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RESEARCH ARTICLE

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Hesitancy, reactogenicity and immunogenicity of the mRNA and whole-virus inactivated Covid-19 vaccines in pediatric neuromuscular diseases

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ABSTRACT

The mRNA-based BNT162b2 and inactivated whole-virus CoronaVac are two widely used COVID-19 vaccines that confer immune protection to healthy individuals. However, hesitancy toward COVID-19 vaccination appeared to be common for patients with neuromuscular diseases (NMDs) due to the paucity of data on the safety and efficacy in this high-risk patient population. Therefore, we examined the underlying factors associated with vaccine hesitancy across time for NMDs and assessed the reactogenicity and immunogenicity of these two vaccines. Patients aged 8–18 years with no cognitive delay were invited to complete surveys in January and April 2022. Patients aged 2–21 years were enrolled for COVID-19 vaccination between June 2021 and April 2022, and they recorded adverse reactions (ARs) for 7 days after vaccination. Peripheral blood was obtained before and within 49 days after vaccination to measure serological antibody responses compared to healthy children and adolescents. Forty-one patients completed vaccine hesitancy surveys for both timepoints, while 22 joined the reactogenicity and immunogenicity arm of the study. Two or more family members vaccinated against COVID-19 was positively associated with intention of vaccination (odds ratio 11.7, 95% CI 1.81–75.1, $p = .010$). Pain at the injection site, fatigue, and myalgia were the commonest ARs. Most ARs were mild (75.5%, $n = 71/94$). All 19 patients seroconverted against the wildtype SARS-CoV-2 after two doses of either vaccine, similar to 280 healthy counterparts. There was lower neutralization against the Omicron BA.1 variant. BNT162b2 and CoronaVac were safe and immunogenic for patients with NMDs, even in those on low-dose corticosteroids.

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Introduction

Since the onset of the COVID-19 pandemic, infection by the SARS-CoV-2 virus has been associated with significant morbidity, mortality, and negative socioeconomic impact throughout the world[1–3] Certain patient populations, such as those with neuromuscular diseases (NMDs), have greater risks of severe disease and death from infections due to their muscle weakness of the chest wall or diaphragmatic muscle, cardiac involvement, and immunosuppressed state.[4] Vaccination is highly effective against symptomatic infection, hospital admission, and severe COVID-19 in healthy adults and children.[5–10] As such, the mRNA-based BNT162b2 and inactivated whole-virus CoronaVac vaccines are amongst the most widely used COVID-19 vaccines globally since authorization for emergency use by World Health Organization.[11–13] Based on these findings in healthy individuals, several national neurology associations, and neuromuscular disease networks recommend COVID-19 vaccination for those with NMDs, but data on this important high-risk patient population specifically remain scarce.[4]

Although COVID-19 vaccination is expected to reduce infectious disease severity in the NMD population, vaccine hesitancy appears to be a major potential barrier.[14] As an example, our group found that in mid-2021 when the COVID-19 vaccines initially became available for adolescents, only 39% of healthy adolescents planned for vaccination.[15] For NMDs, only 69.0% of the parents would want their children vaccinated during the early pandemic period in December 2020.[16] It is also concerning that as little as 42.6% of those with Duchenne muscular dystrophy (DMD) were vaccinated against COVID-19 by November 2021 in Poland.[17] Their reasons for not opting for vaccination during this early, pre-Omicron variant period included the potential for reduced efficacy due to their use of immunosuppressive or immunomodulating therapies and uncertainties regarding possible interactions between the vaccines and treatments for NMDs.[18–20] Despite the availability of two different COVID-19 vaccine types, BNT162b2 and CoronaVac, in our locality, our NMD patients also appeared reluctant on vaccination. Some of these patients had cited the

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risks of adverse effects, disease complications, and reduced efficacy as some of their main concerns.

The reason that there has been a paucity of NMD-specific safety and immunogenicity data despite the rollout of the many types of COVID-19 vaccines is because NMD is a group of rare diseases and NMD patients are hesitant to volunteer for receiving novel vaccines, and so large-scale studies had not yet been possible. In fact, the prevalence of NMDs is as low as 1–10 per 100,000 of the total population.[21] Therefore, scientific evidence on COVID-19 vaccination in NMD patients have been based on small cohorts only thus far. For 14 adult NMD patients, BNT162b2 and mRNA-1273 vaccines generally seemed safe and immunogenic, and similar outcomes were observed in 53 adult inpatients with muscular dystrophies who received 2 doses of BNT162b2.[22,23] The mRNA-1273 vaccine achieved robust humoral and cellular immune responses in 100 adult patients with myasthenia gravis.[24] Unfortunately, there are still no available safety and immunogenicity data on COVID-19 vaccines in children with NMDs. Importantly, there has been no previous research on the inactivated COVID-19 vaccines in adult or pediatric patients with NMDs, including immunogenicity against the novel variants, such as Omicron. Data on both vaccines are essential because some individuals experience significant adverse effects on one vaccine type and are only able to tolerate the other type.[25]

Therefore, this study investigated in-depth the underlying reasons and temporal changes in vaccine hesitancy for pediatric patients with NMDs during the Omicron wave in 2022, using our previously published survey, with an expanded questionnaire tailored specifically for pediatric NMDs.[15] Additionally, we assessed the safety and immunogenicity of two types of COVID-19 vaccines, the BNT162b2 and CoronaVac, by recording adverse effects and measuring serum antibody levels and neutralization against the wild type (WT) SARS-CoV-2 virus and Omicron B.1.1.529 variant.

Patients and methods

Study population

All participants were screened from the Hong Kong (HK) NMD registry.[26] This registry has been approved by the Institutional Review Board (IRB) and collects patient and clinician-reported demographic and clinical information from those with confirmed diagnoses of NMDs after their consent.[26] The diagnosis was determined by clinical pediatric neurologists and supported by genetic testing and/or muscle biopsy results. The neurology clinical study team is based at HK Children's Hospital, Duchess of Kent Children's Hospital at Sandy Bay and Queen Mary Hospital that receives referrals from throughout the entire HK territory for clinical care and research in pediatric NMDs.[26] Participation in the vaccine hesitancy survey required patients to have reached a neurodevelopmental age that could comprehend and provide credible responses to the detailed questionnaire independently without direct parental influence. As such, the inclusion criteria were 8–18 years old and no cognitive deficit in this survey arm of the study. In another arm of this study, which did not necessitate such neurodevelopmental age limitations, patients aged 2–21 years were invited for COVID-19 vaccination to study the reactogenicity and immunogenicity of the BNT162b2 and CoronaVac vaccines. Both arms of the study required at least one parent to accompany the patient during the study process. Potential participants needed to be in stable condition. A patient could join either or both arms of the study, if eligible (Figure 1).

COVID-19 vaccine hesitancy survey

Patients received and completed the first survey through online or phone interviews in January 2022. The survey was based on our previous publication on 2,609 healthy adolescents, supplemented with more tailored queries pertinent to NMD patients and younger age groups that were added into this study.[15] In summary, it included 21 yes/no or multiple-choice questions on patient demographics, presence of medical complexity, history of past COVID-19 infection, influenza and COVID-19 vaccination, intention of receiving COVID-19 vaccination and the reasons for their choice (Supplementary Data). Concerns about receiving COVID-19 vaccination included perception of risks, challenges in access to vaccination centers, adverse effects, less efficacy than their healthy counterparts and vaccine–drug interactions that potentially affect their current NMD treatments. The expected time required to complete the survey was 15 min. At least one parent/legally authorized representative/legal guardian accompanied the child participants in completing the survey. A follow-up survey was sent to patients in April 2022 to longitudinally assess changes in attitudes, hesitancy, and associated reasons shortly after the peak of the first major COVID-19 wave due to the SARS-CoV-2 Omicron variant in HK.

Reactogenicity and immunogenicity study of COVID-19 vaccines

The reactogenicity and immunogenicity arm is a sub-study under the registered Coronavirus disease-19 (COVID-19) Vaccination in Adolescents and Children (COVAC) (NCT04800133). The COVID-19 vaccines were administered at the Community Vaccination Centers research sites supported by the University of Hong Kong (HKU) and the HK Government's COVID-19 Vaccination Program. Patients received two doses of either BNT162b2 or CoronaVac, given 21 or 28 days apart, respectively, followed by an option of either vaccine types as a third dose at least 28 days after their second dose. Dosages of 0.3 mL and 0.1 mL (equivalent to 30 μg and 10 μg of COVID-19 mRNA vaccine embedded in lipid nanoparticles) according to drug regulatory approval by the United States Food and Drug Administration and HK Government were used for aged ≥12 years and 5–11 years, respectively.[5,27] The dosage of CoronaVac was 0.5 mL (600 SU, equivalent to 3 μg, of inactivated SARS-CoV-2 virus as antigen) for all ages.[5]

Vaccine recipients were monitored for 30 min after each injection and reported the types, duration, and severity of adverse reactions (ARs) in a diary using an online or paper format for 7 days after vaccination. Peripheral blood consisting of 15 mL was obtained before the first dose, second dose, 7–43 days after the second dose and 14–49 days after the third dose (if any) for measuring the serological antibody responses. These time intervals as optimal for assessing immunogenicity were based on previous publications and guideline recommendations.[28–31] The SARS-CoV-2 S receptor-binding domain (S-RBD) IgG enzyme linked immunosorbent assay (ELISA) (Chondrex Inc, Redmond, USA) and surrogate virus neutralization test (sVNT) (GenScript, New Jersey, USA) performed in our laboratory on the serum isolated from blood samples of patients had been validated and described in our previous publication.[32] Levels of S-RBD IgG are expressed as optical density (OD_{450}). The cutoff considered as seroconversion was OD_{450} ≥0.50, while values below would be inputted as 0.25.[33] Neutralizing antibodies against SARS-CoV-2 WT and Omicron BA.1 were evaluated by sVNT with inhibition percentages (%) as the readout.[34] The cutoff for positive neutralizing antibody inhibition was ≥30%, and values below 30% would be inputted as 10%. Data from healthy children and adolescents ($n = 280$) were retrieved from our COVAC study for comparison to this NMD cohort, which are available from our previous publication.[28]

Social and contact avoidance was common during this study period when the HK Omicron wave occurred, particularly for vulnerable patients as neurological and respiratory complications surged rapidly.[35] Therefore, some NMD patients were only able to attend our vaccination research sites and provide blood samples at the time-point of 7–43 days after the second dose.

Statistical analysis

Associations between the categorical variables (presence of medically complexity, history of past COVID-19 infection, influenza, and COVID-19 vaccination) and intention of receiving COVID-19 vaccination (i.e., have received or plan to receive *vs* do not plan to receive COVID-19 vaccination) were analyzed by the Fisher's exact test. Intention of receiving COVID-19 vaccination between January and April 2022 was compared by the Cochran's Q test. Reasons for receiving the COVID-19 vaccines in January and April 2022 were compared by the Fisher's exact test. The proportions of ARs reported between NMD patients and the healthy population, also between 2–11 and 12–21 year-old NMD patients were compared by the Fisher's exact test. Age, S-RBD IgG levels, and sVNT% inhibition against WT were compared between NMD patients and the healthy population, also between the two vaccine types, by the Mann-Whitney U-test. S-RBD IgG levels and sVNT% inhibition against WT were compared between different disease subtypes by the Kruskal–Wallis test. Comparisons between the sVNT% inhibition against WT and Omicron BA.1 for each patient were computed using the Wilcoxon matched-pairs signed-rank test. The correlation between ELISA and log10-transformed sVNT% inhibition against WT was evaluated by the Pearson correlation coefficient. $p < .05$ was considered statistically significant. Data analyses and graphing were performed using GraphPad Prism (version 9.3.1).

Standard protocol approval, registration, consent, and assent

The NMD patient registry and COVAC were approved by the HKU/Hospital Authority HK West Cluster IRB Committee (UW19–356 and UW 21–157, respectively). Written informed consent was obtained from adult participants or parents/legally authorized representatives/legal guardians of the child participants. Pediatric patients who were neurodevelopmentally capable (11–21 years old) also provided written assent in the reactogenicity and immunogenicity arm of the study.

Results

Of the 136 patients in the HK NMD registry, 52 were sent invitations to complete the COVID-19 vaccine hesitancy survey, while the others did not fulfill criteria due to age or cognitive delay. Most patients, which were 41 (78.8%) of the 52, completed both the first and follow-up surveys (Figure 1). Eighteen (43.9%) of 41 who filled the survey had spinal muscular atrophy (SMA), while 26 (63.4%) had complex medical needs, including wheelchair mobility, tube or gastrostomy tube feeding, ventilator use, or brace or spinal surgery for scoliosis (Supplementary Table S1).

Two or more family members vaccinated against COVID-19 was positively associated with a higher intention of vaccination (OR: 11.7, 95% CI: 1.81–75.1, $p = .010$) (Table 1). Patients who received an influenza vaccine in the last three consecutive years tended to have higher intention of receiving COVID-19 vaccines, albeit not reaching statistical significance (24 of 30 vs 5 of 11, or 80.0% vs 45.5%, $p = .052$). The major reasons that the NMD patients favored COVID-19 vaccination included their hopes for preventing infection (26 of 40, or 65.0%), protecting their family (16, or 40.0%) and returning to normal life (14, or 35.0%) (Table 2).

Their concerns regarding COVID-19 vaccination included adverse effects that could be potentially worse than the healthy population (9 of 41, 22.0%), safety (9, or 22.0%), suitability (6, or 14.6%), effects on current NMD treatments (4, or 9.8%) and reduced efficacy (4, or 9.8%) (Figure 2). There were also 5 (12.2%) of 41 patients who expressed that their intention of vaccination depended on the progress of the pandemic. Indeed, in April 2022, which was shortly after the peak of the Omicron wave in HK, more respondents had or planned to receive the COVID-19 vaccines than in January 2022 (97.6% vs 73.3%, $p = .003$) (Supplementary Table S2). Also, 30 (73.2%) patients expressed their intention of receiving future boosters, if necessary, in April 2022 (Supplementary Table S2). Twenty (48.8%) of 41 patients expressed a vaccination history/intention of vaccination for at least 1 dose of BNT162b2 (B) or CoronaVac (C) in April 2022 (Supplementary Table S3).

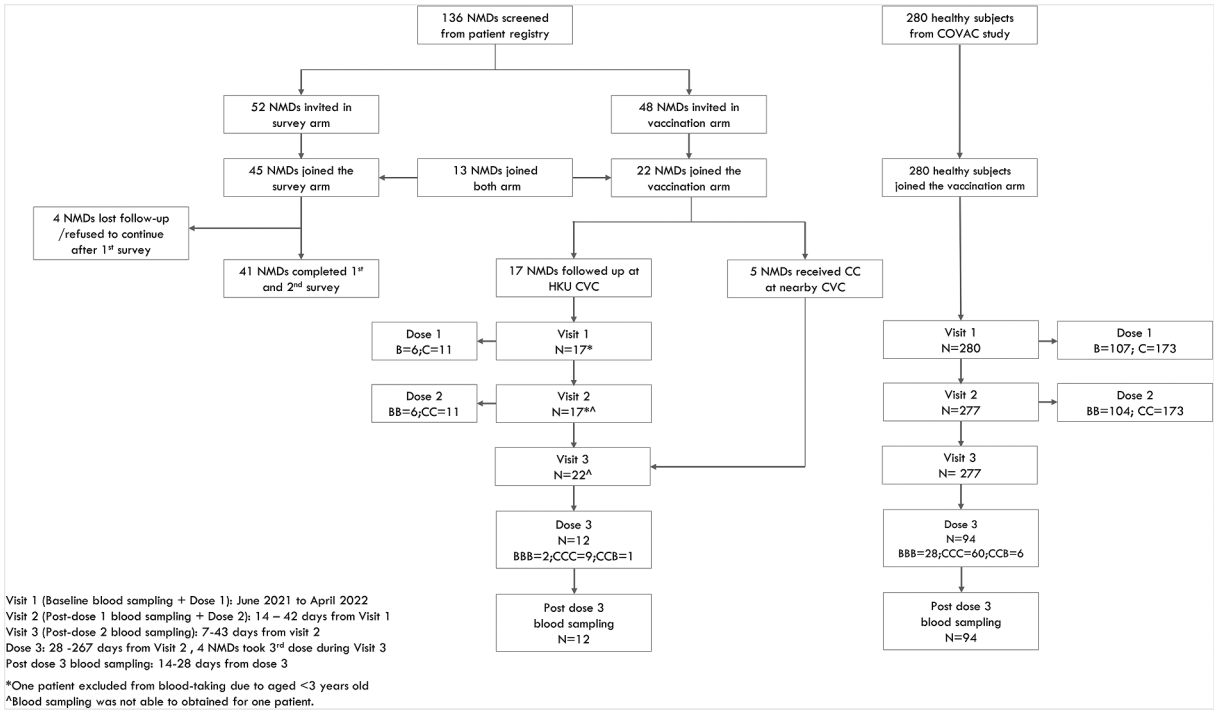

Figure 1. Flow diagram of study participants.
One hundred and thirty-six patients with neuromuscular diseases (NMDs) were screened from the patient registry. Fifty-two patients were invited to complete the hesitancy survey arm, and 48 patients were invited to join the reactogenicity and immunogenicity arm of the study. Forty-five patients completed the first hesitancy survey, and 41 (91.1%) of them completed both first and second surveys. For the reactogenicity and immunogenicity arm of the study, 22 patients joined and 17 were inoculated with BNT162b2 or CoronaVac at our University of Hong Kong (HKU) Community Vaccination Centers (CVCs) research site. These patients recorded adverse reactions in a 7-day diary system after vaccination for reactogenicity/safety analyses and had blood sampling. Additionally, five patients who received two doses of CoronaVac at nearby CVCs and had blood sampling after the second dose. Reactogenicity and immunogenicity data from healthy children and adolescents (n = 280) used for comparisons with patients with NMDs were retrieved from our previous publication.[27] CVCs = Community Vaccination Centers research site, NMDs = patients with neuromuscular diseases, COVAC = Coronavirus disease-19 (COVID-19) Vaccination in Adolescents and Children, HKU = University of Hong Kong. B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; C, 1 dose of CoronaVac; CC, 2 doses of CoronaVac; BBB, 3 dose of BNT162b2; CCC, 3 doses of CoronaVac; CCB, 2 doses of CoronaVac and 1 dose of BNT162b2.

Table 1. Factors associated with intention of receiving COVID-19 vaccination.

	Have received or plan to receive vaccination ($n = 30$)	Do not plan to receive vaccination ($n = 11$)	p-values
Mean age (SD)	14.0 (3.4)	13.4 (3.3)	.648
Female	15 (50.0)	3 (27.3)	.291
Two or more family members are vaccinated against COVID-19^	28 (93.3)	6 (54.5)	.010*
Received the influenza vaccine in the previous year	22 (73.3)	5 (45.5)	.140
Received the influenza vaccine in the last three continuous years	24 (80.0)	5 (45.5)	.052
Know someone diagnosed with COVID-19	0 (0)	2 (18.2)	-
Previously completed compulsory COVID-19 testing	1 (3.3)	3 (27.3)	.052
Wheelchair-mobile	16 (53.3)	6 (54.5)	1.000
Nasogastric or PEG tube feeding use	2 (6.7)	2 (18.2)	.288
Ventilator support	10 (33.3)	4 (36.4)	1.000
Using spinal brace or had spinal surgery	7 (23.3)	1 (9.1)	.412
Presence of one type of disability	7 (23.3))	5 (45.5)	.247
Presence of two or more type of disabilities	11 (36.7)	3 (27.3)	.719

SD = standard deviation, PEG = percutaneous endoscopic gastrostomy.
^odds ratio is presented for those with significant association according to the Fisher's exact test.
*$p < .05$.
Odds ratio = 11.7, 95% confidence interval: 1.81–75.1.

Forty-eight patients were invited from the NMD patient registry to complete the reactogenicity and immunogenicity arm from June 2021 to April 2022, while the others were not recruited due to the age exclusion criterion. Twenty-two (45.8%) patients joined the study (Supplementary Table S4). Nine patients had DMD, seven patients had SMA, three patients had congenital myopathy (CM), and one patient had Becker muscular dystrophy (BMD), chronic inflammatory demyelinating polyneuropathy (CIDP) or myotonic disorder (MD). Fourteen (63.6%) were in the late ambulatory or wheelchair mobile stage. All 9 DMD patients were on corticosteroids (ranges of dosage: 10–30 mg/day or 0.30–0.74 mg/kg/day). Seven SMA patients were on nusinersen or risdiplam. One CIDP patient was on intravenous immunoglobulin therapy

Table 2. Major reasons for receiving COVID-19 vaccination.

	January 2022	April 2022	*p*-values
Planning to vaccinate/already vaccinated	n = 30	n = 40	
Worried to be infected	17 (56.7)	26 (65.0)	.620
To return full-scale face-to-face teaching	16 (53.3)	16 (40.0)	.335
To protect their family	17 (56.7)	14 (35.0)	.091
To return to normal life	19 (63.3)	13 (32.5)	.015*
I think I am high risk group of COVID-19	17 (23.3)	12 (30.0)	.596
Because people around me received vaccination	15 (16.7)	11 (27.5)	.391
I am tired of the social distancing policies	19 (30.0)	10 (25.0)	.787
I want to socialize with large groups of friends	13 (10.0)	10 (25.0)	.132
I want to socialize with participate in large-scale events	112 (6.7)	19 (22.5)	.100
I want to travel	14 (46.7)	18 (20.0)	.022*
I want to play sports at school with friends or in a competition without wearing mask	11 (36.7)	17 (17.5)	.098
To play music safely E.g.: wind instruments, band, choir	16 (20.0)	17 (17.5)	1.000
I want to join study tours E.g.: day trip, school visits or other extra-curricular activities	12 (40.0)	15 (12.5)	.011*

Data presented as number (%). *$p < .05$.

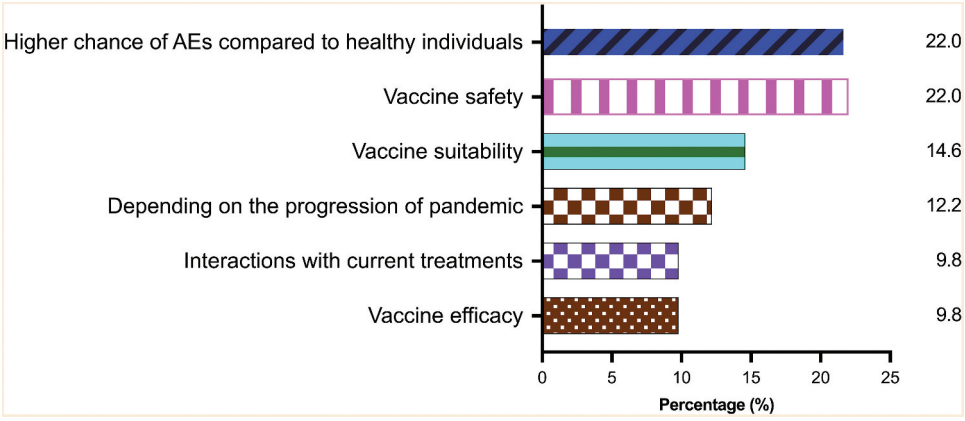

Figure 2. Major concerns about receiving COVID-19 vaccination in patients with neuromuscular diseases.
The three commonest concerns from patients with neuromuscular diseases were having a higher chance of AEs compared to healthy individuals (22.0%), safety (22.0%), and suitability (14.3%). AEs = adverse effects.

Table 3. Reactogenicity for patients with neuromuscular diseases.

Dosage	B	C	BB	CC	BBB	CCC	CCB
Pain at injection site NMDs							
NMDs	5 (83.3)	5 (45.5)	3 (50.0)	6 (54.5)	1 (100)	5 (55.6)	1 (100)
Healthy	93 (89.4)	94 (54.3)	88 (84.6)	89 (51.5)	11 (84.6)	28 (46.7)	6 (100)
p-value	0.509	0.757	0.063	1.000	1.000	0.731	1.000
Swelling, erythema and induration at injection site							
NMDs	0 (0)	2 (18.2)	0 (0)	1 (9.09)	0 (0)	1 (11.1)	0 (0)
Healthy	10 (9.6)	30 (17.3)	11 (10.6)	37 (21.4)	4 (30.8)	1 (1.7)	0 (0)
p-value	1.000	1.000	1.000	0.465	1.000	0.224	N/A
Headache							
NMDs	0 (0)	1 (9.09)	3 (50.0)	1 (9.09)	1 (100)	2 (22.2)	0 (0)
Healthy	22 (21.2)	33 (19.1)	47 (45.2)	22 (12.7)	9 (69.2)	5 (8.3)	3 (50.0)
p-value	0.598	0.692	1.000	1.000	1.000	0.224	1.000
Fatigue							
NMDs	3 (50.0)	4 (36.4)	4 (66.7)	5 (45.5)	0 (0)	5 (55.6)	1 (100)
Healthy	50 (48.1)	74 (42.8)	65 (62.5)	59 (34.1)	9 (69.2)	17 (28.3)	4 (66.7)
p-value	1.000	0.762	1.000	0.518	0.357	0.132	1.000
Myalgia							
NMDs	2 (33.3)	3 (27.3)	1 (16.7)	3 (27.3)	0 (0)	2 (22.2)	0 (0)
Healthy	25 (24.0)	22 (12.7)	16 (15.4)	16 (9.25)	8 (61.5)	4 (6.7)	1 (16.7)
p-value	0.634	0.174	1.000	0.091	0.429	0.172)	1.000
Fever							
NMDs	0 (0)	2 (18.2)	1 (16.7)	1 (9.1)	1 (100)	0 (0)	0 (0)
Healthy	4 (3.9)	2 (1.16)	16 (15.4)	0 (0)	5 (38.5)	0 (0)	1 (16.7)

(*Continued*)

Table 3. (Continued).

Dosage	B	C	BB	CC	BBB	CCC	CCB
p-value	1.000	0.018	1.000	0.060	0.429	1.000	1.000
Abdominal pain							
NMDs	0 (0)	1 (9.09)	0 (0)	1 (9.1)	0 (0)	0 (0)	0 (0)
Healthy	9 (8.7)	17 (9.8)	9 (8.7)	9 (5.2)	1 (7.7)	3 (5.0)	1 (16.7)
p-value	1.000	1.000	1.000	0.469	1.000	1.000	1.000
Antipyretic use							
NMDs	1 (16.7)	0 (0)	2 (33.3)	0 (0)	1 (100)	0 (0)	0 (0)
Healthy	7 (6.7)	2 (1.2)	25 (24.0)	2 (1.2)	3 (23.1)	0 (0)	1 (16.7)
p-value	0.371	1.000	0.634	1.000	0.286	1.000	1.000

Healthy = healthy children and adolescents, NMDs = patients with neuromuscular diseases. B, one dose of BNT162b2; BB, two doses of BNT162b2; C, one dose of CoronaVac; CC, two doses of CoronaVac; BBB, three doses of BNT162b2; CCC, three doses of CoronaVac; CCB, two doses of CoronaVac, and one dose of BNT162b2.

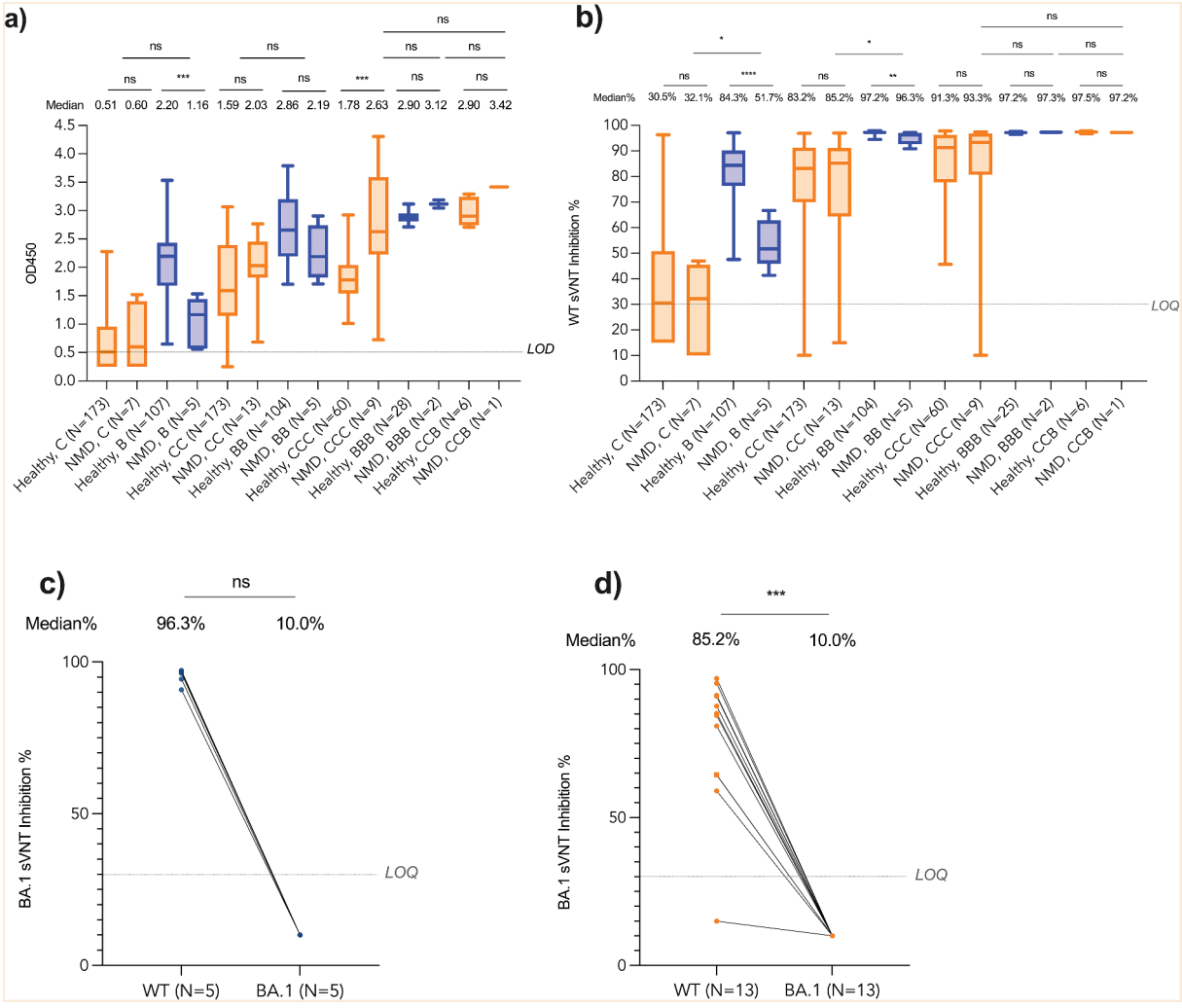

Figure 3. Immunogenicity for patients with neuromuscular diseases.
Antibody responses were determined before the first dose, second dose, 7–43 days after the second dose and 14–49 days after the third dose of BNT162b2 or CoronaVac in patients with neuromuscular diseases (NMDs) (n = 19) and healthy children and adolescents (n = 280). Three NMDs who had COVID-19 infection were excluded from the final analysis. ELISA=enzyme linked immunosorbent assay, LOQ=Limit of quantitation, Healthy=heathy children and adolescents, NMD=patients with neuromuscular diseases, sVNT=surrogate virus neutralization test, WT= wildtype SARS-CoV-2 virus. B, one dose of BNT162b2; BB, two doses of BNT162b2; C, one dose of CoronaVac; CC, two doses of CoronaVac; BBB, three doses of BNT162b2; CCC, three doses of CoronaVac; CCB, two doses of CoronaVac, and one dose of BNT162b2. BNT162b2 was represented as blue while CoronaVac was represented as orange color. Patients with NMDs using corticosteroids (deflazacort or prednisolone) daily were indicated as square dots in (c) & (d). *$p < .05$, **$p < .01$, ***$p < .001$, ****$p < .0001$ or NS (not significant).

infused regularly (dosage: 2 g/kg/3 months). There were 6 (27.3%) and 16 (72.7%) of 22 patients who received two doses of BNT162b2 (BB) or CoronaVac (CC), respectively. One case of CM and DMD each had COVID-19 before enrollment into the study, while 1 patient with SMA reported contracting COVID-19 3 weeks after the first dose, and all three patients fully recovered subsequently. 280 healthy children and adolescents were recruited for the immunogenicity study for comparison (BNT162b2: 107, CoronaVac: 173) (Figure 1). Patients with NMDs were younger than the healthy

controls (B: 11.3 years vs 13.9 years; C: 13.1 years vs 14.0 years) (Supplementary Table S5).

NMD patients had similar proportions of ARs compared to 280 healthy children and adolescents (Table 3). Pain at the injection site (BB: 3 of 6, 50.0%, 6 of 11, CC: 54.5%), fatigue (BB: 4 of 6, 66.7%, 5 of 11, CC: 45.5%), and myalgia (BB: 1 of 6, 16.7%, 3 of 11, CC: 27.3%) were the commonest ARs in NMD patients. Most ARs were mild (75.5%, $n = 71/94$). No severe adverse events, such as apparent NMD deterioration, hospitalization, life-threatening complications, disabilities, or deaths occurred) (Supplementary Figure S1). Similar ARs were reported between patients aged 2–11 and 12–21 years (Supplementary Table S6).

All 19 patients with NMDs seroconverted against WT after BB or CC (Figure 3a). NMD patients had similar antibody responses compared to 280 healthy children and adolescents (ELISA-CC: 2.03 vs 1.59; ELISA-BB: 2.19 vs 2.86; sVNT-CC: 85.2% vs 83.2%) (Figure 3a, 3b). There was a high correlation between ELISA and surrogate virus neutralization in our samples (n = 690, r = 0.897, $p < .0001$) (Supplementary Figure S2). Although after receiving CC, DMD patients using corticosteroids had slightly lower S-RBD IgG than those not on corticosteroids (OD450: 1.82 vs 2.37, $p = .02$) or other disease subtypes (OD450: 1.82 vs 2.54 (SMA) vs 2.03 (CM) vs 1.97 (BMD) vs 2.43 (MD), $p = .01$), corticosteroids did not affect their seroconversion rates (Supplementary Table S7 and 8). There was lower neutralization against Omicron BA.1. The median sVNT % inhibition against WT and Omicron BA.1 was 96.3% and 10.0% after BB ($p = .063$) (Figure 3c), respectively, while it was 85.2% and 10.0% after CC ($p < .001$) (Figure 3d). The other three patients with COVID-19 were excluded from the main immunogenicity analyses (Supplementary Table S9).

Discussion

This is the first in-depth study to understand the underlying reasons for vaccine hesitancy in NMDs, who have specific concerns based on their particular disease, treatments, and prognosis. The findings revealed COVID-19 vaccination in family members is highly influential on the intention of receiving the vaccines for pediatric patients with NMDs, and those who received either the mRNA-based or inactivated whole-virus vaccines did not encounter severe ARs and had antibody responses similar to their healthy counterparts. This is consistent with the notion that family decision and support are key factors on COVID-19 vaccination for pediatric populations, as several recent studies observed this finding for healthy adolescents and children with neurodevelopmental disorders.[15,36,37] Additionally, patients who received the influenza vaccines in the recent consecutive years tended toward having the greater intention of COVID-19 vaccination, and we speculate this was due to higher vaccine confidence and complacency.[14,38] This information will be useful for patient counseling as they continued to raise questions in our clinic regarding the need for the third dose and subsequent boosters in the future.

This is the first study to investigate the safety of both the novel mRNA-based and inactivated-whole virus COVID-19 vaccines in children with NMDs, which showed BNT162b2 and CoronaVac were well tolerated. There were similar profiles of ARs between pediatric patients with NMDs, our healthy cohort, as well as adolescents and adults with NMDs and multiple sclerosis who received two doses of BNT162b2 or mRNA-1273.[22,27,39,40] This is also the first study to demonstrate the CoronaVac is immunogenic in pediatric patients with NMDs. Antibody responses were robust, an observation which was consistent with adolescent and adult patients with NMDs and myasthenia gravis who were able to generate antibody responses against WT.[22–24, 40] It is reassuring that even for pediatric patients with NMDs and on corticosteroids, all patients had successful seroconversion after at least two doses of BNT162b2 or CoronaVac, which was also observed in adolescent and adult patients who received BNT162b2.[22,40] Additionally, there were no apparent interactions between the COVID-19 vaccines and treatments for NMDs, and our cohort of patients did not encounter NMD-related complications or hospitalization.

This study included immunogenicity against Omicron, which is important as some studies showed reduced vaccine effectiveness (VE) of BNT162b2 and CoronaVac against infection or mild COVID-19 due to this variant.[7,8,41–43] Indeed, our findings revealed reduced neutralizing activity against Omicron BA.1 in pediatric patients with NMDs. As neutralization correlates with protective efficacy against symptomatic COVID-19, we expect breakthrough infections to be more common in NMD patients due to Omicron than pre-Omicron variants, as similar to the rest of the population. However, although recent studies indicated that VE of BNT162b2 and CoronaVac against infection due to Omicron were merely~50% after two doses of vaccination in healthy adolescents, both vaccines remained highly protective against hospitalization and moderate-to-severe COVID-19 according to our population studies.[5, 44–46] This is likely because T cell responses are preserved against Omicron,[47,48] which is correlated with clinical protection against severe diseases.[49] Therefore, this study supports the notion that patients with NMDs should become vaccinated with either BNT162b2 or CoronaVac to attain protection against severe COVID-19. Further boosters may enhance neutralization responses against Omicron subvariants for maximal protection.

There were several limitations in this study. First, it was not possible for participants to be enrolled into a study with a blinded and randomized design because these patients are already hesitant to receive novel vaccines and restriction on their choice on the type of vaccine would be an additional deterrent. There can be potential selection bias because more older males with NMDs favored BNT162b2. Also, patients with NMDs were younger than the healthy controls and likely received a higher dosage based on age or size, which could have contributed to the higher antibody responses after 3 injections of CoronaVac. This observation should be investigated in more detail in the future. However, the current findings have more real-life applicability and reflect the reality of outcomes for patients who can choose between vaccines. Reactogenicity and immunogenicity results were not available for all the timepoints, as we encouraged patients to receive the vaccines as soon and conveniently as possible for protection from severe COVID-19. This is because informed choice and prompt preventative treatment for overcoming a surging wave

of infection-related deaths in high-risk patients during the peak of our pandemic period is paramount and should be respected. Additionally, this study was able to evaluate common adverse effects, but a different study design, such as large-scale post-market surveillance, will be required for reporting on rare adverse reactions. Finally, the current small sample size limits the generalizability of the study conclusions. Due to the small size of each group, it is difficult to derive strong data. Nevertheless, this is the largest COVID-19 vaccine study in pediatric NMDs to date, with comparison to as many as 280 healthy individuals on immunogenicity after 2 vaccine doses and comprises a total of 690 blood samples. The results from this study greatly contribute to the currently available scientific evidence that serves as the basis for appropriate clinical practice recommendations and policy-making decisions for patients with NMDs.

Taken together, these present findings and overall evidence support the routine schedule of vaccination for patients with NMDs, and the dosages of immunosuppressives used for the treatment of NMDs in relation to the BNT162b2 and CoronaVac vaccines are inconsequential.[4] We recommend that counseling for these patients should incorporate these informative points and to include several close relatives, if possible, because their decisions appear to be strongly influential toward vaccine hesitancy. Reassurance by reminding the patients about their tolerance to other vaccines, such as influenza, can also be considered. The in-depth understanding on the reasons for vaccine hesitancy in specific, rare diseases acquired from this study is necessary to devise future follow-up research on interventions. Future studies are required to confirm that these counseling techniques are effective on addressing vaccine hesitancy. Additionally, questions remain in terms of the safety, efficacy, long-lasting T cell immunity, and durability of booster doses against other emerging variants,[50] such as Omicron BA2.75, BA.5, XBB, BQ1.1, and BF.7 for these patients.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Jaime S Rosa Duque, upon reasonable request.

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