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Temporal patterns of all-cause mortality among U.S. nursing home residents across COVID-19 vaccination strata, May 2022–June 2023

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ABSTRACT

Background: Most research on COVID-19 vaccine safety and efficacy has focused on working-age adults and disease-specific outcomes, with limited evidence concerning impacts on overall mortality in the elderly. This clinical-epidemiological study examines all-cause mortality in U.S. long-term-care facilities, addressing a critical gap in understanding the associations between COVID-19 vaccination and total mortality among frail residents.

Methods: We analyzed publicly available facility-level Medicare data from 15,022 nursing homes, reported weekly to the U.S. Centers for Disease Control from May 2022 to June 2023, including residents' all-cause deaths and SARS-CoV-2 test results stratified by vaccination status. We modeled mortality relative to COVID-19-positive case counts using mixed Poisson regression adjusted for time-invariant and -varying confounders. Lagged and reverse-lagged models examined and validated temporal directionality.

Results: All-cause mortality rates rose during weeks with more COVID-19-positive residents. Relative to unvaccinated residents, mortality elevations persisted for about three weeks in partially vaccinated and five weeks in fully vaccinated groups. Asymmetry between forward- and reverse-lag models suggested that mortality followed rather than preceded infection peaks.

Conclusions: These findings demonstrate time-linked mortality associations consistent with patterns seen in other population-level datasets and warrant individual-level investigation into potential mechanisms and clinical determinants.

Keywords: nursing homes, aged, SARS-CoV-2, vaccine efficacy, all-cause mortality.

Introduction

In early 2020, the World Health Organization declared COVID-19 a public health emergency of international concern[1]. In response, the United States and many other countries launched mass vaccination campaigns that prioritized older individuals because of their high vulnerability to infectious diseases. However, frail older individuals with multiple comorbidities—whose immunosenescence often results in sub-optimal responses to both infection and vaccination—were under-represented in registration trials. Consequently, a substantial knowledge gap persists regarding real-world health outcomes in this group[2-4]. The present study addresses this gap by examining mortality among nursing-home residents, a population characterized by a high prevalence of age-related conditions that predict both impaired resistance to SARS-CoV-2 infection and a weakened immune response to vaccination[5].

The CDC's National Healthcare Safety Network, in partnership with the Centers for Medicare & Medicaid Services, maintained a nationwide registry that publicly reported weekly COVID-19 and mortality rates among residents in U.S. nursing homes[6]. Such national surveillance data enable monitoring of mortality among older persons. While vulnerable to ecologic bias[7-9], reduction of such bias can be achieved if attention is paid to the longitudinal ordering of time-varying confounding factors[10], an approach that can offer insights when individual data remain largely inaccessible.

The concept of evaluating vaccines by their impact on all-cause mortality rather than disease-specific outcomes is supported by decades of population-based research, showing that vaccines may exert non-specific effects on overall health, beneficial for some live vaccines but potentially adverse for certain non-live formulations[11]. Since COVID-19 mRNA vaccines fall into the latter category and were not evaluated for their effect on total mortality, and since a meta-analysis of phase 3 trials showed divergent mortality of mRNA (non-live) versus adenovector (live) vaccines, with a relative risk for mRNA at 1.03 (0.63–1.71) vs 0.37 (0.19–0.70) for adenovector ($p = 0.015$)[12], the present study aimed at assessing associations between SARS-CoV-2 infection counts and all-cause mortality among nursing-home residents during the 2022–2023 period, when mRNA vaccines accounted for over 98% of all COVID-19 vaccinations administered nationwide[13]. In doing so, we respond to previously articulated calls for system-level surveillance of older populations[4], using methods suitable for ongoing population monitoring.

Methods

DESIGN, SAMPLE AND SETTING

We performed a longitudinal facility-level analysis using publicly available weekly data of population-level mortality across more than 15,000 U.S. nursing homes. The "Nursing Home COVID-19 Public File" is a registry that includes data reported by Medicare/Medicaid Certified Long Term Care facilities (i.e. nursing homes) to the CDC's National Healthcare Safety Network's Long Term Care Facility COVID-19 Module titled "Surveillance Reporting Pathways and COVID-19 Vaccinations". Each record represents one nursing-home week containing incidence and prevalence of several COVID-19-related and vaccination-related variables, gathered from the end of May 2022 through June 2023, a period covering the fourth vaccination round, which was authorized for older people two months before[14], and is referred to in the data set as "second booster administration". At that time, most vaccinated residents had received ancestral (monovalent) or—since September 2022 onward—bivalent BA.4/BA.5-targeted mRNA formulations, while circulating variants were by late 2022 and into early 2023 increasingly XBB and recombinant Omicron sublineages. As a publicly available data file, no ethical approval is required for analysis.

VARIABLES AND MEASUREMENT

The *outcome* variable of this study, "weekly all-cause death counts" (residents dying either in the facility or elsewhere), was collected as the weekly number of residents who died in the facility or at another location as reported by each facility. The *exposure* consisted of weekly counts of residents with Polymerase Chain Reaction-confirmed SARS-CoV-2 infection, stratified by vaccination status (fully, partially, unvaccinated). Vaccination status was based on the following CDC criteria: 1) those who were up-to-date with COVID-19 vaccinations were classified as fully vaccinated (i.e. COVID-19-

positive residents who had received a second booster ≥ 14 days after the first booster); 2) those individuals not up-to-date with the COVID-19 vaccination schedule were considered partially vaccinated (≤ 13 days after most recent dose); and 3) those unvaccinated (no doses or < 14 days since first dose).

In addition to tracking the weekly percentage of residents by vaccination status for descriptive analysis, we also recorded the weekly number of occupied beds. The following time-varying confounders reported on a weekly basis were considered: the number of admissions with COVID-19 into the nursing home, the percentage of completely vaccinated residents, the number of personnel with a confirmed positive COVID-19 test, and staff shortages.

We used county-level socio-demographic and geographic variables as time-invariant confounders, specifically the county's latitude and the percentage of residents identifying as white (a proxy for broader socioeconomic characteristics)[15]. We further mitigated potential unmeasured confounding through baseline mortality adjustment using monthly county death counts from 2020 (as a reference year reflecting the pre-intervention baseline)[16].

STATISTICAL ANALYSES

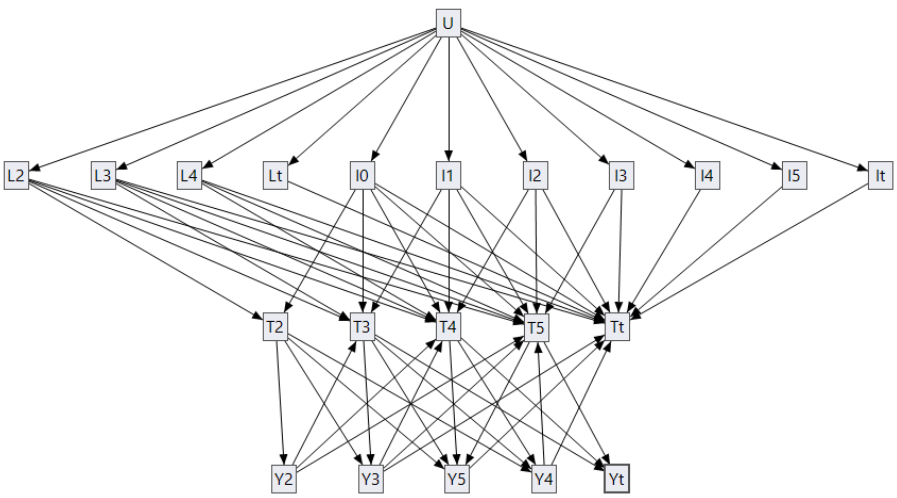
We fit mixed Poisson regression models for facility-week mortality counts as a function of vaccination-specific COVID-19 positivity, using robust inference. Weekly repeated measures were implicitly nested within centers, with random intercepts for centers added to account for baseline facility heterogeneity. Quadratic terms were included if the main effect was statistically significant.

Time-invariant and time-varying confounders were balanced by generalized propensity scores and their squared term,[17] an established alternative to inverse probability weighting with similar bias-reduction performance in longitudinal data.[18,19] Generalized propensity scores values for each week were generated from models incorporating confounders of concurrent and four preceding weeks (including vaccination numbers and mortality history).

Lagged associations (1 to 6 weeks) between infection and mortality were tested with sequential models. We made the models nested, meaning that preceding lags were kept when fitting a further lag, so that incremental effects could be estimated. Equivalent reverse-lag ('falsification') models evaluated residual confounding by examining whether associations persisted when temporal order was inverted.

Figure 1 represents a directed acyclic graph that guided us in the modeling. This figure illustrates potential sources of confounding in the association between COVID 19 test positivity (T) and weekly mortality (Y). Injection status (I) is indirectly measured through its stratified assessment by T; time varying and invariant confounders (L) were adjusted for explicitly, whereas unmeasured U represents potential residual bias. Feedback between T and Y was modeled up to 4 weeks apart.

Figure 1: Directed acyclic graph representing model assumptions



Technical algorithms with variable construction and annotated SAS code are provided in the appendix to allow methodological transparency. Because the U.S. nursing-home dataset previously hosted by CMS is no longer publicly accessible, a reproducible analytic excerpt of the data is archived at the Zenodo research repository.

Results

DESCRIPTIVE STATISTICS

From June 1st 2022 on, the nursing home file contained 15,022 long-term care providers, followed-up for a median of 53 weeks (table 1) and representing jointly approximately 1.21 million residents. Across all weeks, the mean percentage of residents reported as vaccinated against COVID-19 was 88.2%, and 11.8% were unvaccinated. At any given week the mean number of residents who tested positive for SARS-CoV-2 was 0.59 among the partially vaccinated, 0.08 among the fully vaccinated and 0.10 among the unvaccinated. In comparison, the distribution of positive tests by vaccination category indicates that ≈ 13% of unvaccinated tested positive [0.10/(0.10+0.08+0.59)], consistent with the overall unvaccinated proportion (11.8%).

Table 1: Sample characteristics U.S. Nursing Homes, May 2022 to June 2023

Variable	N	Mean (SD)	Median (IQR)	Range	Total
Number of measurements per nursing home (active reporting weeks per facility)	15,022	51.79 (4.84)	53.00 (1.00)	0-53	793013
Number of occupied beds	15,022	80.41 (50.07)	73.00 (52.00)	6-1060	/
Number of total deaths	15,022	17.76 (20.05)	14.00 (23.00)	0-521	281817
Weekly death rate per 100 occupied beds per facility	15,018	0.48 (0.48)	0.41 (0.60)	0-13.40	/
Percentage of residents vaccinated/not vaccinated at any time					
- vaccinated	793,013	88.16 (9.78)	90.14 (11.89)	9.80-100	/
- not vaccinated	793,013	11.79 (9.79)	9.80 (12.06)	0-90.20	/
Number of positive COVID-19 cases by vaccination status at any time					
- partially vaccinated	793,013	0.59 (2.61)	0 (3.42)	0-136.36	6828
- fully vaccinated	793,013	0.08 (0.75)	0 (0)	0-33.33	877
- unvaccinated	793,013	0.10 (0.63)	0 (0)	0-33.33	1253

Notes. SD = standard deviation; IQR = interquartile range. Totals (right column) represent counts aggregated over all nursing homes

MODEL ESTIMATES

Table 2 shows adjusted model predictions of all-cause mortality as a function of the number of positive COVID-19 tests. When no infections were reported, the model intercept indicated a weekly mortality rate of 0.27% per 100 residents (about one death every 3-4 weeks in a 100-resident-sized nursing home). During weeks with COVID-19-positive residents, mortality rose by ≈ 2.2% for each additional positive case regardless of vaccination status, with a slight effect plateauing at higher counts as reflected by significant quadratic terms. Among unvaccinated residents, increased mortality was detectable only in the week of infection and returned to baseline afterwards. Among partially vaccinated residents, elevated mortality persisted for three weeks, and among fully vaccinated residents for five weeks.

Reverse-lag ("falsification") analyses yielded only concurrent but no associations between past mortality and later COVID-19 positivity. Unadjusted analyses are added in table 3 for comparison.

Table 2: Adjusted forward and reverse prediction of weekly mortality counts by number of positive COVID-19 positive residents, stratified by vaccination status

Adjusted incidence rate ratios (95% CI)	Concurrent	Week 2	Week 3	Week 4	Week 5	Week 6
Forward prediction						
# fully vaccinated	*1.0204 (1.0144-1.0264)*	*1.0218 (1.0165-1.0272)*	*1.0192 (1.0141-1.0243)*	*1.0129 (1.0076-1.0182)*	*1.0071 (1.0016-1.0125)*	1.0052 (0.9993-1.0111)
# partially vaccinated	*1.0220 (1.0160-1.0281)*	*1.0249 (1.0181-1.0317)*	*1.0088 (1.0029-1.0147)*	1.0014 (0.9978-1.0051)	1.0037 (0.9999-1.0076)	0.9993 (0.9957-1.0028)
# unvaccinated	*1.0231 (1.0027-1.0439)*	1.0104 (0.9992-1.0217)	1.0078 (0.9961-1.0197)	1.0031 (0.9928-1.0136)	1.0003 (0.9914-1.0093)	0.9989 (0.9896-1.0083)
# fully vaccinated²	*0.9994 (0.9991-0.9997)*	*0.9995 (0.9992-0.9997)*	*0.9996 (0.9993-0.9998)*	*0.9995 (0.9993-0.9998)*	1.0000 (0.9997-1.0002)	1.0000 (0.9997-1.0003)
# partially vaccinated²	*0.9997 (0.9994-1.0000)*	*0.9994 (0.9990-0.9998)*	0.9999 (0.9996-1.0002)			
# unvaccinated²	0.9987 (0.9958-1.0016)	0.9998 (0.9989-1.0007)				
N facilities (records)	14463 (644189)	14463 (644189)	14463 (644189)	14463 (644189)	14463 (644189)	14458 (628273)
Pearson χ^2/DF (model fit)	0.99	0.99	0.99	0.99	0.99	0.98
Reverse prediction (validation)						
# fully vaccinated	*1.0188 (1.0131-1.0245)*	0.9967 (0.9916-1.0019)				
# partially vaccinated	*1.0192 (1.0130-1.0255)*	0.9938 (0.9876-1.0001)				
# unvaccinated	*1.0209 (1.0030-1.0392)*	0.9961 (0.9874-1.0049)				
# fully vaccinated²	*0.9995 (0.9992-0.9998)*	1.0001 (0.9997-1.0002)				
# partially vaccinated²	0.9997 (0.9995-1.0000)	0.9999 (0.9996-1.0002)				
# unvaccinated²	0.9991 (0.9968-1.0014)					
N facilities (records)	14466 (644137)	14466 (644137)				
Pearson χ^2/DF (model fit)	0.99	0.99				

Notes. Incidence-rate ratios (IRR) represent the multiplicative change in expected weekly death counts per resident for each additional resident testing SARS-CoV-2 positive in the same facility. The intercept of these models corresponds to a baseline weekly mortality of 0.0027 per occupied bed (= 0.27 per 100 residents). An IRR of 1.02 indicates a 2 % increase above baseline. Forward models estimate mortality up to 6 weeks after infection; reverse models test for residual confounding by predicting mortality backwards in time. All models include generalized propensity scores (GPS, GPS²) and facility random intercepts; only statistically quadratic terms of significant main effects are included. Subsequent models incorporated lags cumulatively (e.g., week 4 model contains Weeks 1–4 predictors).

Table 3: Unadjusted forward and reverse prediction of weekly mortality counts by number of positive COVID-19 positive residents, stratified by vaccination status

Unadjusted incidence rate ratios (95% CI)	Concurrent	Week 2	Week 3	Week 4	Week 5	Week 6
Forward prediction						
# fully vaccinated	*1.0252 (1.0196-1.0307)*	*1.0318 (1.0267-1.0370)*	*1.0303 (1.0253-1.0353)*	*1.0232 (1.0183-1.0281)*	*1.0098 (1.0050-1.0147)*	*1.0056 (1.0007-1.0105)*
# partially vaccinated	*1.0285 (1.0227-1.0343)*	*1.0361 (1.0300-1.0423)*	*1.0263 (1.0205-1.0321)*	*1.0131 (1.0079-1.0183)*	*1.0007 (1.0023-1.0118)*	1.0003 (0.9970-1.0037)
# unvaccinated	*1.0297 (1.0096-1.0502)*	*1.0259 (1.0139-1.0381)*	*1.0118 (0.9958-1.2081)*	*1.0058 (0.9948-1.0170)*	*1.0009 (0.9926-1.0092)*	*1.0007 (0.9920-1.0095)*
# fully vaccinated²	*0.9992 (0.9989-0.9995)*	*0.9991 (0.9988-0.9994)*	*0.9992 (0.9989-0.9995)*	*0.9992 (0.9989-0.9995)*	0.9999 (0.9996-1.0001)	1.0000 (0.9997-1.0002)
# partially vaccinated²	*0.9994 (0.9991-0.9997)*	*0.9992 (0.9988-0.9996)*	*0.9996 (0.9993-0.9999)*	0.9997 (0.9995-1.0000)	0.9999 (0.9996-1.0001)	
# unvaccinated²	0.9984 (0.9955-1.0012)	0.9990 (0.9977-1.0002)	1.0002 (0.9981-1.0024)			
N facilities (records)	15017 (775713)	15008 (760696)	14998 (745688)	14984 (730690)	14983 (715703)	14977 (700720)
Pearson χ^2/DF (model fit)	1.01	1.01	1.01	1.01	1.01	1.00
Reverse prediction (validation)						
# fully vaccinated	*1.0252 (1.0196-1.0307)*	*1.0131 (1.0079-1.0183)*	1.0023 (0.9971-1.0076)			
# partially vaccinated	*1.0285 (1.0227-1.0343)*	*1.0099 (1.0045-1.0154)*	1.0002 (0.9946-1.0059)			
# unvaccinated	*1.0297 (1.0096-1.0502)*	1.0018 (0.9936-1.0100)	1.0005 (0.9960-1.0141)			
# fully vaccinated²	*0.9992 (0.9989-0.9995)*	*0.9994 (0.9991-0.9997)*				
# partially vaccinated²	*0.9994 (0.9991-0.9997)*	*0.9995 (0.9992-0.9998)*				
# unvaccinated²	0.9984 (0.9955-1.0012)					
N facilities (records)	15017 (775713)	15008 (760696)	14998 (745688)			
Pearson χ^2/DF (model fit)	1.01	1.02	1.01			

Note: the baseline weekly mortality is 0.0027 per occupied bed (= 0.27 per 100 residents)

Discussion

In this longitudinal, facility-level analysis of approximately 15,000 U.S. nursing homes, we observed temporal associations between weeks with reported COVID-19 positivity among residents and increased all-cause mortality. The facility-level mortality rate rose in parallel with incident infections, even after adjustment for time-varying confounders and baseline mortality differences. Notably, the persistence of elevated mortality differed by vaccination status, which normalized after one week in unvaccinated residents, but remained through approximately five weeks post-infection among fully vaccinated residents.

Reverse-lag validation showed no substantial evidence of remaining confounding influences. However, our capacity to control for confounders was limited to temporal variation within facilities, whereas differences between vaccine-status groups could not be fully addressed. For this reason, we mapped possible biases likely to influence such comparative patterns.

First, facility vaccination campaigns typically prioritized more frail and comorbid residents, producing an *indicator bias* whereby those at greatest baseline risk of death could be overrepresented among fully vaccinated categories. Conversely, relatively healthier residents who remained unvaccinated or deferred additional doses form a positively selected reference group, attenuate apparent mortality among the unvaccinated[20]. This bias was described for the primary COVID-19 vaccine series, although subsided with the boosters[21].

Second, a *healthy-vaccinee bias* is also possible, because residents judged too frail or terminal could be excluded from vaccination, whereas comparatively healthier individuals continued to receive booster doses[20]. If present, as has been suspected in some nursing-home studies[22], it would tend to reduce observed mortality among vaccinated residents, thereby diminishing the true group contrasts.

Third, classification practices introduced inherent timing biases: in the dataset, residents moved from "partially" to "fully" vaccinated status only ≥ 14 days after the last dose, creating a brief *immortal-time window* in which recent recipients cannot be coded as vaccinated despite elevated short-term vulnerability, thereby lowering mortality numbers among vaccinated[23].

Fourth, a further source of attenuation is *measurement error* in infection counts, reflected by the consistent higher-order (curvilinear) terms in our models. The Polymerase Chain Reaction protocols had limited positive predictive value, particularly under low-prevalence conditions[24,25], meaning that the practice of mass testing even in the absence of overt clinical infections, undoubtedly contributed to false positive infections, likely diluting true associations to mortality.

Relation to Previous Work

Evidence from epidemiological studies provides a broader context for interpreting our findings. Comparisons across nursing-home cohorts, population-wide surveillance, and individual-level evaluations help situate the mortality patterns observed here within the continuum of COVID-19 vaccine research.

OTHER NURSING-HOME AND ELDERLY COHORT STUDIES

Observational studies in older or institutionalized populations have consistently noted that the protection conferred by mRNA vaccination wanes rapidly—within weeks in many analyses—and that this decline is most pronounced among residents of long-term-care facilities[26,27]. Other studies not only report declining but negative effectiveness. In the United Kingdom, a nursing-home study using a machine-learning-based causal-inference framework on a dataset comparable to ours, reported that higher vaccination coverage was accompanied by elevations in all-cause mortality[28]. Similar patterns have been documented in meta-analyses and national registries showing that, despite high vaccine uptake compared to younger adults, those ≥ 80 years old carry greater post-booster risk of severe or fatal outcomes[29-31]. Individual-level data from Dutch nursing homes further demonstrated recurrent waves of excess mortality among residents aged 85–95 years—particularly toward the end of 2021—when vaccination coverage was near-universal[32]. Taken together, these reports describe mortality trajectories within elderly or institutionalized populations that resemble the temporal extensions observed in our analysis.

POPULATION-LEVEL AND EXCESS- MORTALITY ANALYSES

Population-level surveillance also provides complementary evidence to the nursing-home data. Across Europe and Asia, 2021–23 excess-mortality patterns paralleled vaccination phases, and showed a lingering population-wide vulnerability despite declining vaccination activity in 2023[33]. In northern Europe, mortality began rising in mid-2021 and remained above expected values through spring 2022[34], with EuroMOMO data indicating that the sharpest increases occurred among individuals > 80 years[35], a pattern that is also documented in Germany[36,37]. Japan showed a reversal of its pre-pandemic downward mortality trend from 2021 onward, particularly among people over 70 years old[38,39]. Together, these findings portray a recurring pattern of post-pandemic mortality exceeding baseline expectations, aligning with the temporal extensions in all-cause mortality observed within our long-term-care cohort.

INDIVIDUAL-LEVEL STUDY DESIGNS AND THEIR LIMITATIONS

To address recognized weaknesses of bias in aggregated-level and conventional observational analyses, several groups have evaluated vaccine effectiveness using individual-level frameworks such as target-trial emulations, which extending the logic of causal inference beyond what could be achieved by pairing vaccinated individuals with unvaccinated comparators, all under assumptions mimicking randomization[40]. Target-trial emulations in large health-system cohorts of mainly elderly individuals have reported absent or steadily declining protection estimates with extended follow-up, sometimes turning negative for overall mortality, while early positive effects often appear within days of vaccination before protection is supposed to kick in[41-44], suggestive of residual healthy-vaccinee bias rather than biological protection[40,45]. These considerations illustrate that current setups of individual-level designs do not necessarily provide the protection against bias often assumed. Our aggregated longitudinal approach monitoring population-level temporal dynamics can help to understand the full spectrum of vaccine-related outcomes.

PREVALENCES OF ADVERSE EVENTS IN OLDER ADULTS

Adverse-event surveillance studies and large population databases have documented increased reporting of serious and moderate clinical events following administration of COVID-19 mRNA vaccines, particularly among older individuals[46,47]. Across pharmacovigilance systems, signal analyses have described higher incidence ratios for arrhythmias, thromboembolic phenomena, and certain cardiovascular or coagulation disorders compared with reference vaccines such as influenza formulations. Other cohort and registry studies have identified associations with myo-/pericarditis, myocardial infarction, pulmonary embolism, and cerebrovascular events—including intracranial hemorrhage and thrombocytopenic syndromes—as well as immune-mediated conditions such as Guillain–Barré syndrome[48-51]. Autopsy reports have occasionally attributed myocarditis-related deaths with vaccination due to temporal proximity, though such occurrences remain rare in absolute terms[52]. Collectively, published evidence indicates that severe or life-threatening outcomes are disproportionately represented among adults ≥ 65 years, with the very elderly experiencing the greatest rates of hospitalization and cardiovascular complications[53-58].

Biological plausibility

Our analysis cannot establish direct biological mechanisms; nonetheless, prior research offers plausible pathways through which repeated mRNA vaccinations and SARS-CoV-2 infection might intersect with health outcomes in older adults[59]. Studies have described transient systemic inflammation, endothelial activation, and thrombotic changes following spike-protein exposure or mRNA vaccination, particularly among individuals with pre-existing cardiovascular risk factors[60,61]. Independent investigations have documented shifts in antibody subclass distribution and immune-regulatory signaling that may occasionally be associated with autoimmune or inflammatory phenomena[62,63], observations that fit within the well-characterized processes of immunosenescence and “inflammaging”, in which age-related decline in innate and adaptive immunity, chronic low-grade inflammation, and multimorbidity heighten susceptibility to vascular and metabolic stress[3,53,54,64].

In addition, possible non-specific effects of non-live formulations may influence the immune system in ways that extend beyond protection

against a target pathogen, sometimes affecting overall mortality and susceptibility to unrelated diseases[11,12]. Such observations call for parallel inquiry into the biological mechanisms that could generate these cross-systemic outcomes. In line with this reasoning, emerging immunologic studies have explored how repeated mRNA vaccination and breakthrough infection might modulate immune pathways. Hybrid immunity — from infection preceding vaccination — tends to generate broadly neutralizing antibodies, whereas infection soon after vaccination can elicit lower-affinity immature IgG responses that may transiently enhance inflammatory reactions through immune-escaping variants[65,66]. Repeated exposure to the spike antigen has also been associated with a class-switch toward the IgG4 antibodies and corresponding modulation of immune tolerance[61,67]. Potential links to autoimmune responses have been suggested through adjuvant-induction or via structural similarity between spike peptides and select human proteins hypothesized to enable molecular mimicry[62,68,69]. Finally, several in-vitro investigations have reported impeding type I interferon signaling following mRNA vaccine exposure, an effect that could induce suppression of innate immunity[70].

While no single mechanism has been demonstrated to account for the mortality patterns observed here, collectively these findings outline biologically plausible avenues through which immune modulation might interact with infection dynamics and mortality patterns observed in institutionalized elderly populations.

Strengths and weaknesses

The main strength of this study is it analyses a comprehensive, nationally representative dataset encompassing every Medicare-certified nursing home in the United States, allowing for longitudinal observation across more than one million residents. Applying forward- and reverse-lag validation strengthens inference regarding temporal directionality and reduces the likelihood that the associations observed are artifacts of residual confounding. This work responds to previous requests for structured vaccine-safety assessment systems for older adults[4], using routinely collected surveillance in a way that is transparent and corresponds to a need for methods that surpass mere correlational research[71].

Nevertheless, important limitations merit mention. The aggregated, facility-level structure of the dataset precludes resident-level control for comorbidities, vaccination timing, or prior infection history. Potential misclassification of vaccination status and delayed updating of facility reports could attenuate true differences between strata. It needs to be noted that the analytic period, although covering the major Omicron waves and the rollout of bivalent boosters, did not include subsequent formulation updates or the post-XBB period. Results may also not fully generalize to privately run or non-Medicare-certified facilities that differ in staffing ratios, data reporting practices etc.

Conclusion

In summary, our analysis of national nursing-home surveillance data revealed consistent temporal associations between COVID-19 positivity and all-cause mortality, with the duration of elevated mortality graded according to vaccination dosage, warranting further individual-level investigation to corroborate our findings and if applicable into mechanisms and clinical determinants.

Conflict of Interest Statement:

All authors declare no conflicts of interest in this paper.

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Data availability:

Data are available at
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Appendix:

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Author contributions

KD and RW analyzed the data. KD and NM wrote and edited the original draft, with further editing by RW.; all authors reviewed the manuscript critically for important intellectual content.

References:

1. WHO. COVID-19 Public Health Emergency of International Concern. World Health Organization. Accessed 23Nov2023, https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum

2. Boretti A. mRNA vaccine boosters and impaired immune system response in immune compromised individuals: a narrative review. *Clin Exp Med*. Jan 27 2024;24(1):23. doi:10.1007/s10238-023-01264-1

3. Andryukov BG, Besednova NN. Older adults: panoramic view on the COVID-19 vaccination. *AIMS Public Health*. 2021;8(3):388-415. doi:10.3934/publichealth.2021030

4. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. *Age Ageing*. Feb 26 2021;50(2):279-283. doi:10.1093/ageing/afaa274

5. Meyers E, De Rop L, Deschepper E, et al. SARS-CoV-2 seroreversion and all-cause mortality in nursing home residents and staff post-primary course vaccination in Belgium between February and December 2021. *Vaccine*. Feb 20 2025;51:126865. doi:10.1016/j.vaccine.2025.126865

6. CMS. COVID-19 Nursing Home Data. Updated 24Jan2023. Accessed 24Oct2023, https://data.cms.gov/covid-19/covid-19-nursing-home-data

7. Robinson WS. Ecological Correlations and the Behavior of Individuals. *American Sociological Review*. 1950;15(3):351–357. doi:doi.org/10.2307/2087176

8. Chen YC, Chow-In Ko P, Lee WC, Lien WC. Ecological fallacy in COVID-19 epidemiological inference: Influenza vaccination rate as an example. *J Formos Med Assoc*. Aug 2021;120(8):1655-1656. doi:10.1016/j.jfma.2021.03.011

9. Greenland S. Ecologic Inference Problems in Studies Based on Surveillance Data. In: Brookmeyer R, Stroup DF, eds. *Monitoring the Health of Populations: Statistical Principles and Methods for Public Health Surveillance*. Oxford University Press; 2004:315-340.

10. Hernán MA, Robins JM. *Causal Inference: What If*. Chapman & Hall/CRC; 2020.

11. Benn CS. Non-specific effects of vaccines: The status and the future. *Vaccine*. Apr 2 2025;51:126884. doi:10.1016/j.vaccine.2025.126884

12. Benn CS, Schaltz-Buchholzer F, Nielsen S, Netea MG, Aaby P. Randomized clinical trials of COVID-19 vaccines: Do adenovirus-vector vaccines have beneficial non-specific effects? *iScience*. May 19 2023;26(5):106733. doi:10.1016/j.isci.2023.106733

13. Our World in Data. Official data collated by Our World in Data, "COVID-19, vaccinations (broken down by manufacturer)" [original data]. Accessed 2025Dec04, 2024. https://github.com/owid/covid-19-data/blob/master/public/data/vaccinations/vaccinations-by-manufacturer.csv

14. FDA. Coronavirus (COVID-19) Update: FDA Authorizes Second Booster Dose of Two COVID-19 Vaccines for Older and Immunocompromised Individuals. Accessed 02Feb2023, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-second-booster-dose-two-covid-19-vaccines-older-and

15. Simplemaps. United States Counties Database Updated January 24, 2025. Accessed Feb 14, 2025, https://simplemaps.com/data/us-counties

16. Kirsch S. Accessed 16Apr2025, https://github.com/skirsch/covid/blob/2ea4cfed34611a6172f5327487dc258aea91f43e/debate/ACM/all_counties_ACM_regression_analysis.xlsx

17. Imbens G, Hirano K. The Propensity Score with Continuous Treatments. In: Meng Ga, ed. *Applied Bayesian Modelling and Causal Inference from Missing Data Perspectives*. Wiley; 2004.

18. Ertefaie A, Stephens DA. Comparing approaches to causal inference for longitudinal data: inverse probability weighting versus propensity scores. *Int J Biostat*. 2010;6(2):Article 14. doi:10.2202/1557-4679.1198

19. Moodie EE, Stephens DA. Estimation of dose-response functions for longitudinal data using the generalised propensity score. *Stat Methods Med Res*. Apr 2012;21(2):149-66. doi:10.1177/0962280209340213

20. Jedlicka P. Failure to address crucial biases other than the healthy vaccinee effect. *Int J Infect Dis*. Sep 2024;146:107143. doi:10.1016/j.ijid.2024.107143

21. Westberg C, Wang H, Sambamoorthi U. Multimorbidity and COVID-19 Vaccine and Booster Uptake among Adults in the United States. *Medical Research Archives*. 2025;13(8):1-11. doi:10.18103/mra.v13i8.6837

22. Malignac M, Besseiche A, Cloppet-Fontaine A, et al. COVID-19 vaccine safety and effectiveness at 3 months in institutionalized old people. *BMC Geriatr*. Dec 23 2024;24(1):1032. doi:10.1186/s12877-024-05609-7

23. Alessandria M, Trambusti G, Malatesta GM, Polykretis P, Donzelli A. Classification bias and impact of COVID-19 vaccination on all-cause mortality: the case of the Italian region Emilia-Romagna. *Autoimmunity*. Dec 2025;58(1):2562972. doi:10.1080/08916934.2025.2562972

24. Jaafar R, Aherfi S, Wurtz N, et al. Correlation Between 3790 Quantitative Polymerase Chain Reaction-Positives Samples and Positive Cell Cultures, Including 1941 Severe Acute Respiratory Syndrome Coronavirus 2 Isolates. *Clin Infect Dis*. Jun 1 2021;72(11):e921. doi:10.1093/cid/ciaa1491

25. Gunther M, Rockenfeller R, Walach H. A calibration of nucleic acid (PCR) by antibody (IgG) tests in Germany: the course of SARS-CoV-2 infections estimated. *Front Epidemiol*. 2025;5:1592629. doi:10.3389/fepid.2025.1592629

26. Chemaitelly H, Ayoub HH, AlMukdad S, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. *Nat Commun*. Jun 2 2022;13(1):3082. doi:10.1038/s41467-022-30895-3

27. Katz MA, Cohuet S, Bino S, et al. COVID-19 vaccine effectiveness against SARS-CoV-2-confirmed hospitalisation in the eastern part of the WHO European Region (2022-2023): a test-negative case-control study from the EuroSAVE network. *Lancet Reg Health Eur*. Dec 2024;47:101095. doi:10.1016/j.lanepe.2024.101095

28. Girma S, Patton D. Using double-debiased machine learning to estimate the impact of Covid-19 vaccination on mortality and staff absences in elderly care homes. *European Economic Review*. 2024;170doi:10.1016/j.euroecorev.2024.104882

29. Adhikari B, Bednash JS, Horowitz JC, Rubinstein MP, Vlasova AN. Brief research report: impact of vaccination on antibody responses and mortality from severe COVID-19. *Front Immunol*. 2024;15:1325243. doi:10.3389/fimmu.2024.1325243

30. Otto M, Burrell AJC, Neto AS, et al. Clinical characteristics and outcomes of critically ill patients with one, two and three doses of vaccination against COVID-19 in Australia. *Intern Med J*. Mar 2023;53(3):330-338. doi:10.1111/imj.15884

31. Agrawal U, Bedston S, McCowan C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet*. Oct 15 2022;400(10360):1305-1320. doi:10.1016/S0140-6736(22)01656-7

32. Sluiskes MH, Koster EAS, Goeman JJ, Rodriguez-Girondo M, Putter H, de Wreede LC. A new framework for disentangling different components of excess mortality applied to Dutch care home residents during Covid-19. *BMC Med Res Methodol*. May 10 2025;25(1):126. doi:10.1186/s12874-025-02579-1

33. Okoro EO, Ikoba NA, Okoro BE, Akpila AS, Salihu MO. Paradoxical increase in global COVID-19 deaths with vaccination coverage: World Health Organization estimates (2020-2023). *Int J Risk Saf Med*. Apr 23 2025:924647925133661O. doi:10.1177/09246479251336610

34. Forthun I, Madsen C, Emilsson L, et al. Excess mortality in Denmark, Finland, Norway and Sweden during the COVID-19 pandemic 2020-2022. *Eur J Public Health*. Aug 1 2024;34(4):737-743. doi:10.1093/eurpub/ckae091

35. EuroMOMO. 14Sep2023. https://www.euromomo.eu/

36. Kuhbandner C, Reitzner M. Estimation of Excess Mortality in Germany During 2020-2022. *Cureus*. May 2023;15(5):e39371. doi:10.7759/cureus.39371

37. Kuhbandner C, Reitzner M. Regional patterns of excess mortality in Germany during the COVID-19 pandemic: a state-level analysis. *R Soc Open Sci*. Nov 2025;12(11):250790. doi:10.1098/rsos.250790

38. Tanaka H, Togawa K, Katanoda K. Impact of the COVID-19 pandemic on mortality trends in Japan: a reversal in 2021? A descriptive analysis of national mortality data, 1995-2021. *BMJ Open*. Aug 31 2023;13(8):e071785. doi:10.1136/bmjopen-2023-071785

39. Tanaka H, Nomura S, Katanoda K. Changes in Mortality During the COVID-19 Pandemic in Japan: Descriptive Analysis of National Health Statistics up to 2022. *J Epidemiol*. Mar 5 2025;35(3):154-159. doi:10.2188/jea.JE20240158

40. Pearce N, Cerqueira-Silva T, Vandenbroucke JP. Re: Comparison of the Test-negative Design and Cohort Design With Explicit Target Trial Emulation for Evaluating COVID-19 Vaccine

Effectiveness. *Epidemiology*. Mar 1 2025;36(2):e1. doi:10.1097/EDE.0000000000001812

41. Ioannou GN, Bohnert ASB, O'Hare AM, et al. Effectiveness of mRNA COVID-19 Vaccine Boosters Against Infection, Hospitalization, and Death: A Target Trial Emulation in the Omicron (B.1.1.529) Variant Era. *Ann Intern Med*. Dec 2022;175(12):1693-1706. doi:10.7326/M22-1856

42. Ioannou GN, Locke ER, O'Hare AM, et al. COVID-19 Vaccination Effectiveness Against Infection or Death in a National U.S. Health Care System: A Target Trial Emulation Study. *Ann Intern Med*. Mar 2022;175(3):352-361. doi:10.7326/M21-3256

43. Ioannou GN, Berry K, Rajeevan N, et al. Effectiveness of the 2023-to-2024 XBB.1.5 COVID-19 Vaccines Over Long-Term Follow-up : A Target Trial Emulation. *Ann Intern Med*. Feb 4 2025; doi:10.7326/ANNALS-24-01015

44. McConeghy KW, Hur K, Dahabreh IJ, et al. Early Mortality After the First Dose of COVID-19 Vaccination: A Target Trial Emulation. *Clin Infect Dis*. Mar 20 2024;78(3):625-632. doi:10.1093/cid/ciad604

45. Hulme WJ, Williamson E, Horne EMF, et al. Challenges in Estimating the Effectiveness of COVID-19 Vaccination Using Observational Data. *Ann Intern Med*. May 2023;176(5):685-693. doi:10.7326/M21-4269

46. Fraiman J, Erviti J, Jones M, et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. *Vaccine*. Sep 22 2022;40(40):5798-5805. doi:10.1016/j.vaccine.2022.08.036

47. Kim HJ, Suh JH, Kim MH, Choi MG, Chun EM. Broad-Spectrum Adverse Events of Special Interests Based on Immune Response Following COVID-19 Vaccination: A Large-Scale Population-Based Cohort Study. *J Clin Med*. Mar 6 2025; 14(5) doi:10.3390/jcm14051767

48. Montano D. Frequency and Associations of Adverse Reactions of COVID-19 Vaccines Reported to Pharmacovigilance Systems in the European Union and the United States. *Front Public Health*. 2021;9:756633. doi:10.3389/fpubh.2021.756633

49. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med*. Sep 16 2021; 385(12):1078-1090. doi:10.1056/NEJMoa2110475

50. Faksova K, Walsh D, Jiang Y, et al. COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. *Vaccine*. Apr 2 2024;42(9):2200-2211. doi:10.1016/j.vaccine.2024.01.100

51. Roh JH, Jung I, Suh Y, Kim MH. A potential association between COVID-19 vaccination and development of Alzheimer's disease. *QJM*. Oct 1 2024;117(10):709-716. doi:10.1093/qjmed/hcae103

52. Hulscher N, Hodkinson R, Makis W, McCullough PA. Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis. *ESC Heart Fail*. Jan 14 2024;doi:10.1002/ehf2.14680

53. Santoro A, Bientinesi E, Monti D. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? *Ageing Res Rev*. Nov 2021;71:101422. doi:10.1016/j.arr.2021.101422

54. Ciarambino T, Crispino P, Minervini G, Giordano M. COVID-19 and Frailty. *Vaccines (Basel)*. Mar 7 2023;11(3)doi:10.3390/vaccines11030606

55. Kountouras J, Gialamprinou D, Kotronis G, et al. Ofeleein i mi Vlaptin-Volume II: Immunity Following Infection or mRNA Vaccination, Drug Therapies and Non-Pharmacological Management at Post-Two Years SARS-CoV-2 Pandemic. *Medicina (Kaunas)*. Feb 17 2022;58(2)doi:10.3390/medicina58020309

56. Xiong X, Yuan J, Li M, Jiang B, Lu ZK. Age and Gender Disparities in Adverse Events Following COVID-19 Vaccination: Real-World Evidence Based on Big Data for Risk Management. *Front Med (Lausanne)*. 2021;8:700014. doi:10.3389/fmed.2021.700014

57. Li X, Ostropolets A, Makadia R, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. *BMJ*. Jun 14 2021;373:n1435. doi:10.1136/bmj.n1435

58. Botton J, Jabagi MJ, Bertrand M, et al. Risk for Myocardial Infarction, Stroke, and Pulmonary Embolism Following COVID-19 Vaccines in Adults Younger Than 75 Years in France. *Ann Intern Med*. Sep 2022;175(9):1250-1257. doi:10.7326/M22-0988

59. Mead MN, Rose J, Seneff S, et al. Compound Impacts of COVID-19 modRNA Vaccination and SARS-CoV-2 Infection: A Convergence of Diverse "Spikeopathies" and Other Hybrid Harms. Medical Research Archives, [online] 2025; 13(11) https://esmed.org/MRA/mra/article/view/7087

60. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends Mol Med*. Jul 2022;28(7): 542-554. doi:10.1016/j.molmed.2022.04.007

61. Plume J, Galvanovskis A, Smite S, Romanchikova N, Zayakin P, Line A. Early and strong antibody responses to SARS-CoV-2 predict disease severity in COVID-19 patients. *J Transl Med*. Apr 15 2022;20(1):176. doi:10.1186/s12967-022-03382-y

62. Irrgang P, Gerling J, Kocher K, et al. Class switch toward noninflammatory, spike-specific IgG4 antibodies after repeated SARS-CoV-2 mRNA vaccination. *Sci Immunol*. Jan 27 2023;8(79):eade 2798. doi:10.1126/sciimmunol.ade2798

63. Rodriguez Y, Rojas M, Beltran S, et al. Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review. *J Autoimmun*. Oct 2022; 132:102898. doi:10.1016/j.jaut.2022.102898

64. Palacios-Pedrero MA, Jansen JM, Blume C, et al. Signs of immunosenescence correlate with poor outcome of mRNA COVID-19 vaccination in older adults. *Nat Aging*. Oct 2022;2(10):896-905. doi:10.1038/s43587-022-00292-y

65. Vanden Bossche G. *The Inescapable Immune Escape Pandemic*. Pierucci Publishing; 2023.

66. Parry PI, Lefringhausen A, Turni C, et al. 'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA. *Biomedicines*. Aug 17 2023;11(8)doi:10.3390/biomedicines11082287

67. Uversky VN, Redwan EM, Makis W, Rubio-Casillas A. IgG4 Antibodies Induced by Repeated Vaccination May Generate Immune Tolerance to the SARS-CoV-2 Spike Protein. *Vaccines (Basel)*. May 17 2023;11(5)doi:10.3390/vaccines11050991

68. Rojas M, Herran M, Ramirez-Santana C, et al. Molecular mimicry and autoimmunity in the time of COVID-19. *J Autoimmun*. Sep 2023;139:103070. doi:10.1016/j.jaut.2023.103070

69. Chaufan C, Manwell L, Heredia C, McDonald J. COVID-19 vaccines and autoimmune disorders: A scoping review. *AIMS Medical Science*. 2025; 12(4):325–349. doi:10.3934/medsci.2025023

70. Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs. *Food Chem Toxicol*. Jun 2022;164:113008. doi:10.1016/j.fct.2022.113008

71. Mostert S, Hoogland M, Huibers M, Kaspers G. Excess mortality across countries in the Western World since the COVID-19 pandemic: 'Our World in Data' estimates of January 2020 to December 2022. *BMJ Public Health*. 2024;2(e000282) doi:10.1136/bmjph-2023-000282

