Infection Control & Hospital Epidemiology (2024), **45**, 393–399
doi:10.1017/ice.2023.245

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Research Brief

Longitudinal trends in 30-day mortality attributable to SARS-CoV-2 among vaccinated and unvaccinated US veteran patients

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Surveillance is a cornerstone of public health practice. Accurate monitoring of deaths and hospitalizations caused by coronavirus disease 2019 (COVID-19) is important for informing public policy responses. In 2020, COVID-19 was the third leading cause of death in the United States. As of June 2023, >1 million deaths have been attributed to severe acute respiratory coronavirus virus 2 (SARS-CoV-2).[1,2]

During the early phases of the pandemic, prior to the availability of medical countermeasures, death within a window period following a positive microbiologic test for SARS-CoV-2 had high predictive value as a surveillance tool for measuring COVID-19–attributable deaths. However, following increasing access to testing including for asymptomatic patients, acquisition of widespread immunity in the population and advances in medical therapeutic options, the attribution of a death due to COVID-19 has become more complex. Thus, we examined trends in the percentage of deaths attributable to COVID-19 in both vaccinated and unvaccinated patients with a documented positive SARS-CoV-2 test in a multicenter, retrospective cohort.

Methods

We applied an electronic measurement tool, previously developed using a chart reviewed sample of cases from a national cohort using Veterans' Affairs (VA) data and validated on manually adjudicated cases at Tufts Medical Center, to classify deaths as attributable to or not attributable to COVID-19.[3] Within the VA, all deaths in vaccinated patients that occurred within 90 days of a positive SARS-CoV-2 test between January–February 2022 and June–August 2022 were identified. Then, a random sample of 300 cases were selected for manual review to determine attribution by 2 physicians. At Tufts Medical Center, all deaths in hospitalized patients with a positive SARS-CoV-2 test were identified during the period from January 2021 to October 2022, and all cases underwent manual review for attribution to COVID-19. During the manual review process, cases were classified into COVID-19 attributable (eg, directly caused by respiratory disease secondary to SARS-CoV-2 infection), COVID-19 contributory (eg, SARS-CoV-2 accelerated decline in a frail patient), or COVID-19 nonattributable (eg, patient in a motor vehicle collision who subsequently died secondary to trauma).

After the chart review sample was created, a tool was designed to identify deaths in which COVID-19 contributed to or was the primary cause of death, both of which were classified as COVID-19–related deaths. Aligned with prior work,[3] the tool was designed to be easily defined using structured variables available in the electronic health record (EHR). The electronic measurement tool comprises a 3-point index with 1 point given for each of the following: (1) receipt of remdesivir; (2) receipt of anti-inflammatory drugs (dexamethasone, baricitinib, or tocilizumab); and (3) hypoxemia with $SpO_2 < 90\%$ or supplementary oxygen >2 L, with or without addition of mechanical ventilation. A score of 2–3 has high positive predictive value for COVID-19–related death: overall (PPV, 0.82–0.95), January–February 2022 (PPV, 0.89 and NPV, 0.55), and June–August 2022 (PPV, 0.73 and NPV, 0.70).[4]

To assess longitudinal trends in mortality associated with COVID-19, we applied the tool to classify deaths among VA patients within 30 days of a first positive SARS-CoV-2 test between January 2021 and March 2023.

This study was approved by the VA Boston Research and Development Committee prior to data analysis.

Results

The cohort consisted of 10,778 veterans who died within 30 days of a positive SARS-CoV-2 test during the study period. This included 6,081 vaccinated veterans and 4,697 unvaccinated veterans. Unvaccinated veterans who died were younger: median age, 74.3 vs 77.6 years in vaccinated veterans ($P < .001$) (Table 1, demographics).

From August 2021 to March 2023, an overall decrease in the proportion of deaths attributable to COVID-19 was identified (P value for trend, <.001). Despite a higher absolute number of deaths attributable to COVID-19 in the vaccinated population (6,081 vs 4,697 and 2,650 vs 488 in the 12 months starting March 2022) (Fig. 1A), the proportions of deaths attributable to COVID-19 (Fig. 1B) were similar in both cohorts, trending from >70% at the start of the study period to <50% at the end of the study period.

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Cite this article: Trottier CA, *et al.* (2024). Longitudinal trends in 30-day mortality attributable to SARS-CoV-2 among vaccinated and unvaccinated US veteran patients. *Infection Control & Hospital Epidemiology*, 45: 393–395, https://doi.org/10.1017/ice.2023.245

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Table 1. Demographics of Vaccinated and Unvaccinated Patients Who Died Within 30 Days of a Positive SARS-CoV-2 Diagnostic Test

Variable	Unvaccinated (N = 4,697), No. (%)[a]	Vaccinated (N = 6,081), No. (%)[a]	*P* Value
Age at COVID-19 diagnosis, median y (IQR)	74.3 (68.0–81.5)	77.5 (72.7–86.2)	<.001
Sex, male	4,526 (96.4)	5,962 (98.0)	<.001
Race and ethnicity			<.001
White	3,124 (66.5)	4,233 (69.6)	
Black	833 (17.7)	1,037 (17.1)	
Hispanic	274 (5.8)	378 (6.2)	
Asian/Pacific Islander	96 (2.0)	315 (5.2)	

Note. IQR, interquartile range.
[a]Units unless otherwise specified.

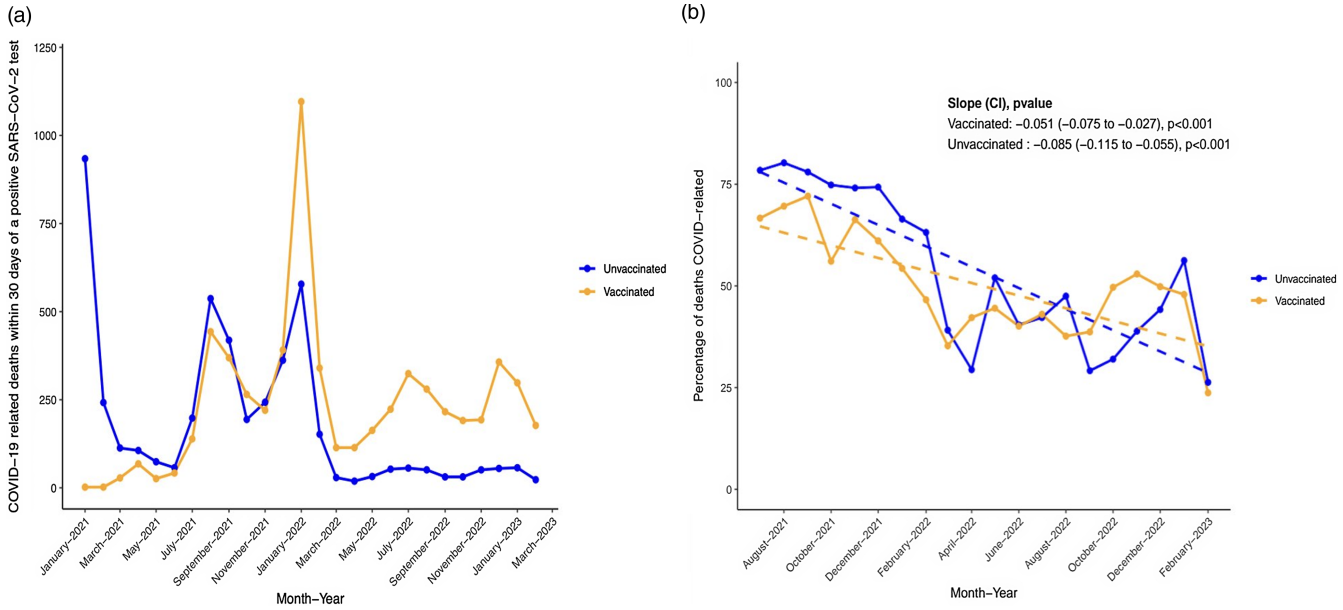

Figure 1. (A) Number of deaths in the VA healthcare system within 30 days of a positive COVID-19 test from January 2021 to March 2023. (B) Proportion of deaths that were related to COVID-19 among unvaccinated and vaccinated patients from August 2021 to March 2023.

Discussion

Throughout the pandemic, myriad measures have been used to guide the ongoing public health response including case rates, hospitalization rates, and death rates. Because determining whether a hospitalization or death is caused by COVID-19 (either directly or indirectly) or not requires manual chart review, data obtained through simpler means, such as by counting deaths within a specified period after a positive test for SARS-CoV-2 have been used by many state and territorial health departments, but these surrogate metrics are imperfect. Our electronic tool, which gives a closer approximation to what is obtained by chart review than other commonly used measures, reveals that the proportion of deaths attributed to COVID-19 within 30 days following a positive test has decreased in both vaccinated and unvaccinated patients and that in an era with widespread immunity and effective therapies, the attributable proportion of COVID-19 deaths within a 30 day window following a diagnosis is similar between the 2 groups. These findings expand upon our prior work evaluating COVID-19 hospitalization data, in which we detected decreasing rates of severe disease following identification of medical countermeasures, which led to the addition of a new surveillance metric that was implemented statewide in Massachusetts in January 2022.[3,5] Notably, in this study, we focused only on individuals who died within 30 days of a positive test, and we did not assess the question of the effectiveness of the vaccine for preventing death.

The official national COVID-19 death toll, which is based on death certificate review, is inherently delayed. In future waves, a simple and easily implemented scoring system, such as this one, would allow state and territorial health authorities to quickly recognize whether new variants or waning population immunity are contributing to increasing attributable mortality. Additionally, integration of more accurate methods of ascertaining attributable cases may improve comparisons of mortality with other respiratory viruses, which has been a subject of debate throughout the pandemic.

As of March 2022, ~68% of veterans engaged in VA healthcare were documented to have received at least a primary vaccination series. Thus, it is important to interpret findings considering the high levels of vaccine uptake in the VA; the greater number of deaths in the vaccinated group is due in part to larger population size. Additionally, veterans who opted not to get vaccinated are systematically different from those who received the COVID-19

https://doi.org/10.1017/ice.2023.245 Published online by Cambridge University Press

vaccine. Unvaccinated patients tended to be younger and with fewer complex comorbidities; thus, they were at lower baseline risk of severe COVID-19 than vaccinated veterans, which also affected the distribution of attributable mortality.[6] By September 2022, the US Centers for Disease Control and Prevention (CDC) estimated that >96% of the US population had at least some degree of immunity to SARS-CoV-2, acquired from vaccination, infection, or both.[7] Unvaccinated veterans identified during later periods are likely to have immunity from infection that reduced their risk of severe disease during subsequent infections.

This study had several limitations. Firstly, the study was conducted in the VA; thus, women, children, and people of Asian and native American race were underrepresented in this sample. Trends in these populations may be different. Second, we were only able to assess SARS-CoV-2–positive cases that were diagnosed at or were reported to the VA. Home tests and tests conducted at outside facilities that were not reported to the VA could not be measured or evaluated for death attribution. However, cases that were diagnosed at home and not documented within healthcare systems would not be attributed to COVID-19; these limitations are similar to those encountered in other public health surveillance systems. Third, patients vaccinated within the VA may be more regular users of VA healthcare, meaning that the VA has more complete data about their medical history. Thus, some degree of misclassification of vaccinated patients as unvaccinated is possible, although the COVID-19 shared data resource does attempt to capture receipt of vaccination outside the VA if it is documented during clinical encounters.

In summary, over the course of the pandemic, COVID-19 severity, as measured by hospitalizations and deaths within 30 days of a positive test, have decreased as population immunity has increased and therapeutics have been developed. Mortality attributable to COVID-19 in patients who recently tested positive for SARS-CoV-2 has also decreased in both vaccinated and unvaccinated populations, and to a similar extent. Simple metrics for determining death attribution can be applied to improve the speed and accuracy of public health surveillance metrics.

Acknowledgments. The views expressed are those of the authors and do not necessarily represent those of the US Department of Veterans' Affairs or the US federal government.

Financial support. No financial support was provided relevant to this article.

Competing interests. W.B.E. and P.M. report research funds from Gilead Sciences (funds to institution). W.B.E. also reports research funding from the VA Health Services Research and Development Service.

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Impact of an electronic medical-record–embedded clinical-decision support tool on duration of antibiotics for outpatient pediatric skin and soft-tissue infections

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Up to 90% of human antibiotic use occurs in the ambulatory setting.[1,2] In the United States, ~50% of outpatient antibiotic prescriptions are unnecessary or inappropriate when accounting for antibiotic selection, dose, and duration.[3–7] In addition to driving antimicrobial resistance, unnecessary antibiotic use results in increased adverse drug events and increased risk of *Clostridioides difficile* infection.[8]

Most ambulatory stewardship interventions reported in the literature have targeted respiratory infections, although skin and soft-tissue infections (SSTIs) are a common indication for outpatient

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Cite this article: Lloyd EC, *et al.* (2024). Impact of an electronic medical-record–embedded clinical-decision support tool on duration of antibiotics for outpatient pediatric skin and soft-tissue infections. *Infection Control & Hospital Epidemiology*, 45: 395–397, https://doi.org/10.1017/ice.2023.232