Clinical Outcomes in Hospitalized Vaccine-Breakthrough Coronavirus Disease 2019 Cases Compared With Contemporary Unvaccinated Hospitalized Adults

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The present array of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have variable efficacy in clinical trials and effectiveness in national “real-world” vaccination programs. Their preventive performance can be evaluated by avoidance of symptomatic infection and severity of disease, the latter often inferred from the required level of care (hospitalization, critical care unit [CCU] admissions, ventilator use, or mortality). Messenger RNA (mRNA)–based vaccines have shown the most potent preventive effect for both the ancestral SARS-CoV-2 strain and subsequent variants such as Delta and Omicron [1, 2]. Nonetheless, breakthrough cases occur, since vaccines do not confer sterilizing immunity; cases following mRNA-based vaccination are far less likely to become severe.

Chile has implemented an early and expansive vaccination program that enabled 2-dose immunization in 88% of its population of 19.5 million (older children included) by the end of the third quarter of 2021 [3]. CoronaVac (Sinovac Biotech Ltd, Beijing, China), is an inactivated vaccine that has been the cornerstone of the program, used in 75% of vaccinated adults. The BNT162b2 mRNA vaccine (Pfizer with BioNTech and Fosun Pharma, New York, New York) has been used mostly in immunocompromised adults and minors, to a much lesser degree. CoronaVac immunogenicity is comparatively less robust, though substantial antibody levels are achieved; real-world effectiveness was assessed in a Chilean study of 4 million vaccinees, demonstrating a 65.9% (95% confidence interval [CI], 65.2%–66.6%) preventive effect for symptomatic infection and a much higher prevention of hospitalization (87.5% [95% CI, 86.7%–88.2%]), CCU admissions (90.3% [95% CI, 89.1%–91.4%]), and death (86.3% [95% CI, 84.5%–87.9%]) in the short run [4]. Effectiveness declined with time [5], suggesting the benefit of boosting doses.

The objective of this study was to compare major outcomes in preboosted fully vaccinated and unvaccinated adult persons hospitalized for coronavirus disease 2019 (COVID-19) in a private general hospital in Santiago, Chile, during mid-2021.

METHODS

We reviewed clinical and demographic information of disease characteristics in 2 groups: (1) fully vaccinated (Fvac; at least 14 days post–second dose, but not boosted) and (2) unvaccinated adults (Unvac), aged >17 years, admitted for COVID-19 in a 353-bed private hospital. We used data extracted from a disease-specific database created at the beginning of the COVID-19 pandemic and enhanced data with relevant information incorporated in real time. Data were extracted from 27 March 2021 (the day the first fully vaccinated case was admitted) to 31 August 2021; this Southern Hemisphere winter season coincided with the second wave of COVID-19 in Chile. Data included age, sex, CCU admission, use of invasive mechanical ventilation, length of hospitalization, and intrahospital death.

A case of COVID-19 was defined by a positive polymerase chain reaction (PCR) test or characteristic clinical and radiologic findings. Accurate information of the type, number, and date of vaccination doses was provided from a mandatory nationwide registry. Our local ethics committee authorized use of these data for outcome research and waived the need for informed consent, under conditions guaranteeing data confidentiality and patient anonymity. Quantitative variables were compared by Student t test, and categorical variables were analyzed with proportional z test using Stata 13 software (StataCorp LLC, College Station, Texas). Comorbidities at time of admission were not evaluated and no genetic characterization of SARS-CoV-2 strains was performed.

RESULTS

During the study period, there were 998 adult COVID-19 admissions (2.5% with undocumented positive PCR, excluding partially vaccinated cases): 260 (26.1%) in Fvac patients, 507 (50.8%) in Unvac patients, and 231 (23.1%) with incomplete vaccination either by dose or timing. Data for persons with
incomplete vaccination were excluded from the study. Vaccine courses were overwhelmingly CoronaVac (251 [96.5%]), with the rest BNT162b2 (3.1%) or Covidecia (Ad5-nCoV, CanSinoBIO, Tianjin, China) (0.4%). Median age was 64.8 (interquartile range [IQR], 57–75) years for Fvac and 45 (IQR, 35–53) years for Unvac (P < .001). Fvac hospitalized patients were more likely than Unvac patients to be >60 years of age (69% vs 15.6%, P < .001). Despite the older age, Fvac admission to CCU was less common than for Unvac (33.8% vs 43.1%, P = .012). Similarly, the need for mechanical ventilation was 13.8% for Fvac and 26.4% for Unvac (P < .001). Unadjusted for age, there were 45 deaths in Fvac (17.3%) and 65 in Unvac (13.4%) (P = .15). A stratified analysis of death by decade is informative (Table 1). Total mean length of stay in days was 11.7 (median, 9) for Fvac and 12.6 (median, 10) for Unvac; for those aged 260 years, length of stay in days was 12.8 (median, 10) for Fvac and 17.8 (median, 15) for Unvac (P < .001; Table 1).

**DISCUSSION**

This study of adults hospitalized for COVID-19 during the second wave in Chile found that hospitalizations, CCU admissions, and ventilator use were all more common in unvaccinated people, at a time when the majority of the adult population had been vaccinated with inactivated SARS-CoV-2 vaccine. When age is considered, deaths are also lower with immunization. The United States Centers for Disease Control and Prevention has reported similar results with mRNA vaccine use [6]. We believe that the good performance of the less potent inactivated vaccine is important for China and the >45 low- and middle-income countries (LMICs) that use World Health Organization–approved inactivated vaccines as the backbone of their vaccine efforts [7]. Chilean data have confirmed inactivated vaccine efficacy in clinical trials [8] and effectiveness for multiple outcomes from a state-sponsored vaccination program in several million people. Our study demonstrates the value of inactivated vaccines in reducing severity of disease in hospitalized patients with COVID-19 at multiple age strata. Among the hospitalized COVID-19 cases, 1 in 4 had received full primary vaccination, overwhelmingy CoronaVac (96.5%), much higher than its 75% participation in the mix of vaccines used in the country, consistent with the superior hospitalization prevention effect found with BNT162b2 in the country compared with the former during the same period of this study (97.2% vs 86%) [5]. Our vaccinated hospitalized subjects were 2 decades older, on average, than the unvaccinated hospitalized subjects, almost certainly representing a population with more baseline comorbidities and naturally more prone to have severe disease and death when infected compared to younger people. The higher mortality in the vaccinated group as a whole is misleading; once age is controlled for by stratum-specific analysis, death rates in each decade group from the 40s to the 70s were lower in vaccinees, with too few cases aged ≥80 years in the unvaccinated group for meaningful comparison. This older cohort also had fewer admissions to the CCU, less need for mechanical ventilation, and shorter length of hospital stay as a whole; these differences were more pronounced and statistically significant in those aged ≥60 years. These clinical outcomes data suggest that full prior vaccination with the inactivated vaccine provides significant protection from serious disease. At a national level, the aggressive vaccination program in Chile of early 2021 seems to have blunted the magnitude of the epidemic, including the more salutary consequences for those with breakthrough disease, reinforcing confidence in the vaccines used. We will be unable to

| Characteristic | Fully Vaccinated | Unvaccinated | P Value |
|---------------|-----------------|--------------|---------|
| Enrollment, No. (% total COVID-19 admissions) | 260 (26.1) | 507 (50.7)* | <.001 |
| Mean age, y (median) [IQR] | 64.8 (67) [57–75] | 45.5 (49) [35–53] | <.001 |
| Age ≥60 y | 69% | 15.6% | <.001 |
| Female sex | 36.9% | 39.6% | .484 |
| CCU admission | 33.8% | 43.1% | .012 |
| Mechanical ventilation | 13.8% | 26.4% | <.001 |
| Total mortality, No. (%) | 45 (17.3) | 68 (13.4) | .150 |
| Age ≥80 y | 13/38 (34.2) | 2/9 (22.2) | .488 |
| Age 70–79 y | 12/69 (17.4) | 6/21 (28.6) | .262 |
| Age 60–69 y | 15/72 (20.8) | 16/44 (36.3) | .066 |
| Age 50–59 y | 3/39 (7.7) | 19/104 (18.3) | .119 |
| Age 40–49 y | 1/21 (4.8) | 18/141 (12.8) | .288 |
| Age 30–39 y | 1/17 (5.9) | 7/134 (5.2) | .909 |
| Age <30 y | 0/4 (0) | 0/54 (0) | .097 |
| Age ≥60 y | 40/179 (22.3) | 24/74 (32.4) | <.001 |
| Mean (median) length of hospitalization, d | 11.7 (9) | 12.6 (10) | .345 |
| In age ≥60 y | 12.8 (10) | 17.8 (15) | <.001 |

Abbreviations: CCU, critical care unit; COVID-19, coronavirus disease 2019; IQR, interquartile range.

*There were 231 (23.1%) COVID-19 admissions in adults with incomplete vaccination and/or <14 days of last dose at COVID-19 diagnosis; these patients were not eligible for the study.
follow up this study since unvaccinated persons are now scarce, due to special incentives toward vaccination and restrictions on the unvaccinated being put in place for adults and children in a national effort to maximize immunization in these populations. A vigorous booster vaccination campaign for all persons with full primary vaccination, beginning with the elderly, has been conducted in late 2021 and 2022. We intend to compare COVID-19 cases in vaccinated people with and without booster doses. Limitations of our study include lack of evaluation of comorbidities and viral variants, being a single-site study, risk of patients’ profile not being an accurate representation of the COVID-19 population at large, and portraying a situation prior to the Omicron surge. Our study does not evaluate the decline of the preventive effect of CoronaVac over time. We believe that Chilean data are reassuring for LMICs since there are many countries with vaccination programs in their infancy, which are or will be heavily dependent on CoronaVac, and these findings add necessary relevant information to complete its profile performance. The global community may wish to consider mRNA-based vaccines, or others of similar robust immunogenicity, for heterologous boosters for persons with primary vaccination with inactivated vaccines given highly favorable immunological results of these combinations noted from the Dominican Republic [9] and enhanced preventive effectiveness reported from Chile [10], to maintain the beneficial effects in hospitalized breakthrough COVID-19 cases found in this study.

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