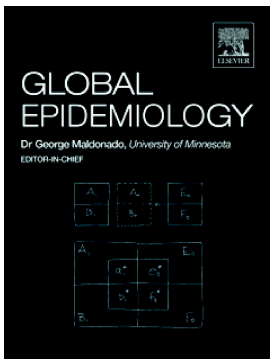
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Twelve-Month All-Cause Mortality after Initial COVID-19 Vaccination with Pfizer-BioNTech or mRNA-1273 among Adults Living in Florida: Statewide Cohort Study

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Short Title: Twelve-Month All-Cause Mortality after Initial COVID-19 Vaccination

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ABSTRACT

Background: Comparative effects of the mRNA COVID-19 vaccines on health outcomes are uncertain. The study objective was to compare all-cause and non-COVID-19 mortality between recipients of BNT162b2 (Pfizer) and mRNA-1273 (Moderna).

Methods: Matched cohort analysis of 1,962,822 adults living in Florida who received a first dose of either BNT162b2 or mRNA-1273 between December 18, 2020, and August 31, 2021, was used to examine 12-month risk of all-cause, cardiovascular, COVID-19, and non-COVID-19 mortality. Matching was performed on seven criteria, including age group, sex, race, ethnicity, calendar month of vaccination, nine types of vaccination sites, and 4,832 census tracts. Kaplan-Meir estimators and Cox proportional hazards regressions were used.

Results: Compared with mRNA-1273 recipients, BNT162b2 recipients had higher hazard of all-cause mortality (784 vs. 562 deaths per 100,000; hazard ratio, HR [95% CI]: 1.40 [1.36, 1.45]), cardiovascular mortality (226 vs. 145 deaths per 100,000 persons; HR [95% CI]: 1.57 [1.47, 1.68]), COVID-19 mortality (61 vs. 32 deaths per 100,000 persons; HR [95% CI]: 1.91 [1.67, 2.19]) and non-COVID-19 mortality (722 vs. 530 deaths per 100,000 persons; HR [95% CI]: 1.37 [1.32, 1.42]). Negative control outcomes and robustness analyses did not show any indication of meaningful unobserved residual confounding likely to alter the results, although there was evidence of potential small residual imbalance among adults 60 years and older.

Conclusions: Florida residents receiving the BNT162b2 vaccine in the initial months of the campaign had h cardiovascular, and COVID-19 mortality compared to matched mRNA-1273 recipients, with differ COVID-19 mortality driven by the results findings suggest that COVID-19 vaccine outcomes should be considered when SARS-CoV-2.

Primary Funding Source:

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Keywords:

COVID-19, mRNA, comparative effectiveness, public health, health policy

INTRODUCTION

A growing number of both randomized and observational studies, including a systematic review commissioned by the World Health Organization's Strate Group of Experts, suggest vaccines may have beneficial or harmful non-specific effects, including potential impact on all-cause mortality, beyond their effect on the target disease.[1-4] In the context of the initial messenger RNA (mRNA) COVID-19 vaccination series, relatively little is known about their effect on all-cause mortality. While findings from the mRNA COVID-19 vaccines trials suggested that both vaccines

reduced the risk of death due to COVID-19, pooled analysis that compared all-cause mortality between the vaccine and placebo arms did not show any differences. In contrast, the trials of the adenovirus COVID-19 vaccines did show a reduction in all-cause mortality.[1, 5] Moreover, no trial was conducted to compare the effects of different vaccines. Cardiac deaths in the mRNA COVID-19 vaccine trials were more frequent, with a relative increase of 50% and 40% compared to the placebo groups among BNT162b2 and mRNA-1273 vaccine recipients, respectively, but these differences did not seem meaningful.[5]

Nonspecific vaccine effects can be directly assessed in observational studies by evaluating a vaccine's impact on all-cause mortality and other outcomes. However, the results of these studies that typically compare vaccinated to unvaccinated cohorts are prone to multiple biases, including healthy vaccinee bias, i.e., observed and unobserved characteristics that have a confounding effect on the decision to vaccinate and an outcome.[6] As a result, they often have relatively low reliability. Moreover, healthy vaccinee bias, likely the result of substantial unobserved differences between vaccinated and unvaccinated individuals, were demonstrated in observational studies of COVID-19 vaccination and other vaccines, even in studies using matching or risk adjustment.[6-10] For example, in a recent extensive study using data from France, vaccinated individuals had a lower mortality risk from transportation-related accidents compared to unvaccinated individuals, which seems highly unlikely to be explained by protective effects of vaccination.[11]

Nonspecific vaccine effects may also be indirectly assessed by evaluating health outcomes among patients who receive different vaccines for the same indication.[12]

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This type of comparison is less likely to be vulnerable to healthy vaccinee bias and has already been used to compare different COVID-19 vaccines. A study using a target trial emulation design with data from the U.S. Department of Veterans Affairs, showed that initial vaccination with BNT162b2 was associated with higher risk of multiple cardiovascular adverse events compared to initial vaccination with mRNA-1273, over a 266-day follow-up period.[13] Another study based on Veterans Affairs data using a similar methodological approach found improved outcomes against COVID-19 infection, hospitalization and intensive care unit admission among U.S. veterans who received a first dose of mRNA-1273 versus BNT162b2, but no difference in non-COVID-19 mortality.[14] To further assess comparative effects of the BNT162b2 vaccine and mRNA-1273 vaccine on 12-month all-cause, cardiovascular, COVID-19, and non-COVID-19 mortality, this study evaluated mortality outcomes among a cohort of adult Florida residents using state-level public health databases.

METHODS

Data

This study analyzed state-level public health databases with data's st records about COVID-19 vaccination, sociodemographic characteristics of vaccine recipients, and vital statistics. Florida SHOTS is a statewide, centralized online immunization information system (IIS) with immunization records for patients of all ages.[15] As a program of the Florida Health Immunization Section, it is authorized by Section 381.003, Florida Statutes. Healthcare practitioners who administer vaccinations to children are required by Florida statute t vaccine registry, unless a parent chooses to opt out of the registry. All COVID-19

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vaccinations were also required to be recorded in Florida SHOTS. The Bureau of Vital Statistics collects vital records data (birth, deaths, marriages, etc.) at the Florida Department of Health. The vital records data for deaths includes primary and underlying cause of death, health-related and other information about individuals residing in Florida at the time of their death.[16] These data are part of the National Death Index (NDI). Data on cardiac hospitalizations, as an additional measure of cardiac risk, was obtained from Florida's Agency for Health Care Administration, which maintains an inpatient data collection program, as directed by Section 408.061, Florida Statutes, and Chapter 59E-7 of the Florida Administrative Code. This study was reviewed by the Florida Department of Health institutional review board and deemed exempt as public health practice.

Study Population and Design

The study population included noninstitutionalized adult Florida residents (ages 18-99 years) receiving a first dose of either the BNT162b2 or mRNA-1273 mRNA vaccine between December 18, 2020, and August 31, 2021, inclusive. Institutionalized individuals living in nursing homes or correctional facilities, as well as those identified as homeless in the Florida SHOTS database or with missing or unknown sex, were excluded from the analysis (See Supplement for the method used to identify nursing home residents and correctional facility residents). Institutionalized individuals were excluded so that the cohort would be representative of a community-dwelling population, similar to the populations enrolled in the initial, pivotal randomized trials evaluating the BNT162b2 and mRNA-1273 COVID-19 vaccines.[17, 18] To minimize baseline differences between BNT162b2 and mRNA-1273 vaccine recipients, a

matched cohort was formed, with a 1:1 ratio and exact matching according to 5-year age bins, sex, race, ethnicity, vaccination site (9 types), calendar month of vaccination with first dose, and census tract of residential address. Vaccination sites included private pharmacies, county health departments, private physician clinics, federally qualified health centers, hospital sites, and other locations. The total number of census tracts was 4,832. The selected matching criteria were hypothesized to have a potential effect on the type of vaccine received or mortality risk. A cohort of Florida residents who were unvaccinated was not constructed because these individuals were not captured in our database.

Outcomes

The primary outcome of the study was 12-month all-cause mortality in the matched cohort, defined as any death within 12 months after the first COVID-19 vaccine dose. The Florida Vital Statistics database was used to identify all deaths and included data through August 31, 2022. A multistep algorithm was then used to match records from Florida SHOTS with death records from the Vital Statistics database. Details about the matching algorithm are available in the Supplement.

Secondary outcomes were cardiovascular, COVID-19, and non-COVID-19 deaths. The classification of subcategories of death was determined by the primary cause of the death on each decedent's death c Classification of Diseases, Tenth Revision (ICD-10) codes (Supplement Table 1). Deaths were attributed to COVID-19 if a corresponding ICD-10 code was listed either as the primary or underlying cause of death on the death certificate. Decedents without an

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ICD-10 code corresponding to COVID-19 on their death certificates were classified as non-COVID-19 deaths.

Negative Control Outcomes

To further evaluate the potential existence of residual confounding, several negative control outcomes were assessed.[19] We assessed (1) deaths from suicide or homicide and (2) deaths from cancer within 12 months of vaccination with the first dose as negative control outcomes. These negative control outcomes were chosen because they are unlikely to be affected by the type of vaccination an individual receives but may be affected by potential unobserved confounders of health outcomes. These deaths were defined and identified based on their corresponding ICD-10 codes being listed as a primary cause of death on the death certificate. To further assess potential residual unobserved confounding factors, the occurrence of SARS-CoV-2 infection (based on documented positive tests) before December 20, 2020, the start of COVID-19 vaccination, was considered as an additional negative control outcome.

Statistical Analysis

Kaplan–Meier cumulative incidence curves were used to compare the risk of mortality outcomes among BNT162b2 and mRNA-1273 vaccine recipients in the matched cohort. Further risk adjustment was conducted using Cox proportional hazards models with an outcome of 1 if death occurred within 12 months of vaccination and 0 otherwise. The follow-up started at the time of receiving the first dose of the vaccine and ended at time of death in those with the outcome and at 12 months in those without the outcome. In addition to an indicator variable corresponding to the type of vaccine received (1 for BNT162b2 and 0 for mRNA-1273), the regression models included the

covariates used for matching (not including indicator variables for census tracts), as well as covariates corresponding to components of the census tract-level social vulnerability index scores (socioeconomic, housing and transportation components) and ZIP code-level five-year average mortality rate specific for t While we adjusted for census tract-level social vulnerability, we did not include indicator variables for census tracts because their high number (4,832) would substantially increase the dimensionality of the regression model and increase the risk of overfitting, collinearity, and spurious estimates. Further stratification was conducted with similar risk-adjusted regression models estimated on age groups 18-39 years-old, 40-59 years-old, and 60 years-old and older. Proportional hazards assumptions were assessed by examining the Schoenfeld residuals over time. The Schoenfeld residual plots are shown in the Supplement (Supplement Figure 5) and did do not demonstrate evidence of a substantial violation of the proportional hazards assumption. In a post hoc sensitivity analysis to further address confounding by pre-vaccination risk, we adjusted for a history of hospitalization due to cardiovascular disease (principal diagnosis with ICD-10 codes: I00-I78), defined as any hospitalization between January 1, 2019, and the first vaccination date.

Negative control outcomes were assessed with similar Cox proportional hazards regressions or logistic regression models. For the negative control outcome of SARS-CoV-2 infections prior to December 20, 2020, the standardized mean difference was calculated to assess balance among the matched cohort. In addition, a logistic regression model with SARS-CoV-2 infections prior to December 20, 2020 was estimated as a negative control outcome, adjusting for the same set of covariates as our

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primary models. As a post-hoc analysis, similar regression models with an additional covariate indicator that captures SARS-CoV-2 infection prior to receiving dose 1, were estimated. Additional post hoc robustness analyses excluded patients with SARS-CoV-2 infection prior to vaccination.

To assess the plausibility of the hypothesis that differences in outcomes between the vaccines could be attributable to differential protective effects against SARS-CoV-2 infection, the analyses were repeated with a more expansive definition of COVID-19+ deaths. Specifically, COVID-19+ deaths were defined as deaths with COVID-19 listed either as the primary or underlying cause of death on the death certificate, or decedents with documented SARS-CoV-2 infection after their first vaccine dose. Decedents without COVID-19 on their death certificates or a SARS-CoV-2 infection after the first dose were classified as non-COVID-19+ deaths.

Additional sensitivity analysis was conducted to assess the robustness of the matched cohort analysis to the presence of residual unobserved confounding covariates. The sensitivity analysis estimates thresholds on the association levels (quantified through odds ratio) between a potential unobserved confounder and the exposure and outcome, respectively, that would render the 95% CI interval of the BNT162b2 vs. Moderna mRNA-1273 vaccination covariate to include 1. Upper bounds on the respective p-values were calculated using methods proposed by Rosenbaum for matched observational studies.[20] (See Supplement for more detailed description.) A post hoc analysis aimed to partially assess whether the results could be related to subsequent mRNA COVID-19 vaccine doses. It assessed the proportion of individuals who received a second dose, and the proportion who received a third dose within 6

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months of their initial dose. Confidence intervals were calculated using the Wald method. Statistical analyses were performed in SAS (version 9.4). All codes and output files are available as a supplemental file.

RESULTS

A total of 11,288,333 adult Florida residents met inclusion criteria with 6,575,206 BNT162b2 vaccine recipients and 4,713,127 mRNA-1273 vaccine recipients. Of those, a total of 1,962,822 vaccine recipients, including 981,411 recipients each for BNT162b2 and mRNA-1273, were matched (1:1) across all seven criteria (Figure 1). Characteristics of vaccine recipients in the full and matched cohorts are shown in Table 1. In the full cohort, BNT162b2 recipients were younger, more likely to be Hispanic and had a higher social vulnerability index (SVI) than mRNA-1273 recipients. Compared to the full cohort, the matched cohort was slightly younger and had lower 12-month mortality risk (Tables 1 and 2).

Overall, BNT162b2 was the dominant vaccine for all age groups in every month with the exception of January for all age groups less than 80 years, December 2020 to April 2021 for the age group 70-79 years, and February to April, 2021 for age group 80 years and older (Supplement Figure 1). Vaccine allocation to different vaccination sites shifted over time. In January 2021, 15% of COVID-19 vaccines were administered in hospitals and 10% were administered in outpatient pharmacies. By August 2021, this distribution had shifted to less than 1% being administered in hospitals and about 80% in pharmacies (data not shown).

Mortality Outcomes

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Table 2 shows the number of deaths in the full and matched cohorts, and Table 3 reports the respective mortality risk (per 100,000 persons) of BNT162b2 and mRNA-1273 recipients in the matched cohort, as well as the risk ratio (RR), risk difference (RD) and the unadjusted and adjusted hazard ratios (HRs). BNT162b2 recipients had higher hazard of all-cause mortality compared to mRNA-1273 recipients (Hazard ratio, HR [95% CI]: 1.40 [1.36, 1.45]), with an excess of 221 deaths per 100,000 persons (95% CI: [198, 244]; Table 3). The corresponding risk ratio was 1.39 (95% CI: [1.35, 1.44]). Similarly, BNT162b2 recipients had a higher hazard ratio for cardiovascular mortality compared to mRNA-1273 recipients (HR [95% CI]: 1.57 [1.47, 1.68]), with an excess of 80 deaths (95% CI: [68, 92]) per 100,000 persons. This corresponded with a risk ratio of 1.55 (95% CI: [1.45, 1.66]).

The COVID-19 mortality risk was higher in BNT162b2 recipients compared to mRNA-1273 recipients (HR [95% CI]: 1.91 [1.67, 2.19]), with an excess of 29 deaths (95% CI: [23, 35]) per 100,000 persons. The corresponding risk ratio was 1.90 (95% CI: [1.70, 2.18]). Non-COVID-19 mortality risk was also higher in BNT162b2 recipients compared to mRNA-1273 recipients (HR [95% CI]: 1.37 [1.32, 1.42]), with an excess of 192 deaths (95% CI: [170, 214) per 100,000 persons. This corresponded with a risk ratio of 1.36 (95% CI: [1.32, 1.41]).

Results of the mortality analysis stratified by age are shown in Supplement Tables 3 and 7. These stratified analyses demonstrated that increased cardiovascular and COVID-19 mortality among BNT162b2 recipients was primarily driven by outcomes in adults 60 years and older. However, all-cause mortality was higher among BNT162b2

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recipients compared to mRNA-1273 recipients for all age groups. Analogous findings from the full cohort are shown in Supplement Table 4.

Cumulative Mortality Incidence Curves

Cumulative incidence curves for all-cause, cardiovascular, COVID-19, and non-COVID-19 mortality in the matched cohort are shown in Figure 2. For all-cause, cardiovascular, and non-COVID-19 deaths, the corresponding curves show clear separation starting 30-40 days post vaccination with dose 1. For COVID-19 mortality, there was a pronounced separation in incidence curves between recipients of BNT162b2 versus mRNA-1273 initially after vaccination and a second divergence that began approximately 200 days after vaccination. The latter period may correspond to the Delta wave which began in Florida around July 2021, when the Delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became the dominant variant in Florida. Results from the full cohort are shown in Supplement Figure 3.

Sensitivity Analysis

Repeating the analysis with COVID-19+ and non-COVID-19+ deaths yielded results similar to the primary analysis with non-COVID-19+ deaths having a hazard ratio of 1.35 (95% CI: [1.30, 1.40) for BNT162b2 as compared to mRNA-1273 recipients in the matched cohort (Table 4 and Supplement Figure 4). Additional post hoc analysis excluding patients with prior SARS-CoV-2 infection showed results similar to the primary analysis (Supplement Table 5). Similarly, a post hoc analysis of mortality outcomes that adjusted for history of SARS-CoV-2 infection prior to vaccination (any infection before the first vaccine dose) showed similar results as the main analysis

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(Supplement Table 7). In addition, adjusting for major cardiovascular disease hospitalization did not meaningfully affect our findings (Supplement Table 8).

Negative Control Outcomes

Similar cumulative incidence curves were constructed for the negative control outcome of homicide and suicide within the matched cohort (Supplement Figure 2). The hazard ratio of homicide and suicide mortality in the matched cohort was 1.22 (95% CI: [0.94, 1.59]) (Table 3). The hazard ratio of cancer mortality in the matched cohort was 1.05 (95% CI: [0.98, 1.13]). Similarly, the hazard ratio for the 40-59 age group was 0.96 (95% CI: [0.78, 1.18) (see Supplement Table 3).

The prevalence of SARS-CoV-2 infection prior to December 20, 2020, was 3.55% for BNT162b2 recipients and 3.49% for mRNA-1273 recipients. The standardized mean difference, which represents the difference between these two mean prevalences expressed in units of standard deviation, was 0.008, suggesting very high level of balance. Logistic regression models, with SARS-CoV-2 infection prior to December 20, 2020 as an outcome, yielded an odds ratio of 1.02 (95% CI: [1.00, 1.05]) for BNT162b2 as compared to mRNA-1273 recipients in the matched cohort. Stratification by age showed no meaningful difference for the 18-39 and 40–59-year-old groups and was significant only among individuals 60 years or older (OR [95% CI]: 1.096 [1.05, 1.15]) (Supplement Table 6).

Robustness Analysis

A sensitivity analysis assessing the influence of unmeasured confounding demonstrated that the matched cohort findings were robust. For example, an unmeasured binary confounder with a 2.0-fold higher prevalence among BNT162b2

recipients relative to mRNA-1273 recipients would need to increase the odds of mortality by at least 2.8-fold to render the estimated 95% CIs to include 1. Full sensitivity analysis results are provided in the Supplementary Material (Supplementary Table 9).

In the matched cohort, 94% of vaccine recipients (93% for BNT162b2 after a mean of 30 days and 94% for mRNA-1273 after a mean of 36 days from the first dose) completed their second dose with the same vaccine. The proportion of vaccine recipients who did not complete a second dose was 6.0% for BNT162b2 and 4.7% for mRNA-1273. The proportion of individuals in our cohort who received a third dose within 6 months of their initial dose was 1.3%.

D I S C U S S I O N

This study compared 12-month mortality outcomes of noninstitutionalized adult Florida residents who received a first dose of BNT162b2 or mRNA-1273 for initial vaccination against COVID-19. The findings demonstrate that vaccination with BNT162b2 was associated with higher 12-month all-cause, cardiovascular, COVID-19, and non-COVID-19 mortality compared to mRNA-1273. The increase in mortality risk was present in all age groups but was most pronounced among vaccine recipients over 60 years of age, with differences in cardiovascular and COVID-19 mortality primarily driven by this age group.

There are several hypothesized (potentially not mutually exclusive) explanations and interpretations for the observed results of this study. First, like any observational study, it is not possible to exclude the existence of residual unobserved confounding

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factors. Second, the demonstrated improved protection provided by the Moderna vaccine (mRNA-1273) compared to the Pfizer vaccine (BNT162b2) against COVID-19 infection, hospitalization and mortality, could theoretically also explain a reduction in non-COVID-19 mortality, caused by sequala of SARS-CoV-2 infection or COVID-19 hospitalization. Third, the findings of this study could support the hypothesis that the Moderna mRNA-1273 and Pfizer BNT162b2 COVID-19 vaccines have different non-specific effects, including on non-COVID-19 mortality.

The subsequent discussion highlights several findings of this study that relate to these three hypotheses, but without further studies and a comparable unvaccinated cohort, conclusive interpretability is limite importance of considering non-specific vaccine effects when evaluating vaccines.

Residual unobserved confounding factors. This study compares outcomes between recipients of two different vaccines, and consequently typical unobserved confounding factors that exist in studies comparing vaccinated to unvaccinated cohorts are less likely to have meaningful impact. The distribution of the Pfizer BNT162b2 and Moderna mRNA-1273 vaccines over time and to different vaccination locations could be a source of biases, for example, because of their different cold supply chain requirements. However, the matching scheme employed by this study directly matches on month of vaccination and the type of vaccination location, which should provide reasonable control of these potential biases.

Nonetheless, there is a valid concern that Pfizer BNT162b2 and Moderna mRNA-1273 cohorts differ on important covariates that affect mortality risk, such as health

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comorbidities and behaviors, that are not directly controlled for in the matching algorithm. There are other studies that also used similar matching between Pfizer BNT162b2 and Moderna mRNA-1273 vaccine recipients, based on the data from Veteran Affairs (VA) System. These studies used matching based on coarser features than the current study but nevertheless, demonstrated that the matched cohorts were very similar (balanced) with respect to relevant comorbidities and health behaviors (e.g., historical vaccination frequencies), despite not being directly matched on these characteristics.[13, 14] This provides reassuring support that the matched Pfizer BNT162b2 and Moderna mRNA-1273 cohorts in this study have similar balance. In addition, results changed minimally when we adjusted for prior major cardiovascular disease hospitalization as a measure of pre-vaccination risk.

Additionally, the analysis of negative control outcomes did not demonstrate existence of meaningful residual bias, particularly compared to the observed effect size of increased mortality risk. In addition, in the current study, the prevalence of SARS-CoV-2 infection prior to the start of the vaccination campaign was very balanced between BNT162b2 and mRNA-1273 recipients, although there was evidence of potential small residual imbalance among adults 60 years and older. Further, the robustness analysis indicated that only substantial unobserved confounding will undo the observed differences in mortality risk between the matched Pfizer BNT162b2 and Moderna mRNA-1273 vaccinees.

Another potential source of confounding could relate to the potential impact of subsequent mRNA COVID-19 vaccines doses, including booster doses, and other changes in vaccine status. Regarding second doses, 94% of vaccine recipients (93%

for BNT162b2 after a mean of 30 days and 94% for mRNA-1273 after a mean of 36 days from the first dose) completed their second dose with the same vaccine, and these individuals represent nearly the entirety of our cohort. We believe that in the context of adverse events such as mortality it is appropriate to start follow-up with the first exposure. Moreover, limiting the analysis to individuals who completed two doses could introduce confounding related to differences between one-dose and two-dose vaccine recipients (for example, individuals who received only a single dose may have experienced more severe adverse reactions and subsequently chosen not to receive a second dose). Regarding booster doses, patients who received a booster dose had to wait at least 6 months after the second dose, per CDC guidelines.[21] By inspecting the 12-month Kaplan-Meier curves presented in Figure 2, it is apparent that the study findings remain valid for a 7-month follow-up window (6 months plus the 21- to 28-day minimum waiting period between a first and second dose). Moreover, the proportion of individuals in our cohort who received a third dose within 6 months of their initial dose was small at 1.3%, and likely represents individuals for whom the CDC recommended an "additional" primary series dose due to co protective immune response.[22]

Potential protective effect of the Moderna mRNA-1273 vaccines. The observed difference in the 12-month mortality risk between the Pfizer BNT162b2 and Moderna mRNA-1273 cohorts could be potentially attributed to improved protection from SARS-CoV-2 infections and subsequent severe outcomes (e.g., hospitalization). There are known potential sequela of infections and especially COVID-19 hospitalization that in some cases could lead to death from a non-COVID-19 causes. The sensitivity

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analysis that considered COVID-19 death as any death that occurred after confirmed SARS-CoV-2 infections post first dose of vaccination suggests that protection against documented SARS-CoV-2 infections may provide only a partial explanation of the findings. While this study and others found that mRNA-1273 was more effective than BNT162b2 for COVID-19-related outcomes, it is important to note that other recent studies have found the vaccines to have similar effectiveness.[23, 24] However, potentially increased effectiveness of mRNA-1273 could explain both early and late separation in the curves of COVID-19 mortality. These time points may correspond to periods of higher community incidence of SARS-CoV-2 infections, specifically with respect to the Alpha variant at the end of 2020 and the Delta variant in the summer of 2021.

Different non-specific effects of Pfizer BNT162b2 and Moderna mRNA-1273 vaccines. The biological mechanisms that may explain a potential difference in overall health outcomes after vaccination with BNT162b2 versus mRNA-1273 are still unclear. Prior studies that compared non-specific effects of vaccines included vaccines that were based on different technologies, for example live and inactivated vaccines. Notably, this study considers two vaccines that are based on similar technology, and consequently, potentially hypothesized mechanisms are likely to be more nuanced. The two vaccines include different quantities of mRNA but there are also differences in the mRNA sequences, quality control of the manufacturing process, delivery systems including type and quantity of lipid nanoparticles, temperature storage requirements, and schedule for administration, in terms of time between the first and second dose.[25, 26] There may also be differences related to biodistribution and other pharmacokinetic and

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pharmacodynamic aspects of the vaccines. To the best of our knowledge, while more recent versions of the mRNA COVID-19 vaccines have been updated to target new virus variants, other vaccine ingredients—including the lipid nanoparticles, salts, and acids used in their formulation—have not changed since the initial series.[27, 28] However, it is important to note that our findings do not inform the comparative safety of newer versions of the mRNA COVID-19 vaccines.

Comparison to existing literature. Several prior studies compared different outcome endpoints between recipients of the BNT162b2 and mRNA-1273 vaccines. Three studies based on data from the U.S. Veterans Affairs system are the most closely related to the current study because they also used matching between BNT162b2 and mRNA-1273 recipients. The first of these studies compared COVID-19-related outcomes including infection, hospitalization, admission to the intensive care unit and death.[14] It conducted up to 6-month follow-up on a matched cohort that included 219,842 individuals in each cohort after administration of the first vaccine dose. The matching was conducted based on calendar date (five-day bins), age (five-year bins), race, urbanicity of residence and coarse geographical region. The results showed that BNT162b2 recipients were at higher risk of documented SARS-CoV-2 infection, as well as COVID-19 hospitalization, although the difference in COVID-19 deaths was relatively small (0.02 per 1000 persons over 24 weeks). One of the negative control outcomes used in this study was non-COVID-19 deaths, for which the study did not find differences. A second study, also focused on COVID-19 outcomes, had similar results using Veterans Affairs and Medicare data, and applied a more nuanced matching scheme to match 902,235 BNT162b2 recipients with 656,736 mRNA-1273

recipients.[29] An important finding of this analysis is that the difference between the BNT162b2 and mRNA-1273 cohorts increased with time, which is consistent with the finding of the current study with respect to COVID-19 deaths.

The third of these studies used a similar one-to-one matching method to conduct 266-day follow-up of multiple adverse event outcomes experienced after vaccination.[13] It showed that BNT162b2 recipients were at a higher risk for several cardiovascular-related outcomes, such as myocardial infraction, ischemic stroke, thromboembolic disease, and myocarditis. Consistent with the studies from the Veterans Affairs, the current study detected increased cardiovascular mortality among recipients of the Pfizer-BioNTech's BNT162b2 compared to Mod

Regarding myocarditis and pericarditis, the comparative effect of BNT162b2 versus mRNA-1273 on disease incidence and subsequent cardiac mortality is unclear. Generally, studies point toward higher risk o mRNA-1273 than Pfizer-BioNTech's [30, 31] However, the Dickerman et al study reported a higher incidence of myocarditis among recipients of BNT162b2.[13] Nonetheless, a broader concern is the limited examination of subclinical myocarditis or elevated cardiac troponin, which has been demonstrated to occur after mRNA COVID-19 vaccination at considerably higher rates than clinical myocarditis.[32, 33] Overall, we identified 5 deaths in the matched cohort with a primary cause of death of myocarditis or pericarditis, but other deaths attributable to acute cardiac arrythmia or sudden cardiac death with an underlying cause of subclinical myocarditis would not be identified in the absence of autopsy, which is uncommonly performed.

Limitations. Because the current study did not include an unvaccinated comparator cohort, conclusive interpretability of the findings is limited, as they may represent a higher rate of non-specific harm associated with BNT162b2 or a higher rate of non-specific benefit associated with mRNA-1273. However, the sensitivity analysis that considered only deaths that occurred without prior documented infection suggests that if such a mechanism exists, it would have to involve a highly nontrivial impact of asymptomatic infections.

Like any observational study, there is always a concern regarding the existence of unobserved confounding that could bias the results, such as differences in unobserved health-seeking behaviors or clinical status. The study would be strengthened by linking to claims data or electronic health records, which could provide details about risk factors such as smoking, obesity, and comorbidities, but these data were not available. Matching also necessarily reduced the size of the studied population, particularly because of the large number of characteristics used to match. It is therefore possible that, similar to clinical trials and cohort studies using matching procedures, the findings may not generalize to segments of the excluded population. While it is possible that the results are generalizable outside of Florida, particularly due to their general congruence with findings from Dickerman et al which assessed patients in the U.S. Veterans Affairs, a conclusion cannot be reached without analysis of other U.S. state-level databases. Some of the health outcomes, such as COVID-19 deaths and cardiovascular deaths, could be subject to misclassification due to errors on death certificates. In addition, in some clinical scenarios, it may be unclear whether COVID-19 was the immediate cause of death or exacerbated an underlying condition, and some

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COVID-19 deaths may have been misclassified due to lack of testing. While misclassification would introduce error, it would not be expected to differ between recipients of BNT162b2 or mRNA-1273.

Despite these limitations, the magnitude of this analysis, rigorousness of the our findings with prior studies support Florida adults who received the BNT162b2 in late series appear to have had higher risk cardiovascular, and COVID-19 mortality compared mRNA-1273 recipients, with differences mortality primarily driven by additional suggest that COVID-19 related health outcomes should be considered when evaluating

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Ethics Approval

This study was reviewed by the Florida Department of Health institutional review board and deemed exempt as public health practice. Data were stored in secure systems in accordance with departmental and statutory regulations.

Contributor statement

RL and JL conceived and designed the study, identified the study population, and defined the outcomes, MJ and FM obtained the data. RL, JL, and FM designed the study methods. FM conducted the statistical analyses. RL and JL drafted the manuscript, which was subsequently reviewed, revised and approved by all authors. RL and JL are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: MJ, FM, and JL were supported by the Florida Department of Health and JL serves as State Surgeon General; RL was a member of the Advisory Committee on Immunization Practices (ACIP) and has a financial relationship with Bluebell Foundation/Chicago Community Trust; there are no other relationships or activities that could appear to have influenced the submitted work.

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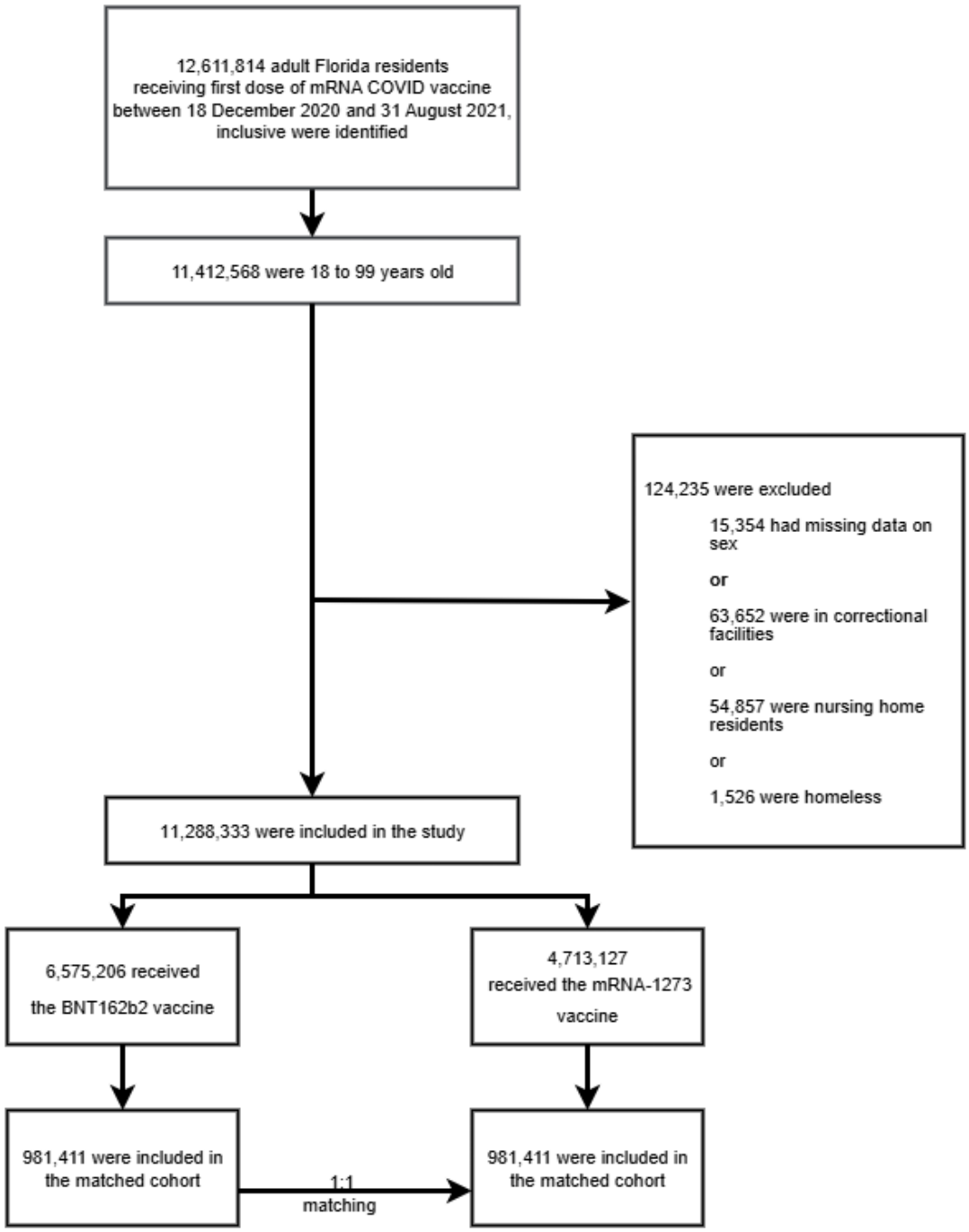
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Figure 1. Selection of participants in study

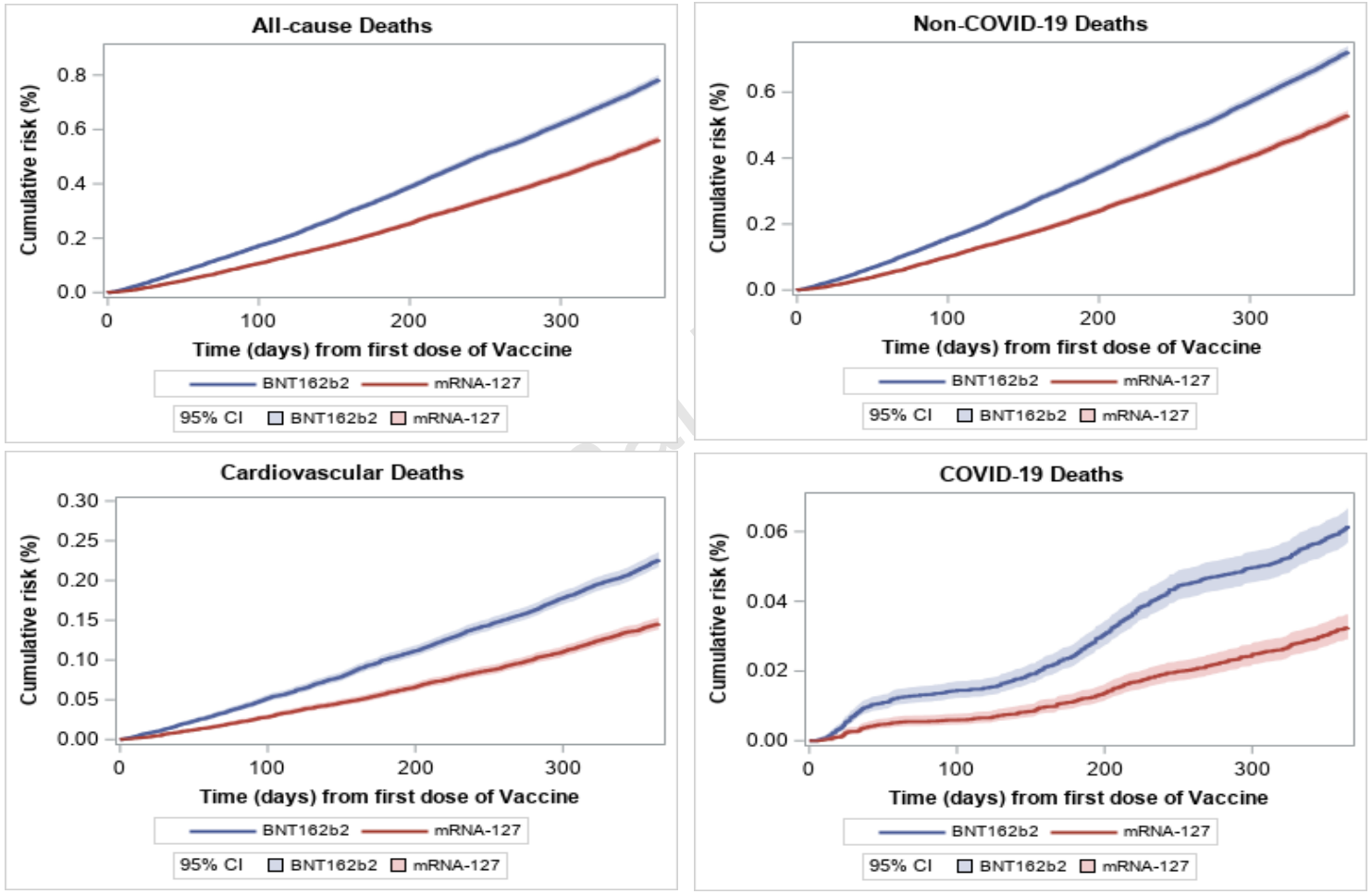


Note: The study included noninstitutionalized adult Florida residents (ages 18-99 years)

receiving a first dose of either the BNT162b2 or mRNA-1273 COVID-19 vaccine between December 18, 2020, and August 31, 2021. Absolute numbers are shown for each inclusion and exclusion criterion

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Figure 2. Cumulative incidence of all-cause, cardiovascular, COVID-19, and non-COVID-19 mortality in matched cohort.



Note: The cumulative incidence up to 365 days after the First dose of vaccine for all cause, cardiovascular, COVID-19, and non-COVID-19 are shown in the top left, top right, bottom left, and bottom right panels, respectively. Cumulative incidence was calculated using Kaplan Meier method and the follow-up ended either at the date of death or end of study observation period (365 days from first dose of vaccine). For cause-specific cumulative incidence, deaths from all other causes were censored at the time of death.

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Table 1. Demographic and vaccine characterist

Variables	Full cohort				Matched cohort			
	BNT162b2 N (%)	mRNA-1273 N (%)	Total N (%)	Standardized Difference	BNT162b2 N (%)	mRNA-1273 N (%)	Total N (%)	Standardized Difference
Total	6,575,206 (58.3)	4,713,127 (41.8)	11,288,333		981,411 (50.0)	981,411 (50.0)	1,962,822	
Age				0.28				0.0
Median (Q1, Q3)	52 (37, 66)	60 (43, 71)	56 (39, 69)		56 (39, 67)	56 (39, 67)	56 (39, 67)	
18-39	1,906,280 (29.0)	990,032 (21.0)	2,896,312 (25.7)		246,242 (25.1)	246,242 (25.1)	492,484 (25.1)	
40-49	1,050,560 (16.0)	561,018 (11.9)	1,611,578 (14.3)		127,577 (13.0)	127,577 (13.0)	255,154 (13.0)	
50-59	1,186,370 (18.0)	777,253 (16.5)	1,963,623 (17.4)		189,474 (19.3)	189,474 (19.3)	378,948 (19.3)	
60-69	1,152,961 (17.5)	1,044,834 (22.2)	2,197,795 (19.5)		212,722 (21.7)	212,722 (21.7)	425,444 (21.7)	
70-79	844,380 (12.8)	923,425 (19.6)	1,767,805 (15.7)		153,096 (15.6)	153,096 (15.6)	306,192 (15.6)	
80+	434,655 (6.6)	416,565 (8.8)	851,220 (7.5)		52,300 (5.3)	52,300 (5.3)	104,600 (5.3)	
Sex				0.02				0.0
Female	3,578,944 (54.4)	2,514,975 (53.4)	6,093,919 (54.0)		522,702 (53.3)	522,691 (53.3)	1,045,393 (53.3)	
Male	2,996,262 (45.6)	2,198,152 (46.6)	5,194,414 (46.0)		458,709 (46.7)	458,720 (46.7)	917,429 (46.7)	
Race				0.43				0.0
Black	645,949 (9.8)	353,416 (7.5)	999,365 (8.9)		62,607 (6.4)	62,601 (6.4)	125,208 (6.4)	
Others	1,459,955 (22.2)	702,248 (14.9)	2,162,203 (19.2)		137,196 (14.0)	137,190 (14.0)	274,386 (14.0)	
Unknown	247,985 (3.8)	720,500 (15.3)	968,485 (8.6)		30,111 (3.1)	30,111 (3.1)	60,222 (3.1)	
White	4,221,317 (64.2)	2,936,963 (62.3)	7,158,280 (63.4)		751,497 (76.6)	751,509 (76.6)	1,503,006 (76.6)	
Ethnicity				0.50				0.0
Hispanic	2,056,323 (31.3)	685,958 (14.6)	2,742,281 (24.3)		194,063 (19.8)	194,067 (19.8)	388,130 (19.8)	
Not Hispanic	3,730,586 (56.7)	2,769,752 (58.8)	6,500,338 (57.6)		688,449 (70.2)	688,439 (70.2)	1,376,888 (70.2)	
Unknown	788,297 (12.0)	1,257,417 (26.7)	2,045,714 (18.1)		98,899 (10.1)	98,905 (10.1)	197,804 (10.1)	
Vaccination site				0.47				0.0

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Variables	Full cohort				Matched cohort			
	BNT162b2 N (%)	mRNA-1273 N (%)	Total N (%)	Standardized Difference	BNT162b2 N (%)	mRNA-1273 N (%)	Total N (%)	Standardized Difference
CHD OR DOH	1,049,292 (16.0)	826,335 (17.5)	1,875,627 (16.6)		115,927 (11.8)	115,927 (11.8)	231,854 (11.8)	
Doctor's clinic	1,235,108 (18.8)	469,804 (10.0)	1,704,912 (15.1)		158,314 (16.1)	158,314 (16.1)	316,628 (16.1)	
Fire Rescue Or EMS	347,376 (5.3)	104,593 (2.2)	451,969 (4.0)		16,350 (1.7)	16,350 (1.7)	32,700 (1.7)	
FQHC OR RHC OR CHC	237,351 (3.6)	186,131 (4.0)	423,482 (3.8)		13,488 (1.4)	13,488 (1.4)	26,976 (1.4)	
Hospital Clinic	446,202 (6.8)	366,792 (7.8)	812,994 (7.2)		52,674 (5.4)	52,674 (5.4)	105,348 (5.4)	
Hospital ER	42,689 (0.7)	83,983 (1.8)	126,672 (1.1)		2,945 (0.3)	2,945 (0.3)	5,890 (0.3)	
Other Pharmacies	188,232 (2.9)	556,815 (11.8)	745,047 (6.6)		40,756 (4.2)	40,756 (4.2)	81,512 (4.2)	
Others Or Misc.	388,330 (5.9)	335,533 (7.1)	723,863 (6.4)		91,400 (9.3)	91,400 (9.3)	182,800 (9.3)	
Publix, CVS, or Walgreens	2,640,626 (40.2)	1,783,141 (37.8)	4,423,767 (39.2)		489,557 (49.9)	489,557 (49.9)	979,114 (49.9)	
Month of receiving COVID-19 Vaccine Dose 1				0.28				0.0
Dec	127,641 (1.9)	118,059 (2.5)	245,700 (2.2)		9,920 (1.0)	9,920 (1.0)	19,840 (1.0)	
Jan	736,922 (11.2)	797,497 (16.9)	1,534,419 (13.6)		143,684 (14.6)	143,684 (14.6)	287,368 (14.6)	
Feb	628,580 (9.6)	648,219 (13.8)	1,276,799 (11.3)		87,037 (8.9)	87,037 (8.9)	174,074 (8.9)	
Mar	1,609,563 (24.5)	1,195,638 (25.4)	2,805,201 (24.9)		295,057 (30.1)	295,057 (30.1)	590,114 (30.1)	
Apr	1,463,665 (22.3)	900,505 (19.1)	2,364,170 (20.9)		211,246 (21.5)	211,246 (21.5)	422,492 (21.5)	
May	585,561 (8.9)	349,067 (7.4)	934,628 (8.3)		66,581 (6.8)	66,581 (6.8)	133,162 (6.8)	
Jun	359,369 (5.5)	138,060 (2.9)	497,429 (4.4)		24,830 (2.5)	24,830 (2.5)	49,660 (2.5)	
Jul	454,750 (6.9)	215,792 (4.6)	670,542 (5.9)		48,517 (4.9)	48,517 (4.9)	97,034 (4.9)	
Aug	609,155 (9.3)	350,290 (7.4)	959,445 (8.5)		94,539 (9.6)	94,539 (9.6)	189,078 (9.6)	
SVI Score								
Overall (Median (IQR))	46.9 (25.0, 71.8)	43 (20.6, 66.4)	46.3 (23.3, 69.6)	0.15	42.4 (20.3, 62.6)	42.4 (20.3, 62.6)	42.4 (20.3, 62.6)	0.0
Socioeconomic status (Median (IQR))	45.3 (22.8, 68.9)	42.9 (20.6, 65.8)	44.4 (21.8, 67.6)	0.07	41.2 (19.1, 60.5)	41.2 (19.1, 60.5)	41.2 (19.1, 60.5)	0.0

Variables	Full cohort				Matched cohort			
	BNT162b2 N (%)	mRNA-1273 N (%)	Total N (%)	Standardized Difference	BNT162b2 N (%)	mRNA-1273 N (%)	Total N (%)	Standardized Difference
Housing and transportation (Median (IQR))	47.4 (24.3, 72.5)	44.1 (21, 69.2)	47.1 (22.9, 71.8)	0.11	44.3 (20.4, 65.9)	44.3 (20.4, 65.9)	44.3 (20.4, 65.9)	0.0

Notes: Q1= 25th percentile, Q3= 75th percentile, CHD = County Health Department, DOH = Department of Health, EMS= Emergency Medical Services, Hospital ER = Hospital Emergency Room, FQHC = Federally Qualified Health Center, CHC = Community health Center, RHC = Rural Health Clinic

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Table 2. All-cause, Cardiovascular (CV), COVID-19, non-COVID-19, Suicide or Homicide, and Cancer mortality in matched and full cohorts over 12 months.

	All-causes	**Cardiovascular**	COVID-19	non-COVID-19	Suicide or Homicide	Cancer
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Full cohort	114,265 (1.01)	34,918 (0.31)	8,455 (0.07)	105,810 (0.94)	1,514 (0.01)	24,021 (0.21)
Matched cohort	13,209 (0.67)	3,639 (0.19)	921 (0.05)	12,288 (0.63)	224 (0.01)	3,204 (0.16)

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Table 3. Risk, risk difference (RD), crude and adjusted hazard ratios (HR) and rate ratios (RR) of cardiovascular, non-COVID-19, COVID-19, non-COVID-19, suicide or homicide, and cancer death in the matched cohort over 12 months.

	Matched Cohort [a] Outcome – Death					
	All cause	**Cardiovascular**	**COVID-19**	**non-COVID-19**	**Suicide or Homicide**	**Cancer**
BNT162b2 vs. mRNA-1273 N						
Crude model HR (95% CI)	1.40 (1.35, 1.44)	1.56 (1.46, 1.66)	1.90 (1.66, 2.17)	1.36 (1.32, 1.41)	1.22 (0.94, 1.59)	1.05 (0.98, 1.12)
Adjusted model [b] HR (95% CI)	1.40 (1.36, 1.45)	1.57 (1.47, 1.68)	1.91 (1.67, 2.19)	1.37 (1.32, 1.42)	1.22 (0.94, 1.59)	1.05 (0.98, 1.13)
BNT162b2 risk (per 100,000)	783.6 (766.1, 801.0)	225.6 (216.2, 235.0)	61.4 (56.5, 66.3)	722.1 (705.4, 738.9)	12.5 (10.3, 14.7)	166.9 (158.8, 175)
mRNA-1273 risk (per 100,000)	562.4 (547.6, 577.1)	145.2 (137.7, 152.7)	32.4 (28.8, 36.0)	530.0 (515.6, 544.3)	10.3 (8.3, 12.3)	159.6 (151.7, 167.5)
(BNT162b2 - mRNA-1273) RD (95% CI) per 100,000	221.2 (198.3, 244.1)	80.4 (68.4, 92.4)	29.0 (23.0, 35.1)	192.2 (170.1, 214.2)	2.2 (-0.7, 5.2)	7.3 (-4, 18.6)
(BNT162b2/mRNA-1273) RR (95% CI)	1.39 (1.35, 1.44)	1.55 (1.45, 1.66)	1.90 (1.70, 2.18)	1.36 (1.32, 1.41)	1.22 (0.94, 1.58)	1.05 (0.98, 1.12)

Notes:

Risks were estimated using Kaplan Meier method and hazard ratios were estimated using Cox Proportional hazards model

[a] Matched-on age, sex, race, ethnicity, vaccination site, month of receiving vaccine dose 1 and census tract

[b] Adjusted for age, sex, race, ethnicity, vaccination site, SVI scores at census tract level, average mortality rate at zip code level (2015-2019), and month of receiving vaccine dose 1

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Table 4. COVID-19 deaths, with (COVID+) and without (non-COVID+) prior SARS-CoV-2 infection, in matched cohort

Models	Matched Cohort BNT162b2 vs. mRNA-1273 (First Dose)	
	COVID-19 Death or non-COVID-19 Death after prior SARS-CoV-2 infection HR (95% CI)	**Non-COVID-19 Death with no prior SARS-CoV-2 infection HR (95% CI)**
Unadjusted model	1.86 (1.68, 2.06)	1.34 (1.29, 1.39)
Adjusted model [b]	1.88 (1.70, 2.08)	1.35 (1.30, 1.40)
Adjusted Model by Age [b]		
18-39	1.92 (0.95, 3.85)	1.31 (1.02, 1.68)
40-59	1.34 (1.01, 1.78)	1.13 (1.01, 1.26)
60+	1.98 (1.77, 2.21)	1.38 (1.33, 1.44)
BNT162b2 risk (per 100,000)	108.5 (102.0, 115.0)	675.0 (658.8, 691.2)
mRNA-1273 risk (per 100,000)	58.3 (53.5, 63.1)	504.1 (490.1, 518.1)
(BNT162b2 - mRNA-1273) RD (95% CI) per 100,000	50.2 (42.2, 58.3)	171.0 (149.6, 192.4)
(BNT162b2/mRNA-1273) RR (95% CI)	1.86 (1.68, 2.06)	1.34 (1.29, 1.39)
Notes:		
a Matched-on age, sex, race, ethnicity, vaccination site, month of receiving vaccine dose 1 and census tract		
b Adjusted for age, sex, race, ethnicity, vaccination site, SVI scores at census tract level, average mortality rate at zip code level (2015-2019) , and month of receiving vaccine dose 1		

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: MJ, FM, and JL were supported by the Florida Department of Health and JL serves as State Surgeon General; RL was a member of the Advisory Committee on Immunization Practices (ACIP) and has a financial relationship with Bluebell Foundation/Chicago Community Trust; there are no other relationships or activities that could appear to have influenced the submitted work.

'This paper has been uploaded to Medrxiv as a preprint: https://www.medrxiv.org/content/10.1101/2025.04.25.25326460v2

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