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Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial



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Summary

Background The safety and immunogenicity profile of COVID-19 vaccines when administered concomitantly with seasonal influenza vaccines have not yet been reported. We therefore aimed to report the results of a substudy within a phase 3 UK trial, by evaluating the safety, immunogenicity, and efficacy of NVX-CoV2373 when co-administered with licensed seasonal influenza vaccines.

Methods We did a planned exploratory substudy as part of the randomised, observer-blinded, placebo-controlled, phase 3 trial of the safety and efficacy of the COVID-19 vaccine (NVX-CoV2373) by co-administering the influenza vaccine at four study hospitals in the UK. Approximately, the first 400 participants meeting the main study entry criteria—with no contraindications to influenza vaccination—were invited to join the substudy. Participants of the main study were randomly assigned (1:1) to receive two intramuscular injections of either NVX-CoV2373 (5 µg) or placebo (normal saline) 21 days apart; participants enrolled into the substudy were co-vaccinated with a single (0·5 mL) intramuscular, age-appropriate (quadrivalent influenza cell-based vaccine [Flucelvax Quadrivalent; Seqirus UK, Maidenhead] for those aged 18–64 years and adjuvanted trivalent influenza vaccine [Fluad; Seqirus UK, Maidenhead] for those ≥65 years), licensed, influenza vaccine on the opposite deltoid to that of the first study vaccine dose or placebo. The influenza vaccine was administered in an open-label manner and at the same time as the first study injection. Reactogenicity was evaluated via an electronic diary for 7 days after vaccination in addition to monitoring for unsolicited adverse events, medically attended adverse events, and serious adverse events. Immunogenicity was assessed with influenza haemagglutination inhibition and SARS-CoV-2 anti-spike protein IgG assays. Vaccine efficacy against PCR-confirmed, symptomatic COVID-19 was assessed in participants who were seronegative at baseline, received both doses of study vaccine or placebo, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic COVID-19 from the first dose until 6 days after the second dose (per-protocol efficacy population). Immunogenicity was assessed in participants who received scheduled two doses of study vaccine, had a baseline sample and at least one post-vaccination sample, and had no major protocol violations before unmasking (per-protocol immunogenicity population). Reactogenicity was analysed in all participants who received at least one dose of NVX-CoV2373 or placebo and had data collected for reactogenicity events. Safety was analysed in all participants who received at least one dose of NVX-CoV2373 or placebo. Comparisons were made between participants of the substudy and the main study (who were not co-vaccinated for influenza). This study is registered with ClinicalTrials.gov, number NCT04583995.

Findings Between Sept 28, 2020, and Nov 28, 2020, a total of 15 187 participants were randomised into the main phase 3 trial, of whom 15 139 received treatment (7569 received dose one of NVX-CoV2373 and 7570 received dose one of placebo). 431 participants were co-vaccinated with a seasonal influenza vaccine in the substudy (217 received NVX-CoV2373 plus the influenza vaccine and 214 received placebo plus the influenza vaccine). In general, the substudy participants were younger, more racially diverse, and had fewer comorbid conditions than those in the main study. Reactogenicity events were more common in the co-administration group than in the NVX-CoV2373 alone group: tenderness (113 [64·9%] of 174 vs 592 [53·3%] of 1111) or pain (69 [39·7%] vs 325 [29·3%]) at injection site, fatigue (48 [27·7%] vs 215 [19·4%]), and muscle pain (49 [28·3%] vs 237 [21·4%]). Incidences of unsolicited adverse events, treatment-related medically attended adverse events, and serious adverse events were low and balanced between the co-administration group and the NVX-CoV2373 alone group. No episodes of anaphylaxis or deaths were reported within the substudy. Co-administration resulted in no change to influenza vaccine immune response although a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. NVX-CoV2373 vaccine efficacy in the substudy (ie, participants aged 18 to <65 years) was 87·5% (95% CI –0·2 to 98·4) and in the main study was 89·8% (95% CI 79·7–95·5).

Lancet Respir Med 2021

Published Online
November 17, 2021
[https://doi.org/10.1016/S2213-2600\(21\)00409-4](https://doi.org/10.1016/S2213-2600(21)00409-4)

See Online/Comment
[https://doi.org/10.1016/S2213-2600\(21\)00438-0](https://doi.org/10.1016/S2213-2600(21)00438-0)

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See Online for appendix

Interpretation To our knowledge, this substudy is the first to show the safety, immunogenicity, and efficacy profile of a COVID-19 vaccine when co-administered with seasonal influenza vaccines. Our results suggest concomitant vaccination might be a viable immunisation strategy.

Funding Novavax.

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Introduction

More than a year has passed since the start of the COVID-19 pandemic due to SARS-CoV-2. COVID-19 has been a devastating disease worldwide, with more than 247 million cases and 5 million deaths reported as of Nov 2, 2021.¹ Seasonal influenza epidemics also occur globally, and WHO estimates that 290 000–650 000 individuals die from influenza each year, with the highest numbers of death occurring in adults older than 65 years and children younger than 2 years.² Public health recommendations in many countries include yearly influenza vaccination as a key preventative strategy.³

Global COVID-19 vaccination efforts are now well underway with more than 6·9 billion vaccine doses administered as of Nov 2, 2021.¹ This continued mass COVID-19 vaccination programme will certainly coincide with influenza vaccination programmes. With the initiation of booster campaigns and the continuation of primary series vaccination, the timing of such doses would likely overlap with the 2021–22 influenza season in many settings. Currently, no data exist for the co-administration of COVID-19 vaccines with other vaccines, as most phase 3 trials of COVID-19 vaccines either excluded participants with recent or planned receipt of other licensed vaccines or required an interval of at least 1 week between them. In particular, information about the effects of co-administration on immune responses and safety is needed to formulate public health policy in light of simultaneous vaccination programmes. This information is particularly important as immuno-

senescence might leave older adults more vulnerable to influenza infection, complications, and mortality, as well as reduce their immune responses to standard influenza vaccines.⁴ Current guidance in the UK is to separate the administration of any deployed COVID-19 and influenza vaccines by at least 7 days to avoid incorrect attribution of potential adverse events.³ The US Centers for Disease Control (CDC) recommends a 14-day interval between these vaccines.⁵ However, the need for multiple clinic visits might lead to reduced compliance and hence reduced vaccination uptake. To ensure adequate vaccine uptake of both COVID-19 and influenza vaccines, co-administration would encourage the public to take up these vaccines in one visit rather than returning 7 days or more later.

Herein, we report the results of a substudy of a phase 3 UK trial that assessed the safety and efficacy of two doses of NVX-CoV2373 compared with placebo.⁶ In the main study, a total of 15 187 participants underwent randomisation, of whom 15 139 participants received at least one dose of NVX-CoV2373 (n=7569) or placebo (n=7570), and 14 039 were included in the per-protocol efficacy population. Of the per-protocol efficacy population, 3910 (27·9%) were 65 years or older, and 3117 (44·6%) had coexisting illnesses. A vaccine efficacy of 89·7% (95% CI 80·2–94·6) against symptomatic PCR-proven COVID-19 was observed. The reactogenicity was generally mild and transient, and the incidence of serious adverse events was low and similar in the two groups.⁶ In this substudy, we aimed to evaluate the safety,

Research in context

Evidence before this study

We searched PubMed for research articles published from Dec 1, 2019, to April 1, 2021, with no language restrictions using the terms “SARS-CoV-2”, “COVID-19”, “vaccine”, “co-administration”, and “immunogenicity”. No peer-reviewed publications describing the simultaneous use of any SARS-CoV-2 vaccine and another vaccine were reported. Several vaccine manufacturers had publications on phase 3 trials SARS-CoV-2 vaccine results (Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, and the Gamaleya Research Institute of Epidemiology and Microbiology). Neither these publications nor their clinical trials’ protocols (when publicly available) described co-administration, and they often had trial criteria specifically excluding those with recent or planned vaccination with any licenced vaccine near or at the time of any study injection.

Added value of this study

Immune interference and safety are always a concern when two vaccines are administered at the same time. To our knowledge, this substudy is the first to show the safety and immunogenicity profile and clinical vaccine efficacy of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine.

Implications of all the available evidence

This study provides much needed information to help guide national immunisation policy decision making on the important issue of concomitant use of COVID-19 vaccines with influenza vaccines.

immunogenicity, and efficacy of NVX-CoV2373 when co-administered with a licensed seasonal influenza vaccine.

Methods

Study design and participants

This influenza and COVID-19 vaccine co-administration study was a planned exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial that was aimed to evaluate the safety and efficacy of two 5 µg doses of NVX-CoV2373, administered intramuscularly 21 days apart, compared with placebo.⁶ Briefly, this main study enrolled participants at 33 sites in the UK beginning in September, 2020. Eligible participants for the main study were men and non-pregnant women aged 18–84 years who were healthy or had stable chronic medical conditions. Health status was assessed at screening and based on medical history, vital signs, and physical examination. Key exclusion criteria included a history of documented COVID-19, treatment with immunosuppressive therapy, or diagnosis with an unstable medical condition. 15 187 participants were randomly allocated to either the vaccine or placebo, with 15 139 participants receiving at least one dose of NVX-CoV2373 or placebo. Full details about the methods and design of the main study are reported elsewhere.⁶ The protocol is available with the full text of this article online.

Regarding this co-administration substudy of the COVID-19 and influenza vaccines, approximately the first 400 participants who met the additional substudy criteria were invited to participate. The additional specific inclusion criteria were as follows: have not already received a 2020–21 seasonal, licensed influenza vaccine and have no previous history of allergy or severe reaction to influenza vaccines. All participants were excluded from receipt of any live vaccine within 4 weeks or any vaccine within 2 weeks of the first dose of study vaccine or placebo co-administered with the influenza vaccine. Substudy enrolment was not randomised (ie, consecutive patients were enrolled into the substudy from the main study before randomisation) or stratified by age (ie, all patients were allocated to the influenza vaccine; therefore, stratification was not applicable).

We obtained written informed consent from all participants before enrolment in the trial. The trial protocol was approved by the North West–Greater Manchester Central Research Ethics Committee (20/NW/03/99) and was performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines. Safety oversight was performed by an independent safety monitoring committee.

Randomisation and masking

Participants of the seasonal influenza vaccine co-administration substudy were selected before study vaccine randomisation. Approximately 400 consecutive, non-randomised, eligible participants from four study hospitals in the main study were enrolled into the

substudy. Participants were then randomly assigned (1:1) via block randomisation to receive either two intramuscular injections (0.5 mL) of NVX-CoV2373 or placebo (normal saline), 21 days apart. Randomisation was stratified by site and by age (≥ 65 years). Participants in the seasonal influenza vaccine co-administration substudy then received a concomitant dose of seasonal influenza vaccine with the first study injection only. This dose comprised a single intramuscular injection (0.5 mL) of a licensed influenza vaccine in the opposite deltoid to that of the study vaccine or placebo and was given at the same time. Although the main study was observer-blinded, the substudy of the influenza vaccine was administered in an open-label manner.

Procedures

The study vaccine NVX-CoV2373 consisted of 5 µg of SARS-CoV-2 rS with 50 µg matrix-M adjuvant (Novavax; Gaithersburg, MD, USA). Two different influenza vaccines were used in the substudy to comply with national influenza vaccination recommendations:⁷ the quadrivalent influenza cell-based vaccine (Flucelvax Quadrivalent; Seqirus UK, Maidenhead) for those aged 18–64 years, and the adjuvanted trivalent influenza vaccine (Fluad; Seqirus UK, Maidenhead) for those 65 years or older (appendix p 7).

For immunogenicity assessments, blood was collected from all trial participants at baseline and at day 21 for those in the influenza substudy and for all trial participants at baseline and day 35 (14 days after the second dose of study vaccine). To assess the possible effect of the study vaccine on the immunogenicity of the influenza vaccine, a haemagglutination inhibition assay antibody was performed in all influenza substudy participants at baseline and at day 21. To assess humoral immune response to the study vaccine, an ELISA for SARS-CoV-2 anti-spike protein IgG was performed at baseline and on day 35 in approximately 900 non-randomised participants from two study sites in the main study (as part of an immunogenicity cohort) as well as in those in the influenza substudy.

As part of the safety assessment, after each study vaccination, participants remained under observation at the study site for at least 30 min to monitor for the presence of any acute reactions. Solicited local and systemic adverse events were collected via an electronic diary for 7 days after each injection for approximately 2000 non-randomised participants from four study sites in the main study (as part of a reactogenicity cohort) as well as those in the influenza substudy. Participants in the influenza substudy were instructed to record local reactogenicity for the study vaccine (ie, NVX-CoV2373 or placebo) injection site only. All participants from the main study and substudy were assessed for unsolicited adverse events from the first injection or injections through 21 days; serious adverse events, adverse events of special interests including those relevant to COVID-19

For the study protocol of the main study see <https://www.novavax.com/resources/protocols>

and potentially immune-mediated medical conditions (appendix pp 9–10), and medically attended adverse events were assessed from the first injection to the end of the study period (Feb 23, 2021), whereas only treatment-related medically attended adverse events were analysed from the first injection to day 35. Unsolicited adverse events and other safety events were reported for all participants who provided informed consent and received at least one injection in the main study and a co-administered influenza vaccine in the substudy. Data from this ongoing phase 3 trial for the purpose of this analysis were assessed at a median of approximately 4 months after the first study injection (ie, the dose with which influenza vaccine was co-administered). The safety follow-up period was the same for both the main study and substudy. Participants in the influenza vaccine co-administration substudy, the main study immunogenicity cohort, and main study reactogenicity cohort were all enrolled at separate, distinct locations.

The primary efficacy endpoint was the first occurrence of virologically confirmed symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after the second vaccination in participants who were seronegative at baseline. Symptomatic COVID-19 was defined according to the US Food and Drug Administration (FDA) criteria.⁶ Symptoms of possible COVID-19 were assessed throughout the trial and collected using an electronic symptom diary for at least 10 days from symptom onset. At the onset of suspected COVID-19 symptoms, participants called their study site and, when instructed, mucosal specimens from the nose and throat were collected daily over a 3-day period to assess for SARS-CoV-2 infection. Virological confirmation was performed using PCR testing. Daily temperature self-measurements were recorded at home for at least 10 days and participants were evaluated for an initial clinical assessment (in 1–3 days). A follow-up assessment was conducted (in 7–10 days) where physical examinations were done and vital signs were collected.

Outcomes

The outcomes of the substudy were the immunogenicity assessments (ie, haemagglutination inhibition assay antibody in all influenza substudy participants at baseline and at day 21; and ELISA for SARS-CoV-2 anti-spike protein IgG at baseline and on day 35 in approximately 900 non-randomised participants from two study sites in the main study; both prespecified), safety and reactogenicity assessments (ie, local and systemic reactogenicity in the influenza substudy; unsolicited adverse events from the first injection or injections through 21 days in all participants; and serious adverse events, adverse events of special interest including those relevant to COVID-19 and potentially immune-mediated medical conditions, and medically attended adverse events from the first injection to the end of the study

period [Feb 23, 2021], whereas only treatment-related medically attended adverse events were analysed from the first injection to day 35; prespecified), and efficacy assessment (ie, the first occurrence of virologically confirmed symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after the second vaccination in participants who were seronegative at baseline; post-hoc).

Statistical analysis

In the safety analysis, unsolicited adverse events, serious adverse events, medically attended adverse events, and adverse events of special interest were analysed in all participants who received at least one dose of NVX-CoV2373 or placebo for the main study and one dose of NVX-CoV2373 or placebo plus one dose of influenza vaccine for the substudy (all prespecified). Safety events were summarised descriptively. Solicited local and systemic adverse events after the first injection were also summarised by the US FDA toxicity grading criteria and duration after each injection (appendix p 11). Unsolicited adverse events were coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (version 23.1) and summarised by severity and relationship to study vaccine. In analysis for safety, participants in the substudy were then compared with participants in the main study, by study vaccine and influenza vaccine received (ie, NVX-CoV2373 plus influenza vaccine, NVX-CoV2373 alone, placebo plus influenza vaccine, and placebo alone).

For the immunogenicity analysis for the influenza vaccine, strain-specific immune responses to the influenza vaccine were assessed in participants who received the influenza vaccine in the intention-to-treat population, as measured by the haemagglutination inhibition assay and reported as geometric mean titres, geometric mean fold rise comparing at day 0 (baseline) and at day 21, and seroconversion rates (defined as the proportion of participants with either a baseline reciprocal titre of less than ten and a post-vaccination reciprocal titre ≥ 40 , or a baseline titre of ten or more and a post-vaccination titre of four folds or higher). For influenza strain-specific geometric mean titres according to group (influenza vaccine concomitantly administered with NVX-CoV2373 or with placebo), titres reported below the lower limit of quantitation (ie, below the starting dilution of assay reported as less than ten) were set to half that limit (ie, ten divided by two).

In immunogenicity analysis to the study vaccine, using SARS-CoV-2 anti-spike protein IgG antibody concentrations measured by the ELISA assay, geometric mean ELISA units at each study visit (day 0 and day 35), the geometric mean fold rises comparing at day 0 and at day 35, along with the 95% CIs, were summarised by vaccine group (ie, NVX-CoV2373 plus influenza vaccine, NVX-CoV2373 alone, placebo plus influenza vaccine, and placebo alone; prespecified). A post-hoc assessment of

the ratio between the geometric means adjusting for baseline titre, age, and treatment group was also performed. Data were also assessed by age group (ie, 18 to <65 years and ≥ 65 to 84 years) and corresponding influenza vaccine types (ie, quadrivalent influenza cell-based vaccine and adjuvanted trivalent influenza vaccine). The seroconversion rate for the IgG antibody was defined as a proportion of participants with four-fold rises or more. ELISA units reported below the lower limit of quantitation (ie, below the starting dilution of assay reported as <200) were set to half that limit (ie, 200 divided by two).

For both the haemagglutination inhibition assay and anti-spike protein IgG antibody measured 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 geometric mean titres or geometric mean ELISA units and geometric mean fold rises. The seroconversion rates, along with the 95% CIs based on the Clopper-Pearson method, were summarised by vaccine group. The per-protocol immunogenicity analysis set for the substudy and main study was defined as those who received two doses of vaccine, had all immunology samples available, had no major protocol deviations, and did not have a laboratory confirmed SARS-CoV-2

infection before any visit where serology was measured.

Non-randomised comparisons of the day 35 anti-spike protein IgG antibody ELISA units were performed using a geometric mean ratio defined as the ratio of two geometric mean ELISA units. An analysis of covariance on log transformed values with group, age, and baseline ELISA units was performed. The ratios of geometric least square means and 95% CIs for the ratios were calculated by back transforming the mean differences and 95% CIs for the differences of log-transformed ELISA units between the two groups. The two-sided 95% CIs for the absolute rate difference between two groups were constructed using the Newcombe method.

The main study was designed and driven by the total number of events expected to achieve statistical significance for the primary efficacy endpoint—ie, a target of 100 mild, moderate, or severe COVID-19 cases for the main study. The target number of 100 cases for the final analysis provides more than 95% power for 70% or higher vaccine efficacy. The main (hypothesis testing) event-driven analysis for the final analyses of the primary objective was done at an overall one-sided type I error rate of 0.025 for the primary endpoint. The primary endpoint (ie, the per-protocol population) was analysed in participants who were seronegative at baseline, received both doses of study vaccine or placebo, had no

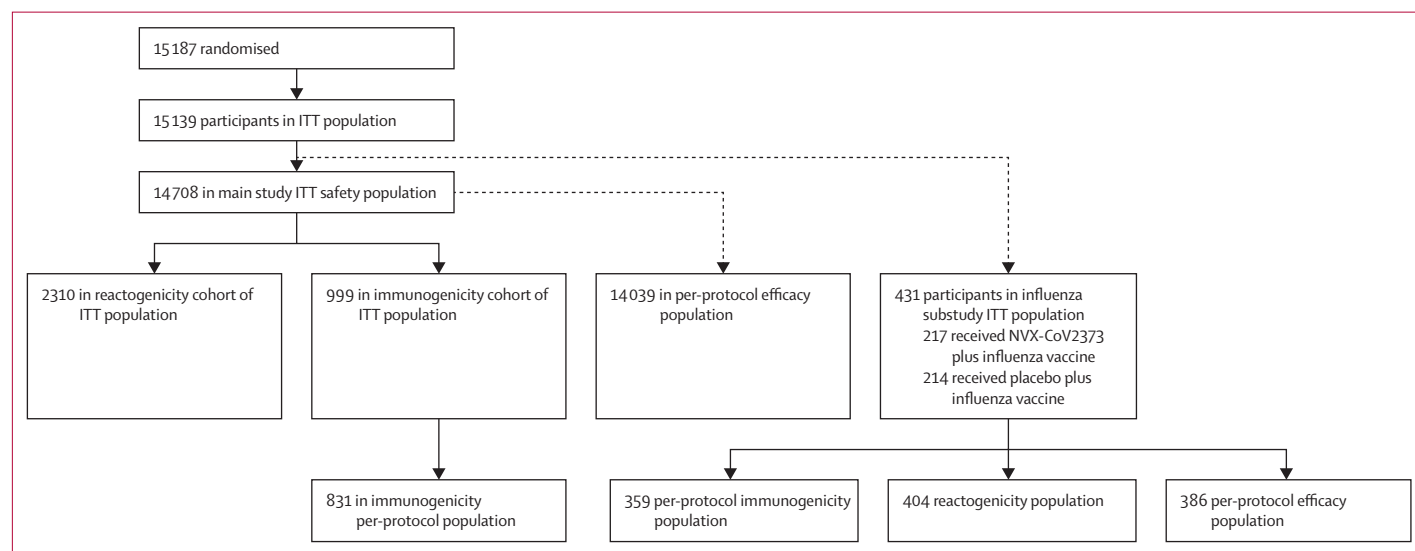


Figure 1: Main study, influenza vaccine substudy, and study cohorts

The main study ITT population (n=15 139) were all participants who received at least one dose of NVX-CoV2373 or placebo. Those who were enrolled in the influenza substudy (n=431) were then removed to create the main study safety population (n=14 708) used to make safety comparisons with the substudy. The main study per-protocol efficacy population included all participants who were seronegative at baseline, received both doses of study vaccine, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic COVID-19 from the first dose until 6 days after the second dose. The influenza substudy total ITT population included all those who received at least one dose of NVX-CoV2373 or placebo and any influenza vaccine (n=431). This entire group was assessed for immunogenicity (haemagglutination inhibition assay and ELISA testing for anti-spike protein IgG) and safety. Of these individuals, 404 (93.7%) recorded data into the 7-day reactogenicity diary (influenza substudy reactogenicity population). Those who did not record data included those who were unable to download the electronic diary or were non-compliant with its use. Of the 431 substudy participants, 386 (89.6%) also met the per-protocol efficacy definition as defined above. The immunogenicity cohort ITT population included all participants from the main study who received at least one dose of NVX-CoV2373 or placebo and underwent ELISA testing for anti-spike protein IgG. The per-protocol immunogenicity subset from the main study included those who received two doses of vaccine, had all immunology samples available, had no major protocol deviations, and did not have a laboratory confirmed SARS-CoV-2 infection before any visit in which serology was measured. The reactogenicity cohort of the ITT population included all individuals from the main study who received at least one dose of NVX-CoV2373 or placebo and recorded data into the electronic diary. The influenza substudy was enrolled at four unique study hospitals, the immunogenicity cohort of the ITT population was enrolled at four unique study hospitals, and the reactogenicity cohort of the ITT population was enrolled at two unique study hospitals who had the resources to manage the additional study requirements. ITT=intention-to-treat.

major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic COVID-19 from the first dose until 6 days after the second dose (ie, the per-protocol efficacy population). Vaccine efficacy was defined with the following equation:

$$\text{Vaccine efficacy (\%)} = (1 - \text{relative risk}) \times 100$$

where the relative risk (RR) of incidences were between the two study groups (ie, NVX-CoV2373 or placebo).

The estimated RR and its 95% CI for the main study were derived using Poisson regression with robust error variance.⁸ Hypothesis testing of the primary endpoint was done against the null hypothesis (ie, vaccine efficacy \leq 30%). The study met the success criterion by rejecting of the null hypothesis to demonstrate a significant vaccine efficacy. As the influenza co-administration substudy was an exploratory objective, no formal power calculation was done to assess any specific endpoint.

We did all statistical analyses with SAS (version 9.4). This study is registered with ClinicalTrials.gov, number NCT04583995.

Role of the funding source

The funder of the study had primary responsibility for the study design, study vaccines, protocol development, study monitoring, data management, and statistical analyses.

Results

Between Sept 28, 2020, and Nov 28, 2020, a total of 15 187 participants were randomised into the main phase 3 trial; of whom 15 139 participants received at least one dose of NVX-CoV2373 (n=7569) or placebo (n=7570), of which 431 were co-vaccinated with a seasonal influenza vaccine (217 received NVX-CoV2373 plus the quadrivalent influenza cell-based vaccine or adjuvanted trivalent influenza vaccine, depending on age, and 214 received placebo plus the quadrivalent influenza cell-based vaccine or adjuvanted trivalent influenza vaccine; figure 1). Those who were enrolled in the influenza substudy (n=431) were removed from the main study intention-to-treat population (n=15 139), resulting in the main study intention-to-treat safety population (n=14 708) used to make safety comparisons with the influenza substudy participants. In the influenza substudy group, 190 (43.3%) of 431 were female, 327 (75.1%) were white, 98 (22.7%) were from ethnic minorities or reported multiple races, and 117 (27.1%) had at least one comorbid condition based on the US CDC definitions.⁵ The median age of substudy participants was 39 years, 142 (32.9%) of 431 were 50 years or older, and 29 (6.7%) were 65 years or older (appendix p 12). Within the substudy, 29 (6.7%) of 431 participants received the adjuvanted trivalent influenza vaccine with a median age of 66 years (n=16) in the NVX-CoV2373 group and 69 years (n=13) in the placebo group, and 402 (93.3%) received the quadrivalent influenza cell-based vaccine with a median age of 38 years (n=201) in the NVX-CoV2372 group and 37 years (n=201) in the placebo group (table 1).

A total of 431 participants were assessed for unsolicited adverse events, serious adverse events, medically attended adverse events, and adverse events of special interest, and 404 participated in the assessment of reactogenicity. All 431 participants were part of the evaluable immunogenicity population for both the haemagglutination inhibition assay and anti-spike protein IgG assay. The substudy group overall was younger, more racially diverse, and had fewer comorbid conditions than participants in the main study as well as in the main study reactogenicity and immunogenicity cohorts (table 1; appendix pp 12–13). The main study immunogenicity cohort for the anti-spike protein IgG assay included 999 participants in the intention-to-treat population who had received either the NVX-CoV2373

	NVX-CoV2373 plus aTIV (n=16)	NVX-CoV2373 plus QIVc (n=201)	Placebo plus aTIV (n=13)	Placebo plus QIVc (n=201)	Total (ITT population; n=15 139)
Age, years					
Mean	66.9 (1.86)	40.3 (12.72)	69.3 (3.73)	40.2 (11.57)	53.1 (14.91)
Median	66.0 (65–71)	38.0 (20–64)	69.0 (65–77)	37.0 (23–64)	55.0 (18–84)
Age group					
18–64 years	0	201 (100%)	0	201 (100%)	11 014 (72.8%)
≥65 years	16 (100%)	0	13 (100%)	0	4125 (27.2%)
Sex					
Male	6 (37.5%)	117 (58.2%)	4 (30.8%)	114 (56.7%)	7808 (51.6%)
Female	10 (62.5%)	84 (41.8%)	9 (69.2%)	87 (43.3%)	7331 (48.4%)
Race or ethnic group					
White	12 (75.0%)	151 (75.1%)	11 (84.6%)	153 (76.1%)	14 280 (94.3%)
Black or African American	0	4 (2.0%)	0	2 (1.0%)	60 (0.4%)
Asian	0	14 (7.0%)	1 (7.7%)	22 (10.9%)	462 (3.1%)
Multiple	4 (25.0%)	25 (12.4%)	0	23 (11.4%)	136 (0.9%)
Not reported	0	3 (1.5%)	1 (7.7%)	1 (0.5%)	176 (1.2%)
Other	0	3 (1.5%)	0	0	17 (0.1%)
Missing	0	1 (0.5%)	0	0	8 (<0.1%)
Hispanic or Latinx	1 (6.3%)	9 (4.5%)	1 (7.7%)	4 (2.0%)	125 (0.8%)
SARS-CoV-2 serostatus					
Negative	15 (93.8%)	183 (91.0%)	12 (92.3%)	184 (91.5%)	14 362 (94.9%)
Positive	1 (6.3%)	18 (9.0%)	0 (0.0%)	13 (6.5%)	643 (4.2%)
Missing	0	0	1 (7.7%)	4 (2.0%)	134 (0.9%)
Comorbidity status*					
Yes	5 (31.3%)	50 (24.9%)	7 (53.8%)	55 (27.4%)	6767 (44.7%)
No	11 (68.8%)	151 (75.1%)	6 (46.2%)	146 (72.6%)	8372 (55.3%)

Data are mean (SD), median (range), or n (%). Percentages are based on the ITT dataset within the seasonal influenza vaccine substudy by vaccine type (aTIV for those ≥65 years and QIVc for those <65 years of age) and overall. aTIV=adjuvanted trivalent influenza vaccine. ITT=intention to treat. QIVc=quadrivalent influenza cell-based vaccine. *Participants with comorbidities were those identified who have at least one of the comorbid conditions reported as a medical history or have a screening body-mass index value greater than 30 kg/m².

Table 1: Demographics and baseline characteristics of participants in the influenza vaccine co-administration substudy and entire study populations

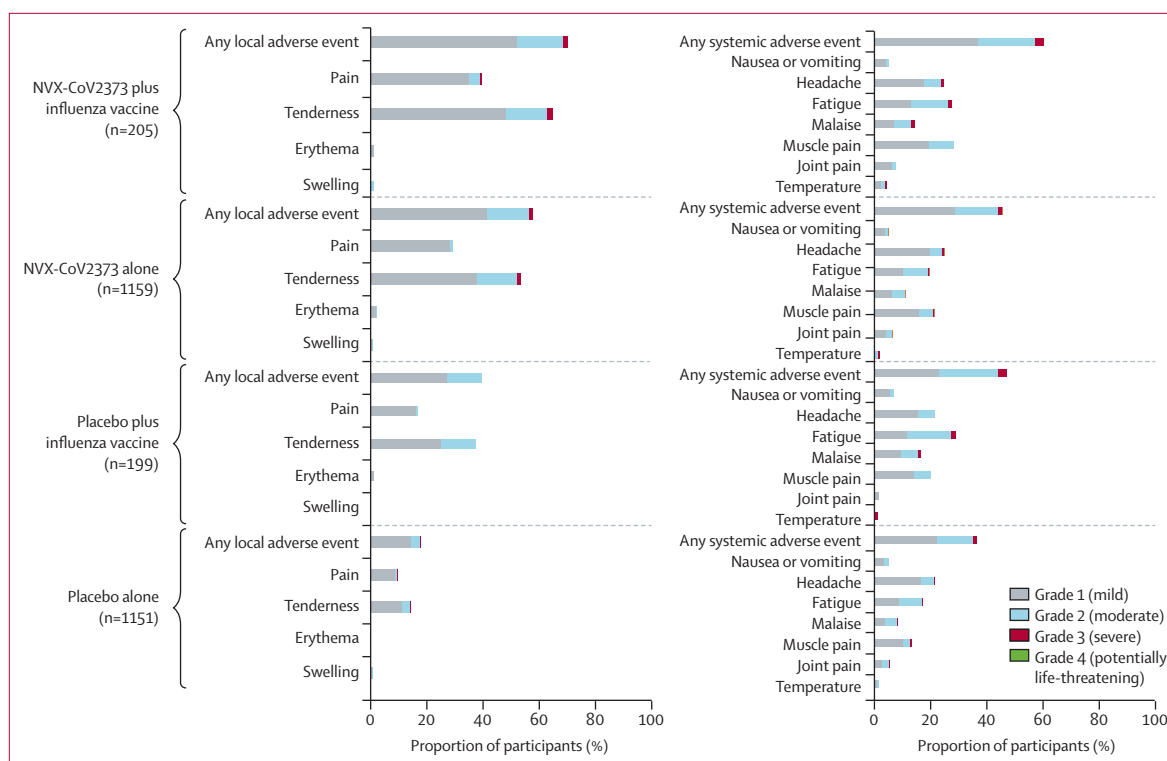


Figure 2: Reactogenicity data from participants in the influenza vaccine co-administration substudy and participants in the reactogenicity cohort of the main study after dose one

The percentage of participants in each treatment group with solicited local and systemic adverse events during the 7 days after each vaccination is plotted according to the maximum toxicity grade (mild, moderate, severe, or potentially life-threatening) in participants included in the seasonal influenza vaccine substudy and those included in the reactogenicity cohort of the main study.

vaccine or placebo alone. The main study reactogenicity cohort included 2310 from the safety population who had received at least one dose of the NVX-CoV2373 vaccine or placebo alone (figure 1).

Overall, local reactogenicity (assessed only at the non-influenza vaccine injection site) was largely absent or mild in the co-administration group, NVX-CoV2373 alone group, and placebo plus influenza vaccine group (figure 2). Any local adverse event was reported in 122 (70.1%) of 174 co-vaccinated (three [1.7%] were severe), 640 (57.6%) of 1111 in the NVX-CoV2373 alone group (11 [1.0%] severe), 71 (39.4%) of 180 in the placebo plus influenza vaccine group (0% severe), and 195 (17.9%) of 1092 in the placebo alone group (two [0.2%] severe). The most commonly reported local adverse events were injection site tenderness (113 [64.9%] of 174 co-vaccinated and 592 [53.3%] of 1111 given NVX-CoV2373 alone) and injection site pain (69 [39.7%] co-vaccinated and 325 [29.3%] given NVX-CoV2373 alone).

Any systemic adverse event was reported in 104 (60.1%) of 173 co-vaccinated (five [2.9%] were severe), 506 (45.7%) of 1108 in the NVX-CoV2373 alone group (14 [1.3%] severe), 85 (47.2%) of 180 in the placebo plus influenza vaccine group (five [2.8%] severe), and 397 (36.3%) of 1093 in the placebo alone group (12 [1.1%] severe). In

	Influenza substudy (n=431)		Main study participants (n=14 708)*	
	NVX-CoV2373 plus influenza vaccine (n=217)	Placebo plus influenza vaccine (n=214)	NVX-CoV2373 alone (n=7352)	Placebo alone (n=7356)
Any adverse event	40 (18.4%)	31 (14.5%)	1297 (17.6%)	1030 (14.0%)
Any severe adverse event	1 (0.5%)	0	33 (0.4%)	33 (0.4%)
Serious adverse event	1 (0.5%)	0	43 (0.6%)	44 (0.6%)
Medically attended adverse event	17 (7.8%)	18 (8.4%)	279 (3.8%)	288 (3.9%)
Treatment-related medically attended adverse event	3 (1.4%)	0	34 (0.5%)	17 (0.2%)
Potentially immune-mediated medical condition	0	0	5 (<0.1%)	8 (0.1%)
Adverse event of special interest related to COVID-19	0	0	8 (0.1%)	22 (0.3%)

Unsolicted adverse events and severe adverse events are those within 21 days of study dose one (with or without co-administration of influenza vaccine). Serious adverse events, medically attended adverse events, adverse events of special interest, and potentially immune-mediated medical conditions are assessed for the entire study period.
*The main study intention-to-treat population (n=15 139) were all participants who received at least one dose of NVX-CoV2373 or placebo; those who were enrolled in the influenza sub-study (n=431) were then removed to create the main study safety population (n=14 708) for comparison with the substudy participants.

Table 2: Safety data from participants in the influenza vaccine co-administration substudy and participants in the entire intention-to-treat study population (without substudy participants)

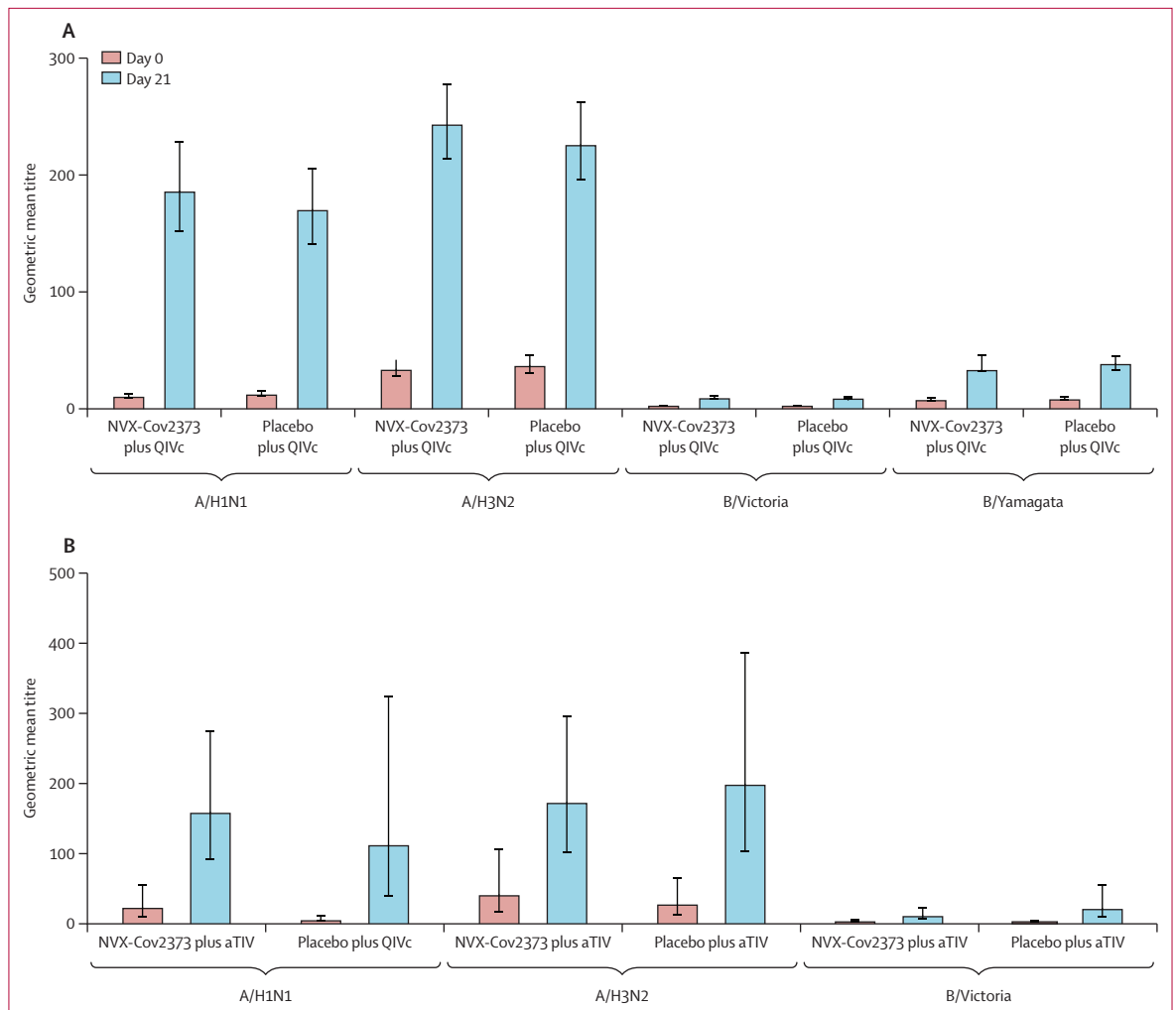


Figure 3: Geometric mean titres of haemagglutination inhibition on day 0 and day 21 in the QIVc group (A) and in the aTIV group (B)

Error bars are 95% CIs. Comparison of the geometric mean titres of haemagglutination inhibition at baseline (day 0) and 21 days after vaccination with NVX-CoV2373 or placebo with either the QIVc or aTIV influenza vaccine by influenza strain (n=178 for the NVX-CoV2373 plus QIVc group, n=179 for the placebo plus QIVc group, n=13 for the NVX-CoV2373 plus aTIV group, and n=11 for the placebo plus aTIV group). Immunogenicity was assessed in the per-protocol immunogenicity population. aTIV=adjuvanted trivalent influenza vaccine. QIVc=quadrivalent influenza cell-based vaccine.

general, the incidence of specific systemic reactogenicity events was similar within all of these groups (figure 2). The most commonly reported systemic adverse events were muscle pain (49 [28.3%] of 173 co-vaccinated and 237 [21.4%] of 1108 given NVX-CoV2373 alone) and fatigue (48 [27.7%] of 1108 co-vaccinated and 215 [19.4%] given NVX-CoV2373 alone), with muscle pain also occurring more frequently in the co-administration group than in the placebo plus influenza vaccine group (49 [28.3%] of 173 vs 36 [20.0%] of 180). Notably, fever (ie, temperature $\geq 38^{\circ}\text{C}$) was reported in seven (4.3%) of 163 in the co-vaccinated group, 21 (2.0%) of 1067 in the NVX-CoV2373 alone group, three (1.7%) of 172 in the placebo plus influenza vaccine group, and 16 (1.5%) of 1061 in the placebo alone group (appendix pp 14–17).

When assessed by specific influenza vaccine type (ie, the quadrivalent influenza cell-based vaccine in

those <65 years and the adjuvanted trivalent influenza vaccine in those ≥ 65 years) among those administered concomitantly with NVX-CoV2373, a trend towards lower rates of local and systemic reactogenicity was observed in the older group who received the adjuvanted trivalent influenza vaccine. Of note, the median duration of reactogenicity events was generally 1–2 days for local adverse events and approximately 1 day for systemic adverse events in both the co-vaccinated group and the NVX-CoV2373 alone group; when assessed by specific influenza vaccine type, a general trend was observed for a shorter duration of reactogenicity among those 65 years or older (ie, adjuvanted trivalent influenza vaccine recipients; data not shown).

Unsolicited adverse events reported up to 21 days after first vaccination were predominantly mild in severity and were similarly distributed across the co-vaccinated

and NVX-CoV2373 alone groups (table 2). The frequency of all adverse events (40 [18.4%] of 217) and all severe adverse events (one [0.5%]) in the co-vaccinated group was similar to those in the NVX-CoV2373 alone group (1297 [17.6%] of 7352 for all adverse events and 33 [0.4%] for all severe adverse events). These rates were also similar to the rates of all adverse events (31 [14.5%] of 214) and all severe adverse events (none) in the placebo plus influenza vaccine group and placebo alone group (1030 [14.0%] of 7356 for all adverse events and 33 [0.4%] for all severe adverse events; table 2). The unsolicited adverse events occurring in more than 1% of the co-vaccinated group included headache (five [2.3%] of 217), fatigue (four [1.8%]), and oropharyngeal pain (three [1.4%]). The number of all medically attended adverse events was 17 (7.8%) of 217 in those co-vaccinated and 279 (3.8%) of 7352 in those who received NVX-CoV2373 alone, whereas the number of medically attended adverse events was 18 (8.4%) of 214 in the placebo plus influenza vaccine group and 288 (3.9%) of 7356 in the placebo group alone. The number of treatment-related medically attended adverse events were lower and balanced in all groups (table 2). The number of serious adverse events was also low and balanced among the substudy participants and those not involved in the substudy. No treatment-related serious adverse events were reported in substudy participants. No potentially immune-mediated medical conditions or adverse events of special interests relevant to COVID-19 were seen in the influenza co-administration substudy, with resulting event rates similar to those not involved in the substudy. No episodes of anaphylaxis or deaths were reported within the substudy.

No significant differences were observed in the baseline geometric mean titres of haemagglutination inhibition between those in the substudy co-vaccinated with NVX-CoV2373 plus influenza vaccine group and those in the placebo plus influenza vaccine group (figure 3). In the quadrivalent influenza cell-based vaccine groups, geometric mean titres of haemagglutination inhibition were significantly higher after vaccination on day 21 compared with day 0 (appendix pp 18–19). No difference was seen in day 21 geometric mean titres of haemagglutination inhibition between the NVX-CoV2373 plus influenza vaccine group and the placebo plus influenza vaccine group for any individual influenza strain (A/H1N1, A/H3N2, B/Victoria, or B/Yamagata) for either influenza vaccine. Geometric mean fold rise values followed the same pattern (appendix pp 18–19). For both the quadrivalent influenza cell-based vaccine and adjuvanted trivalent influenza vaccine, haemagglutination inhibition seroconversion rates were generally higher for the influenza A strains than for the influenza B strains (figure 4).

Baseline anti-spike protein IgG ELISA units were similar in participants in the substudy co-vaccinated with NVX-CoV2373 plus influenza vaccine and those who

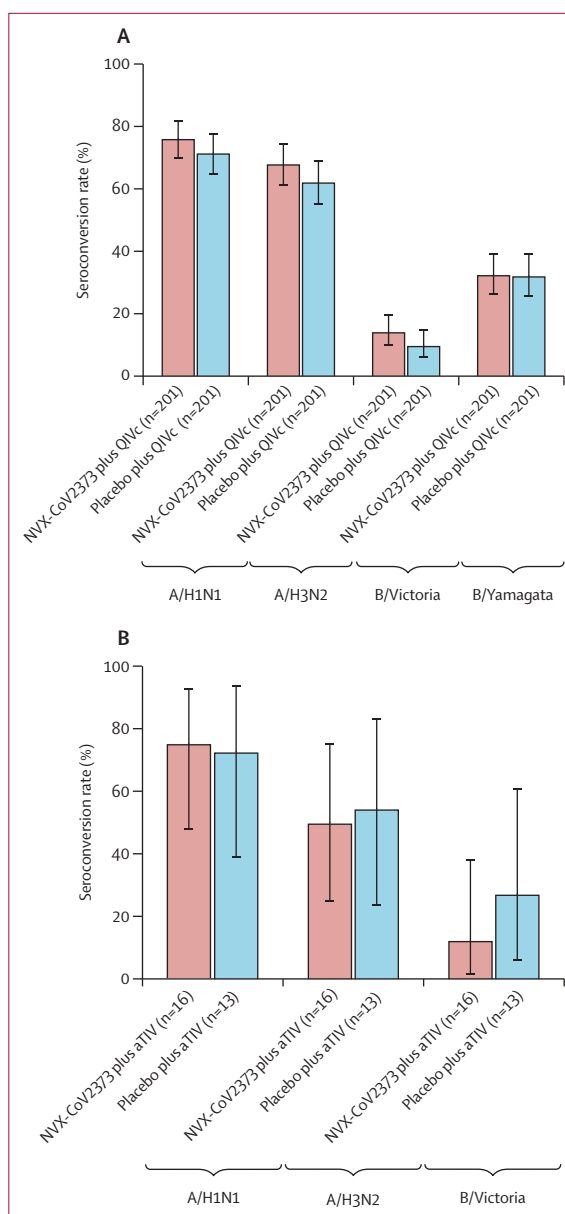


Figure 4: Haemagglutination inhibition seroconversion rates on day 21 in the QIVc group (A) and in the aTIV group (B)

Error bars are 95% CIs. Comparison of the haemagglutination inhibition seroconversion rates 21 days after vaccination with NVX-CoV2373 or placebo with the QIVc or aTIV influenza vaccine by influenza strain. aTIV=adjuvanted trivalent influenza vaccine. QIVc=quadrivalent influenza cell-based vaccine.

received placebo plus influenza vaccine as well as in those vaccinated in the main study immunogenicity cohort with NVX-CoV2373 alone or placebo alone (data for the immunogenicity per-protocol population are shown in table 3). In the groups vaccinated with NVX-CoV2373 plus influenza vaccine or with NVX-CoV2373 alone, the day 35 geometric mean ELISA units were significantly higher than those at baseline. A difference in geometric mean ELISA units was observed between the two per-protocol

	NVX-CoV2373 plus influenza vaccine			Placebo plus influenza vaccine			NVX-CoV2373 alone			Placebo alone		
	n	Day 0	Day 35	n	Day 0	Day 35	n	Day 0	Day 35	n	Day 0	Day 35
Geometric mean ELISA unit												
Inactivated influenza vaccine plus NVX-CoV2372 or placebo (all ages)	n=178	116.3 (107.7-125.6)	31236.1 (26295.5-37104.9)	n=181	111.4 (105.1-118.1)	115.7 (106.1-126.1)	n=414	112.2 (107.5-117.0)	44678.3 (40352.2-49468.2)	n=417	110.3 (106.3-114.5)	113.2 (106.8-120.0)
QIVc plus NVX-CoV2373 or placebo (18 to <65 years)	n=168	115.8 (107.2-125.0)	31516.9 (26316.2-37745.3)	n=170	112.2 (105.4-119.3)	116.8 (106.5-128.0)	n=300	111.9 (106.2-117.9)	47564.3 (43327.3-53449.4)	n=310	109.7 (105.2-114.4)	113.5 (105.6-122.0)
aTIV plus NVX-CoV2373 or placebo (≥65 years)	n=10	125.6 (75.0-210.3)	26876.1 (15374.6-46981.5)	n=11	100.0 (100.0-100.0)	100.0 (100.0-100.0)	n=114	112.8 (105.0-121.2)	37892.8 (30833.3-46568.5)	n=107	112.1 (103.4-121.4)	112.3 (103.1-122.3)
Geometric mean fold rise												
Inactivated influenza vaccine plus NVX-CoV2372 or placebo (all ages)	n=178	NA	268.6 (221.0-326.4)	n=181	NA	1.0 (1.0-1.1)	n=414	NA	398.4 (358.6-442.6)	n=417	NA	1.0 (1.0-1.1)
QIVc plus NVX-CoV2373 or placebo (18 to <65 years)	n=168	NA	272.3 (222.3-333.5)	n=170	NA	1.0 (1.0-1.1)	n=300	NA	425.0 (375.7-480.8)	n=310	NA	1.0 (1.0-1.1)
aTIV plus NVX-CoV2373 or placebo (≥65 years)	n=10	NA	214.0 (96.5-474.6)	n=11	NA	1.0 (1.0-1.0)	n=114	NA	335.9 (274.4-411.1)	n=107	NA	1.0 (1.0-1.0)
Seroconversion rate												
Inactivated influenza vaccine plus NVX-CoV2372 or placebo (all ages)	n=178	NA	97.8 (94.3-99.4)	n=181	NA	0.6 (0.0-3.0)	n=414	NA	99.0 (97.5-99.7)	n=417	NA	0.7 (0.1-2.1)
QIVc plus NVX-CoV2373 or placebo (18 to <65 years)	n=168	NA	97.6 (94.0-99.3)	n=170	NA	0.6 (0.0-3.2)	n=300	NA	99.0 (97.1-99.8)	n=310	NA	1.0 (0.2-2.8)
aTIV plus NVX-CoV2373 or placebo (≥65 years)	n=10	NA	100.0 (69.2-100.0)	n=11	NA	0.0 (0.0-28.5)	n=114	NA	99.1 (95.2-100.0)	n=107	NA	0.0 (0.0-3.4)

Data are n or assay result (95% CI). Inactivated influenza vaccine included both aTIV and QIVc. Influenza vaccine co-administration substudy participants were compared with the per-protocol immunogenicity population (data are shown for participants who consented to have IgG concentrations assessed). Comparison of the anti-spike protein IgG geometric mean ELISA units at baseline (day 0) and day 35 as well as day 35 geometric mean fold rise and seroconversion rate after vaccination with NVX-CoV2373 or placebo with either aTIV, QIVc, or alone. aTIV=adjuvanted trivalent influenza vaccine; NA=not applicable; QIVc=quadrivalent influenza cell-based vaccine.

Table 3: Anti-spike protein IgG on day 0 and day 35 in the influenza vaccination substudy and in the immunogenicity cohort of the per-protocol population

groups (31236.1 [95% CI 26295.5–37104.9] for the NVX-CoV2373 plus influenza vaccine group [n=178] vs 44678.3 [40352.2–49468.2] for the NVX-CoV2373 alone group [n=414]). A post-hoc assessment of the ratio between the two geometric means when adjusted for baseline ELISA units, age, and treatment group was 0.57 (95% CI 0.47–0.70). This difference between the NVX-CoV2373 plus influenza vaccine cohort and the NVX-CoV2373 alone cohort was also reflected in the geometric mean fold rises, but not in the seroconversion rates. The day 35 geometric mean ELISA units were numerically lower in those aged 65 years or more (ie, those who received the adjuvanted trivalent influenza vaccine) concomitant vaccination group compared with those aged 18 to less than 65 years (ie, those who received the quadrivalent influenza cell-based vaccine) concomitant vaccination group, although the number of participants in the concomitant adjuvanted trivalent influenza vaccine group was small. However, the geometric mean fold rises in both groups were large with more than 200 times compared with day 0, and the seroconversion rates were both more than 97%. This diminution in immunogenicity with increasing age was also seen in the main study immunogenicity cohort. The subgroup of participants receiving concomitant NVX-CoV2373 and any influenza vaccine who were seropositive (n=19) at baseline achieved day 35 geometric mean ELISA units that were significantly greater than those in similar participants who were seronegative (n=198) at baseline (71115.6 [95% CI 46813.0–108032.8] vs 30439.1 [25713.4–36033.5]; appendix p 20).

Among 386 participants in the influenza substudy who were included in the efficacy per-protocol population, two (1%) of 191 participants were reported to have virologically confirmed, symptomatic COVID-19 with onset at least 7 days after the second dose among vaccine recipients and eight (4%) of 195 among placebo recipients. A post-hoc analysis of the primary endpoint showed a vaccine efficacy of 74.8% (95% CI –19.7 to 94.7) in the influenza substudy group. Among 360 participants who were aged 18 to less than 65 years, one (<1%) of 178 participants was reported to have virologically confirmed, symptomatic COVID-19 with onset at least 7 days after the second dose among vaccine recipients and eight (4%) of 182 among placebo recipients; vaccine efficacy of 87.5% (95% CI –0.2 to 98.4; appendix p 22). Too few cases were reported among those in the per-protocol population who were 65 years or older to calculate a vaccine efficacy. All influenza substudy COVID-19 cases in the per-protocol group were due to the Alpha (B.1.1.7) variant. Among 431 participants in the influenza substudy intention-to-treat population, vaccine efficacy was 80.6% (95% CI 13.3–95.7; appendix p 22). Vaccine efficacy in the main study per-protocol population (those aged 18 to <65 years) was 89.8% (95% CI 79.7–95.5) while vaccine efficacy against the Alpha variant alone in the main study per-protocol population was 86.3% (71.3–93.5).

Discussion

To our knowledge, this substudy is the first to show the safety, immunogenicity, and efficacy of any COVID-19 vaccine when co-administered with a seasonal influenza vaccine or any other vaccination. Most COVID-19 vaccine trials have excluded participants receiving other vaccinations at the time or near the time of injection with study vaccine and therefore have no interaction studies addressed in their labels.^{9–11} Although no specific comparative immunogenicity endpoints were prespecified in this exploratory substudy, we found no evidence for interference of the COVID-19 vaccine with the quadrivalent influenza cell-based vaccine. Definitive conclusions about the adjuvanted trivalent influenza vaccine were not possible because of the small number of participants aged 65 years or more. We did, however, observe an effect of concomitant administration of an influenza vaccine on the absolute magnitude of the anti-spike protein IgG antibody response. This effect did not seem to be clinically meaningful, as vaccine efficacy appeared to be preserved. Co-administration also appeared to have no clinically meaningful effect on systemic or local reactogenicity and no additional safety concerns were found to be associated with co-vaccination. Solicited local and systemic reactogenicity events after co-administration were generally similar to the incidence and severity of those for each vaccine when administered separately. The incidence of more subjective local reactogenicity (ie, pain and tenderness) was elevated in the co-vaccinated group above the level of either the NVX-CoV2373 alone or placebo plus influenza vaccine groups, but the incidences for more objective local events (ie, erythema and swelling) were low and indistinguishable between all groups. These increased incidences were largely driven by an increase in mild symptoms. Whether participants were biased in their assessment of pain and tenderness at the study injection site having received two co-administered vaccinations is unclear; the fact that placebo injections were assessed as causing more local pain or tenderness when given concomitantly with an influenza vaccine (administered in the opposite arm) compared with placebo injections, when given alone, would suggest this is likely to be the case. Another explanation is that participants recorded additive local symptoms from the influenza injection site in error despite being instructed to record symptoms at the injection site of the study vaccine only. The incidence for any systemic reactogenicity event in those co-vaccinated was modestly elevated over the incidence for either NVX-CoV2373 or influenza vaccine alone, consistent with an overall higher vaccine immunogen load and the relatively younger participant population in the substudy. This effect was seen mainly for the events of muscle pain and fever, yet despite the relative increase in the incidence of fever, the absolute fever rate in those who received two co-administered vaccinations was modest (4.3%). Incidences of severe events were low in all groups and showed no clinically

meaningful pattern of increased reactogenicity. The elevation in some reactogenicity events might, in part, have been due to the overall younger age of the influenza vaccine substudy participants compared with the main study reactogenicity cohort (median age 39.0 years [93.3% aged 18 to <65 years] vs 52.0 years [80.1% aged 18 to <65 years]). Those who were 65 years or older who received two adjuvanted vaccines (ie, the adjuvanted NVX-CoV2373 and adjuvanted trivalent influenza vaccine) compared with those younger than 65 years who received one adjuvanted vaccine (ie, the adjuvanted NVX-CoV2373 and unadjuvanted quadrivalent influenza cell-based vaccine) had lower rates of reactogenicity; this effect of age was also seen in the NVX-CoV2373 alone group and in previous NVX-CoV2373 studies^{6,12,13} and is consistent with immunosenescence.

The incidences of adverse events, serious adverse events, and adverse events of special interest were low and balanced between those given NVX-CoV2373, influenza vaccine, or both. The incidence of any medically attended adverse events was higher in substudy participants compared with non-substudy participants. This difference was less apparent when assessing treatment-related medically attended adverse events only. The increased rate of all medically attended adverse events in the substudy might represent a health care seeking bias in those desiring an influenza vaccine rather than a true increase in medical visits due to adverse events related to co-vaccination or receipt of the influenza vaccine plus placebo; an assessment of these excess medical visits revealed that most were general practice visits associated with health maintenance concerns (data not shown).

The magnitude of the humoral response to either influenza vaccine was not affected by co-administration with NVX-CoV2372 when assessed at 21 days after dosing, although care should be used in generalising this observation to adjuvanted trivalent influenza vaccine because of the small sample size. The post-vaccination increase in geometric mean titres and seroconversion rates for each strain were high when either influenza vaccine was administered with placebo or NVX-CoV2373, although a generally lower response to the influenza B strains was observed in all influenza vaccine recipients. The humoral immune response to influenza B strains is dependent upon numerous factors, including age and previous influenza vaccine exposure.¹⁴ Low influenza B seroconversion rates¹⁵ and lower seroconversion rates relative to influenza A strains^{16,17} have been seen with previous immunogenicity studies of quadrivalent inactivated influenza vaccines.

By contrast, a modest reduction in the anti-spike protein IgG ELISA units was observed with the co-administration of NVX-CoV2373 and an influenza vaccine. Whether this reduction was due to vaccine interference or due to the non-randomised nature of the studied groups is unclear. In the absence of a correlate

of protection, interpretation of the significance of this finding is difficult. The post-hoc assessment of vaccine efficacy in this substudy in those aged 18 to less than 65 years was 87·5% compared with the vaccine efficacy of 89·8% in the same age group from the per-protocol efficacy populations in the main study. The similar vaccine efficacy for the co-administration substudy group and the main study group would suggest that the reduction in the anti-spike protein IgG ELISA units as a result of co-administration might not be clinically meaningful. In fact, the concentrations of anti-spike protein IgG ELISA units in those receiving both vaccines (in either those 18 to <65 years or ≥65 years) was still more than three-fold greater than the anti-spike protein IgG ELISA units found in convalescent serum, suggesting that ELISA units in this range found in substudy participants might be protective.^{18,19} It should be also noted that no difference in the rates of seroconversion were seen between those co-vaccinated and those who received NVX-CoV2373 alone.

The extent of the reduction in anti-spike protein IgG ELISA units might be less relevant in participants who are seropositive at baseline, as they achieved high values after vaccination with co-administration of influenza vaccine with a mean of 71115 ELISA units in co-vaccinated seropositive participants of all ages compared with a mean of 46679 ELISA units in the per-protocol NVX-CoV2373 alone recipients of all ages (yet this finding was not as large as the mean of 125490 ELISA units in seropositive NVX-CoV2372 alone recipients). One possible explanation for this finding is that seropositive individuals have pre-existing T-cell and B-cell populations with immune memory against the SARS-CoV2 spike protein minimising any possible effect of immune interference. Therefore, influenza vaccine co-administration might affect priming but have no effect on the immune response in previously primed individuals. An implication of this finding is that influenza vaccine co-administration with the second dose of any two-dose COVID-19 vaccine schedule, or with a subsequent booster dose of COVID-19 vaccine, might overcome any potential immune interference. This effect should be assessed further as it has important implications for public health vaccination strategies.

Although this substudy is the first to evaluate the co-administration of a COVID-19 vaccine with a seasonal influenza vaccine, influenza vaccine co-administration in other settings has been well studied. Our study used two different influenza vaccines for different age groups in compliance with the UK influenza vaccination guidelines.³ For those younger than 65 years, a cell culture-derived, inactivated quadrivalent influenza vaccine was used. The quadrivalent influenza cell-based vaccine was approved in the UK in December, 2018, for individuals 9 years and older and extended to 2 years and older in 2020. For the older cohort, an MF59 squalene-based, oil-in-water adjuvanted trivalent influenza vaccine

was administered. This adjuvanted trivalent influenza vaccine was approved in the UK in August, 2017. In two studies of the MF59 adjuvanted trivalent influenza vaccine given concomitantly with a pneumococcal vaccine, antibody responses to either vaccine were not affected, and the safety data were consistent with expected rates of adverse events for both vaccines.^{20,21} No interference or safety concerns have been reported with a quadrivalent influenza vaccine co-administered with pneumococcal and herpes zoster vaccines.^{22,23}

The strengths of our substudy include the placebo-controlled study design and its alignment with the UK's national influenza vaccine policy in the use of both adjuvanted and unadjuvanted influenza vaccines in different age groups. Study limitations include the small overall substudy size (with few participants ≥65 years owing to the high rate of routine influenza vaccination among participants in this age group at study start), small number of substudy efficacy endpoints, the absence of formal prespecified non-inferiority statistical assessment of immunogenicity, and the absence of randomisation in recruiting the influenza substudy, immunogenicity, and reactogenicity cohorts. A stronger study design could have involved four randomised groups, consisting of NVX-CoV2373 plus influenza vaccine, NVX-CoV2373 plus placebo, influenza vaccine plus placebo, and placebo plus placebo. Another limitation was the open-label study design in administering the influenza vaccine, but this design was required to allow participants to consider only the study vaccine injection site for assessment of local symptoms. Finally, the assessment of neutralising antibody titres might have benefitted the immunogenicity investigation, yet previous studies with NVX-CoV2373 have shown a strong correlation between the anti-spike protein and wild-type microneutralisation results.¹⁸

In conclusion, this substudy is the first to show the safety, immunogenicity, and efficacy profile of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine. These data show no early safety concerns with the concomitant administration of NVX-CoV2373 with an influenza vaccine. Immunogenicity of the influenza vaccine was preserved with concomitant administration although a modest decrease in the immunogenicity of the NVX-CoV2373 vaccine was found. Vaccine efficacy in those aged 18 to less than 65 years appeared to be preserved in those receiving both vaccines compared with those vaccinated with NVX-CoV2373 alone. Future clinical trials and post-licensure studies of COVID-19 vaccines should include safety and immunogenicity data for co-administration with common adult and paediatric vaccines. More research on the concomitant vaccination of COVID-19 and influenza vaccines is needed, especially in those older than 65 years, to help guide national immunisation policy on this important issue.

Contributors

PTH is the chief investigator. ST, PTH, JSP, LK, FD, GG, IC, and AR contributed to the protocol and study design. EG, CC, ALG, JG, FB,

AMM, and PAS are study site principal investigators. EG, CC, ALG, JG, FB, AMM, and PAS contributed to the study or data collection. IC and AR verified the data and reviewed the statistical analysis. ST (representing the funder) and PTH (representing the trial sites) interpreted the data, wrote the manuscript, and decided to submit for publication. All authors reviewed, commented on, and approved this manuscript before submission for publication.

Declaration of interests

ST, JSP, LK, FD, GG, IC, AR, and EJR are Novavax employees; and SR, JE, and AG-J are Seqirus employees, as they receive a salary for their work. All other authors declare no competing interests.

Data sharing

Only the data presented in this paper and the appendix will be shared for this study.

Acknowledgments

This study was funded by Novavax. Editorial assistance in the preparation of this manuscript was provided by Phase Five Communications, funded by Novavax. We thank all the study participants for their commitment to this study. We also acknowledge the investigators and their study teams for their hard work and dedication. In addition, we thank the National Institute for Health Research (NIHR) Clinical Research Network, the NIHR Oxford Cognitive Health Clinical Research Facility, NHS Digital, and the UK Vaccine Task Force; and we are grateful to the Wellcome Trust funding for the Northern Ireland Clinical Research Facility.

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