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Immunogenicity, safety, and reactogenicity of concomitant administration of the novavax vaccine against Omicron XBB.1.5 (NVX-CoV2601) and a 20-valent pneumococcal conjugate vaccine in adults aged ≥60 years: A randomised, double-blind, placebo-controlled, non-inferiority trial

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SUMMARY

Objectives: There is conflicting evidence as to whether the combined administration of two vaccines can lead to poorer immunogenicity and reactogenicity. The co-administration of the Omicron-adapted COVID-19 vaccine from Novavax (NVX-CoV2601) and a 20-valent pneumococcal conjugate vaccine (PCV20) has not been previously investigated.

Methods: In this randomised, double-blind, placebo-controlled, non-inferiority trial, immunocompetent participants aged ≥60 years were randomised in a 1:1:1:1 ratio to four groups: NVX-CoV2601 plus PCV20 (combination group); NVX-CoV2601 plus placebo (NVX-only group); PCV20 plus placebo (PCV20-only group); or placebo plus placebo (placebo group). The primary outcome was Omicron-specific anti-spike protein IgG ELISA units at day 28 in the combination group compared with the NVX-only group. Non-inferiority was established if the lower limit of the two-sided 95% CI of the geometric mean titre ratio was above the non-inferiority margin of 0.67. Secondary outcomes included anti-pneumococcal capsular polysaccharide (PCP) IgG ELISA units. Solicited local and systemic adverse events were collected for 7 days after vaccination. This study was registered with ClinicalTrials.gov, number NCT05767606, and the EU Clinical Trials Register, EudraCT number 2022–004118-12.

Results: All 256 randomised participants completed the study. The baseline characteristics were similar in the four groups. Overall, the median age was 64 (IQR 61 to 69) and 105 (41%) of 256 were male. At day 28, the geometric mean anti-spike protein IgG ELISA units were 534 U/mL (95% CI 432–660) in the combination group and 556 U/mL (95% CI 460–672) in the NVX-only group, resulting in a geometric mean titre ratio of 0.96 (95% CI 0.73–1.27), thereby meeting the criteria for non-inferiority.

Anti-PCP IgG ELISA units at day 28 were 507 U/mL (95% CI 416–619) in the combination group and 592 U/mL (95% CI 485–723) in the PCV20-only group. Local and systemic reactogenicity was similar in the three active treatment groups. No safety concerns or serious adverse events were observed.

Conclusions: Immunogenicity following co-administration of NVX-CoV2601 with PCV20 was non-inferior to administration of NVX-CoV2601 alone. Given the similar safety and reactogenicity profile, our

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findings may help to overcome concerns about concomitant vaccination and pave the way for combination vaccines.

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Introduction

Although COVID-19 is no longer classified as a public health emergency of international concern by the World Health Organization, it continues to pose a global health burden.[1] The current variants of COVID-19 are less dangerous than previous strains, but can still cause serious illness, especially in susceptible patients, such as the elderly.[2] In this vulnerable patient group, vaccination against SARS-CoV-2 remains one of the most important strategies for reducing morbidity and mortality. Another important group of pathogens causing serious respiratory infection are the various serotypes of *Streptococcus pneumoniae*, commonly referred to as pneumococci. A large prospective cohort study from the UK found that pneumococci are detectable in around 10% of patients hospitalised with a lower respiratory tract infection.[3] In this study, 75% of the serotype would have been covered by the commonly used 20-valent polysaccharide conjugate pneumococcal vaccine (PCV20), which is recommended for adults aged 60 or 65 years and older, depending on the country or geographical region. Given the overlapping risk populations, combined administration of Novavax's (NVX) new Omicron-adapted vaccine (NVX-CoV2601) and the PCV20 could be a viable immunisation strategy for a large proportion of the population. Despite extensive literature on the topic of concurrent vaccination, there is still conflicting evidence as to whether the administration of COVID-19 vaccines in combination with other vaccines is associated with worse immunogenicity and reactogenicity. Co-administration of the NVX-CoV2601 and PCV20 vaccines has not yet been investigated. The primary aim of this investigator-initiated, randomised, double-blind, placebo-controlled study was to investigate whether combined administration of NVX-COV2601 and PCV20 vaccine is non-inferior to administration of NVX-COV2601 alone in terms of immunogenicity against SARS-CoV-2 in adults aged 60 years or older.

Methods

Study design and participants

This randomised, placebo-controlled, non-inferiority trial was conducted in a single study centre in Vienna, Austria (Medical University of Vienna, University Hospital Vienna). This study included immunocompetent volunteers aged 60 years or older, who were eligible for a SARS-CoV-2 vaccination with NVX-COV2601 and a pneumococcal vaccination with PCV20. Owing to the high vaccination coverage rate in the population, we only included subjects who had already received at least two COVID-19 vaccines, the last of which was an mRNA vaccine (BNT162b2 or mRNA-1273) and was given at least 12 weeks prior to study inclusion. For women, the last menstrual period had to be more than one year ago. Key exclusion criteria comprised the use of immunosuppressive medication, congenital or acquired immunodeficiencies, any chronic condition that may significantly interfere with the immune response in the opinion of the investigator, history of COVID-19 within 16 weeks before study vaccination. Participants with a previous pneumococcal vaccination of any kind were excluded. Pneumococcal vaccination status was determined by interview and inspection of vaccination records. Vaccination in early childhood was very unlikely in this cohort, as population-wide vaccination programs against pneumococci were only introduced later[4].

Written informed consent was obtained from all participants before enrolment in the trial. The trial protocol was approved by the Ethics Committee of the Medical University of Vienna (EK 2108/2022) and was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines.

Randomisation and masking

All participants were randomly assigned to one of four groups: NVX-COV2601 plus PCV20 (combination group); NVX-COV2601 plus placebo (NVX-only group); PCV20 plus placebo group (PCV20-only group); or placebo plus placebo group (placebo group) in a ratio of 1:1:1:1. Randomisation was stratified by age (< 70 versus ≥70 years), last immunological event (i.e., last SARS-CoV-2 vaccination or infection ≤6 months versus > 6 months ago), and the agent used for the last SARS-CoV-2 vaccination (BNT162b2 versus mRNA-1273). The aim of this stratification was to achieve balanced anti-spike protein IgG levels in the four groups. To ensure an even distribution within the strata, a permuted block with a size of 4 was used. Randomisation and preparation of study medication was performed by an independent, unblinded team. The randomisation process also determined the side (left or right deltoid muscle) for administering the individual study drugs, using an independent unrestricted 1:1 randomisation ratio. Participants and other study personnel who administered vaccinations, collected data and assessed adverse events were blinded. All treatments (0.5 mL NVX-COV2601, 0.5 mL PCV20 and 0.5 mL normal saline 0.9% as placebo) were administered in identical non-transparent syringes.

Procedures

The COVID-19 vaccine NVX-COV2601 (Nuvaxovid®) consisted of 5 μg of SARS-CoV-2 (Omicron XBB.1.5) spike protein with 50 μg Matrix-M™ adjuvant. The PCV20 (Prevenar 20®, previously Apexxnar®) consisted of capsular saccharides from 20 pneumococcal serotypes (1, 3, 4, 5, 6 A, 6B, 7 F, 8, 9 V, 10 A, 11 A, 12 F, 14, 15B, 18 C, 19 A, 19 F, 22 F, 23 F, and 33 F) conjugated to CRM_{197} carrier protein (51 μg per dose) and adsorbed on aluminium phosphate (125 μg aluminium per dose). Normal saline 0.9% was used as a solution for the placebo injection. Each participant received a 0.5-mL injection in the left deltoid muscle and a 0.5-mL injection in the right deltoid muscle in immediate succession on Day 0.

For immunogenicity assessments, blood was collected from all trial participants at baseline (day 0) and at day 28. To assess humoral immune response to the NVX-COV2601 vaccine and PCV20, ELISA for Omicron-specific SARS-CoV-2 anti-spike protein IgG (EuroImmun®), and an enzyme immunoassay for pneumococcal capsular polysaccharide (PCP) IgG (VaccZyme®) was performed, respectively. To assess the SARS-CoV-2 infection status, anti-nucleocapsid activity was assessed using the Elecsys® Anti-SARS-CoV-2 immunoassay from Roche®.

As part of the safety assessment, participants remained under observation at the study site for at least 20 min after vaccination to monitor for the presence of any acute reactions. Solicited local and systemic adverse events were collected via a paper-based diary for 7 days. Each participant was given a thermometer for the daily measurement of body temperature and a ruler for the daily measurement of redness or swelling. Solicited adverse events were classified

according to the FDA toxicity grading scale for clinical abnormalities (Table S1). All participants were assessed for unsolicited adverse events from the first injection through 28 days. Serious adverse events were defined as any event that resulted in death, were life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in permanent disability.

After the final blood sample was taken and adverse events were documented, all participants were given the opportunity to receive the COVID-19 or pneumococcal vaccines that they had not received during the study period due to receiving a placebo. This post-study vaccination was not assessed for immunogenicity and reactogenicity.

Outcomes

The primary endpoint of this non-inferiority trial was the Omicron-specific anti-spike IgG ELISA units at day 28 in the combination and NVX-alone groups. Secondary immunogenicity endpoints included anti-spike and anti-PCP IgG ELISA units at day 28 and the fold-increase from baseline to day 28 in the four study groups. Safety endpoints included serious adverse events, severe adverse events, unsolicited adverse events, need for medical consultation, need for medication, and cases of COVID-19 after vaccination through day 28. Reactogenicity was systematically assessed using solicited local and systemic adverse events through day 7 after vaccination.

Statistical analysis

For the immunogenicity analysis, non-inferiority was established if the lower limit of the two-sided 95% confidence interval (CI) of the geometric mean titre (GMT) between the combination arm and the NVX-only arm at day 28 ($28\text{-d-GMT}_{\text{NVX-only}}/28\text{-d-GMT}_{\text{combination}}$) was above the pre-defined non-inferiority margin of 0.67.[5] Moreover, GMTs with 95% CIs were calculated for baseline and day 28 anti-spike protein and anti-PCP IgG ELISA units. The relative increase in antibody levels is reported as geometric mean fold increase comparing day 0 (baseline) with day 28. For both the anti-spike protein and anti-PCP IgG antibody levels by treatment group, the 95% CIs were calculated based on the *t* distribution of the log-transformed values, then back transformed to the original scale for presentation as GMTs or geometric mean ELISA units and geometric mean fold increases.

The analyses of safety and reactogenicity were largely descriptive. Statistical comparisons were performed using Fisher's exact test for the frequency of adverse events or the Wilcoxon signed-rank test for ordinal severity of adverse events, but these should be interpreted as exploratory analyses that were not corrected for multiple testing. We performed the analyses of immunogenicity, safety and reactogenicity in the subgroups of participants younger than 70 years and 70 years or older.

Sample size calculation

The sample size calculation was based on the primary objective of demonstrating the non-inferiority of the combination group to the NVX-only group in terms of immunogenicity against SARS-CoV-2. Considering the results of the trial by Toback et al., we expected a data distribution of $\log_{10}$-transformed mean (non-omicron-specific) anti-spike protein IgG levels of 4.65 U/mL with a standard deviation of 0.4.[6] Using the WHO-defined non-inferiority margin of 0.67 for GMT ratios (which equals a −0.176 difference in $\log_{10}$-transformed antibody levels), a sample size of 64 per group provided an 80% power to show the non-inferiority of combined administration of NVX-COV2601 with PVC20 to NVX-COV2601 alone, at a two-sided alpha of 0.05.

All statistical analyses and visualisations were performed using the R statistical software, version 4.1.2 (R Foundation). This study is registered with ClinicalTrials.gov, number NCT05767606, and the EU Clinical Trials Register, EudraCT number 2022–004118-12.

Role of the funding source

This Investigator-Initiated Study received financial support and study medication from Novavax, Inc.®.

Results

Participants

Between December 13, 2023, and May 7, 2024, a total of 279 people were assessed for eligibility. Of these, 256 were randomised to receive either NVX-COV2601 plus PCV20 (combination group, n=64), NVX-COV2601 plus placebo (NVX-only group, n=65), PCV20 plus placebo (PCV20-only group, n=64) or placebo plus placebo (placebo group, n=63). All randomised participants completed the study and were included in the immunogenicity, safety, and reactogenicity analyses. Fig. 1 shows the flowchart of the study. The follow-up visit (i.e. day of immunogenicity assessment) was conducted at a median of 28 days (IQR 28 to 28) post-vaccination. Baseline characteristics and comorbidities were similar in the four study groups (Table 1). The median age of the participants was 64 years (IQR 61 to 69), 105 (41%) of the 256 participants were male. Of the 256 participants, 218 (85.2%) had a history of SARS-CoV-2 infection, as shown by nucleocapsid antibody reactivity in vitro. Most participants (231 [90.2%] of 256) had at least one co-existing medical condition, with hypertension (47.7%), hyperlipidaemia (40.6%) and allergies (25.0%) being the most common.

Immunogenicity

Table 2 and Fig. 2 show the geometric mean anti-spike protein and anti-PCP IgG ELISA units at baseline and 28 days post-vaccination and the fold increase in antibody levels in the four groups. The primary endpoint (geometric mean anti-spike protein IgG ELISA units at day 28) was 534 U/mL (95% CI 432 to 660) in the combination group (NVX-COV2601 plus PCV20) and 556 U/mL (95% CI 460 to 672) in the NVX-only group (NVX-COV2601 plus placebo). The GMT ratio between the combination group and the NVX-only group was 0.96 (95% CI 0.73 to 1.27), with the lower bound of the two-sided 95% confidence interval being 0.73, which was above the predefined non-inferiority threshold of 0.67. Anti-spike protein IgG baseline levels and the fold-increase were similar between the combination group and the NVX-only group (Tables 2 and 3, Fig. 2). Geometric mean anti-spike protein IgG ELISA units decreased from baseline to day 28 in the PCV20-only group (Day 0, 336 [95% CI 259 to 435]; Day 28, 309 [95% 242 to 395]) and the placebo group (Day 0, 377 [95% CI 287 to 497]; Day 28, 347 [95% 269 to 449]) (Table 2, Fig. 2).

Anti-PCP IgG ELISA units were similar at baseline and day 28 between the combination group and the PCV20-only group (Table 2 and Fig. 2), resulting in a GMT ratio at day 28 of 0.86 (0.65 to 1.13) and a geometric mean ratio of fold-increase of 1.09 (0.77 to 1.54) (Table 3). Immunogenicity results were similar in the subgroups of participants younger than 70 years and 70 years or older (Table S2).

Safety and reactogenicity

Table 4 summarises the safety and reactogenicity findings of this study. The rate of adverse events was higher in the active treatment groups (combination group, 57 [89%] of 64; NVX-only group, 53 [82%] of 64; PCV20-only group, 55 [86%] of 64) than in the placebo

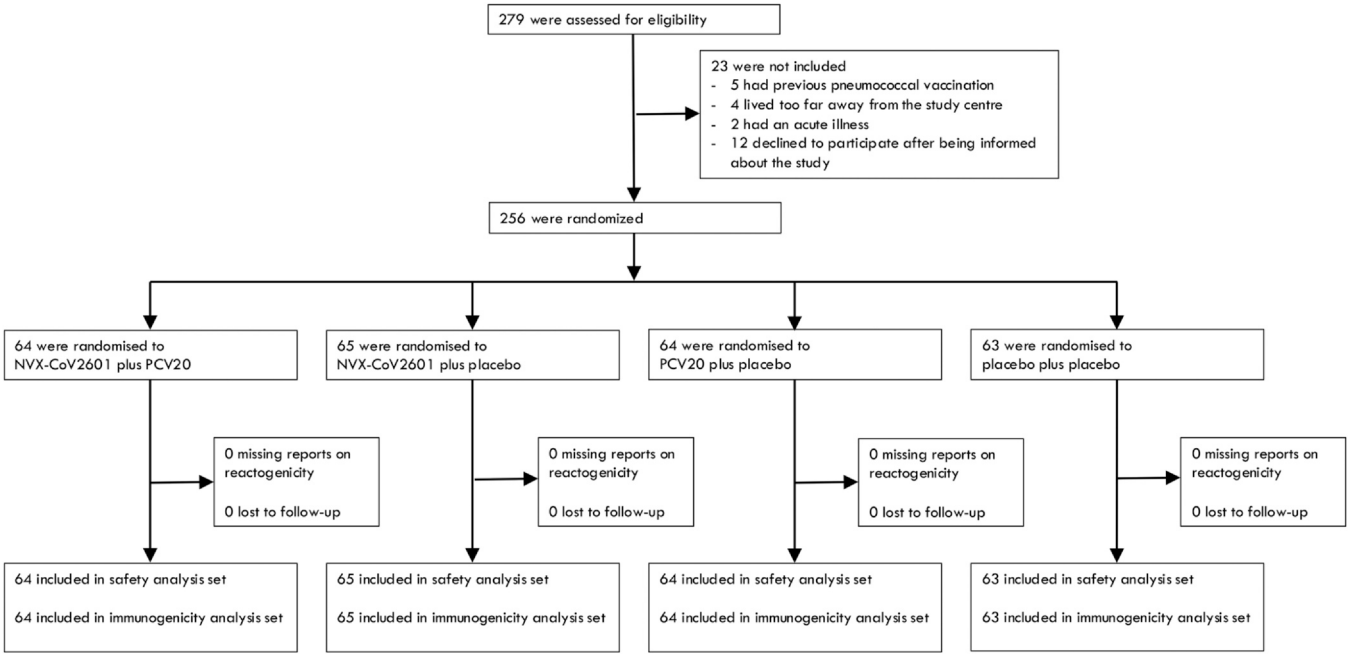

Fig. 1. Flowchart of the study population.

Table 1
Baseline characteristics.

	Overall	NVX-COV2601 plus PCV20	NVX-COV2601 plus Placebo	PCV20 plus Placebo	Placebo plus Placebo	p
n=	256	64	65	64	63	
Age (years) - median (IQR)	64 [61,69]	63 [61,68]	64 [62,69]	64 [61,69]	64 [62,69]	0.459
Male sex - n (%)	105 (41.0)	19 (29.7)	31 (47.7)	28 (43.8)	27 (42.9)	0.181
Weight (kg) - mean (SD)	79.7 (19.5)	80.1 (22.2)	78.1 (16.1)	82.2 (22.0)	78.4 (17.1)	0.599
BMI (kg/m^2) - mean (SD)	27.1 (5.8)	27.6 (6.6)	26.2 (5.0)	28.0 (6.6)	26.6 (4.5)	0.283
Caucasian - n (%)	256 (100)	64 (100)	65 (100)	64 (100)	63 (100)	NA
History of COVID-19 according to Nucleocapsid-Ab status - n (%)	218 (85.2)	53 (82.8)	57 (87.7)	55 (85.9)	53 (84.1)	0.875
Any comorbidity - n (%)	231 (90.2)	58 (90.6)	60 (92.3)	56 (87.5)	57 (90.5)	0.831
Cardiovascular Disease - n (%)	17 (6.6)	7 (10.9)	3 (4.6)	3 (4.7)	4 (6.3)	0.434
Hypertension - n (%)	122 (47.7)	29 (45.3)	27 (41.5)	37 (57.8)	29 (46.0)	0.280
Hyperlipidaemia - n (%)	104 (40.6)	32 (50.0)	24 (36.9)	23 (35.9)	25 (39.7)	0.347
Diabetes - n (%)	24 (9.4)	3 (4.7)	5 (7.7)	5 (7.8)	11 (17.5)	0.075
Neurological disorder - n (%)	24 (9.4)	5 (7.8)	2 (3.1)	5 (7.8)	12 (19.0)	0.016
Psychiatric disorder - n (%)	44 (17.2)	14 (21.9)	10 (15.4)	11 (17.2)	9 (14.3)	0.680
Pulmonary disorder - n (%)	26 (10.2)	9 (14.1)	5 (7.7)	6 (9.4)	6 (9.5)	0.665
Urological disorder - n (%)	25 (9.8)	6 (9.4)	6 (9.2)	5 (7.8)	8 (12.7)	0.820
Gastrointestinal disorder - n (%)	30 (11.7)	10 (15.6)	8 (12.3)	4 (6.2)	8 (12.7)	0.411
Allergy - n (%)	64 (25.0)	16 (25.0)	19 (29.2)	14 (21.9)	15 (23.8)	0.801
Thyroid disorder - n (%)	40 (15.6)	14 (21.9)	9 (13.8)	11 (17.2)	6 (9.5)	0.267
Musculoskeletal - n (%)	16 (6.2)	5 (7.8)	2 (3.1)	4 (6.2)	5 (7.9)	0.639
Metabolic or endocrinologic disorder - n (%)	13 (5.1)	5 (7.8)	2 (3.1)	4 (6.2)	2 (3.2)	0.534

Table 2
Immunogenicity data.

	NVX-COV2601 plus PCV20	NVX-COV2601 plus Placebo	PCV20 plus Placebo	Placebo plus Placebo
Anti-SARS-CoV-2 immunogenicity				
Geometric mean (95% CI) anti-spike protein IgG ELISA units at Day 0	361.4 (272.7–479)	366.9 (287.8–467.7)	335.9 (259.3–435)	377.4 (286.8–496.6)
Geometric mean (95% CI) anti-spike protein IgG ELISA units at Day 28	534 (432.3–659.7)	555.8 (459.9–671.7)	309.1 (242–395)	347.3 (268.7–448.9)
Geometric mean (95% CI) anti-spike protein fold increase	1.48 (1.25–1.75)	1.52 (1.33–1.72)	0.92 (0.88–0.96)	0.92 (0.88–0.96)
Anti-pneumococcal immunogenicity				
Geometric mean (95% CI) anti-pneumococcal capsular polysaccharide IgG ELISA units at Day 0	44.6 (36.2–55)	51.4 (40.1–65.9)	56.8 (46.4–69.5)	41.3 (34.1–50)
Geometric mean (95% CI) anti-pneumococcal capsular polysaccharide IgG ELISA units at Day 28	507.1 (415.6–618.7)	51.6 (40.3–65.9)	592.4 (485.4–722.9)	40.9 (33.8–49.5)
Geometric mean (95% CI) anti-pneumococcal capsular polysaccharide fold increase	11.37 (8.75–14.77)	1 (0.98–1.02)	10.43 (8.31–13.1)	0.99 (0.97–1.01)

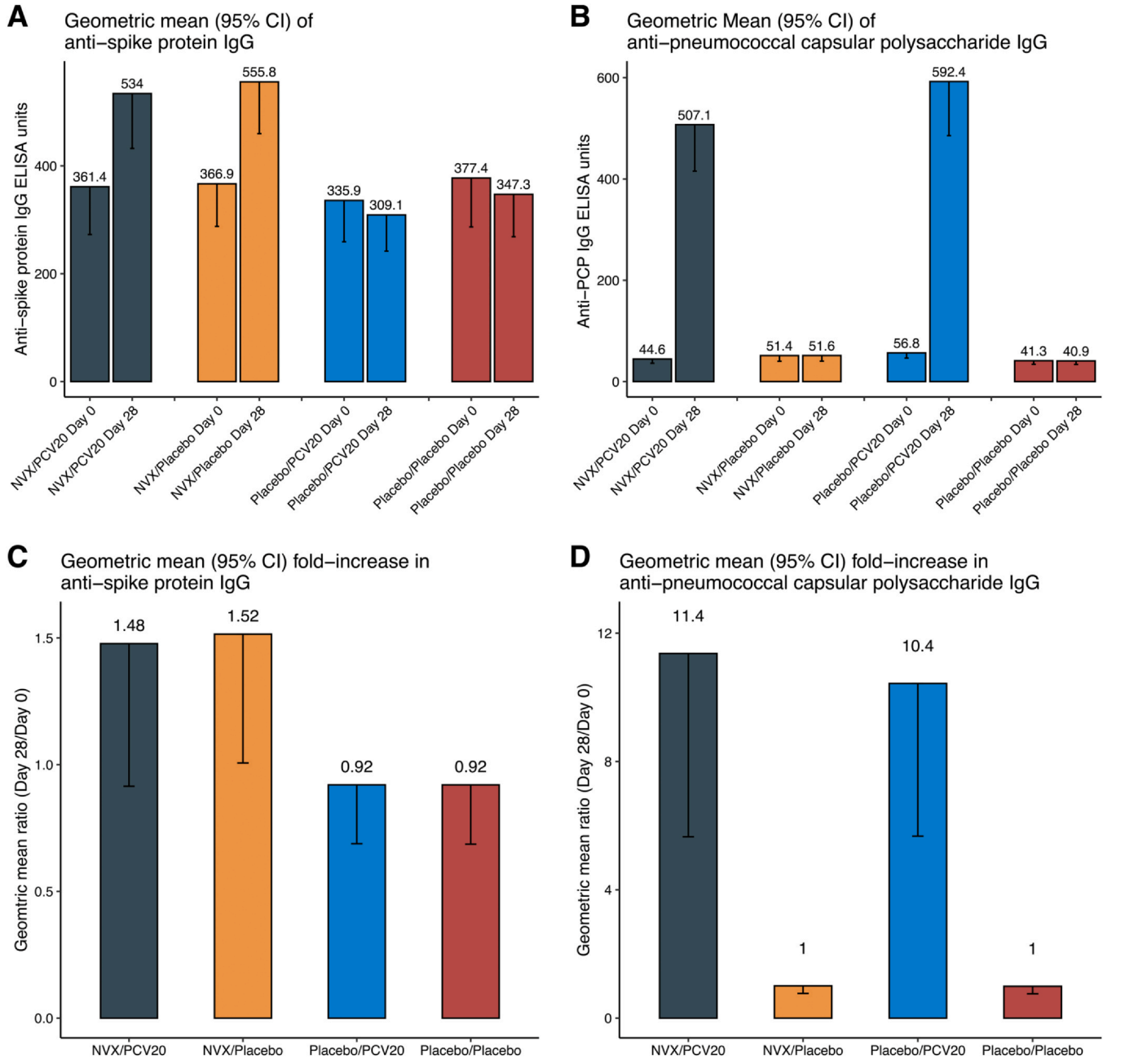

Fig. 2. Geometric mean anti-spike protein (A and C) and anti-pneumococcal capsular polysaccharide (B and D) IgG ELISA units at baseline and 28 days post-vaccination and the fold increase in antibody levels in the four groups. Abbreviations: anti-PCP, anti-pneumococcal capsular polysaccharides; NVX, NVX-CoV2601; PCV20, 20-valent pneumococcal conjugate vaccine.

group (36 [57%] of 63), mainly due to a higher incidence of local adverse events in the active treatment groups (combination group, 84%; NVX-only group, 63%; PCV20-only group, 84%; placebo group, 18%). Overall, severe solicited adverse events occurred in 6 (2.3%) of the 256 study participants; no serious adverse event occurred. The frequency of adverse events requiring medical consultation (0%, 3.1%, 0% and 1.6%, respectively) or drug treatment (10.9%, 13.8%, 23.4% and 12.7%, respectively) was similar in the four groups. A total of 4 (1.6%) of the 256 participants developed COVID-19, three of which were symptomatic and confirmed by PCR and one of which was detected by the change from negative to positive anti-nucleocapsid reactivity after 28 days. Two of these cases were in the combination group and two in the placebo group. Fig. 3 shows the frequency and grading of solicited local and systemic adverse events per group. The exact absolute and relative numbers of each solicited adverse event can be found in Tables S2 to S4. Local adverse events were more frequent in the groups receiving the PCV20 vaccination (combination group, 84%; PCV20-only group, 84%) than in the NVX-only (63%) and the placebo group (17%). Of the 4 subjects experiencing severe local adverse events in this study, 2 (3.1%) were in the combination group (1 subject experiencing severe itch and warmth and 1 subject experiencing severe tenderness and pain) and 2 (3.1%) in the PCV20-only group (1 subjects experiencing severe redness and swelling and 1 subject experiencing severe tenderness) (Table S3). In addition, in the 64 participants randomised to the combination group, all categories of solicited local adverse reactions, with the exception of itching, were significantly more severe in the shoulder muscle injected with PCV20 (Table S5).

Unsolicited adverse events were reported by 60 (23.4%) of the 256 participants (combination group, 23.4%; NVX-only group, 29.2%;

Table 3
Statistical comparison of immunogenicity outcomes between the active treatment groups including the primary endpoint.

	NVX-COV2601 plus PCV20	NVX-COV2601 plus Placebo	PCV20 plus Placebo	Geometric Mean Ratio (95% CI)
Anti-SARS-CoV-2 immunogenicity				
Geometric mean (95% CI) anti-spike protein IgG ELISA units at Day 0	361.4 (272.7–479)	366.9 (287.8–467.7)	-	0.99 (0.68–1.42)
Geometric mean (95% CI) anti-spike protein IgG ELISA units at Day 28	534 (432.3–659.7)	555.8 (459.9–671.7)	-	0.96 (0.73–1.27)
Geometric mean (95% CI) anti-spike protein fold increase	1.5 (1.2–1.7)	1.5 (1.3–1.7)	-	0.98 (0.79–1.2)
Anti-pneumococcal immunogenicity				
Geometric mean (95% CI) anti-pneumococcal capsular polysaccharide IgG ELISA units at Day 0	44.6 (36.2–55)	-	56.8 (46.4–69.5)	0.79 (0.59–1.05)
Geometric mean (95% CI) anti-pneumococcal capsular polysaccharide IgG ELISA units at Day 28	507.1 (415.6–618.7)	-	592.4 (485.4–722.9)	0.86 (0.65–1.13)
Geometric mean (95% CI) anti-pneumococcal capsular polysaccharide fold increase	11.37 (8.75–14.77)	-	10.43 (8.31–13.1)	1.09 (0.77–1.54)

Table 4
Safety and reactogenicity outcomes.

	Overall	NVX-COV2601 plus PCV20	NVX-COV2601 plus Placebo	PCV20 plus Placebo	Placebo plus Placebo	p
N=	256	64	65	64	63	
Any serious adverse event[a] - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Any solicited adverse event - n (%)	201 (78.5)	57 (89.1)	53 (81.5)	55 (85.9)	36 (57.1)	< 0.001
Any solicited systemic adverse event - n (%)	122 (47.7)	34 (53.1)	33 (50.8)	26 (40.6)	29 (46.0)	0.502
Any solicited local adverse event - n (%)	160 (62.5)	54 (84.4)	41 (63.1)	54 (84.4)	11 (17.5)	< 0.001
Any solicited severe adverse event - n (%)	6 (2.3)	2 (3.1)	1 (1.5)	3 (4.7)	0 (0.0)	0.334
Any unsolicited adverse - n (%)	60 (23.4)	15 (23.4)	19 (29.2)	16 (25.0)	10 (15.9)	0.346
Any adverse event requiring medical consultation - n (%)	3 (1.2)	0 (0.0)	2 (3.1)	0 (0.0)	1 (1.6)	0.302
Any adverse event requiring medication - n (%)	39 (15.2)	7 (10.9)	9 (13.8)	15 (23.4)	8 (12.7)	0.198
COVID-19 after vaccination - n (%)	4 (1.6)	2 (3.1)	0 (0.0)	0 (0.0)	2 (3.2)	0.248

[a] Serious adverse events were defined as any event that resulted in death, were life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in permanent disability.

PCV20-only group, 25%; placebo group, 15.9%) (Table S6). The most common unsolicited adverse event was a common cold (combination group, 7.8%; NVX-only group, 9.2%; PCV20-only group, 6.2%; placebo group, 6.3%). Safety and reactogenicity results were similar in the subgroups of participants younger than 70 years and 70 years or older (Table S8).

Discussion

This randomised, placebo-controlled, double-blind vaccine trial was the first trial to investigate the immunogenicity, safety, and reactogenicity of a co-administration of the omicron-adapted Novavax vaccine (NVX-COV2601) and PCV20 vaccines. We found that in participants aged 60 years or older, combined administration of the NVX-COV2601 and PCV20 vaccines was non-inferior to administration of NVX-COV2601 alone in terms of immunogenicity against Omicron-specific anti-spike protein. Importantly, this age group is particularly susceptible to severe illness from SARS-CoV-2 and pneumococcal infections, where both vaccines remain an important strategy to reduce morbidity and mortality.[7,8] Regarding the immune response against pneumococci, our study was not designed and powered for formal hypothesis testing, but similar immunogenicity was observed between the combination group and the PCV20-only group.

Owing to the promising benefits, various combinations of simultaneously administered vaccines have previously been investigated.[9] Most of these studies suggest that immunogenicity is similar between co-administered vaccines and vaccines administered alone, particularly for non-live vaccines like the NVX vaccine and PCV20, compared to live vaccines.[9] However, with the new vaccine technologies developed during the COVID-19 pandemic, the question regarding the efficacy and safety of co-administered vaccines has resurfaced. With regard to mRNA-based SARS-CoV-2 vaccines, Fitz-Patrick and colleagues conducted a descriptive randomised controlled trial in which participants aged ≥65 years were randomised 1:1:1 to PCV20 plus BNT162b2, PCV20 alone or BNT162b2 alone.[10] The safety and immunogenicity of co-administered PCV20 and BNT162b2 were similar to those of PCV20 or BNT162b2 alone. Two other studies from China investigated the administration of inactivated quadrivalent influenza vaccine and 23-valent pneumococcal polysaccharide vaccine in combination with inactivated SARS-CoV-2 vaccines (CoronaVac and Sinopharm BBIBP-CorV, respectively) and also found no evidence of significant interference with immunogenicity and tolerability.[11,12] Even more evidence is available on the co-administration of SARS-CoV-2 vaccines and influenza vaccines. Izikson and colleagues found no difference in immunogenicity after simultaneous administration of a booster dose of mRNA-1273 with influenza vaccines in a randomised controlled trial; however, without formal statistical testing.[13] By contrast, two large observational studies in health-care workers found that co-administration of influenza vaccines with mRNA vaccines were associated with significantly decreased immunogenicity against SARS-CoV-2.[14,15] Similarly, Toback and colleagues found a modest reduction in the anti-spike antibody levels with the co-administration of NVX-CoV2373 and influenza vaccines in an exploratory sub-study of a phase 3 trial.[6] Overall, most evidence for the immunogenicity and reactogenicity of combined administration of SARS-CoV-2 vaccines, including the NVX vaccines, stems from observational studies and exploratory trials, which did not perform formal hypothesis testing in the form of non-inferiority trials.

In the active treatment groups, the 1.5-fold increase in anti-spike protein antibodies was far less than the 10-fold increase in

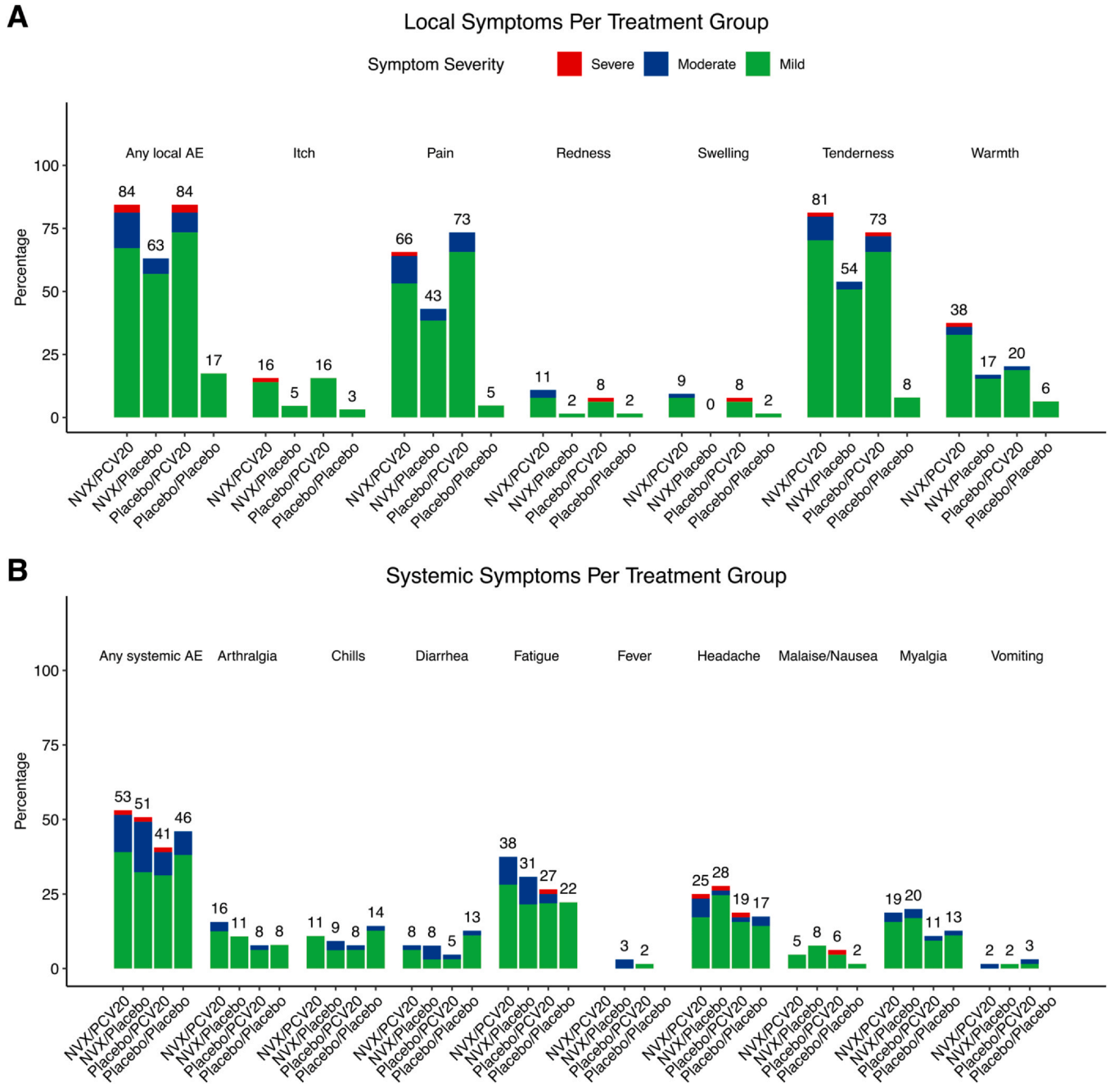

Fig. 3. Frequency (%) of local (A) and systemic (B) adverse events during the 7 days in each group is plotted according to the maximum toxicity grade.

anti-pneumococcal antibodies, which is likely since participants had already received at least a complete primary series of SARS-CoV-2 vaccines prior to the study and had not received a pneumococcal vaccine. In addition, previous studies have shown that the short-term increase in antibody levels is lower with the protein-based Novavax vaccines than with the mRNA-based vaccines.[16] In a study evaluating the immunogenicity of a heterologous boost with NVX-CoV2373, an approximately 5-fold increase in Omicron-specific antibodies was observed.[17] A direct comparison of antibody levels observed in our study with other studies is not possible as different assays were used to quantify the antibodies.

Our study did not raise any safety concerns associated with a concomitant administration, which is in line with previous investigations. Solicited local and systemic adverse events were frequent but mostly mild, indicating a low symptom burden for participants. In particular, systemic adverse events occurred in almost half of the participants, both in the three active treatment groups and in the placebo-only group. This finding emphasises the value of a double-blind study design with a placebo-only group to obtain a realistic assessment of the safety and reactogenicity of vaccines and other drugs, especially when daily diaries with solicited adverse events are used. Regarding local adverse events, groups receiving the PCV20 vaccine (i.e. the combination group and the PCV20-only group) had higher rates of local adverse events, including few cases of severe local adverse events. This numerical trend was observed for each of the individual solicited adverse events. The poorer local reactogenicity of PCV20 was also confirmed by the comparison between the NVX and PCV20 vaccines within the

combination group. In this paired analysis, local adverse events were more frequent and graded higher on the side of the shoulder where the PCV20 vaccine was injected.

The wastewater surveillance in Austria showed that population-wide SARS-CoV-2 viral loads peaked in December 2023, followed by a progressive decline until May 2024, indicating a generally low incidence of COVID-19 throughout most of the study period.[18,19] The XBB Omicron subvariant predominated until January 2024, after which the JN.1 Omicron subvariant became the leading circulating strain.[19] Although overall case numbers remained low, the possibility remains that incidental infections may have influenced immunogenicity results. However, through a combination of privately performed PCR testing and assessment of anti-nucleocapsid antibody changes, only four cases of COVID-19 were identified in the entire study cohort, suggesting that any impact on study results is unlikely to be significant.

Despite the potential benefits of simultaneously administering COVID-19 and other vaccines, significant concerns from both patients and healthcare professionals have resulted in a considerable number of vaccinations being postponed.[20] While our study is largely of confirmatory nature, we still believe it provides valuable evidence to overcome concerns of concomitant administration of the NVX-COV2601 and PCV20 vaccines and potentially other similar non-live vaccines. Strengths of this study include the randomised, double-blind study design and the fact that there were no dropouts; all randomised subjects completed the study and were included in the full analysis. We have also included a homogenous study population of older people in whom the efficacy and safety of the vaccine is of particular interest. Our results suggest that co-administration of NVX-COV2601 and PCV20 could simplify vaccination schedules without compromising safety or immunogenicity. In the real-world setting, this approach may increase vaccine uptake in older adults and improve protection against both SARS-CoV-2 and pneumococcal disease.

Limitations

Firstly, as with all immunogenicity studies, it is assumed that a similar antibody response reliably correlates with similar protection against transmission and severe disease, but this is not known. Secondly, the sample size of this study only allowed a descriptive comparison of adverse events and was only able to detect common adverse events. Rare but potentially serious adverse events (e.g. myocarditis, immune-mediated prothrombotic conditions), which are equally if not more important than common vaccine reactions, could not be assessed in this study. Third, this was a single-centre study in Austria (Europe), which lacked ethnic and racial diversity. Fourth, we analysed antibody levels after 28 days, but an effect of concomitant administration at longer follow-up periods cannot be excluded based on our results. Finally, because the immunogenicity assessment in this study used an assay based on the spike protein of the early Omicron subvariants, activity against the newer subvariants (JN.1, KP.2 and KP.3) was not assessed. In addition, although we quantified anti-spike antibody levels, we did not perform neutralising antibody assays, which are considered better predictors of protection.[21] Notably, the aim of this study was to investigate the effects of a co-administered vaccine on immunogenicity rather than to assess the level of protection after vaccination.

Conclusions

In conclusion, this trial is the first to show the immunogenicity, safety and reactogenicity profile of the Omicron-adapted Novavax vaccine when co-administered with a polysaccharide-conjugated pneumococcal vaccine. Compared with the administration of NVX-COV2601 alone, immunogenicity against Omicron-specific anti-spike protein was non-inferior after concomitant administration of NVX-COV2601 with a PCV20 vaccine in participants aged 60 years or older. Our data showed no safety concerns with the concomitant administration of NVX-COV2601 with a PCV20 vaccine. Given the similar immunogenicity, safety, and reactogenicity profile, our findings may help to overcome concerns about concomitant vaccination.

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Author contributions

All listed authors meet all four criteria for authorship in the ICMJE Recommendations. AJ and MZ conceived the study idea. AJ, MW, PK, TP, AD, VJ, PH, EY, MJ, MP, LP, FB, and MZ performed the research. AJ and MZ performed the statistical analysis and had direct access to the data. AJ prepared the figures and tables. AJ analysed the data and drafted the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

Data availability

Data will be shared upon reasonable request.

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.

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None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106405.

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