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Breakthrough infections due to SARS-CoV-2 Wild type, the Delta variant and the Omicron variant in early fourth wave of epidemics in Myanmar

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The "severe acute respiratory syndrome coronavirus type 2" (SARS-CoV-2) is also known as "coronavirus disease 19" (COVID-19). It originated in Wuhan, Hubei province, People's Republic of China, in December 2019; and, it spread worldwide causing a global pandemic. Genetic variants of SARS-CoV-2 have been emerging and circulating around the world throughout the COVID-19 pandemic namely the original (wild-type), the Alpha variant, the Beta variant, the Delta variant, and the Gamma variant. In third wave, the notorious variant was the Delta variant; it was well-known for quick transmissibility, causing high morbidity and mortality. In late November 2021, the Omicron variant was first detected in South Africa.

According to vaccination record, nearly half of the world population had completed vaccination (World Health Organization, 2022). In Myanmar, the vaccine coverage in end of November 2021 was as follows: 30% of population received one dose of vaccination; and, 21% had completed vaccination- two doses. Then, the coverage rose to nearly 40% and 30% respectively in early January 2022 (Our World in Data, 2022). The morbidity and mortality of SARS-CoV-2 infected cases may be better with increasing COVID-19 vaccine coverage; nonetheless, the transmissibility and virulence of several variants and old Wild type leads to breakthrough infections **(**BTIs). Therefore, information on BTIs following COVID-19 vaccination was required in Myanmar; vaccination status, the duration of symptom onset to last dose of vaccination, clinical severity and outcome of BTIs in relation to wild type, the Delta variant and the Omicron variant. The findings will give some advice to the national vaccine program particularly the requirement for booster dose.

There were several reports on BTIs in relation to different variant of SARS-CoV-2. The study from UK pointed out that "the third/booster dose of vaccination offers substantial additional protection against the risk of symptomatic COVID-19 for being infected with the Omicron variant when compared to ≥ 25 weeks post second vaccine dose" (Sheikh et al., 2021). In the outbreak report from Norway, the SARS-CoV-2 Omicron variant was highly transmissible among fully vaccinated young and middle-aged adults (Brandal et al., 2021). Hansen et al. (2021) found that the Omicron variant invaded COVID-19 vaccine more than the Delta variant.

The transmissibility of the Omicron variant compared to other variants is not clearly known (World Health Organization, 2021). The study from Norway, Brandal et al., (2021) revealed that the SARS-CoV-2 Omicron variant was highly transmissible even among fully vaccinated young and middle-aged adults. The omicron variant was at least twice as contagious as delta and at least four times as contagious as the original version of the coronavirus (UK Health Security Agency, 2021). A new study on recent Ontario COVID-19 cases suggests the Omicron variant is less likely to cause hospitalization or death than the Delta variant, but could still significantly impact health-care systems due to its high transmissibility (Public Health Ontario, 2021).

According to report on BTIs among physicians from Myanmar during the third wave, the Delta epidemic, the common symptoms were aches and pain, sneezing, runny nose, headache, cough, and sore throat (Pyar et al., 2021).

Running nose, sneezing (stuffy nose), sore throat, fatigue and headache were top 5 symptoms found with the Omicron variant infected persons, reported by (Zoe Covid Study Group, 2022). They also found that the symptoms of the Omicron variant infected persons were not statistically different from those infected with the Delta variant where only 50% of people experiencing the classic three symptoms of fever, cough, or loss of sense of smell or taste. According to (UK Health Security Agency, 2021), sore throat was seen in half of the cases with the Omicron variant; however, it was noted in one-third of the cases with the delta variant. They also compared the symptoms; a loss of smell and taste was less common among omicron cases compared to delta variant cases.

Regarding the clinical severity of the variant, patients infected with the Delta variant had moderate to severe status with variable mortality depending mainly on clinical severity and co-morbid status. Of clinical severity of the Omicron variant, the reports were contradictory. The preliminary data from South Africa suggested that not only the number of the Omicron infected cases but also the number of cases to keep in hospital were high; the cases were reported as severe (World Health Organization, 2021). On the other hand, in Scotland, early national data revealed that the Omicron variant was associated with a two-thirds reduction in the risk of COVID-19 hospitalisation when compared to Delta variant (Sheikh et al., 2021). Hospitalisation risk from Omicron infection was nearly one-third of Delta (UK Health Security Agency, 2021). The researchers from California also pointed out that the Omicron infected cases were less severe (Lewnard et al., 2022); and, it was proved by one preprint study (Wang et al., 2022). Omicron infections were associated with a 91% reduction in risk of death compared to the Delta variant (Lewnard et al., 2022). BTIs among physicians from Myanmar during the third wave possibly the Delta epidemic revealed that 90% of cases were mild; only 10% were severe and none of them was fatal (Pyar et al., 2021).

Based on WHO severity score, the clinical severity of COVID-19 infection was classified into four types: mild, moderate, severe and critical. In mild category, patients have symptoms only, CXR is normal and, SaO_2 on air is normal. In moderate category, CXR shows pneumonias and SaO_2 on air is $\geq 90\%$. In severe category, respiratory rate is > 30/min and, SaO_2 on air is < 92%. In critical disease category, the patient has ARDS; he may have sepsis with multi-organ dysfunction or septic shock or acute thrombosis (pulmonary embolism, acute coronary syndrome, acute stroke).

Nasopharyngeal swabs were taken from both clinically suspicious cases, contacts of COVID-19 PCR positive cases, and healthy travelers coming to Myanmar at Mingaladon airport, No.(1) Defence Services General Hospital (1000-Bedded) and Defence Services Liver Hospital (300-Bedded), Mingaladon COVID-19 treatment Hospital, from October 2021 to early January 2022; then, they were proceeded with both Abbot COVID-19 Antigen Rapid Test Device and RT-PCR. Then, they were differentiated with special tests for variant.

Nasopharyngeal swabs were collected using plastic swab with nylon flocked swabs, it was placed in a 3ml viral transport media (Himedia, India). The virus RNA was extracted using the magnetic beads method, according to the instruction of the nucleic acid extraction kit (Bioer MagaBioplus Virus DNA/RNA purification Kit II, China). SARS CoV-2 RNA detection was done by bioPerfectus Nucleic Acid Detection Kit (bioPerfectus, Jiangsu bioPerfectus Biotech Co.,Ltd, China). All SARS CoV-2 positive samples were tested with abTES^{TM} COVID-19 Variant qPCR I kit (AIT biotech Pte-Ltd, Singapore), using Applied Biosystem 7500 Fast Real Time PCR System according to the manufacturer's instruction. abTES^{TM} COVID-19 variant qPCR I kit differentiates wild and variant SARS CoV-2 infection among all positive samples. After that, SARS CoV-2 Alpha, Beta, Gamma, Delta & Omicron variant infection among all SARS CoV-2 variant samples were tested by GenXPro SARS CoV-2 ABGD variant Detection Kit (GenXPro, Germany) and SARS CoV-2 variant Omicron (B.1.1.529) Real Time PCR Kit (bioPerfectus, Jiangsu bioPerfectus Biotech Co.,Ltd, China). SARS CoV-2 variant Omicron (B.1.1.529) Real Time PCR Kit detect Orf1ab gene and mutations E484A, N679K, L981F, 69-70del and H655Y of S gene. A sample was considered as Omicron (B.1.1.529) if any two of the three specific targets (E484A, N679K and L981F) with cycle threshold (Ct) less than 40 and Δ Ct values were detected in manufacturer's reference range. Clinical severity/symptoms, travel history, vaccination history and co-morbid status was taken either face to face (if they came to No.(1) DSGH or Mingaladon COVID-19 treatment Hospital (300 Bedded)) or viber/ telecommunication (if they did not come to No.(1) DSGH or Mingaladon COVID-19 treatment Hospital (300 Bedded). Then, clinical, chest radiograph (mild, moderate and severe cases) and variant parameters were analyzed. Those requiring hospital admission at Mingaladon COVID-19 treatment Hospital (300-Bedded) were treated according to hospital/National guideline: antiviral drugs, antibiotics, oxygen therapy, steroid therapy, heparin therapy, fluids and electrolyte and supportive care. The blood tests were done according to guideline and monitored till discharge from Mingaladon COVID-19 treatment Hospital (300-Bedded) or death.

During this period, among 50,842 nasopharyngeal swab samples were tested and 770 (1.5%) samples were SARS CoV-2 test positive. The total number of positive samples on October, November, December and January were 321, 272, 149 and 28 respectively. In these 770 positive samples, Ct value less than 30 were selected (n = 150). Table (1) shows clinical severity status of cases infected with different variant.

Wild type was seen in 2 cases (2/150 = 1.3 %) and Delta variant 138 cases (138/150= 92.0 %). The Omicron variant was detected only in January 2022; the number was 10 (10/150= 6.7 %) over five months. Table (2) reveals the survival status of BTIs with different variant.

There were two cases infected with the Wild type in this study; the first case was fully vaccinated with Covaxin and the second case had incomplete vaccination. The first case, BTIs with the wild type, was fully vaccinated; the second dose was taken 6 months ago. Thus, it was clear that the protective efficacy of vaccine decreased by 6 months. The study from Israel revealed that the prevention effect reduced at 2 months after vaccination and finally disappeared at 6 months or longer after vaccination (Levine-Tiefenbrun et al., 2021). It again highlighted the need for booster vaccination. Likewise, El Sahly provided the evidence that the mRNA-1273 vaccine was efficacious in preventing Covid-19 illness and severe disease at more than 5 months (El Sahly et al., 2021). Their symptoms were fever, loss of smell and cough. The finding was comparable with the earlier study done in second wave of epidemics in Myanmar at the end of 2020, probably the wild type; it revealed that 81.5% were symptomatic patients; the most common presenting symptoms were fever 54.1%, loss of smell 50.3%, and cough 30.9% (Htun et al., 2021). As a severity, 20.7% of patients had signs of severe pneumonia; however, in this study, both were mild form and not fatal. It pointed out the report by CDC; the age-adjusted rate of hospitalization among US adults aged 18 years or older was 83.6 per $100,000$ for unvaccinated persons compared with 4.5 per $100,000$ for fully vaccinated persons (Danza et al., 2022). Likewise, Tenforde and colleagues demonstrated that patients vaccinated with an mRNA COVID-19 vaccine was significantly less likely for hospitalization and disease progression to death or mechanical ventilation (Tenforde et al., 2021)

In this study, the Delta variant infected BTIs occupied the majority of cases (92%); it produced mild 36.2% (50 cases), moderate 52.2% (72 cases), severe 10.9% (15 cases) and critical 0.7% (1 case) infection. The common presentations of them were fever (40%), dyspnea (30%), cough (20%), loss of smell (20%), loss of taste (13%), myalgia (13%), sore throat (13%), runny nose (13%), and loose motion (13%). The findings were comparable with the previous study on BTIs among physicians caring COVID-19 cases in Myanmar (Pyar et al., 2021). They did the study in the third wave of epidemics in Myanmar in July 2021; probably the Delta variant epidemics. The top symptoms were a headache, sore throat, runny nose, fever and cough (Pyar et al., 2021). The number of cases required hospital admission was 88 (63.8%), all were infected with the Delta variant; moderate, severe and critical cases.

In this study, the Delta variant infected BTIs did not cause severe illness generally owing to protective effect of vaccine; mild 36.2% (50 cases) and moderate 52.2% (72 cases). It provided another evidence for previous report. The report from Vietnam among BTIs in health care workers highlighted that BTIs due to the Delta variant following Oxford-AstraZeneca vaccination were associated with high viral loads, prolonged PCR positivity and low levels of vaccine-induced neutralizing antibodies; however, they were asymptomatic or mild disease in terms of severity (Chau et al., 2021). Likewise, multicenter Cohort study from China showed that the mRNA vaccines were highly effective at preventing symptomatic and severe COVID-19 associated with the Delta infection; and, vaccination is associated with faster decline in viral RNA load and a robust serological response (Jin et al., 2022). Moreover, study on BTIs done in Day-Care center of South Korea again confirmed that the Delta variant had high infection rate, high transmissibility; however, clinical severity was mild (Yi et al., 2022). The beauty of BTIs including infection with the Delta variant was reported as follows. They were less likely to develop symptoms and their symptoms were not severe even if they acquired infection (Chia et al., 2021) (Shah et al., 2021) (de Gier et al., 2021). In addition, those with BTIs rarely need hospital admission; and their rate of recovery was faster than nonvaccinated (Eyre et al., 2021)(Tartof et al., 2021).

In this study, the mortality rate was 5.8% (7 severe and one critical case); non-survivors were due to the Delta variant. COVID-19 related death in 6 cases and COVID-19 unrelated death in 2 cases. The one and only one critical case was brought to hospital in state of deep coma (Glasgow Coma Scale 3/15) on admission; moreover, he had associated co-morbidities like old age (63 year), hypertension with moderate cardiomegaly, diabetes mellitus, acute kidney injury (creatinine 1.8 mg %), very high D dimer (> 10,000 ng/ml), SaO_2 85% on air and right upper lobe collapse in chest radiograph. Two out of six fatal cases had COVID-19 related gastrointestinal complications. One case had gastrointestinal hemorrhage, thrombocytopenia (platelet count 20 x 10^9/ L) and hypothyroidism; and another case had duodenal perforation, age 65year, died on 4th post-operative day. Two out of six non-survivors had diabetes mellitus and chronic obstructive airway disease. The last fatal case was female, 47 years having many co-morbid conditions such as brain tumor, congenital heart disease- atrial septal defect and diabetes mellitus; she died of COVID-19 pneumonia. The cause of death was unrelated to COVID-19 in 2 cases: acute myeloblastic leukemia, age 33 year; and, cerebrovascular hemorrhage (basal ganglia hemorrhage, 70-year male, died on post-operative day 4 following Burr Hole surgery).

Nearly 90% (122/138) of cases with the Delta variant infection were fully vaccinated. And 11% (16/138) of cases did not get vaccine received vaccination; hence, they had

severe (10.9%, 15/138) and critical (0.7%, 1/138) infections. The mild (36.2%, 50/138) and moderate (52.2%, 72 /138) cases had completed vaccination; nonetheless, the time of symptom onset to vaccination second dose to was 6 months. Thus, it proved the requirement for booster dose as the efficacy for protection decreased gradually over 6 months; it was also reported in other studies. The prevention effect reduced at 2 months after vaccination and finally disappeared at 6 months or longer after vaccination in Israel study (Levine-Tiefenbrun et al., 2021). Likewise, the mRNA-1273 vaccine continued to be efficacious in preventing Covid-19 illness and severe disease at more than 5 months (El Sahly et al., 2021). Furthermore, the effectiveness of the coronavirus disease 2019 (COVID-19) BNT162b2 vaccine in preventing disease and reducing viral loads of breakthrough infections (BTIs) was said to be decreasing especially with the Delta variant; analysis of viral loads of over 16,000 infections during the Delta-variant-dominated pandemic wave in Israel revealed that BTIs in recently fully vaccinated individuals had lower viral loads than infections in unvaccinated individuals. In addition, the study in Qatar gave another evidence that BNT162b2-induced protection against SARS-CoV-2 infection appeared to wane rapidly following its peak after the second dose, but protection against hospitalization and death persisted at a robust level for 6 months after the second dose (Chemaitelly et al., 2021).

Infection due to the Omicron variant was seen in 10 cases in this study. Regarding clinical presentations, although the Omicron variant caused more of upper respiratory symptoms as its main habitus was upper airways; all were asymptomatic in this study. Two out of ten cases, mother and her child 4 years old, did not have vaccine; they came back from India for corrective surgery for congenital heart disease- ventricular septal defect. Eight out of ten cases (80%) had completed vaccination; however, they got second dose 6 months ago. It also confirmed that the vaccine efficacy waned after 6 months; and, the need for booster dose. It proved United Kingdom study which pointed out that "the third/booster dose of vaccination offers substantial additional protection against the risk of symptomatic COVID-19 for being infected with the Omicron variant when compared to ≥ 25 weeks post second vaccine dose" (Sheikh et al., 2021). Only one case completed booster dose. It confirmed the finding from Norway; the SARS-CoV-2 Omicron variant was highly transmissible even among fully vaccinated young and middle-aged adults (Brandal et al., 2021). Likewise, Hansen et al. (2021) confirmed that the Omicron variant invaded COVID-19 vaccine more than the Delta variant. According to the UK study, sore throat was commonly reported as common presentation of the omicron virus cases; loss of smell and taste were less common among omicron cases compared to delta variant cases. In this study, cases infected with the Omicron variant were asymptomatic; and, they did not need hospital stay or oxygen. Therefore, it provided the evidence for report from Ontario; they found that the Omicron variant less likely to cause hospitalization or death than the Delta variant, but could still significantly impact health-care systems due to its high transmissibility (Public Health Ontario, 2021).

It can be concluded that BTIs due to the wild type was not rare; however, it caused mild infection if there was no co-morbidity. BTIs due to the Delta variant were the most common BTIs; nonetheless, the majority of them (88%) had mild to moderate severity. Mortality rate of BTIs due to the Delta variant was 5.6% (8/138); these non-survivors had poor prognostic factors like associated co-morbidities (diabetes mellitus, hypertension, chronic obstructive airway disease), old age, late referral, associated malignancy, gastrointestinal bleeding, duodenal ulcer perforation, thrombocytopenia, and multi-organ failure. BTIs due to the Omicron variant was seen in 10 cases who came back from abroad; they were asymptomatic. In view of duration of symptom onset to timing of vaccination second dose, all BTIs cases took second dose 6 months ago; it showed falling efficacy of protective effect of vaccine if longer than 6 months and the requirement for booster dose particularly 4 to 5 months after second dose.

Table 1. Clinical severity status of cases infected with different variant (n = 150)

Type of SARS CoV-2 virus	Number of cases	Asymp-tomatic	Mild	Moderate	Severe	Critical	Survived	Non-survived	Imported
Wild	2		2				2		
Delta	138		50	72	15	1	130	8	2 Malaysia, 1 Syri lanka
Omicron	10	10					10		9 India, 1 Russia
	150						142	8	

Table 2. Survival status of BTIs cases infected with different variant (n = 132)

Type of SARS CoV-2 virus	Total number of cases	Number of BTIs (percent)	Number of survivors (percent)	Number of non-survivors (percent)
Wild	2	1(50%)	2 (100%)	0
Delta	138	123 (89.1%)	130 (95.4%)	8 (5.6%)
Omicron	10	8 (75%)	10 (100%)	0
Total	150	132	142	8

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