Presenting clinical symptoms of post-COVID-19 breakthrough infection: Predictors of mortality in a Middle Eastern population

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ABSTRACT

Objective: Breakthrough COVID-19 infections are common following immunisation with various types of vaccines. The patterns of infections have not been well established. We aimed to analyse the signs and symptoms of post vaccination infections in addition to the need for hospital admission, ER visit and supplemental oxygen in relation to age and gender.

Methods: A cross-sectional cohort study was conducted in JUH from March 2021 to August 2022, we interviewed 1479 individuals who are >15 years of age and got a breakthrough infection. The statistical analysis was performed using STATA statistical software.

Results: Out of the 1479 cases, 50.2 % and 69.4 % were females and less than 45 years of age respectively. Symptoms of cough, fever and headache were reported by nearly 50 % of the patients, while one-third complained of dyspnoea. We found that participants older than 45 years had worse clinical outcomes (P-value < 0.001). 13 deaths were identified in this study due to breakthrough infection, 92.3 % of them were older than 45 years (P-value < 0.001). Participants ≥45 years who experienced a breakthrough infection of COVID-19 were 0.7 times less likely to be females using adjusted logistic regression.

Conclusion: This study indicates that despite more severe symptoms reported in younger patients, the major clinical outcomes were worse among older patients, which makes age a major risk for poor outcomes regardless of symptoms. Thus, older people should be evaluated carefully when presenting with mild symptoms of COVID-19 breakthrough infection. The study also confirms that there is no difference in the incidence of COVID-19 breakthrough infections between males and females. Prospective studies are needed to risk stratify COVID-19 breakthrough infections, which should take into account variants of the virus and comorbidities.

Introduction

The introduction of COVID-19 vaccines represented an important milestone in the response to the COVID-19 pandemic. However, there has been emerging reports describing breakthrough COVID-19 infections on fully vaccinated individuals (i.e. received all recommended doses of an FDA-authorised COVID-19 vaccine). According to the literature, vaccines lose effectiveness overtime and there has been evidence suggesting the appearance of new SARS-CoV-2 variants, which is the causative organism of COVID-19 infections [1,2].

The vaccines that were approved for use in Jordan were BNT162b2, ChOdOx-1 S, and BBIBP-CorV [3]. In a fully vaccinated population, studies showed that mRNA vaccines were 97.84 % effective in preventing symptomatic disease. Other types such as non-replicating vector

and protein subunit vaccines had lower but similar rates of efficacy [4]. Against asymptomatic infection, the efficacy rates varied according to the type of vaccine and the COVID-19 strain, but were all considered to be effective [4].

Gender differences in the incidence of post-COVID vaccination infection showed variable results, although more reports state that males are more likely to develop breakthrough infection [5–8]. Older age is an independent risk factor for poor clinical outcome in patients who develop post vaccination infection, although the incidence is higher in younger age groups [2,7,9,10].

Although the literature has established the aforementioned importance of vaccination in various countries across Europe, Asia, and North America [10–13], little supporting data exists in the Gulf region on the matter. In Jordan, COVID-19 vaccine side effects were studied but not the COVID-19 breakthrough infection symptoms and outcome among fully vaccinated individuals [14]. In this proposed study, the reported symptoms and clinical outcome including hospital and emergency admissions, use of supplemental oxygen therapy and mortality of post COVID-19 vaccination infection were studied with special consideration of its relation to age and gender of the studied patients.

Material and methods

Participants

This cross-sectional cohort study was conducted at Jordan university hospital, (JUH), Amman, Jordan from March 2021 to August 2022. We included all patients who are older than 15 years and who had breakthrough infections following completion of the recommended COVID-19 vaccine series. COVID-19 breakthrough infections were defined as instances of SARS-CoV-2 infection that occurred at least 14 days after the final vaccine dose, regardless of whether the person had a previous COVID-19 infection or not. The exclusion of the paediatric age group (under 15 years old) was since their immunity and clinical manifestations differ from those of adults. Additionally, the paediatric group has a higher exposure to the virus due to their lifestyle, but the risk of life-threatening complications is lower than in adults, particularly the elderly. COVID-19 related data were collected from the hospital's electronic medical record and telephonic call interviews conducted by trained interviewers. COVID-19 infection is defined as a confirmed positive SARS-CoV-2 infection, determined through RT-PCR testing conducted at the University of Jordan laboratory. All patients who had COVID-19 breakthrough infection with a confirmed positive SARS-CoV-2 were interviewed regardless of their infection status prior to getting the vaccine.

Data collection

The data collection involved two steps. Initially, we identified all patients who had positive SARS-CoV-2 testing through RT-PCR testing at the Jordan University Hospital PCR laboratory. Their electronic medical records were then reviewed and the following data were collected: names, age, gender, dates of SARS-CoV-2 RT-PCR positive testing, the date of the last COVID-19 vaccine dose, vaccine type, and number of doses. In the second step, patients who experienced breakthrough infections were identified. Subsequently, trained medical students conducted phone call interviews with patients or their families to collect the following data: self-reported symptoms of infection, including fever, cough, headache, fatigue, and gastrointestinal symptoms. Additionally, information regarding post-COVID-19 breakthrough infection outcomes such as death, hospitalization, ICU admission, and the need for supplemental oxygen therapy (including home oxygen therapy) was obtained through phone calls and cross-verified by reviewing electronic medical records.

Informed verbal consent was obtained during the phone call from all patients or their family members. This study was approved by the Institutional Review Board (IRB) at JUH (https://doi.org/10/2021/29094).

Statistical analysis

All statistical analyses were performed using STATA statistical software, version 16 (Stata Corp. LLC, College Station, TX, USA). Categorical variables were presented as percentages. Differences between age group categories including baseline characteristics, symptoms and major clinical outcomes were assessed using a Chi-squared test for categorical variables. A logistic regression analysis for prediction of gender differences in COVID-19 breakthrough baseline characteristics and symptoms was done. Potential factors affecting COVID-19 breakthrough were assessed using unit-variable regression analysis. Only significant variables were subsequently included in the final multivariable regression model. The confidence interval was set at 95 % and p values of ≤ 0.05 were considered to indicate statistical significance.

Results

Out of 1479 of COVID-19 confirmed cases with breakthrough infection, the majority were female 743 (50.2 %) and younger than 45 years of age 1027 (69.4 %). Furthermore, the vast majority of breakthrough infections occurred after 3 months of receiving the last dose of the vaccine 1,360 cases (92 %).

Out of the participants, 834 individuals, accounting for 56.4 % of the cohort, received the BNT162b2 vaccine and 93.3 % of participants received two doses of the vaccine and 191 (12.9 %) they have previous COVID-19 infection [Table 1].

Nearly half of the participants complained of cough, fever, and headache. Around one-third complained of dyspnoea and 63.6 % of them were 15–45 years (P-value = 0.003). We found that 46.5 % of the participants complained of joint pain and 65.7 % of them were 15–45 years (P-value = 0.003) [Table 2].

In addition, 7 % of participants complained of chest pain and 62 % of them were 15–45 years with a (P-value = 0.005) and 46.9 % of

Table 1
Characteristics of participants with COVID 19 breakthrough (n = 1479) age groups.

Baseline characteristics	Total number	15–45 year N = 1027 (69.4 %)	≥ 46 N = 452 (30.6 %)	P value
Gender				0.003 *
Male	736 (49.8 %)	485 (65.9 %)	251 (34.1 %)	
Female	743 (50.2 %)	542 (73 %)	201(27 %)	
Type of vaccines				0.001 *
Sinopharm (BBIBP-CorV)	504 (34.1 %)	349 (69.3 %)	155(30.8 %)	
Pfizer-BioNTech (BNT162b2)	834 (56.4 %)	600 (71.9 %)	234 (28.1 %)	
AstraZeneca (ChOdOx-1 S)	95 (6.4 %)	50 (52.6 %)	45 (47.4 %)	
Mixed types of vaccines	46 (3.11 %)	28 (60.9 %)	18 (39.1 %)	
Number of doses				0.1
Two doses	1,379 (93.3 %)	963 (69.8 %)	416 (30.2 %)	
Three doses	100 (6.7 %)	64 (64 %)	36 (36 %)	
Infections relation to vaccine				0.3
Before receiving vaccine	191 (12.9 %)	123 (64.4 %)	68 (35.6 %)	
After receiving vaccine	1,288 (86.7 %)	897 (69.6 %)	391 (30.4 %)	

* Statically Significant.

Table 2

COVID-19 breakthrough symptoms of participants (n = 1479) according to age groups.

Symptoms (Yes %)	Total Number	15–45 year N = 1027(69.4 %)	≥ 46 N = 452 (30.6 %)	P value
Fever	810 (54.8 %)	547 (67.5 %)	263 (32.5 %)	0.08
Cough	809 (54.7 %)	552 (68.2 %)	257 (31.8 %)	0.3
Runny nose	643 (43.5 %)	457 (71.1 %)	186 (28.9 %)	0.2
Dyspnoea	404 (27.3 %)	257 (63.6 %)	147 (36.4 %)	0.003*
Headache	793 (53.6 %)	550 (69.4 %)	243 (30.6 %)	0.9
Anosmia	465 (31.4 %)	327 (70.3 %)	138(29.7 %)	0.6
Ageusia	451 (30.5 %)	318 (70.5 %)	133 (29.5 %)	0.5
Sore throat	701 (47.4 %)	491 (70 %)	210 (30 %)	0.6
Fatigue	948 (64.1 %)	653 (68.9 %)	295 (31.1 %)	0.5
Joint pain	687 (46.5 %)	451 (65.7 %)	236 (34.4 %)	0.003*
Chest pain	253 (17.1 %)	157 (62.1 %)	96 (37.9 %)	0.005*
GI symptoms	236 (16.0 %)	165 (69.9 %)	71 (30.1 %)	0.9
Muscle Aches	546 (36.9 %)	355 (65 %)	191 (35 %)	0.005*

GI: gastroenterology.
*Statically significant.

Table 3

Major clinical outcomes related to COVID-19 breakthrough according to age group.

	Total Number	15–45 year N = 1027 (69.4 %)	≥ 46 N = 452 (30.6 %)	P value
Hospitalization related to COVID				<0.001 *
Yes	105 (7 %)	43 (41 %)	62 (59 %)	
No	1374 (93 %)	984 (71.6 %)	390 (28.4 %)	
Visited to Emergency room				<0.001 *
Yes	93 (6 %)	36 (38.7 %)	57 (61.3 %)	
No	1386 (94 %)	991 (71.5 %)	395 (28.5 %)	
Admission to ICU				<0.001 *
Yes	18 (1 %)	5 (27.8 %)	13 (72.2 %)	
No	1461 (99 %)	1022 (70 %)	439 (30 %)	
In hospital O₂ therapy requirements				<0.001 *
Yes	67 (5 %)	19 (28.4 %)	48 (71.6 %)	
No	1412 (95 %)	1008 (71.4 %)	404 (28.6 %)	
Home O₂ therapy required				<0.001 *
Yes	41 (3 %)	13 (31.7 %)	28 (68.3 %)	
No	1438 (97 %)	1014 (70.5 %)	424 (29.5 %)	
Mortality				<0.001 *
Yes	13 (0.9 %)	1 (7.7 %)	12(92.3 %)	
No	1446 (99.1 %)	1026(70 %)	440 (30 %)	

* Statically significant.

Table 4

Logistic Regression Analysis for prediction of gender differences in COVID-19 breakthrough baseline characteristics and symptoms.

Variables	Odd Ratio (OR)	95 % Confidence interval CI	p value
Age group ≥ 46	0.7	0.55–0.87	0.001*
Type of vaccine			
Sinopharm		Reference	
Pfizer	1.2	0.9–1.4	0.2
AstraZeneca	0.9	0.6–1.5	0.9
Different types of vaccine	2.2	1.1–4.2	0.02*
Cough (Yes)	1.3	1.1–1.7	0.02*
Runny nose (Yes)	1.1	0.8–1.3	0.6
Dyspnoea (Yes)	0.9	0.7–1.3	0.9
Headache (Yes)	1.04	0.8–1.3	0.7
Sore throat (Yes)	0.9	0.8–1.3	0.9
Fatigue (Yes)	1.02	0.8–1.4	0.9
Joint pain (Yes)	1.15	0.8–1.5	0.4
Chest pain (Yes)	1.5	1.1–2.1	0.03*
Gastrointestinal symptoms (Yes)	1.21	0.9–1.7	0.2
Muscular aches (Yes)	1.1	0.8–1.5	0.6

* Statically significant.

participants complained of muscle aches of which 65 % were 15–45 years with a (*P*-value = 0.005).

We found that participants who were older than 45 years had worse major clinical outcomes including emergency room visits, hospitalisation, ICU admission and the need for oxygen therapy with a (*P*-value < 0.001).

In this study 13 patients (0.9 %) died from COVID-19 breakthrough infection, 92.3 % of them were older than 45 years (*P*-value < 0.001) [Table 3].

Adjusted logistic regression presented in Table 4 showed older participants (≥45) were 0.7 times less likely to be females compared to males [OR (95 % CI) 0.7 (0.55–0.87), (*P*-value 0.001)]. Female participants were 2.2 times more likely to be vaccinated with mixed vaccine types [OR (95 % CI) 2.2 (1.1–4.2), (*P*-value 0.02)]. Females were 1.3 times more likely to complain of cough [OR (95 % CI) 1.3 (1.1–1.7), (*P*-value 0.02)] and 1.5 times more likely to experience chest pain [OR (95 % CI) 1.5 (1.1–2.1), (*P*-value 0.03)] [Table 4].

Discussion

In this study, we investigated the COVID-19 breakthrough infection in relation to age group. We found in this study that males and females were almost equally likely to develop a breakthrough COVID-19 infection, despite that older females are less likely to be infected than males. Previously published studies found that males are more likely to get infected [5,6,8]. Another study done in the United States found that females are more likely to get infected [7], this can be due to the different baseline genetics, ethnicity and demographics of our population. In addition, we found that the incidence of COVID-19 breakthrough infection was higher in the 15–45 age group, and this is similar to what was reported in a study done in the United States that showed the average age of infection is 44.5 years old [7]. Reopening of schools and universities likely explains this finding, in addition to maintaining limited social activities for the older population. Moreover, the majority of participants received BNT162b2 (56.4 %), which can be explained by

the preference of BNT162b2 over other types of vaccines in the Jordanian population [14].

It appears that symptoms of COVID-19 breakthrough infection are changing from natural COVID-19 infection. Fever was a common presenting symptom in natural infection compared to breakthrough infection [15–18]. Waning immune response from the vaccine, the development of new mutations and the reduction in viral load after vaccination may explain this finding [19,20]. The most common post vaccination COVID-19 infection symptom in this study was fatigue, followed by fever, cough, and headache, which is consistent with the

findings of the study done by Pollet et al. [21], which found that the most common symptoms were rhinitis, followed by cough and headache. The dissimilarity in fatigue could be due to the subjectivity of fatigue as a symptom [22].

Our study found that among the patients that reported a feeling of dyspnoea, chest pain, arthralgia, and myalgia 63.6 % of them were between the ages of 15 and 45, compared to 36.4 % in the older population (age >=46). Conversely, Stouten et al found that dyspnoea had higher odds of occurring in patients older than 65 years of age. This can be explained by the different age group categories used in this study compared with their study [23].

We studied patients' reported major clinical outcomes including emergency room visits, hospital and ICU admissions, supplemental oxygen therapy and death. We found that patients who are younger than 45 years of age were less likely to have these clinical outcomes. This is similar to what was reported by Taquet et al who investigated 10,024 individuals with SARS-CoV-2 breakthrough infection and found a substantial effect of age on the results with lower absolute risks for most clinical outcomes (death and respiratory failure, intubation, hypoxaemia, seizures, and ICU admissions) among younger individuals (age <60 years) [21]. Similar studies reported the same findings [2,9,10].

This finding highlights that although the reported symptoms by the older population were milder than those reported by the younger population, the outcome was worse among the older age group, indicating that age is an independent risk factor for poor post vaccination clinical outcome.

Our study showed that female patients were more likely to report chest pain. This is consistent with the findings of a study done in Vietnam among healthcare workers, which found that women were more likely to develop chest pain as well [24]. This finding can be explained by the fact that females are likely to suffer from higher anxiety levels that can be the cause of the chest pain, especially that chest pain among our cohort didn't translate into poor outcome and the older population who had poor outcome didn't report chest pain as frequently.

The mortality among the studied population was 0.9 %. This is a descriptive study and thus this result cannot be compared with mortality from natural COVID-19 infection given the absence of control group in our study as well as the presence of many confounders [25].

This is the first study in Jordan that investigated COVID-19 breakthrough infection symptomatology and clinical outcome, but it has several limitations. Firstly, we couldn't include a control group in the study, which could have measured the effectiveness of the vaccine. Secondly, the use of self-reported symptoms and outcomes would leave room for recall bias. Thirdly, we did not perform virus isolation to assess the duration of viral shedding, the subtype of the virus or the viral load in the patients, relying instead on PCR Ct values as a marker of infectivity. Fourthly, this study was conducted during the transition period from the Alpha variant to the Omicron variant. The emergence of the newer Omicron variant could have reduced the vaccine's efficacy due to its ability to evade immunity. Finally, we didn't include co-morbidities in the study, which could affect the disease outcome and the symptoms felt by the patients.

Conclusion

In this study, there was no difference in the incidence of COVID-19 breakthrough infections between males and females. Despite more severe symptoms reported in younger patients, the major clinical outcomes were worse among older patients, which makes age a major risk factor for poor outcomes regardless of symptoms. Thus, older people should be evaluated carefully when presenting with mild symptoms of COVID-19 breakthrough infection. Prospective studies are needed to risk stratify COVID-19 breakthrough infections which should take into account variants of the virus and comorbidities.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data associated with this manuscript are available in the Supplementary Material.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100495.

References

[1] Moghadas SM, Moghadas SM, Vilches TN, et al. Clinical Infectious Diseases The Impact of Vaccination on Coronavirus Disease 2019 (COVID-19) Outbreaks in the United States. Clin Infect Dis ® 2021;73(12):2257–64. https://doi.org/10.1093/cid/ciab079.

[2] Scobie HM, Johnson AG, Suthar AB, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status — 13 U.S. Jurisdictions April 4–July 17 2021. https://doi.org/10.1101/2021.08.11.21261885v1.

[3] Basta NE and Moodie EMM on behalf of the VIPER (Vaccines, Infectious disease Prevention and ERGC-19 VD and ATT. COVID-19 Vaccine Development and Approvals Tracker. *covid19.trackvaccines.org.* Published online 2020.

[4] Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Bergman H, et al. Efficacy and safety of COVID-19 vaccines. Cochrane Database Syst Rev 2022 Dec 7;12(12): CD015477. https://doi.org/10.1002/14651858.CD015477.

[5] Velasco JM, Vila V, Diones PC, et al. Clinical characterization of COVID-19 breakthrough infections, Philippines. J Clin Virol December 2021;2022(150–151): 105157. https://doi.org/10.1016/j.jcv.2022.105157.

[6] Liu C, Lee J, Ta C, et al. A Retrospective Analysis of COVID-19 mRNA Vaccine Breakthrough Infections - Risk Factors and Vaccine Effectiveness. medRxiv Prepr Serv Heal Sci. Published online 2021. doi: 10.1101/2021.10.05.21264583.

[7] 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(August):5167–82. https://doi.org/10.2147/IDR.S373183.

[8] Arora G, Taneja J, Bhardwaj P, et al. Adverse events and breakthrough infections associated with COVID-19 vaccination in the Indian population. J Med Virol 2022; 94(7):3147–54. https://doi.org/10.1002/jmv.27708.

[9] Agrawal U, Katikireddi SV, McCowan C, et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): a prospective cohort study. Lancet Respir Med 2021;9(12): 1439–49. https://doi.org/10.1016/S2213-2600(21)00380-5.

[10] 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: 353–8. https://doi.org/10.1016/j.ijid.2021.08.008.

[11] Kissling E, Hooiveld M, Sandonis Martín V, et al. Vaccine effectiveness against symptomatic SARS-CoV-2 infection in adults aged 65 years and older in primary care: I-MOVE-COVID-19 project, Europe, December 2020 to May 2021. Euro Surveill 2021;26(29):2100670. https://doi.org/10.2807/1560-7917.ES.2021.26.29.2100670/CITE/PLAINTEXT.

[12] COVID-19 vaccination effectiveness: a review in early vaccine adopters in Asian Countries.

[13] Rosenberg ES, Dorabawila V, Easton D, et al. Covid-19 Vaccine Effectiveness in New York State. N Engl J Med 2022;386(2):116–27. https://doi.org/10.1056/NEJMOA2116063/SUPPL_FILE/NEJMOA2116063_DISCLOSURES.PDF.

[14] Hatmal MM, Al-Hatamleh MAI, Olaimat AN, et al. Side effects and perceptions following covid-19 vaccination in jordan: A randomized, cross-sectional study implementing machine learning for predicting severity of side effects. Vaccines 2021;9(6):1–23. https://doi.org/10.3390/vaccines9060556.

[15] Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020;133(9):1025. https://doi.org/10.1097/CM9.0000000000000744.

[16] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052. https://doi.org/10.1001/JAMA.2020.6775.

[17] Alsofayan YM, Althunayyan SM, Khan AA, Hakawi AM, Assiri AM. Clinical characteristics of COVID-19 in Saudi Arabia: a national retrospective study. J Infect Public Health 2020;13(7):920–5. https://doi.org/10.1016/J.JIPH.2020.05.026.

[18] Garazzino S, Montagnani C, Donà D, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Eurosurveillance 2020;25(18):1–4. https://doi.org/10.2807/1560-7917.ES.2020.25.18.2000600.

[19] Chia PY, Ong SWX, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine breakthrough infections: a multicentre cohort study. Clin Microbiol Infect 2022;28(4):612.e1–7. https://doi.org/10.1016/J.CMI.2021.11.010.

[20] Petter E, Mor O, Zuckerman N, et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. medRxiv. Published online February 8, 2021, doi: 10.1101/2021.02.08.21251329.

[21] Pollett SD, Richard SA, Fries AC, et al. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mRNA Vaccine-Breakthrough Infection Phenotype Includes Significant Symptoms, Live Virus Shedding, and Viral Genetic Diversity. Clin Infect Dis 2022;74(5):897–900. https://doi.org/10.1093/cid/ciab543.

[22] Aaronson LS, Teel CS, Cassmeyer V, et al. Defining and measuring fatigue. J Nurs Scholarsh 1999;31(1):45–50. https://doi.org/10.1111/j.1547-5069.1999.tb00420.x.

[23] Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. Brain Behav Immun 2022;103(April):154–62. https://doi.org/10.1016/j.bbi.2022.04.013.

[24] Chau NVV, Ngoc NM, Nguyet LA, et al. An observational study of breakthrough SARS-CoV-2 Delta variant infections among vaccinated healthcare workers in Vietnam. eClinicalMedicine 2021;41:101143. https://doi.org/10.1016/j.eclinm.2021.101143.

[25] François Watkins LK, Mitruka K, Dorough L, et al. Characteristics of reported deaths among fully vaccinated persons with coronavirus disease 2019—United States, January–April 2021. Clin Infect Dis 2022;75(1):e645–52. https://doi.org/10.1093/CID/CIAC066.