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Clinical characterization of COVID-19 breakthrough infections, Philippines

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ABSTRACT

We clinically characterized PCR detected breakthrough infections among partially/fully vaccinated cases with majority given an inactivated vaccine, CoronaVac. From 1 March to 15 July 2021, we detected 182 SARS-CoV-2 infections among vaccinated cases with 129 classified as breakthrough infections. Majority were male, 30–39 y.o., and were asymptomatic or mildly symptomatic with few severe cases. Alpha, Beta and Delta VOCs were detected from sequencing breakthrough infections. Healthcare workers had significantly lower Ct values (higher viral loads) versus non-HCWs. Our results underscore the importance of regular PCR screening for HCWs due to the risk of SARS-CoV-2 transmission from asymptomatic breakthrough infections and provide evidence supporting administration of a booster dose especially to HCWs.

1. Introduction

COVID-19 vaccines are critical for controlling the SARS-CoV-2 pandemic. Despite their ability to prevent symptomatic and severe COVID-19, vaccines are less effective at preventing asymptomatic SARS-CoV-2 infection[1]. The clinical presentation and outcome of breakthrough infections range from asymptomatic to severe and, rarely, death[1]. In the Philippines, Coronavac was the first vaccine brand administered in 1 March 2021 followed by ChAdOx1-S(March), Pfizer and Sputnik V(May), Moderna(June), and Janssen(July)(DOH,2021). SARS-CoV-2 vaccines were given by priority to frontline healthcare workers(HCWs), senior citizens, persons with comorbidities, and frontline personnel in essential sectors(uniformed personnel). Here, we clinically characterize SARS-CoV-2 infections among partially vaccinated and breakthrough SARS-CoV-2 infections among fully vaccinated individuals.

2. Methodology

2.1. Data and sample collection

Nasopharyngeal swabs were collected at the Victoriano Luna Medical Center(VLMC), a tertiary military hospital in Quezon City, Philippines. Samples were collected from patients with COVID-19-like-illness or as part of contact tracing. Vaccination (vaccination date, dose, vaccine brand) and clinical outcome data were collected. RT-PCR positive results with vaccination data were analyzed. Swabs were stabilized in Universal Transport Media, temporarily stored at 4°C, transferred to freezers(-80°C), and tested within 24–72 hours.

2.2. SARS-CoV-2 real time RT-PCR

RT-PCR testing was done at VLMC COVID Laboratory. Swabs were heat-inactivated at 65°C for 10 minutes. RNA was extracted using NATCH CS(Sansure, China). Specimens were thawed and a 200 µl aliquot was used for RNA extraction. SARS-CoV-2 semi-quantitative rRT-PCR kits(Sansure, China) were used. Extracted nucleic acids were amplified using SLAN96P and MA6000(Sansure, China). Breakthrough

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infection was defined as a SARS-CoV-2 rRT-PCR positive result in a respiratory specimen collected from a patient ≥14 days after the 2nd vaccine dose.

2.3. Next generation sequencing

Nasopharyngeal/oropharyngeal specimens were randomly selected from individuals fully vaccinated with CoronaVac and with breakthrough infections from 21 April to 6 July 2021. Viral RNA was extracted using a QiAamp viral RNA minikit (Qiagen) and extracted RNA shipped to AFRIMS, Bangkok, Thailand. Sequencing and bioinformatics analysis were performed as previously described [2].

2.4. Statistical analysis

Measures of central tendency/ dispersion and proportion were used to describe quantitative and categorical variables. Two-tailed t-test was used to evaluate continuous variables with p value < 0.05 considered statistically significant.

2.5. Ethics

This study was approved by the AFPHSC Research Ethics Committee. Written informed consent was obtained.

3. Results

From 1 March-15 July 2021, 182 SARS-CoV-2 infections among vaccinated cases were detected with 129 breakthrough infections. Table 1 shows the demographic data, clinical characterization of cases, and clinical/lab outcome. Most of the partial and/or breakthrough infections were male, 30–39 y.o., asymptomatic or mildly symptomatic, and required facility quarantine. Two deaths were recorded in the group with available clinical outcome. Most of the partial and/or breakthrough infections were male, 30–39 y.o., asymptomatic or mildly symptomatic, and required facility quarantine. Two deaths were recorded in the group receiving only 1 vaccine dose. Median age was 46, 32, and 39 for those tested positive after 1 dose, received 2 doses but tested positive <14 days (partial) and ≥14 days (full) after the 2nd dose, respectively. Among HCWs with data, 9(23%), 2(14%), and 31(25%) had partial or breakthrough infections for the 1-dose, 2-dose (partial) and 2-dose (full) groups, respectively, with a mean N-gene Ct value ranging from 28–29 for all 3 groups (Table 1). Among 30 HCWs ([16/30(53%)] female; majority [11/30(37%)] from the 30–39 y.o. group) with breakthrough infections given CoronaVac and tested by RT-PCR, 28/30(93%) and 13/30(43%) had N gene Ct values <35 and ≤25, respectively, while among non-HCWs ([46/60(77%)] male; majority [22/60(37%)] from the 30–39 y.o. group) with breakthrough infections, 47/60(78%) and 14/60(23%) had N-gene Ct values <35 and ≥25, respectively (Table 2). The mean of the Ct values of the N-gene Ct value was 31 (range 30–39 years age group) (28). Among HCWs with data, 9(24%), 7(20%) and 33(26%) had partial or breakthrough infections for the 1-dose, 2-dose (partial) and 2-dose (full) groups, respectively, with a mean N-gene Ct value ranging from 28–29 for all 3 groups (Table 1).

Table 1

| Category                        | No. of specimens with N gene Ct value ≤35 | No. of specimens with N gene Ct value ≥35 |
|---------------------------------|------------------------------------------|------------------------------------------|
| TCRT                             | 31/37 (84)                                | 13/37 (35)                                |
| TCRT + 1 dose                   |                                        | 12/37 (45)                                |
| TCRT + 2 doses                  |                                        | 1/13 (7)                                  |
| Median age (range)              | 19 (6-38)                                 | 15 (7-61)                                 |
| Male (%)                        | 23 (59)                                   | 4 (8)                                     |
| Facility Quarantine (%)         | 13/30 (43)†                               | 6/14 (43)                                 |
| Home Quarantine (%)             | 7/30 (23%)†                               | 5/14 (36)                                 |
| Deaths (%)                      | 2/30 (7%)†                                | 0/14 (0%)                                 |
| Mean Ct value of N gene (range) | 36 (24 - ≥40)                             | 34 (22 - ≥40)                             |
| Mean Ct value of N gene (range) | 29 (20 - 38)                              | 28 (19 - 37)                              |
| Facility Quarantine (%)         | 13/30 (43)†                               | 6/14 (43)                                 |
| Home Quarantine (%)             | 7/30 (23%)†                               | 5/14 (36)                                 |
| Deaths (%)                      | 2/30 (7%)†                                | 0/14 (0%)                                 |
| Mean Ct value of N gene (range) | 36 (24 - ≥40)                             | 34 (22 - ≥40)                             |
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| Deaths (%)                      | 2/30 (7%)†                                | 0/14 (0%)                                 |
| Mean Ct value of N gene (range) | 36 (24 - ≥40)                             | 34 (22 - ≥40)                             |
| Mean Ct value of N gene (range) | 29 (20 - 38)                              | 28 (19 - 37)                              |

*a* 30 out of 39 with available clinical outcome

† 1 mortality; initially presented with no symptoms

‡Received 2 doses but positive <14 days after 2nd dose

| Received any vaccine brand |
|---------------------------|

4. Discussion

Based on September 2021 data, distribution of the vaccines given was CoronaVac (55.66%), ChAdOx1-S (18.07%), Janssen (10.69%), Pfizer (9.53%), Moderna (5.04%), Sputnik V (0.98%), and Sinopharm (0.03%) (DOH, 2021). During the study period, 2,597 SARS-CoV-2 cases were detected at the VLMC COVID lab (% positivity rate), 251,316 and 504,529 cases SARS-CoV-2 cases reported from the National Capital Region and at the national level, with all 4 SARS-CoV-2 variants of concernVOCool(Alpha, Beta, Delta, Gamma) circulating [5]. Most partial and breakthrough infections were male and from the 30–39 y.o. age group. This could be explained by the demographics of the population tested who were mostly active military service members (male:18-56 y.o.). Breakthrough infections among those given CoronaVac and with HCW data, majority were females among HCWs in contrast to non-HCWs where majority were males. Most of the partial and breakthrough infections were also asymptomatic or mild, though 10/94(11%) required hospitalization but eventually recovered, similar to results from CoronaVac trials [4,5]. There were patients who presented with severe symptoms, 4(10%) and 1(1%) among those who received only 1 dose and 2 doses of CoronaVac, respectively. There were 2 deaths (CoronaVac–1; ChAdOx1–S–1) in the group infected after 1 dose. Colds (runny nose) was a more frequent symptom versus cough for breakthrough infections which is comparable with reports citing the changing symptomatology of COVID-19 [6].

When the Ct value is >34, live virus is undetectable in vitro [7,8].
is probably a substantial underestimation given the large proportion of associated with higher exposure risk.

HCWs, use of boosters, and continued compliance to non-sequenced samples.

Since a Ct value of <35 is associated with infectivity [7, 8], we can assume that fully vaccinated persons with asymptomatic breakthrough infections and those with low Ct values (i.e., <25) can shed and transmit infectious virus [9]. In our study, among fully vaccinated asymptomatic individuals positive for SARS-CoV-2, 70%, 42% and 18% had N gene Ct values below 35, 30 and 25, respectively. The possibility of potential infectivity among fully vaccinated breakthrough infections is important for fully vaccinated health care workers infected with SARS-CoV-2 but who are asymptomatic. This is evidenced by the significantly lower Ct values (higher viral loads) of the Orf1ab and N genes among fully vaccinated HCWs with breakthrough infections compared to the Ct values of non-HCWs. The significantly lower Ct values may be attributed to the continuous and sustained exposure of HCWs to COVID-19 infected patients.

The study period coincided with a surge of infections due to alpha and beta VOCs which show increased transmissibility versus earlier SARS-CoV-2 variants [10,11]. Best hospital infection prevention and control practices and strategies were exercised but the risk of hospital-associated transmission should be viewed in the midst of a COVID-19 surge and reflective of a resource-constrained with limited staffing setting.

CoronaVac neutralizing antibody titers were reported to be short-lived and declined below the seropositive cutoff after 6–8 months [12]. Higher rates of breakthrough infections are expected if COVID-19 vaccines with lower efficacy are used and when the predominant variants are VOCs [13]. Alpha and Beta VOCs were dominant during these months [14] with Delta first detected on May 2021 [15]. The Delta VOC became the predominant circulating VOC starting end of July-August 2021, explaining the VOC predominance and distribution among the sequenced samples.

Our results support the importance of regular PCR screening for HCWs, use of boosters, and continued compliance to non-pharmaceutical interventions even after vaccination due to asymptomatic breakthrough infections. Though we recorded lower Ct values among breakthrough infections in HCWs, majority were asymptomatic or mild. We recommend that further studies on booster vaccination strategies be done, particularly on the best combination of vaccine brand/platform and optimal approach (homologous vs heterologous) which will provide the highest protection especially for populations associated with higher exposure risk.

5. Limitations

The number of COVID-19 vaccine breakthrough infections detected is probably a substantial underestimation given the large proportion of asymptomatic infections. SARS-CoV-2 RT-PCR testing was performed at irregular intervals, and we were not able to culture infectious virus or estimate the breakthrough infection rates because the denominator was not well-defined. The data may also not be fully representative of the spectrum of illness present or the variants responsible for breakthrough infections due to the small sample size.

Data Availability

The 9 SARS-CoV-2 genomes from the Philippines were deposited in the GenBank database (accession no. OL629465 to OL629473). The raw reads have been deposited in the NCBI Sequence Read Archive (SRA accession no. SRR17024243 to SRR17024251). The BioProject accession no. is PRJNA783155. The BioSample accession no. is SAMN23419457 to SAMN23419465.

Disclaimer

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Philippines and US Department of the Army or the Department of Defense. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships which could have appeared to influence the work reported in this paper. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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References

[1] Team CC-VBCI, COVID-19 vaccine breakthrough infections reported to CDC - United States, January 1-April 30, 2021, MMWR Morb. Mortal. Wkly. Rep. 70 (21) (2021) 792–793.
[2] JM Velasco, P Chinnawirotpisan, K Joonlasak, W Manasatienkij, A Huang, MT Valderama, et al., Coding-complete genome sequences of 23 SARS-CoV-2 samples from the Philippines, Microbiol. Resour. Announc. 9 (43) (2020).
[3] DOIH, UP-PGC, AND UP-NIH CONFIRM ADDITIONAL COVID-19 VARIANT CASES INCLUDING FIRST CASE OF LAMBDA VARIANT [press release], Manila, 15 Aug 2021 2021.
[4] MD Tamrissor, HL Doganay, M Akova, HR Gumer, A Azap, S Akhan, et al., Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey, Lancet (2021).
[5] A Jara, EA Undurraga, C Gonzalez, F Paredes, T Fontecilla, G Jara, et al., Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile, N Engl. J. Med. (2021).

[6] ZOE Covid Study 2021 [cited 2021 28 September 2021]. Available from: https://covid.joinzoe.com/post/new-top-5-covid-symptoms#part_1.

[7] MM Arons, KM Hatfield, SC Reddy, A Kimball, A James, JR Jacobs, et al., Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility, N Engl. J. Med. 382 (22) (2020) 2081–2090.

[8] B La Scola, M Le Bideau, J Andreani, VT Hoang, C Grimaldier, P Colson, et al., Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards, Eur. J. Clin. Microbiol. Infect. Dis. 39 (6) (2020) 1059–1061.

[9] MC McEllistrem, CJ Clancy, DJ Buehrle, N Singh, A Lucas, V Sirianni, et al., SARS-CoV-2 is associated with high viral loads in asymptomatic and recently symptomatic healthcare workers, PLoS One 16 (3) (2021), e0248347.

[10] NG Davies, S Abbott, RC Barnard, CJ Jarvis, AJ Kucharski, JD Munday, et al., Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England, Science 372 (6538) (2021).

[11] H Tegally, E Wilkinson, M Giovanetti, A Iranzadeh, V Fonseca, J Giandhari, et al., Detection of a SARS-CoV-2 variant of concern in South Africa, Nature 592 (7854) (2021) 438–443.

[12] H Pan, Q Wu, G Zeng, J Yang, D Jiang, X Deng, et al., Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial, medRxiv (2021), 2021.07.23.21261026.

[13] E. Mahase, Covid-19: how many variants are there, and what do we know about them? Bmj 374 (2021) n1971.

[14] JM Velasco, P Chinnawirotpisan, MT Valderama, K Joonlasak, W Manazaienski, A Huang, et al., Coding-complete genome sequences of 11 SARS-CoV-2 B.1.1.7 and B.1.351 variants from metro manila, Philippines, Microbiol Resour Announc. 10 (28) (2021) e0049821.

[15] Morales NJ. Philippines tightens curbs after detecting first local cases of Delta variant 2021 [cited 2021 4 Nov 2021]. Available from: https://www.reuters.com/world/asia-pacific/philippines-detects-first-local-transmission-delta-variant-2021-07-16/.