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Coronavirus Pandemic

Identification of SARS-CoV-2 variants of concern in vaccine-breakthrough infections

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Dear Editor,

The U.S. Food and Drug Administration has issued Emergency Use Authorization (FDA-EUA) for three COVID-19 vaccines targeting the SARS-CoV-2 spike glycoprotein (S) [1]. Emerging SARS-CoV-2 variants of concern (VOCs) such as B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), B.1.427/B.1.429 (Epsilon), and P1 (Gamma) encode mutations in the S protein [2,3]. There are contradictory results regarding the efficacy of these vaccines against VOCs and few population-level analyses are available [4]. The Centers for Disease Control and Prevention (CDC) defined vaccine breakthrough (VBT) as a U. S. resident who has SARS-CoV-2 RNA or antigen detected in a respiratory specimen collected at least 14 days after completing the primary series of an FDA-EUA SARS-CoV-2 vaccine [4]. The aim of this study was preliminary characterization of the SARS-CoV-2 genotypes detected in VBT cases.

Study

To support the public health response, nasopharyngeal specimens were collected from patients diagnosed with COVID-19 by real-time polymerase chain reaction (RT-PCR) at least 14 days after the completion of COVID-19 vaccination series. Samples with a cycle threshold (Ct) of ≤ 28 underwent whole genome sequencing as recommended by the CDC using the ClearLabs Dx system (ClearLabs, San Carlos, CA, USA) following the manufacturer's recommendations. Nextclade version v0.14.2 was used for mutation identification and data analysis [5]. Statistical analysis was performed using Fisher exact and $p < 0.05$ was considered to be statistically significant.

Results and Discussion

There were 62,842 COVID-19 cases in Nebraska from January 1 to July 31, 2021. Of those cases, 1,913 VBT cases (3%) were detected including 1,053 VBT after Pfizer vaccine, and 554, and 306 VBT cases after the completion of the Moderna and Janssen vaccination series, respectively (Table 1). For the VBT cases, there were 1,193 females and 720 males with a median age of 51 years (range, 13-103) (Table 1). In addition, 1,705 of the VBT cases (90.1%) were non-Hispanic and 1,623 cases (84.8%) were white. Of 1,913 VBT cases, 1,148 (60%) of the patients were symptomatic with mild symptoms including cough, fever, and/or shortness of breath while 181 (9.5%) were asymptomatic. Four hundred and fifteen of these patients (21.7%) had underlying medical conditions such as chronic lung, cardiovascular, and metabolic diseases. Based on the criteria of Ct ≤ 28, 577 samples out of 1,913 VBT cases were sequenced and included the following VOCs: 290 Delta, 219 Alpha, 23 Gamma, 12 Epsilon, 4 B.1.526, and 2 Beta. In addition, two of these represented the variant of interest (VOI) Iota, while 27 VBT cases were neither VOC nor VOI. In comparison to COVID-19 cases from unvaccinated patients (2,927 sequences), 1,672 of the cases were the Alpha variant and 501 cases the Delta variant (Table 1). The results of this study demonstrated that the VOC Delta variant represented

the most common strain associated with VBTs with $p \leq 0.0001$.

Conclusions

To the best of our knowledge, this is the first study addressing the effect of VOCs on the protective effectiveness of COVID-19 vaccines in the real world setting especially in the presence of conflicting evidence of vaccine efficacy against VOCs.

The strength of our findings comes from the evaluation of real cases and sequencing samples with high viral loads. In this study, 27 VBT cases belonged to non-VOC/VOI strains suggesting that factors other than mutations in the spike protein may be involved in the vaccine breakthrough process. Other factors that might contribute to VBTs include underlying medical conditions and the administered vaccine (type, dose, handling, and storage), which may result in inability of the immune system to mount immune response to the vaccine [3,6].

The main limitation of this study was the small sample size, especially the number of non-VOC cases. In addition, no serology studies were performed on these patients to measure the antibody titers in response to vaccination, and there was lack of information on pre-vaccination testing to determine previous COVID-19 infections, although high-levels of virus were detected in all individuals suggesting an acute infection at the time of sampling.

Sequencing of additional VBT cases is ongoing, along with serological testing to compare the antibody titers from individuals with natural infection to those without vaccination.

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Table 1. Demographic and epidemiology data for patients that represented vaccine breakthrough infections with COVID-19 from January 1 to July 31, 2021.

Characteristics	n
Age (years)	
Mean	53
Median	51
Range	13-103
Gender	
Male	720
Female	1,193
Ethnicity	
Not Hispanic or Latino	1,705
Hispanic or Latino	127
Unknown	81
Race	
White	1,623
Black or African American	100
Native Hawaiian/Pacific Islander	3
American Indian or Alaska Native	12
Asian	41
Other	110
Unknown	24
Symptom Status	
Symptomatic	1,148
Asymptomatic	181
Unknown	584
Underlying Medical Conditions	
Yes	415
No	540
Unknown	958
COVID-19 Cases	
Unvaccinated	60,929
Vaccinated	1,913
Pfizer	1,053
Moderna	554
Janssen (Johnson & Johnson)	306
Total Cases	**62,842**
Genotypes Identified by Sequencing	
Total Vaccinated	**577**
B.1.617 (Delta)	290
B.117 (Alpha)	219
P.1 (Gamma)	23
B.1.429/427 (Epsilon)	12
B.1.351 (Beta)	2
B.1.526 (Iota)	4
Not a VOC/VOI	27
Total Unvaccinated	**2,927**
B.1.617 (Delta)	501
B.117 (Alpha)	1,672
P.1 (Gamma)	58
B.1.429/427 (Epsilon)	126
B.1.351 (Beta)	25
B.1.526 (Iota)	35
C.37 (Lambda)	3
Not a VOC/VOI	507

VOC: variant of concern; VOI: variant of interest.

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