Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination or infection in Florida residents: a self-controlled case series study

Objective

To evaluate the risks of all-cause and cardiac-related mortality following COVID-19 vaccination.

Methods

Design

The self-controlled case series (SCCS) method adapted to evaluate death as the outcome was used.[1,2] The SCCS method, originally developed to assess vaccine safety, utilizes within-person comparisons to estimate the temporal association between a transient exposure and an acute event.[1] The SCCS method estimates relative incidence (RI) by comparing incidence during a defined high-risk period following exposure with incidence during a control period (i.e., all time in the follow-up period that is not the risk period).[1–4] A major strength of the SCCS method is that fixed-time confounders, such as health related risk-factors, are controlled for.[1,3]

The primary analysis utilized the SCCS method developed for single exposures that cannot be repeated.[1,3,4] Since mRNA vaccinations require a multidose schedule, a simple modification was employed, where the last vaccination preceding death was used as the single exposure.[2] In this method, the within-individual comparison is between the immediate post-exposure period and later post-exposure periods.[3]

Data sources

Data from Florida's reportable disease repository (Merlin), Florida State Health Online Tracking System (FLSHOTS), and death records data from vital statistics were linked.

Setting and study population

For the primary analysis, Florida residents aged 18 years or older who died within 25-weeks of COVID-19 vaccination since the start of the vaccination roll-out (December 15, 2020) were included.

Individuals were excluded if they (1) had a documented COVID-19 infection, (2) experienced a COVID-19 associated death, (3) received a booster, or (4) received their last COVID-19 vaccination after December 8, 2021 (to ensure each individual had the 25-week follow-up period to experience the event of interest).

To allow for death registration, the study end date for both analyses was June 1, 2022.

Exposure and outcomes

The exposure of interest was the 28-day risk period following COVID-19 vaccination.

Two outcomes were assessed. Natural all-cause deaths (i.e., excluding homicides, suicides, and accidents) and cardiac-related deaths. Cardiac-related deaths were included if their death record

contained an ICD-10 code of I30-I52. For the primary analysis, only participants that experienced the exposure and outcome were included in this study.

Statistical analysis

Primary Analyses

Follow-up began on the day of their last COVID-19 vaccination. Participants were not censored upon death, rather, they were followed for the entire 25-week follow-up period.[1–4]

Conditional logistic regression models offsetting by interval-length were used to estimate RIs and 95% confidence intervals (CIs) comparing incidence in the 28-day risk period to incidence in the baseline period (i.e., the rest of the follow-up period).[2,5] Seasonality was controlled for in each model unless the sample size was too small. Potential confounding by age was reduced by limiting the follow-up period to 25-weeks. Separate models were fitted for each outcome and subgroup analyzed. Estimates were considered statistically significant if the 95% CI did not contain 1.

Data were formatted into a stacked dataset, where exposures for each individual are stacked in columns (i.e., multiple rows per individual), using the SCCS package in R. Conditional logistic regression models were estimated using the clogit function from the survival package.

Results

Primary Analysis

Table 1 presents the results for the primary analysis for natural all-cause and cardiac-related deaths following COVID-19 vaccination.

All-cause deaths following vaccination

In the 28 days following vaccination, no increase in risk was observed for all-cause deaths. A statistically significant decrease was observed for participants 60 years or older in the 28 days following vaccination (RI = 0.97, 95% CI = 0.94 - 0.99).

Cardiac-related deaths following vaccination

In the 28 days following vaccination, a statistically significant increase in cardiac-related deaths was detected for the entire study population (RI = 1.07, 95% CI = 1.03 - 1.12). Stratifying by age group revealed RIs were significantly higher for age groups 25 - 39 (RI = 2.16, 95% CI = 1.35 - 3.47) and 60 or older (RI = 1.05, 95% CI = 1.01 - 1.10). The remaining age groups failed to reach statistical significance.

Cardiac-related deaths by age group, vaccination type, and sex following vaccination

To determine which group may be driving the increased risk of cardiac-related deaths in the primary analysis, the vaccination analysis was further stratified by sex, vaccination type, and age groups. Tables 2 and 3 present the sex specific results for cardiac-related deaths following vaccination stratified by age group and vaccination type. Risk was significantly higher during the risk period for males (RI = 1.09, 95% CI = 1.03 - 1.15) but not for females (RI = 1.05, 95% CI = 0.98 - 1.11). Concerning vaccination type, males receiving mRNA vaccination had significantly higher risk (RI = 1.11, 95% CI = 1.05 - 1.18), while males receiving vaccinations that were not mRNA/unknown had significantly lower risk (RI = 0.75, 95% CI = 0.58 - 0.98). RIs for females stratified by vaccination type revealed a similar pattern, with lower, non-

significant estimates. Among the subgroups evaluated, males aged 18 - 39 had the highest risk (RI = 1.97, 95% CI = 1.16 - 3.35).

Discussion/Conclusion

In this statewide study of vaccinated Florida residents aged 18 years or older, COVID-vaccination was not associated with an elevated risk for all-cause mortality. COVID-19 vaccination was associated with a modestly increased risk for cardiac-related mortality 28 days following vaccination. Results from the stratified analysis for cardiac-related death following vaccination suggests mRNA vaccination may be driving the increased risk in males, especially among males aged 18 - 39. Risk for both all-cause and cardiac-related deaths was substantially higher 28 days following COVID-19 infection. The risk associated with mRNA vaccination should be weighed against the risk associated with COVID-19 infection.

Limitations

These data are preliminary, based on surveillance data, and should be interpreted with caution. The results have several limitations:

While this method has been used to assess risk of death following COVID-19 vaccination,[2] it violates the assumption that an event does not affect subsequent exposure (for mRNA vaccines), which may introduce bias.[6] Further, it does not consider the multidose vaccination schedule required for mRNA vaccination.

This study cannot determine the causative nature of a participant's death. We used death certificate data and not medical records. COVID testing status was unknown for those who did not die of/with COVID. Cardiac-related deaths were ascertained if an ACME code of I3-I52 were on their death certificate, thus, the underlying cause of death may not be cardiac-related.

The finding that the Janssen vaccine was more protective than mRNA vaccine against mortality within 28 days of vaccination could be due to confounding and needs to be further evaluated. It is likely that the populations who received COVID-19 mRNA vaccine and the Johnson vaccine are different, something we were not able to ascertain in this analysis. It is possible that the population who received the Johnson vaccine was younger and healthier than those receiving the mRNA vaccines. The Pfizer and Moderna mRNA vaccines were released more than 2 months earlier than the Janssen vaccine when the recommendations were limited to those 65 and older.

Additional studies should be conducted to further understand the risks and benefits of vaccination of males between 25-39. Increased risk in the primary analysis for the 25 - 39 age group was based on a small sample size. Additionally, significant mortality from diagnosed COVID-19 infection occurred among all adult age groups. COVID-19 mortality among asymptomatic or undiagnosed COVID-19 infection is less clear. However, excess overall mortality among 25–44-year-old Americans was significant in a study[1] looking at mortality from January 2020-October 2020. The largest increases were among Hispanic and Latino. It is unclear what the contribution of asymptomatic or undiagnosed COVID-19 infection is to mortality risk, and how this contributes to excess mortality.

[1] https://www.cdc.gov/mmwr/volumes/69/wr/mm6942e2.htm

Confounding by age may be present in the 60 years or older age group, which may explain the slight elevated risk for cardiac-related deaths following vaccination. This may also explain the increased risk for the entire vaccination analysis group for cardiac-related deaths since this group comprises the vast majority of deaths. Removing those aged 60 years or older yielded non-significant results for cardiac-related deaths following vaccination (RI = 1.15, 95% CI = 0.99 - 1.34), mRNA vaccination (RI = 1.17, 95% CI = 1.00 - 1.37), and males with mRNA vaccination (RI = 1.09, 95% CI = 0.89 - 1.34).

Lastly, this analysis was conducted during the first months the vaccines were available. Both COVID-19 mortality due to infection or risk of mortality associated with vaccination have likely changed over time. In the fall of 2022, most people have either been vaccinated or have natural immunity to COVID-19. Many have had multiple vaccine doses, multiple infections or both. Research to assess the current risks and benefits of the COVID-19 vaccine to help update vaccine recommendations should be studied in this context.

Table 1: Relative incidence following COVID-19 vaccination or infection for all-cause and cardiac-related deaths during the risk period vs baseline period

Subgroup, exposure	No. events	Follow-up, 1000 person days	RI (95% CI)
COVID-19 vaccination			
All-cause deaths			
≥ 18			
Baseline period	50947	8912.17	Ref
Risk period	9680	1697.56	0.98 (0.95 - 1.00)
18 - 24*			
Baseline period	47	7.94	Ref
Risk period	7	1.51	0.78 (0.35 - 1.73)
25 - 39			
Baseline period	397	67.77	Ref
Risk period	64	12.91	0.84 (0.63 - 1.11)
40 - 59			
Baseline period	3744	651.06	Ref
Risk period	685	124.01	0.97 (0.89 - 1.06)
≥ 60			
Baseline period	46759	8185.40	Ref
Risk period	8924	1559.12	0.97 (0.94 - 0.99)
Cardiac-related deaths			
≥ 18			
Baseline period	16406	2923.10	Ref
Risk period	3479	556.78	1.07 (1.03 - 1.12)
18 - 24*			
Baseline period	17	3.23	Ref
Risk period	5	0.62	1.54 (0.57 - 4.19)
25 - 39			
Baseline period	75	15.29	Ref
Risk period	29	2.91	2.16 (1.35 - 3.47)
40 - 59			
Baseline period	1034	183.46	Ref
Risk period	214	34.94	1.07 (0.91 - 1.26)
≥ 60			
Baseline period	15280	2721.12	Ref
Risk period	3231	518.31	1.05 (1.01 - 1.10)

*Crude due to sparse data

Table 2: Relative incidence of cardiac-related deaths following COVID-19 vaccination for males by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, male			
Baseline period	8901	1586.72	Ref
Risk period	1893	302.23	1.09 (1.03 - 1.15)
≥ 18, male, mRNA			
Baseline period	8223	1474.12	Ref
Risk period	1805	280.78	1.11 (1.05 - 1.18)
≥ 18, male, not mRNA\unknown			
Baseline period	678	112.60	Ref
Risk period	88	21.45	0.75 (0.58 - 0.98)
18-39, male			
Baseline period	55	11.32	Ref
Risk period	22	2.16	1.97 (1.16 - 3.35)
18-39, male, mRNA			
Baseline period	52	10.58	Ref
Risk period	20	2.02	1.84 (1.05 - 3.21)
40-59, male			
Baseline period	683	120.10	Ref
Risk period	134	22.88	0.98 (0.80 - 1.20)
40-59, male, mRNA			
Baseline period	591	104.81	Ref
Risk period	122	19.96	1.00 (0.81 - 1.24)
40-59, male, not mRNA\unknown*			
Baseline period	92	15.29	Ref
Risk period	12	2.91	0.68 (0.38 - 1.25)
≥ 60, male			
Baseline period	8163	1455.3	Ref
Risk period	1737	277.2	1.08 (1.02 - 1.14)
≥ 60, male, mRNA			
Baseline period	7580	1358.72	Ref
Risk period	1663	258.80	1.10 (1.03 - 1.17)
≥ 60, male, not mRNA\unknown			
Baseline period	583	96.58	Ref
Risk period	74	18.40	0.73 (0.55 - 0.97)

*Crude due to sparse data

†Group 18-39, male, not mRNA\unknown not included due to small sample size (n = 5)

Table 3: Relative incidence of cardiac-related deaths following COVID-19 vaccination for females by age group and vaccination type†

Cardiac-related deaths			
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, female			
Baseline period	7505	1336.38	Ref
Risk period	1586	254.55	1.05 (0.98 - 1.11)
≥ 18, female, mRNA			
Baseline period	6992	1251.41	Ref
Risk period	1521	238.36	1.06 (1.00 - 1.13)
≥ 18, female, not mRNA\unknown			
Baseline period	513	16.18	Ref
Risk period	65	84.97	0.86 (0.63 - 1.17)
18-39, female*			
Baseline period	37	7.20	Ref
Risk period	12	1.37	1.70 (0.89 - 3.27)
18-39, female, mRNA*			
Baseline period	33	6.32	Ref
Risk period	10	1.20	1.59 (0.78 - 3.23)
40-59, female			
Baseline period	351	63.36	Ref
Risk period	80	12.07	1.25 (0.96 - 1.63)
40-59, female, mRNA			
Baseline period	324	58.36	Ref
Risk period	73	11.12	1.25 (0.95 - 1.64)
40-59, female, not mRNA\unknown*			
Baseline period	27	5.00	Ref
Risk period	7	0.95	1.36 (0.59 - 3.13)
≥ 60, female			
Baseline period	7117	1265.82	Ref
Risk period	1494	241.11	1.02 (0.96 - 1.09)
≥ 60, female, mRNA			
Baseline period	6635	1186.73	Ref
Risk period	1438	226.04	1.04 (0.97 - 1.11)
≥ 60, female, not mRNA\unknown			
Baseline period	482	79.09	Ref
Risk period	56	15.06	0.79 (0.57 - 1.10)

*Crude due to sparse data

†Group 18-39, female, not mRNA\unknown not included due to small sample size (n = 6)

References

1. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354:i4515. doi:10.1136/bmj.i4515

2. Nafilyan V, Bermingham C, Ward IL, et al. Risk of death following SARS-CoV-2 infection or COVID-19 vaccination in young people in England: a self-controlled case series study. *medRxiv*. Published online January 1, 2022:2022.03.22.22272775. doi:10.1101/2022.03.22.22272775

3. Whitaker H, Farrington P, Spiessens B, Musonda P. Tutorial in Biostatistics: The self-controlled case series method. *Stat Med*. Published online 2006:1768-1797. doi:https://doi.org/10.1002/sim.2302

4. Hubbard R, Lewis S, West J, et al. Bupropion and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network. *Thorax*. 2005;60(10):848. doi:10.1136/thx.2005.041798

5. Whitaker H. *Using R for Self-Controlled Case Series Studies*.; 2022. https://sccs-studies.info/r.html

6. Weldeselassie, YG, Whitaker, HJ, Farrington, CP. Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice. *Epidemiol Infect*. – 2011;139(12):1805-1817. doi:10.1017/S0950268811001531