

Original Research

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Death Reporting in Breakthrough and Unvaccinated SARS-CoV-2 Infection Cases

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Abstract

Vaccines are undeniably an important tool for controlling infectious disease outbreaks, and they are the most certain way to end the epidemic risk. This brief report describes the characteristics of coronavirus disease 2019 (COVID-19) deaths among breakthrough and unvaccinated cases hospitalized in Fars province in the south of Iran. This cross-sectional study was performed to compare breakthrough and unvaccinated death cases in Fars, Iran (February 2, to August 19, 2021). Among 444,728 fully vaccinated people, 60,800 breakthrough cases were detected. Thus, 501 died, of which 297 (297/501) cases were hospitalized and compared with the unvaccinated dead group. The median age for breakthrough and unvaccinated cases was estimated 79 and 65 y, respectively. All signs and symptoms of COVID-19 were more frequent in the unvaccinated group. Decreasing O₂ saturation (less than 93%) happened more often in the unvaccinated group significantly. Unvaccinated dead patients had significantly shorter hospital stays. These patients received 66.63% Sinopharm, 0.67% Sputnik, 0.67% COVIran Barekat, and 31.99% AstraZeneca vaccines. None of them were health-care staff. Equitable access to safe and effective vaccines is critical to ending the COVID-19 pandemic. As vaccine uptake increases, we observed a decrease in mortality and protection from severe forms of the disease.

Undoubtedly vaccines are a fundamental tool to control the infectious diseases outbreak and are the most confident means to terminate the epidemic risk. Based on various evidence, it routinely needs 5 to 10 y to develop a vaccine for the infectious agents.^{1,2} As we enter the year 2020, a new viral infectious agent engulfs the entire globe in a short time. By looking back at the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, the global burden of coronavirus disease 2019 (COVID-19) infection is estimated at 229,329,042 cases and approximately 4,705,890 deaths (September 20, 2021).³

A remarkable spread for researching and developing vaccines was created by the increasing rate of transmission and death. Hence, all processes from the initial SARS-CoV-2 sequencing to an interim analysis of vaccine efficiency were performed in just 300 d.⁴

Therefore, in the following attempts, 3 first vaccines (Pfizer, Moderna, Janssen) were introduced and approved by emergency by the United States Food and Drug Administration for use authorization publicly. Under the pressure of outbreak, several companies in different regions of world for instance Serum Institute in India for Astra-Zeneca and Novavax, Beijing Bio Institute in China for Sinopharm were licensed for manufacturing vaccines.⁵ These products have the green light from the World Health Organization (WHO) to be rolled out globally for emergency use. Although the vaccination is a very complex and challenging procedure and needs very special platforms to entirely eradicate COVID-19, it is necessary to produce, distribute, and vaccinate people worldwide in a short time.⁶

Iran has gone through 5 waves since the identification and spread of the Delta variant. Despite all efforts made by health-care workers, due to some circumstances, the death rate was reported high in some days of peak. Although the vaccination program was started before the Delta variant, there are some reasons that made the situation worse. This brief report describes the characteristics of death in vaccinated and unvaccinated people hospitalized after 14 d of vaccination in Fars province in the south of Iran.

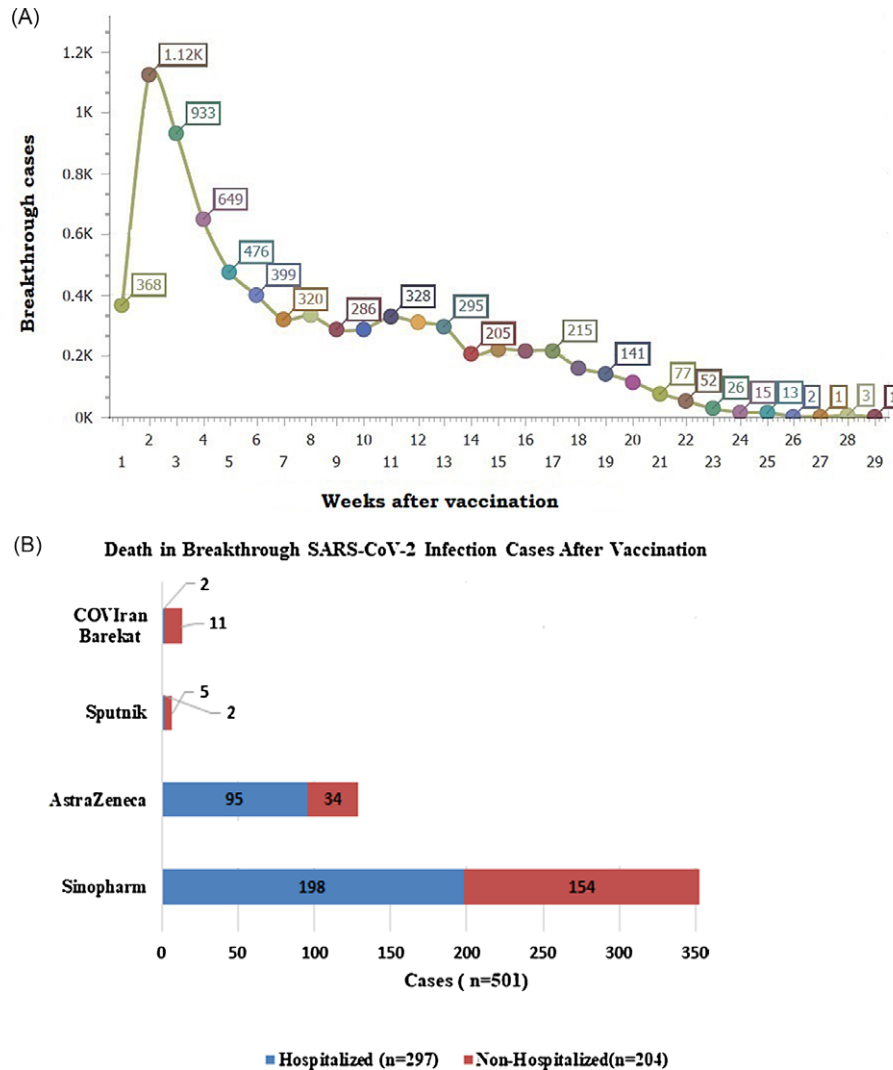


Figure 1. Cumulative breakthrough cases (A), and death count by vaccine type (B).

Methods

Study Design

This cross-sectional study was performed to describe dead breakthrough cases in the study region from the initial time of the vaccination program until now (February 2, to 19 August 2021).

The ethical committee approved this study of Shiraz University of Medical Sciences (Ethical code: IR.SUMS.REC. 1399.022.). We selected a control group for more comparisons, which was age- and sex-matched and double the size of the patient group. The control group included unvaccinated who died in the hospitals from the same database of patients.

Data Collection

For any hospitalized patients who were confirmed with COVID-19, comprehensive information was recorded in electronic database registry data like; demographic data, symptoms of the disease at arrival, underlying chronic health problems, duration of time from onset of symptoms, vaccination status, doses, type, and date of injection and, the clinical outcome as death or discharge. Information was collected and entered into the electronic registry of Shiraz University of Medical Sciences.

Statistical Analysis

The data are described with proper descriptive statistics. The independent sample t-test or Pearson chi-squared test was compared for quantity and qualitative variables, respectively. In univariate analysis, a logistic regression model was fitted for variables with a *P*-value less than 0.2. All statistical analyses were performed with SPSS22, and a *P*-value less than 0.05 was considered the threshold of statistical significance.

Participants

Based on the Center of Disease Control (CDC) definition, a vaccine breakthrough infection is defined as detecting SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person 14 ≥ d after they have completed all recommended doses of COVID-19 vaccine. Participants in this study included 297 dead breakthrough infections, who were hospitalized in Fars, Iran.

Results

All vaccinated people were investigated from the beginning of the vaccination program. According to our findings, 368 cases became

Table 1. Comparison of breakthrough and unvaccinated death cases

Variables	Breakthrough died cases (n = 297)	Unvaccinated died cases (n = 595)	P-Value
Age	74 (19–100)	65 (31–85)	0.25
Sex (female:male)	127:170 (42.8% : 57.2%)	273: 322 (45.8% : 54.11%)	0.37
Fever	86 (29%)	342(57.47%)	P< 0.001
Cough	108 (36.4%)	256 (43.02%)	0.056
Muscle pain	69 (23.2%)	378 (63.52%)	P< 0.001
Respiratory distress	207 (69.7%)	386 (64.87%)	0.15
Headache	13 (4.4%)	189 (31.76%)	P< 0.001
Diarrhea	13 (4.4%)	134 (22.52%)	P< 0.001
Anorexia	30 (10.15%)	127 (21.34%)	P< 0.001
O ₂ saturation less than 93%	262 (88.2%)	545 (91.59%)	0.005
Intubation	131 (44.1%)	284 (47.73%)	0.307
Hypertension	116 (39.1%)	242 (40.67%)	0.64
Diabetes	75 (25.3%)	289 (48.57%)	P< 0.001
Cardiovascular disease	65 (21.9%)	189 (31.76%)	0.002
Cancer	15 (5.1%)	76 (12.77%)	P< 0.001
Liver disease	1 (0.3%)	49 (8.23%)	P< 0.001
Kidney disease	21 (7.1%)	37 (6.21%)	0.62
Neurological disorders	5 (1.7%)	19 (3.19%)	0.18
Immunodeficiency disease	1 (0.3%)	13 (2.18%)	0.03
Length of stay	8.3 ± 1.4	3.6 ± 2.34	0.02

positive for SARS-CoV-2 infection, 1 wk after vaccination. Among 444,728 fully vaccinated people, 60,800 breakthrough cases were detected from the second week onward cumulatively (Figure 1). Overall, 501 patients died, of which 297 patients were hospitalized. These patients ($n = 297$) were described and compared with an age- and sex-matched group. The median age for breakthrough cases and the unvaccinated group was estimated 79 and 65 y, respectively. The sex distribution of dead breakthrough cases was 127 (42.8%) females and 170 (57.2%) males. Furthermore, in the unvaccinated death group, 273 (45.8%) females and 322 (54.11%) males were included. Although all signs and symptoms of COVID-19 were more frequent in the unvaccinated group, fever, muscle pain, headache, and anorexia were significantly different between the 2 groups. Decreasing O₂ saturation (less than 93%) happened more often in the unvaccinated group significantly. The duration of hospital stay was impressively less in the unvaccinated dead patients. It means dying of COVID-19 within a short time. Vaccines type in breakthrough death patients consists of 66.63% Sinopharm, 0.67% Sputnik, 0.67% COVIran Barekat and 31.99% AstraZeneca. Variables with a P -value less than 0.2 in the univariate analysis are included in a regression model. The factors were evaluated in association with breakthrough and unvaccinated death cases. Respiratory distress was more often present (odds ratio [OR] = 5.6; 95% confidence interval [CI]: 1.23, 8.93; $P = 0.001$) in the unvaccinated death population versus breakthrough death. Other variables were not statistically significant. More details are provided in Table 1.

Discussion

This is the first report comparing breakthrough and unvaccinated deaths in Fars, Iran. Vaccines are the most effective tool for controlling this infectious outbreak in the current crisis. Despite the high level of vaccine efficiency (> 85%) for preventing severe forms

of diseases, but various reports published about breakthrough SARS-CoV-2 infections in fully vaccinated individuals.^{7–9} Based on these reports and current results, it was found that vaccines have conferred widespread protection against SARS-CoV-2 infection. As we see in the current results, hospitalization was significantly more in breakthrough cases. Also, fully vaccinated individuals who experienced breakthrough infections reported fewer symptoms than unvaccinated at the time of study. This means vaccines remain a critical tool for providing protection against COVID-19, especially against severe illness and hospitalization. This result supports earlier research demonstrating that vaccination offers considerable protection against the most severe COVID-19 disease signs as well as general infection protection.¹⁰ To evaluate vaccine safety and surveillance, it is important to follow the fully vaccinated individuals to diagnose any serious complications or infections especially severe cases or dead people due to COVID-19 disease. According to the CDC report, a total of 10,262 SARS-CoV-2 vaccine breakthrough infections were diagnosed in 46 states of the United States until April 30, 2021; of those 160 (2%) cases have died.¹¹ Compared with our results, our death rate (501/60800; 0.82%) was lower than published reports. The median age of dead cases in the United States was 82 y old, which is more than our results. We have started the vaccination program simultaneously for the elderly individuals with especial illness in other ages (19–100 y old). This is while in the United States the age range was 71 to 89. Poor immune response, co-existence of multiple comorbidities at older ages, and overall frailty may be the main reasons why they are at higher risk.¹¹ Furthermore, in various reports, it was seen that 85% of breakthrough cases were infected with the B.1.1.7 variant.^{12–15}

Similar to our results, Pre-existing illness and age greater than 60 y were found to be predictors of death in unvaccinated patients in a retrospective study on predictors of death in COVID-19 vaccine breakthrough infections in Brazil.¹⁶

Critically, some reasons may increase the breakthrough infection rate or related death. The most important reason may be in terms of the failure to comply with expected health protocols after vaccination.¹⁷ Various evidence shows people with special medical conditions and lower immunity due to underlying disease may not obtain optimal protection from established vaccines. Moreover, the combined effect of waning immunity and the increased prevalence of the delta variant decreases the efficacy of a vaccine and the booster (third) dose would be helpful in this circumstance. So far, in the countries with high rates of vaccination, booster doses have been started for those who are 60 y of age or older or have an immunodeficiency disease.¹⁸ Another issue that should be pointed out in Iran, is waiting for the home-grown crops of vaccines. Sanctions have caused a lot of difficulties in providing initial equipment and materials. Trying local solutions and modifying the method causes an unexpected delay in manufacturing vaccines.¹⁹ Despite the fact that independent researchers have demonstrated vaccine efficacy, there is evidence of increased SARS-CoV-2 breakthrough rates in vaccinated individuals.^{13,20,21} The main point about the strength of the current study is reporting about death breakthrough cases and comparison with the unvaccinated groups. As a suggestion, it is better to design experimental studies and evaluate the immune responses in different groups of patients and following them. Future studies will help determine the long-term effectiveness of vaccination and even the booster dose against current and emerging variants.

Conclusions

The findings of this study indicated that vaccination was associated with a reduction in the risk of SARS-CoV-2 infection; a severe form of disease and death rate. Equitable access to safe and effective vaccines is critical to ending the COVID-19 pandemic. As vaccine uptake increases, we anticipate a decrease in mortality and increased protection from severe forms of the disease.

References

1. Wolf J, Bruno S, Eichberg M, et al. Applying lessons from the Ebola vaccine experience for SARS-CoV-2 and other epidemic pathogens. *NPJ Vaccines*. 2020;5(1):15.
2. Excler JL, Saville M, Berkley S, et al. Vaccine development for emerging infectious diseases. *Nat Med*. 2021;27(4):591-600.
3. Worldometer D., COVID-19 coronavirus pandemic. World Health Organization, www.worldometers.info, 2020. <https://www.worldometers.info/coronavirus/>
4. Cleve MI. What the lightning-fast quest for Covid vaccines means for other diseases. *Nature*. 2021;589:16-18.
5. Kim JH. SARS-CoV-2 vaccine development, access, and equity. *J Exp Med*. 2020;217(11):e20201288.
6. van Riel D, de Wit E. Next-generation vaccine platforms for COVID-19. *Nat Mater*. 2020;19(8):810-812.
7. Bergwerk M, Gonen T, Lustig Y, et al. Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med*. 2021;385(16):1474-1484.
8. Butt AA, Nafady-Hego H, Chemaitelly H, et al. Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination. *Int J Infect Dis*. 2021;110:353-358.
9. Sankary KM, Sippel JL, Eberhart AC, et al. Breakthrough cases of COVID-19 in vaccinated United States Veterans with spinal cord injuries and disorders. *Spinal Cord*. 2021;59(10):1132-1133.
10. Reynolds MW, Xie Y, Knuth KB, et al. COVID-19 vaccination breakthrough infections in a real-world setting: using community reporters to evaluate vaccine effectiveness. *Infect Drug Resist*. 2022;15:5167-5182.
11. CDC COVID-19 Vaccine Breakthrough Case Investigations Team. COVID-19 vaccine breakthrough infections reported to CDC—United States, January 1–April 30, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(21):792-793.
12. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet*. 2021;397(10287):1819-1829.
13. Kustin T, Harel N, Finkel U, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. *Nat Med*. 2021;27(8):1379-1384.
14. Bouton TC, Lodi S, Turcinovic J, et al. COVID-19 vaccine impact on rates of SARS-CoV-2 cases and post vaccination strain sequences among health-care workers at an urban academic medical center: a prospective cohort study. *medRxiv*. 2021. doi:10.1101/2021.03.30.21254655
15. Jacobson KB, Pinsky BA, Montez Rath ME, et al. Post-Vaccination Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infections and Incidence of the Presumptive B.1.427/B.1.429 Variant Among Healthcare Personnel at a Northern California Academic Medical Center. *Clin Infect Dis*. 2022;74(5):821-828.
16. Estofolete CF, Fares GF, Banho CA, et al. Predictors of death in COVID-19 vaccine breakthrough infections in Brazil. *J Infect*. 2022;84(4):e22-e24.
17. Schaffer DeRoo S, Pudalov NJ, Fu LY. Planning for a COVID-19 vaccination program. *JAMA*. 2020;323(24):2458-2459.
18. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *N Engl J Med*. 2021;385(15):1393-1400.
19. Akbarialiabadi H, Rastegar A, Bastani B. How sanctions have impacted Iranian healthcare sector: a brief review. *Arch Iran Med*. 2021;24(1):58-63.
20. Hacisuleyman E, Hale C, Saito Y, et al. Vaccine breakthrough infections with SARS-CoV-2 variants. *N Engl J Med*. 2021;384(23):2212-2218.
21. Philomina J B, Jolly B, John N, et al. Genomic survey of SARS-CoV-2 vaccine breakthrough infections in healthcare workers from Kerala, India. *J Infect*. 2021;83(2):237-279.