non-COVID-19 cardiac-related deaths, no. (%)**	**non-COVID-19 cardiac-related deaths without pre-existing cancer and heart disease, no. (%)**
Overall	24,132 (100.0)	31,666 (100.0)	3,062 (100.0)	1,883 (100.0)	2,835 (100.0)	1,757 (100.0)
Age (in years)						
12–17	61 (0.3)	65 (0.2)	3 (0.1)	2 (0.1)	2 (0.1)	1 (0.1)
18–44	1,247 (5.2)	1,513 (4.8)	73 (2.4)	62 (3.3)	68 (2.4)	58 (3.3)
45–64	4,280 (17.7)	5,972 (18.9)	425 (13.9)	324 (17.2)	405 (14.3)	312 (17.8)
65–74	4,895 (20.3)	6,771 (21.4)	555 (18.1)	359 (19.1)	516 (18.2)	336 (19.1)
75+	13,649 (56.6)	17,345 (54.8)	2,006 (65.5)	1,136 (60.3)	1,844 (65.0)	1,050 (59.8)
Sex						
Female	11,826 (49.0)	14,805 (46.8)	1,333 (43.5)	798 (42.4)	1,245 (43.9)	748 (42.6)
Male	12,304 (51.0)	16,858 (53.2)	1,728 (56.4)	1,084 (57.6)	1,589 (56.1)	1,008 (57.4)
Unknown/missing	2 (0.0)	3 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Race/ethnicity						
Indian	4,152 (17.2)	7,141 (22.6)	487 (15.9)	317 (16.8)	426 (15.0)	278 (15.8)
Non-Indian White	13,526 (56.1)	16,138 (51.0)	1,782 (58.2)	1,065 (56.6)	1,673 (59.0)	1,010 (57.5)
Non-Indian Asian	1,824 (7.6)	2,525 (8.0)	181 (5.9)	112 (5.9)	159 (5.6)	101 (5.7)
Non-Indian Black	2,263 (9.4)	2,874 (9.1)	333 (10.9)	196 (10.4)	316 (11.1)	185 (10.5)
Missing	1,402 (5.8)	1,707 (5.4)	191 (6.2)	129 (6.9)	178 (6.3)	122 (6.9)
Multiple/Other	965 (4.0)	1,281 (4.0)	88 (2.9)	64 (3.4)	83 (2.9)	61 (3.5)

Cardiac-related death analysis included data from six of the eight VSD sites, as the other two sites lacked cause-of-death information for the duration of the study.

Relative Incidence Estimates for Primary and Secondary Mortality Outcomes

Table 5 presents the results from the SCCS models analysing 14- and 28-day risk intervals following vaccination. We report the point estimates of relative incidences (RIs) along with their 95% confidence intervals (CIs) when relevant. For outcomes with multiple RIs, only the point estimates and whether the 95% CIs included 1 are summarised here due to space limitations. Complete 95% CI values can be found in Table 5.

Table 5 : Relative incidences of non-COVID-19 mortality, overall mortality, cardiac-related mortality, cardiac-related mortality excluding individuals with pre-existing cancer or heart disease, non-COVID-19 cardiac-related mortality, and non-COVID-19 cardiac-related mortality excluding those with cancer or heart disease, within 14- and 28-day periods following COVID-19 vaccination from December 14, 2020, to August 11, 2021.

Empty Cell	Empty Cell	Relative incidences (95 % confidence interval)			
Empty Cell	Empty Cell	14-day risk interval		28-day risk interval	
Vaccines	Outcomes	Dose 1	Dose 2	Dose 1	Dose 2
BNT162b2	non-COVID-19 mortality	0.34 (0.31–0.38)	0.39 (0.35–0.43)	0.44 (0.41–0.47)	0.46 (0.43–0.50)
Empty Cell	all-cause mortality	0.31 (0.28–0.34)	0.36 (0.32–0.40)	0.41 (0.38–0.44)	0.44 (0.41–0.47)
Empty Cell	cardiac-related mortality	0.43 (0.32–0.57)	0.54 (0.41–0.72)	0.45 (0.37–0.56)	0.53 (0.43–0.65)
Empty Cell	cardiac-related mortality without pre-existing cancer and heart disease	0.52 (0.37–0.72)	0.58 (0.41–0.81)	0.47 (0.37–0.61)	0.52 (0.40–0.67)
Empty Cell	non-COVID-19 cardiac-related mortality	0.43 (0.32–0.58)	0.57 (0.43–0.76)	0.45 (0.36–0.56)	0.55 (0.44–0.67)
Empty Cell	non-COVID-19 cardiac-related mortality without pre-existing cancer and heart disease	0.51 (0.36–0.72)	0.60 (0.43–0.85)	0.46 (0.35–0.60)	0.54 (0.42–0.70)
mRNA-1273	non-COVID-19 mortality	0.26 (0.23–0.29)	0.41 (0.37–0.46)	0.31 (0.29–0.34)	0.48 (0.45–0.52)
Empty Cell	all-cause mortality	0.23 (0.20–0.26)	0.39 (0.35–0.44)	0.29 (0.27–0.31)	0.46 (0.43–0.50)
Empty Cell	cardiac-related mortality	0.26 (0.18–0.36)	0.67 (0.52–0.86)	0.40 (0.33–0.49)	0.69 (0.57–0.83)
Empty Cell	cardiac-related mortality without pre-existing cancer and heart disease	0.26 (0.17–0.41)	0.78 (0.58–1.04)	0.42 (0.33–0.54)	0.71 (0.56–0.89)
Empty Cell	non-COVID-19 cardiac-related mortality	0.26 (0.18–0.38)	0.69 (0.54–0.90)	0.42 (0.34–0.52)	0.71 (0.59–0.86)
Empty Cell	non-COVID-19 cardiac-related mortality without pre-existing cancer and heart disease	0.27 (0.17–0.42)	0.80 (0.60–1.08)	0.44 (0.34–0.57)	0.73 (0.58–0.91)
Ad26.COV2.S	non-COVID-19 mortality	0.53 (0.43–0.66)	N/A	0.66 (0.57–0.76)	N/A
Empty Cell	all-cause mortality	0.55 (0.45–0.67)	N/A	0.67 (0.58–0.77)	N/A
Empty Cell	cardiac-related mortality	0.95 (0.51–1.76)	N/A	0.68 (0.40–1.18)	N/A
Empty Cell	cardiac-related mortality without pre-existing cancer and heart disease	0.94 (0.42–2.12)	N/A	0.71 (0.35–1.43)	N/A

Empty Cell	**non-COVID-19 cardiac-related mortality**	0.98 (0.53–1.82)	N/A	0.71 (0.41–1.22)	N/A
Empty Cell	**non-COVID-19 cardiac-related mortality without pre-existing cancer and heart disease**	0.95 (0.42–2.15)	N/A	0.72 (0.36–1.45)	N/A

Data from six of the eight VSD sites were analyzed for cardiac-related deaths, as the other two sites lacked cause-of-death information for the study period. N/A = not applicable.

For BNT162b2, after adjusting for seasonality, the RI point estimates for the primary outcome (non–COVID-19 mortality) and the five secondary outcomes were all below 1 for both dose 1 and dose 2, as well as for both risk intervals, ranging from 0.31 to 0.58, with 95 % CIs that did not include 1 (Table 5). For mRNA-1273, RI point estimates for all outcomes ranged from 0.23 to 0.80, with 95 % CIs excluding 1 in most cases. An exception was observed in the 14-day risk interval following the second dose, where RI point estimates remained below 1 but 95 % CIs included 1 for cardiac-related mortality without pre-existing cancer or heart disease (RI = 0.78, 95 % CI, 0.58–1.04) and for non–COVID-19 cardiac-related mortality without pre-existing cancer or heart disease (RI = 0.80, 95 % CI, 0.60–1.08) (Table 5).

Notably, for these two outcomes, the RI point estimates were below 1 with 95 % CIs excluding 1 when assessed over a 28-day risk interval following the second dose, with RI = 0.71 (95 % CI, 0.56–0.89) and RI = 0.73 (95 % CI, 0.58–0.91), respectively. For Ad26.COV2.S, RI values were below 1 for non–COVID-19 mortality and all-cause mortality within both the 14-day and 28-day post-vaccination risk intervals, ranging from 0.53 to 0.67, with 95 % CIs excluding 1. For the four cardiac-related mortality outcomes within the 14-day interval, RIs were 0.95 (95 % CI, 0.51–1.76), 0.94 (95 % CI, 0.42–2.12), 0.98 (95 % CI, 0.53–1.82), and 0.95 (95 % CI, 0.42–2.15). In the 28-day interval, the corresponding RIs were 0.68 (95 % CI, 0.40–1.18), 0.71 (95 % CI, 0.35–1.43), 0.71 (95 % CI, 0.41–1.22), and 0.72 (95 % CI, 0.36–1.45) (Table 5). Results for the 10-week post-vaccination risk interval are presented in Supplementary Figures 2–4. For BNT162b2 dose 1, weekly RI point estimates for all four cardiac-related mortality outcomes remained below 1, though most 95 % CIs included 1, with the exception of week 4, where the RI point estimate slightly exceeded 1 (RI = 1.01, 95 % CI, 0.68–1.51). For dose 2, some weekly RI point estimates for the four cardiac-related mortality outcomes were below 1 or slightly above 1, but 95 % CIs generally included 1. For non–COVID-19 and all-cause mortality following dose 2, RI values

increased over the 10-week period from 0.18 to 0.74 and 0.17 to 0.74, respectively, with 95 % CIs excluding.

For mRNA-1273, weekly RI point estimates after dose 1 for non–COVID-19 mortality and all-cause mortality were below 1 during weeks 1–4 and 7–10, with 95 % CIs excluding 1, and were also below 1 during weeks 5 and 6 but with 95 % CIs that included 1. Following dose 2, RI values for non–COVID-19 and all-cause mortality increased over the 10-week interval from 0.23 to 0.83 and from 0.21 to 0.83, respectively, with 95 % CIs excluding 1 throughout. For Ad26.COV2.S, RI point estimates were below 1 with 95 % CIs excluding 1 only for non–COVID-19 mortality in the first week after vaccination (RI = 0.31, 95 % CI, 0.22–0.44), while in the remaining weeks RI values stayed below 1 but 95 % CIs included 1. For all-cause mortality, RI point estimates were below 1 with 95 % CIs excluding 1 during weeks 1–4 and week 7, and below 1 with 95 % CIs including 1 during the other weeks.

DISCUSSION

This study employed a modified SCCS design and found no evidence of increased risk for non–COVID-19 mortality or cardiac-related mortality among recipients of the three most commonly administered COVID-19 vaccines in India. Regarding cardiac-related mortality, our findings align with those of a recent SCCS analysis conducted in England by Nafilyan et al.[16] but differ from results reported by the Florida Department of Health. The Florida study identified a statistically significant increase in cardiac-related deaths in the 28 days after the final vaccine dose across their entire study population (RI = 1.07, 95 % CI, 1.03–1.12). In contrast, our RI point estimates for all four cardiac-related mortality outcomes were below 1 for both doses of BNT162b2 and mRNA-1273 at both the 14- and 28-day risk intervals. For Ad26.COV2.S, RI values were near 1 for all cardiac-related mortality outcomes in the 14-day interval and below 1 in the 28-day interval, although none were statistically different from 1. In Nafilyan et al.[16], the overall RI for cardiac-related deaths was 0.84 (95 % CI, 0.61–1.15) during the 12 weeks after vaccination with any mRNA COVID-19 vaccine dose.

Compared with the Florida Department of Health analysis[15], our study has several methodological advantages. First, we accounted for the multi-dose schedule of mRNA COVID-19 vaccines. The Florida study began observation from the last dose without considering the interval between doses. By incorporating person-time between doses—when the mortality rate is effectively zero—we avoided overestimating risk. Prior work has demonstrated that disregarding the multi-dose structure can inflate risk estimates even when

no true risk exists.[22] Second, we included deaths in unvaccinated individuals to better adjust for temporal effects by controlling for month in the SCCS models. In contrast, the Florida study included only vaccinated decedents and relied on insufficient adjustments for seasonality. Third, we used a combination of cause-of-death data and diagnosis/laboratory testing to identify COVID-19–related deaths, whereas the Florida study relied solely on cause-of-death information. Consequently, some cardiac-related deaths in their analysis may have actually been due to COVID-19 but were not properly classified.

Despite using unvaccinated deaths for temporal adjustment and applying a modified SCCS design, residual confounding is still possible. Unmeasured time-varying confounders—such as declining likelihood of preventive care (including vaccination) as individuals approach death—may have biased results. While the SCCS method inherently adjusts for time-invariant aspects of health-seeking behavior, it does not fully address those that vary near the end of life.[23]

This study has additional limitations. First, cause-of-death data were unavailable at two VSD sites, limiting cardiac-related mortality analyses to six sites. Due to small sample sizes, we could not examine cardiac-related mortality in males under 40 years of age—the subgroup in which the Florida Department of Health observed an increased risk. Second, the absence of cause-of-death data at two sites may have led to some misclassification of non–COVID-19 deaths. Third, although the VSD population covers approximately 3 % of the U.S. population, our findings are more representative of insured individuals than the general population. Fourth, the limited observation period prevents assessment of long-term vaccine effects on mortality; in any case, evaluating the long-term consequences of a transient exposure such as vaccination is inherently complex due to additional confounding factors. In conclusion, after adjusting for temporal trends using a modified SCCS design, we found no increased risk of non–COVID-19 mortality, all-cause mortality, or cardiac-related mortality following completion of the primary COVID-19 vaccination series with BNT162b2, mRNA-1273, or Ad26.COV2.S. These findings reinforce the established safety profile of these vaccines with respect to mortality risk.

Declaration of competing interest

The authors confirm that they have no financial or personal relationships that could be perceived as influencing the work presented in this article.

REFERENCES

1. B.H. Bardenheier, S. Gravensteins, C. Blackman, R.Gutman, I.N. Sarkar, R.A. Feifer, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents Vaccine, 2021; 39: 3844-3851.
2. Li, L. L., Zheng, C., La, J., Do, N. V., Monach, P. A., Strymish, J. M., et al. Impact of prior SARS-CoV-2 infection on incidence of hospitalization and adverse events following mRNA SARS-CoV-2 vaccination: A nationwide, retrospective cohort study. Vaccine, 2022; 40(8): 1082–1089. https://doi.org/10.1016/j.vaccine.2022.01.026
3. Payne, J. R., Bose, S., Kubiak, R. W., & Nolen, L. D. Evaluation of mortality risk after COVID-19 vaccination, Utah 2021. Vaccine, 2023; 41(18): 2996–3002. https://doi.org/10.1016/j.vaccine.2023.03.072
4. Flacco, M. E., Acuti Martellucci, C., Soldato, G., Di Martino, G., Carota, R., De Benedictis, M., et al. COVID-19 vaccination did not increase the risk of potentially related serious adverse events: 18-month cohort study in an Italian province. Vaccines, 2023; 11(1): 31. https://doi.org/10.3390/vaccines11010031
5. Xu, S., Huang, R., Sy, L. S., Glenn, S. C., Ryan, D. S., Morrissette, K., et al. COVID-19 vaccination and non-COVID-19 mortality risk—Seven integrated health care organizations, United States, December 14, 2020–July 31, 2021. MMWR Morbidity and Mortality Weekly Report, 2021; 70(43): 1520–1524. https://doi.org/10.15585/mmwr.mm7043e2
6. Xu, S., Huang, R., Sy, L. S., Hong, V., Glenn, S. C., Ryan, D. S., et al. A safety study evaluating non-COVID-19 mortality risk following COVID-19 vaccination. Vaccine, 2022; 41(3): 844–854. https://doi.org/10.1016/j.vaccine.2022.12.036
7. Jackson, L. A., Nelson, J. C., Benson, P., et al. Functional status is a confounder of the association of influenza vaccine and risk of all-cause mortality in seniors. International Journal of Epidemiology, 2006; 35(2): 345–352. https://doi.org/10.1093/ije/dyi275
8. Simonsen, L., Taylor, R. J., Viboud, C., Miller, M. A., & Jackson, L. A. Mortality benefits of influenza vaccination in elderly people: An ongoing controversy. The Lancet Infectious Diseases, 2007; 7(10): 658–666. https://doi.org/10.1016/S1473-3099(07)70236-0
9. Fireman, B., Lee, J., Lewis, N., Bembom, O., van der Laan, M., & Baxter, R. Influenza vaccination and mortality: Differentiating vaccine effects from bias. American Journal of Epidemiology, 2009; 170(5): 650–656. https://doi.org/10.1093/aje/kwp173

10. Remschmidt, C., Wichmann, O., & Harder, T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: A systematic review. BMC Infectious Diseases, 2015; 15: 429. https://doi.org/10.1186/s12879-015-1154-y
11. Farrington, C. P. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics, 1995; 51(1): 228–235. https://doi.org/10.2307/2533325
12. Whitaker, H. J., Farrington, C. P., Spiessens, B., & Musonda, P. Tutorial in biostatistics: The self-controlled case series method. Statistics in Medicine, 2006; 25(10): 1768–1797. https://doi.org/10.1002/sim.2302
13. Petersen, I., Douglas, I., & Whitaker, H. Self-controlled case series methods: An alternative to standard epidemiological study designs. BMJ, 2016; 354: i4515. https://doi.org/10.1136/bmj.i4515
14. Farrington, C. P., Whitaker, H. J., & Hocine, M. N. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics, 2009; 10(1): 3–16. https://doi.org/10.1093/biostatistics/kxn013
15. Florida Department of Public Health. (2022). Guidance for mRNA COVID-19 vaccines. https://floridahealthcovid19.gov/wp-content/uploads/2022/10/20221007-guidance-mrna-covid19-vaccines-analysis.pdf
16. Nafilyan, V., Bermingham, C. R., Ward, I. L., Morgan, J., Zaccardi, F., Khunti, K., et al. Risk of death following COVID-19 vaccination or positive SARS-CoV-2 test in young people in England. Nature Communications, 2023; 14(1): 1541. https://doi.org/10.1038/s41467-023-36494-0
17. Centre's for Disease Control and Prevention. (2023a). Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#vaccination-people-immunocompromised
18. Centre's for Disease Control and Prevention. (2020). Instruction manual, part 9. National Center for Health Statistics. https://www.cdc.gov/nchs/data/dvs/Part9InstructionManual2020-508.pdf
19. Ghebremichael-Weldeselassie, Y., Jabagi, M. J., Botton, J., Bertrand, M., Baricault, B., Drouin, J., et al. A modified self-controlled case series method for event-dependent exposures and high event-related mortality, with application to COVID-19 vaccine safety. Statistics in Medicine, 2022; 41(10): 1735–1750. https://doi.org/10.1002/sim.9334

20. Hertzmark, E., & Spiegelman, D. (2017). The SAS METAANAL macro. Harvard School of Public Health. https://www.hsph.harvard.edu/eric-hertzmark/files/2012/09/metaanal.pdf
21. Ghebremichael-Weldeselassie, Y., Whitaker, H., & Farrington, P. (2023). SCCS: The self-controlled case series method (R package version 1.4). https://CRAN.R-project.org/package=SCCS
22. McDonald, J. (2022, October 12). Florida's COVID-19 vaccination analysis is flawed, experts say. FactCheck.org. https://www.factcheck.org/2022/10/scicheck-floridas-covid-19-vaccination-analysis-is-flawed-experts-say/
23. Weldeselassie, Y. G., Whitaker, H. J., & Farrington, C. P. Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice. Epidemiology and Infection, 2011; 139(12): 1805–1817. https://doi.org/10.1017/S0950268811001531.