Safety and immunogenicity of booster doses of an XBB.1.5 RBD subunit COVID-19 vaccine among individuals aged 5–80 years in India: a phase 3, single-blind, randomised controlled trial

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Summary

Background The SARS-CoV-2 virus continues to evolve with recent variants such as the omicron sub-variants potentially exhibiting increased transmissibility. Of note, the XBB.1.5 variant has been associated with vaccine-breakthrough cases. We utilised the same platform previously used to develop CORBEVAX™, an ancestral Wuhan strain COVID-19 RBD subunit vaccine, to now develop an XBB.1.5 RBD subunit vaccine. We evaluated the safety and immunogenicity of the new XBB.1.5 RBD subunit vaccine compared to an ancestral Wuhan strain RBD subunit vaccine.

Methods This prospective, single-blind, phase 3 randomised controlled trial was conducted in participants aged 5–80 years. Participants who had not received any other approved COVID-19 vaccine within the last 6 months were enrolled and randomised in a 2:1 ratio to receive two booster doses of either the test vaccine or the control vaccine. The vaccines were administered on Day 0 and Day 28 with immunogenicity assessments on Day 0, Day 28, and Day 42. Safety assessments included the collection of solicited and unsolicited adverse events (AEs) up to Day 56. The primary objective of the study was to demonstrate immunogenic superiority of the test vaccine booster series compared to the control vaccine series. This superiority objective was to be met if the lower limit of the two-sided 95% CI of the anti-XBB.1.5.RBD neutralising antibody (nAb) geometric mean titre (GMT) ratio of test: control was >1.0 on either Day 28 or Day 42. Given the emergence of JN.1 as the prevalent SARS-CoV-2 strain during the conduct of this study, Day 42 anti-JN.1 nAb levels were measured in a *post hoc* immunogenicity assessment. In addition, anti-XBB.1.5 RBD protein IgG concentrations were also measured by ELISA on Day 0, Day 28, and Day 42. The trial was registered at Clinical Trials Registry–India as CTRI/2024/01/061423.

Findings A total of 360 participants (32.8% female) were enrolled and randomised across seven sites in India. The nAb GMT ratio of test: control participants was 2.08 (95% CI 1.64–2.63) on Day 28 and 2.91 (95% CI 2.38–3.56) on Day 42. The geometric mean fold rise (GMFR) of neutralising antibodies (nAb) was 7.637 (95% CI 6.090–9.578) on Day 28 and 17.02 (95% CI 13.79–21.01) on Day 42 in the test booster series arm. The nAb GMFRs in the control booster series arm at the same time points were 3.033 (95% CI 2.340–3.932) and 4.824 (95% CI 3.731–6.236), respectively. *Post hoc* analyses revealed an nAb GMT ratio of 1.90 (95% CI 1.56–2.31) for test: control against the JN.1 SARS-CoV-2 strain. The safety profile of the new XBB.1.5 RBD subunit vaccine was found to be very similar to that of the ancestral strain vaccine with 59 AEs (about 1 AE for every 8 doses administered) and 27 AEs (a little less than 1 AE for every 8 doses administered) respectively during the study. No serious AEs or AEs of special interest were reported in either the test or control arm of the study. Two cases of pyrexia required medical attention, one in each arm.

Interpretation The new XBB.1.5 RBD subunit vaccine was found to be both safe and robustly immunogenic when administered as a two-dose booster series in individuals aged 5–80 years. In particular, the vaccine induced a significant rise in neutralising antibodies against the XBB.1.5 strain as well as cross-protective neutralising antibodies against the JN.1 SARS-CoV-2 strain. These data are in line with studies of other XBB.1.5 monovalent

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vaccines and support a positive risk-benefit profile. Real-world studies may provide additional evidence about the effectiveness of this new updated vaccine.

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Keywords: Randomised controlled trial; COVID-19; XBB.1.5 variant; Subunit vaccine; Booster

Research in context

Evidence before this study

The SARS-CoV-2 virus has been circulating worldwide since its emergence in late 2019. Vaccinations have been particularly effective in preventing hospitalisations and deaths even among individuals who acquire COVID-19. Multiple technology platforms, including mRNA and protein subunit platforms, have been utilised to develop vaccines. More recently, immune-evasive SARS-CoV-2 strains have emerged fuelling the need for variant-directed boosters. Several mRNA monovalent boosters and one protein subunit booster, targeting the XBB.1.5 strain, have been approved by various national regulatory agencies across the world.

Added value of this study

In this study, we tested a new XBB.1.5 RBD subunit vaccine developed using an established yeast-expression system. We conducted a single-blinded, randomised, phase 3 study to compare two booster doses of this updated vaccine versus two booster doses of the ancestral strain vaccine developed using the same yeast-expression system. We showed that the safety profiles of the two vaccines were comparable. More than 85 million doses of the ancestral strain vaccine (CORBEVAX™) have now been administered, demonstrating an acceptable safety profile. Additionally, the XBB.1.5 RBD subunit vaccine was found to be superior to the ancestral strain vaccine in inducing neutralising antibodies against the XBB.1.5 strain. Importantly, this updated vaccine also induced neutralising antibodies against the JN.1 strain, which became the most prevalent circulating SARS-CoV-2 strain during and after the conduct of the study. This study demonstrates a favourable risk-benefit profile of the updated monovalent XBB.1.5 RBD subunit vaccine when administered as a booster series across multiple age groups including children aged 5 years and above.

Implications of all the available evidence

Our study adds to the growing body of evidence suggesting that the use of updated monovalent booster vaccines will be beneficial in reducing the morbidity and mortality associated with SARS-CoV-2 infection. Various real-world studies have demonstrated the effectiveness of such updated vaccines in preventing hospitalisations and deaths. Protein subunit vaccines such as ours have been extensively used for many decades and may be more likely to be accepted in an environment of increasing vaccine hesitancy. SARS-CoV-2 vaccines developed on newer platforms, such as mRNA and adenoviral vector platforms, while faster to market, have been associated with rare but serious adverse events, such as myocarditis and thrombosis. Protein subunit SARS-CoV-2 vaccines do not appear to produce as many adverse events, suggesting a superior safety profile.

Introduction

About five years into the COVID-19 pandemic, the SARS-CoV-2 virus continues to evolve and present ongoing challenges to global public health efforts. While COVID-19 has transitioned towards an endemic status, the emergence of novel omicron sub variants, particularly the XBB lineages, has driven new surges in infections worldwide.[1,2] The omicron variant (B.1.1.529) has been the predominant SARS-CoV-2 strain in circulation since January 2022, spawning over 680 sub-lineages.[3] Its high transmissibility and capacity for immune evasion have resulted in widespread vaccine-breakthrough infections and reinfections.[4,5] Among the Omicron subvariants, the WHO designated BQ.1.1 and XBB* (XBB and its sub-lineages, including XBB.1.5) as "Omicron subvariants under monitoring" due to their potential for increased transmissibility and immune escape.[6] Fortunately, no significant increase in disease severity has been observed to date despite these evolving variants.

Of particular concern is the XBB.1.5 subvariant, a recombinant of two omicron predecessors, BA.2.10.1 and BA.2.75. Preliminary research indicates that XBB.1.5 exhibits enhanced immune evasion properties and increased binding affinity to the human ACE2 receptor compared to other circulating omicron subvariants.[7,8] The F486P mutation in the receptor-binding domain of the spike glycoprotein distinguishes XBB.1.5 from its XBB or XBB.1 predecessor and has been associated with increased ACE2 binding.[9] XBB was the most prevalent sub-lineage (63.2%) circulating all over India as of December 2023. The WHO's Technical Advisory Group on COVID-19 Vaccine Composition (TAG–CO–VAC) has recommended that new

formulations of COVID-19 vaccines should aim to induce antibody responses that neutralise XBB descendent lineages to improve protection against XBB.1-related variants. One approach recommended was to use a monovalent XBB.1 descendent lineage, such as XBB.1.5 as the vaccine antigen.[10]

Biological E. Limited (BE) presently has a subunit COVID vaccine, CORBEVAX™ (targeting the ancestral Wuhan strain) that has market authorisation in India and has been granted Emergency Use Listing by the WHO.[11–13]

To contain the spread of the new variant, BE has developed a new XBB.1.5-RBD subunit vaccine on the same platform used for the vaccine against the ancestral strain. Animal toxicity and immunology studies have indicated a favourable risk-to-benefit profile (unpublished data) and the vaccine has been advanced for clinical development. This study describes the design and results of a phase 3 safety and immunogenicity study of a new XBB.1.5-RBD vaccine in individuals aged 5–80 years, when administered as a booster series.

Methods

Trial design and setting

This study was a prospective, multicentre, single-blind, phase 3 randomised controlled trial conducted at seven study sites across India between January and June 2024 (BAPS Pramukh Swami Hospital, Surat, Gujarat; Cheluvamba Hospital, Mysuru, Karnataka; ESIC Medical College and Hospital, Faridabad, Haryana; Gillurkar Multispeciality Hospital, Nagpur, Maharashtra; Guru Teg Bahadur Hospital, Delhi; Lifepoint Multispecialty Hospital, Pune, Maharashtra; and St. Theresa's Hospital, Hyderabad, Telangana). The study was conducted in accordance with the principles defined in the Declaration of Helsinki (2024), the International Conference on Harmonisation guidelines for Good Clinical Practices (GCP), and the New Drugs and Clinical Trial Rules (2019) from the Central Drugs Standard Control Organization, India. The protocol received approval from the Investigational Review Board or Ethics Committee at each study site. All participants and/or their parents provided written informed consent prior to enrolment. No patients or members of the public were involved in the design, conduct, reporting, or dissemination of this research. All study sites were required to have the capacity to store and administer investigational vaccines under cold chain conditions and staff qualified in GCP-compliant clinical trial procedures. Vaccinations were administered by trained personnel licenced according to local regulatory requirements.

The total duration of the study for each participant was 56 days from the day of the first dose of vaccination. Study participants received two doses of test or control vaccine, administered on Day 0 and Day 28. Three participants did not receive the second dose of the vaccine as they dropped out of the study before Day 28. Immunogenicity was assessed at Day 0 (pre-vaccination), Day 28, and at Day 42 (14 days post-second dose) while the safety profile was assessed until 28 days after the second dose (Day 56). A time window of +4 days was allowed for Day 28 and Day 42 visits, and a time window of 14 days was allowed for the Day 56 visit to ensure participant compliance.

During this study, no major protocol deviations were reported at any of the study sites. A few participants reported for their visits outside the window period, but these deviations were not found to be significant and were duly reported to the ethics committees of the respective study sites. No formal interim efficacy or safety analyses or predefined stopping rules were included in the protocol. The trial was registered at Clinical Trials Registry–India as CTRI/2024/01/061423.

Participants

A total of 360 healthy individuals, aged between 5 and 80 years were enrolled in the study. The participants were further stratified into three age subsets: ≥50–≤80 years (older adults), ≥18–≤49 years (younger adults), and ≥5–≤17 years (children and adolescents). Within each age subset, participants were randomised in a 2:1 ratio between the test and control vaccine groups.

Medically stable individuals who were previously vaccinated with any existing COVID-19 vaccine (either as a primary series only or a primary series and a booster dose, with the most recent dose at least 6 months prior to enrolment) were eligible to participate in the study. Health status was assessed during the screening period and included an assessment of medical history, clinical laboratory tests, vital signs, and a physical examination. Other key eligibility criteria included being virologically negative for SARS-CoV-2 infection confirmed by an RT-PCR test at the screening visit (day −1 to −3), seronegative for HIV 1 and 2, hepatitis B virus, and hepatitis C virus. All those with an axillary temperature of more than 38·0 °C, those participating in any other clinical trial, those with a known allergy to vaccine components, those living in the same household of SARS-CoV-2-positive person(s), those with symptoms suggestive of an acute illness, and those with other chronic illnesses or immunodeficient conditions or who were on immunosuppressants were excluded from the study. A complete list of eligibility criteria is provided as Supplementary Information. Licenced or investigational COVID-19 vaccines were prohibited during study follow-up. Medications for symptom relief were permitted, but immunoglobulins or blood products were not allowed within the 3 months prior to enrolment.

Randomisation, allocation concealment, and blinding

Enrolled participants were randomised in a 2:1 ratio to either receive the XBB.1.5 RBD subunit vaccine (test) or

CORBEVAX™ ancestral strain RBD vaccine (control). An interactive web response system-based (IWRS) platform was utilised for randomisation, that occurred after completion of all screening-related activities and prior to the administration of the first booster dose. A participant was considered randomised once they met all the eligibility criteria and received a randomisation number from the IWRS platform. The randomisation scheme was generated by SAS statistical software. Site staff accessed treatment assignments through the IWRS interface, and allocation was concealed until the point of assignment. This was a single-blind study where study participants were unaware of the vaccination group to which they were assigned. The test and control vaccines were prepared in syringes outside the participants' presence to maintain blinding.

Interventions (vaccines)

Biological E's CORBEVAX™—a subunit vaccine containing the receptor-binding domain (RBD) of the ancestral SARS-CoV-2 strain—was used as a control vaccine. The new formulation that contained the XBB.1.5 RBD antigen of SARS-CoV-2 was used as a test vaccine. Both RBD proteins were produced on the same *Pichia pastoris* yeast platform and both the formulated vaccines contained the RBD protein antigen and Aluminium Hydroxide gel as Al^{3+} and CpG1018 as adjuvants.[14] A 0·5 mL dose of the candidate XBB.1.5 RBD antigen of SARS-CoV-2 test vaccine or the CORBEVAX™ vaccine containing RBD from the ancestral strain (control vaccine) was administered via an intramuscular (IM) injection into the deltoid muscle of the non-dominant arm in a two-dose booster schedule with a 28-day interval between doses. Both the vaccines contained 25 μg of RBD Antigen, 750 μg of Aluminium Hydroxide (as Al^{3+}) and 750 μg of CpG1018.

Outcomes

This phase 3 study was designed to assess both the immunogenicity and safety of BE's new XBB.1.5 subunit COVID-19 test vaccine. The primary objective was to assess the immunogenic superiority against the monovalent CORBEVAX™ control vaccine (containing the ancestral Wuhan strain) administered in two doses, with a 28-day interval between doses, in terms of virus neutralising antibodies at Day 28 and Day 42. The primary immunogenicity endpoint was the geometric mean titre (GMT) of anti-XBB.1.5.RBD neutralising antibodies at Day 28 and at Day 42 in cohorts that received the test and control vaccine for superiority demonstration. Superiority was to be concluded if the lower limit of the two-sided 95% confidence interval of the GMT ratio of test: control of anti-XBB.1.5.RBD neutralising antibody titres was >1.0 either at Day 28 or Day 42. The secondary immunogenicity endpoint was to assess GMT at baseline, and to calculate the geometric mean fold rise (GMFR) at Day 28 and at Day 42 in both the test and control groups. Another secondary immunogenicity endpoint was to calculate the proportion of participants at Day 28 and Day 42 with a ≥2-fold rise of neutralising antibodies in those with pre-existing antibody titres, and a ≥4-fold rise in those without pre-existing antibody titres when compared with baseline titres.

The secondary objective was to descriptively assess the overall safety, reactogenicity and tolerability of BE's XBB.1.5-RBD subunit COVID-19 test vaccine in comparison with the CORBEVAX™ control vaccine (containing the ancestral Wuhan strain) for a period of 28 consecutive days after each dose in all enrolled individuals. The secondary safety endpoints were defined as occurrence of any adverse reactions within 60 min post-vaccination after each booster dose, occurrence of any solicited adverse events (AEs) within 7 consecutive days after both doses, and occurrence of any unsolicited AEs; medically attended AEs; AEs of special interest in the 28 days' post-vaccination period.

In April 2024, about midway through the conduct of this study, the WHO's TAG–CO–VAC team, determined that the JN.1 strain of SARS-CoV-2 was the dominant strain circulating worldwide. Hence, additional *post hoc* outcomes relating to protection against the JN.1 strain were included in this study. Briefly, neutralising antibodies directed against the JN.1 strain were assessed on Day 0 and Day 42 in the test and control groups, and descriptively compared.

Safety assessments

The safety assessments were based on a descriptive comparison of incidence rates of solicited local and systemic AEs up to 7 days (Day 0–6), captured through subject diaries after each vaccine dose. Participants were observed for 60 min post-vaccination to assess reactogenicity. Solicited local AEs were pain, redness, swelling, itching or warmth at the injection site. Solicited systemic AEs were fever, headache, chills, myalgia, arthralgia, fatigue, nausea, urticaria, rhinorrhoea, irritability, hypotonic-hyporesponsive episodes, somnolence, seizure, and acute allergic reaction. Unsolicited adverse events (AEs) were assessed up to Day 28 after each dose and serious AEs (SAEs), medically attended AEs (MAAEs), and AEs of special interest (AESIs) were followed up throughout the study duration.

Immunogenicity assessments

Detection of anti-XBB.1.5 RBD IgG concentration

The concentration of IgG that specifically bound to the XBB.1.5 receptor-binding domain (RBD) protein in the serum samples was measured in a sandwich ELISA. Purified XBB.1.5 RBD protein was bound to the 96-well plate and the serum samples were added to the wells to enable attachment of the RBD-specific IgGs. After washing the plate, a secondary antibody directed against human IgG and linked to an enzyme was added

to the plate. Finally, the enzyme substrate was added resulting in a reaction that produced a colour signal which was detected and quantified by spectrophotometry. The intensity of the colour is directly proportional to the concentration of RBD specific IgG in the serum sample. A pooled serum sample was used as a reference standard for comparison and the anti-RBD IgG concentration is reported in ELISA Units/mL (EU/mL). Day 0, Day 28, and Day 42 serum samples of all the clinical trial participants were tested for anti-RBD IgG concentration by ELISA.

Detection of anti-XBB.1.5 neutralising antibody

Neutralising antibodies (nAbs) were measured to assess the level of antibodies capable of blocking the SARS-CoV-2- XBB.1.5 strain from infecting mammalian cells. To enable testing in conventional laboratories, a pseudovirus based on the HIV-1 lentivirus expressing the spike protein prepared via transfection was utilised in this study.[15] This lentivirus expressed the Spike Protein from the SARS-CoV-2-XBB.1.5 strain as well as a reporter enzyme viz. Nano-luciferase. This XBB.1.5-Pseudovirus (PSV) was shown to infect HEK-293T-ACE2 cells, a human cell line that overexpresses the ACE-2 receptor. Once the pseudovirus infects cells, the enzyme Nano-luciferase is produced and can convert the specific substrate into a reaction product that can be detected by a chemiluminescence detector. When the PSV were pre-incubated with serum samples, the nAbs present in the serum blocked the PSV's ability to infect the HEK-293T-ACE2 cells thereby reducing the chemiluminescence signal directly proportional to the degree of neutralisation. Thus, by conducting neutralisation of the PSV at different dilutions of the serum and measuring the observed PSV neutralisation, a dilution (i.e., titre) of the serum that represented 50% neutralisation of the PSV added to the cells was calculated and termed as Pseudo-Virus Neutralization Titer50 or PSVNT (directly proportional to the nAb titre in the serum sample). Day 0, Day 28, and Day 42 serum samples from all the clinical trial participants were tested for PSVNT.

Detection of anti-JN.1 neutralising antibodies and anti-JN.1 RBD IgG antibodies

The JN.1 PSV consisted of the same HIV-1 lentivirus that was utilised to generate the PSV representing the XBB.1.5 strain, except for the use of the JN.1 spike protein sequence. Day 0 and Day 42 sera samples collected from the study were tested and nAb titres against the JN.1 PSV were determined. Similar statistical analysis, as performed for XBB.1.5 PSV nAb titres, was also performed for JN.1 PSV nAb titres.

Sample size calculations

Sample size and power were estimated to evaluate superiority of the XBB.1.5-RBD vaccine over the control using a one-sided, two-sample t-test on log-transformed neutralising antibody titres under a parallel-group design. The primary hypothesis tested whether the GMT ratio (test/control) exceeded 1.0, with superiority concluded if the lower bound of the two-sided 95% confidence interval was >1.0. The calculation assumed a log-transformed mean difference of 0.5 (corresponding to a GMT ratio of 1.6487), selected *a priori* to reflect a realistic and clinically meaningful difference in neutralising antibody levels between the test and control vaccines. A geometric standard deviation of 3.9 (log SD $\approx$ 1.36), derived from prior in-house superiority clinical trial immunogenicity data, and a 2:1 randomisation ratio were used. A total of 351 participants provided 90% power at a one-sided 2.5% significance level. To ensure compatibility with subgroup stratification requirements and simplify site-level enrolment blocks, the sample size was finalised at N of 360 (allowing for a 2.5% dropout rate).

Statistical analysis

Three populations were pre-specified for statistical analyses: the intention-to-treat (ITT) population (all randomised participants), the safety population (those who received at least one vaccine dose), and the according-to-protocol (ATP) population (participants who completed both doses, had no major protocol deviations, and contributed valid immunogenicity data at all protocol-defined time points).

Primary immunogenicity analyses for demonstration of superiority were conducted using the ATP population. Descriptive analyses (e.g., demographics, baseline characteristics) were performed using the ITT population while safety analyses were performed on the safety population. Safety analyses included descriptive summaries of solicited and unsolicited adverse events, serious adverse events, and adverse events of special interest. Missing safety and immunogenicity data were not imputed; all analyses were based on observed and valid data only.

For immunogenicity analyses, the geometric mean titres (GMTs) of the virus neutralisation antibodies for each of the age groups were calculated separately. A two-sided 95% CI for the post vaccination geometric mean titres were calculated. Immunogenicity was compared using a two-sample *t*-test on the means of log-transformed titres at the 2.5% significance level (one-sided) to allow for pairwise comparisons. For each comparison, the ratio of the GMTs along with their corresponding 95% CI was presented. There was no formal allowance for multiplicity in testing two primary outcomes (Day 28 and Day 42 GMTs). All the immunogenicity data were log transformed and anti-logged before interpretation.

Role of the funding source

The study was funded by Biological E. Limited. The funder was involved in the study design, collection,

analysis, interpretation of data, the writing of this article, and the decision to submit it for publication.

Results

Study population and disposition

A total of 372 children and adults were screened of whom 360 participants (32.8% female) were enrolled with 240 randomised to the test vaccine and 120 to the control vaccine. The mean age in subgroup-1, subgroup-2, and subgroup-3 was 55.41 years, 32.53 years, 13.01 years in the group that received the test vaccine, and 55.78 years, 34.06 years, and 13.35 years in the group that received the control vaccine. All participants were Indian by nationality. Participants were predominantly male, comprising nearly 68% in the test vaccine group and 65% in the control vaccine group. These data are summarised in Table 1 and Supplementary Table S1. All 360 participants had received two doses of a primary COVID-19 vaccine series and about 1 in 6 participants had received a booster dose as well.

Of the 240 that received the test vaccine, 1 participant was lost to follow-up. Similarly, 2 of the 120 that received the control vaccine were lost to follow up. Therefore, all immunogenicity analyses on Day 28 and Day 42 included 357 participants while Day 0 included all 360 participants (Trial profile [as per CONSORT 2025] shown in Fig. 1).

Immunogenicity findings

XBB.1.5 subunit test vaccine induced superior immune responses

The primary objective of this phase 3 study was to assess the immunogenicity of the XBB.1.5 subunit test vaccine in comparison with CORBEVAX™ control vaccine directed against the ancestral COVID-19 strain. As primary endpoint, the neutralising antibody titres against the XBB.1.5 strain were measured on Day 28 and Day 42 in participants who received either the test or control vaccine (Fig. 2A). Superiority was to be determined and concluded if the lower limit of the 95% CI of the test: control GMT was >1 on either Day 28 or Day 42. As shown in Table 2, this ratio was 2.08 (lower limit of 1.64) on Day 28 and 2.91 (lower limit of 2.38) on Day 42 (Fig. 2B). These data show that the updated XBB.1.5 subunit vaccine is superior to the vaccine directed against the ancestral Wuhan strain.

One of the secondary immunogenicity objectives was to assess the GMFR of both nAbs as well as IgGs. These data are presented in Table 3 and show that the GMFR for neutralising antibodies on Day 28 is nearly 8 after the XBB.1.5 subunit vaccine while only about 3 after CORBEVAX™. At Day 42, the GMFR levels are more than 17 after the XBB.1.5 subunit vaccine and about 5 after CORBEVAX™. The GMFR differences were more modest when it came to IgG antibody levels with a GMFR of about 8 on Day 42 after the XBB.1.5 subunit vaccine while a little more than 6.5 after CORBEVAX™. (Geometric mean concentrations of anti-XBB.1.5-RBD IgGs presented in Fig. 2C).

Lastly, the proportion of participants that underwent seroconversion on Day 28 (after dose –1) and on Day 42 (after dose–2) were assessed. For the XBB.1.5 subunit vaccine, 79.1% and 89.1% were seroconverted by nAbs on Day 28 and Day 42 respectively. For the CORBEVAX™ arm, the same seroconversion rates 58.5% and 68.6% respectively. Anti-XBB.1.5 IgG seroconversion rates were comparable in the two arms at both time points. Additional measures of 2- and 4-fold-rise in neutralising antibodies are provided in Table 4.

XBB.1.5 subunit vaccine induced cross-reactive neutralising antibodies against the JN.1 strain

Given the emergence of JN.1 during the conduct of the study, neutralising antibodies titres against the JN.1 strain were measured on Day 0 and Day 42 in both arms of the study. *Post hoc* analyses of these data showed that the XBB.1.5 RBD subunit vaccine induced nearly 2-times the levels of neutralising antibodies against the JN.1 strain than the ancestral strain control vaccine (GMT ratio of 1.90 with 95% CI from 1.56 to 2.31). This finding meets the *a priori* superiority criteria drawn up for the XBB.1.5 strain, suggesting significant cross-neutralisation against the JN.1 strain as well (Table 5).

The individual titres and geometric mean titres of those vaccinated with either the XBB.1.5 RBD subunit vaccine or control vaccine against both the XBB.1.5 and JN.1 strains is presented in Fig. 2D. The GMTs induced by the XBB.1.5 RBD subunit vaccine against the JN.1 strain were significantly higher than those induced by the ancestral strain vaccine.

These immunogenicity data when taken together point towards enhanced neutralisation ability by the

Demographic variables Statistics/category	XBB 1.5 vaccine (N = 240)	CORBEVAX™ vaccine (N = 120)
Sex		
Male n (%)	164 (68.3%)	78 (65%)
Female n (%)	76 (31.7%)	42 (35%)
Age (years)		
Mean (SD)	34.2 (18.34)	33.9 (18.27)
BMI		
Median (IQR)	22.9 (17.3, 26.0)	22.4 (18.4, 25.0)
Height (cms)		
Median (IQR)	164.0 (152.0, 167.5)	161.0 (152.0, 167.0)
Weight (kgs)		
Median (IQR)	61.1 (40.3, 72.3)	59.5 (43.2, 68.3)
Ethnicity		
Indian n (%)	240 (100%)	240 (100%)

Percentages were calculated using column header group count as denominator. n = Participant count in specified category. N = Total number of participants. The IQR is reported along with the corresponding q1 and q3 values.

Table 1: **Demographic characteristics.**

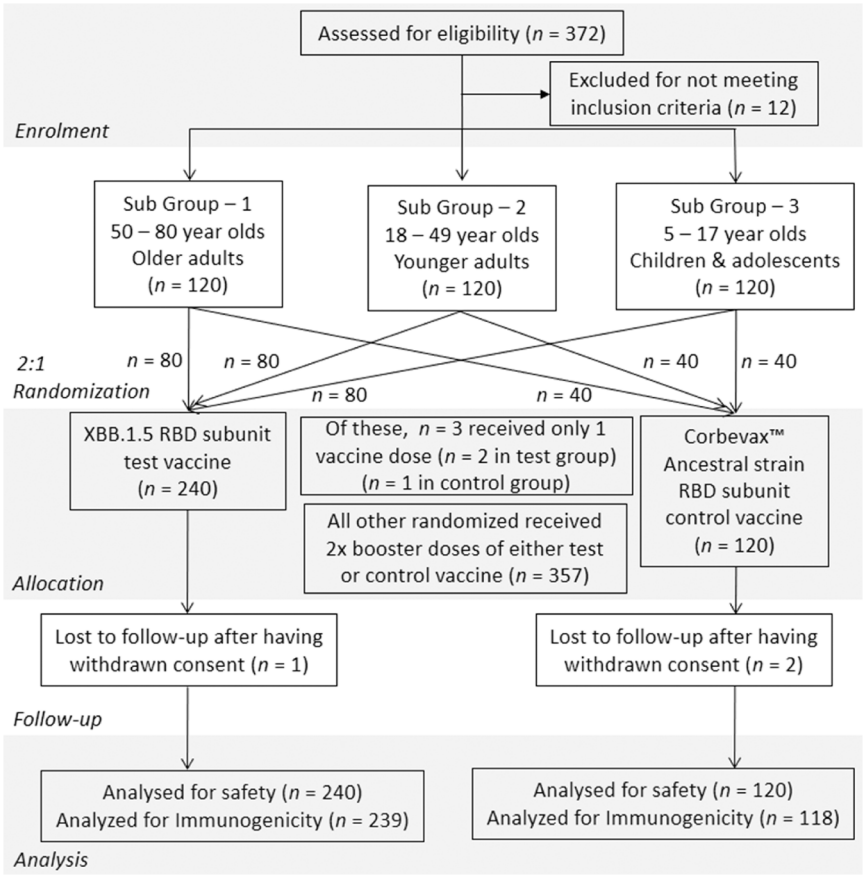

Fig. 1: **Trial profile**.

XBB.1.5 subunit vaccine compared to the CORBEVAX™ control ancestral Wuhan strain vaccine. Additionally, the XBB.1.5 RBD subunit vaccine also provides significant neutralisation of the JN.1 strain of SARS-CoV-2 as well.

Safety findings

Overall, 59 adverse events (AEs) were reported after the XBB.1.5-RBD subunit vaccine with these events being reported in 54 (22.50%) participants. The most frequently reported AEs were injection site pain (30 events in 27 [1.25%] participants), pyrexia (13 events in 13 [5.42%] participants), and headache (9 events in 9 [3.75%] participants). The unsolicited AEs reported after the XBB.1.5-RBD subunit vaccine were headache (2 events in 2 [0.83%] participants), and pyrexia, fatigue, nausea, abdominal pain, cough, and rhinorrhoea all reported in 1 participant each (1 event in 1 [0.41%] participant each).

On the other hand, 27 AEs were reported after CORBEVAX™, the ancestral SARS-CoV-2 strain control vaccine in 27 (22.50%) participants. The most frequently reported AEs in this control arm were injection site pain (14 events in 14 [11.67%] participants), pyrexia (5 events in 5 [4.16%] participants), injection site erythema, and headache [3 events in 3 (2.50%) participants each]. Unsolicited AEs reported after CORBEVAX™ were miliaria (prickly heat), headache, fatigue, pyrexia, and injection site pain (1 event in 1 [0.83%] participant each).

Importantly, no serious AEs were reported in either arm of the study. Only 2 AEs required medical attention of any kind, both were cases of pyrexia with 1 each after CORBEVAX™ and the XBB.1.5 RBD subunit vaccine. While most AEs were found to be causally related to the test vaccine (58 of 59 AEs) and control vaccine (25 of 27 AEs), the severity was mostly mild (56 of 59 AEs in the test vaccine group and 26 of 27 AEs in the control vaccine group). Adverse event data are presented in tabular form in Tables 6 and 7 and additional AE data are presented in Supplementary Tables S2–S5.

Discussion

This phase 3 study was designed to assess the immunogenicity and safety of a new updated XBB.1.5 subunit vaccine. The test vaccine was compared to BE's CORBEVAX™, a subunit vaccine that contains the RBD of the ancestral Wuhan COVID-19 strain. Both these

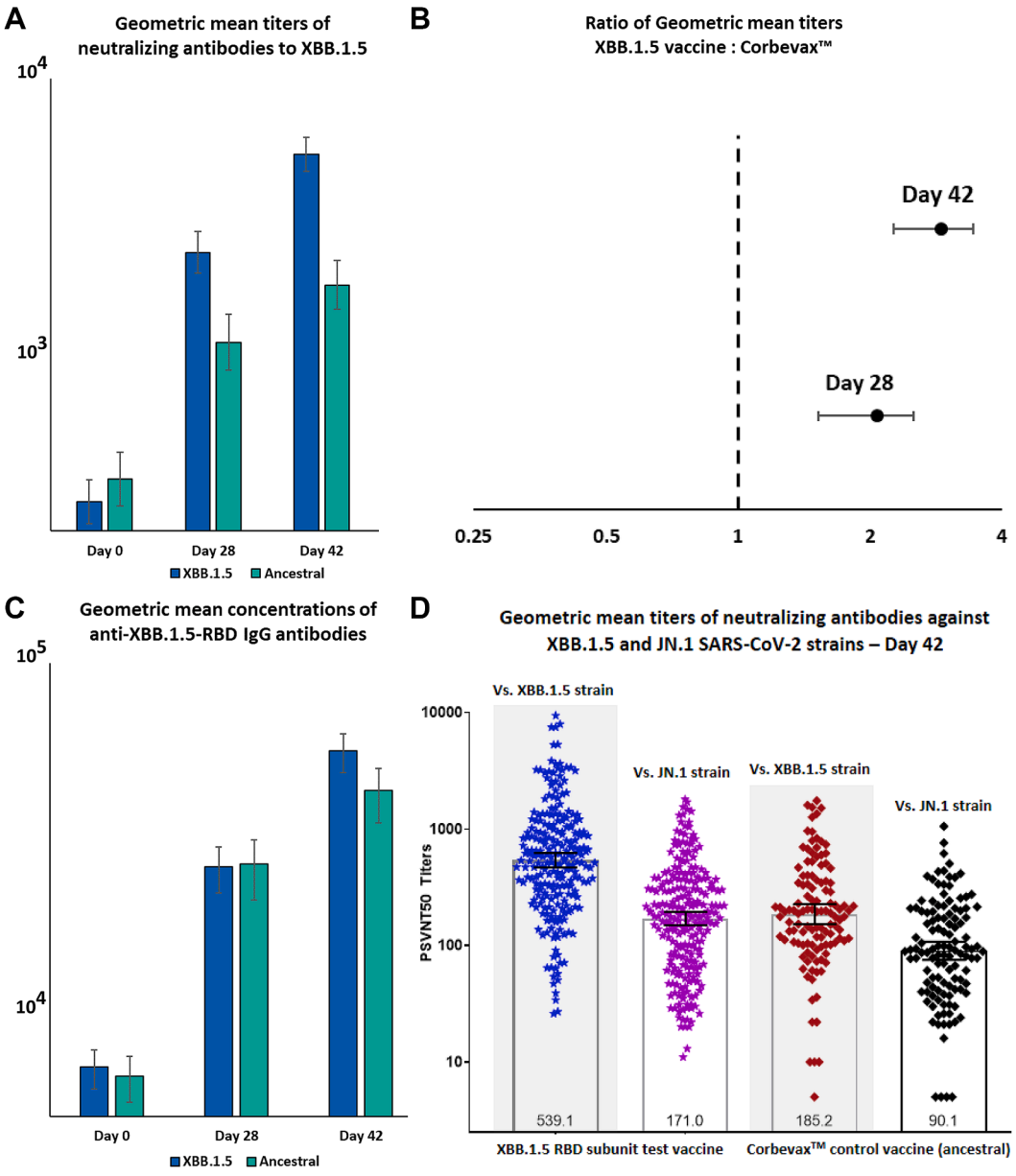

Fig. 2: A) Geometric mean titres. B) Geometric mean titre ratio of XBB.1.5 neutralising antibodies. C) Geometric mean concentration anti-XBB.1.5 IgG antibodies ("XBB.1.5" represents the XBB.1.5 RBD subunit test vaccine and "Ancestral" represents CORBEVAX™, the Ancestral SARS-CoV-2 strain RBD subunit control vaccine). D) Geometric mean titres of neutralising antibodies measured by PSVNT 50 induced against the JN.1 and XBB.1.5 strains of SARS-CoV-2 14 days after the two-dose booster series. PSVNT: Pseudo-Virus Neutralization Titer50.

vaccines have been developed on the same platform which uses a *P. pastoris* yeast expression system.[16–21] The primary objective was to assess whether two booster doses of the XBB.1.5 subunit vaccine were superior to two booster doses of the ancestral strain vaccine by measuring XBB.1.5 RBD neutralising antibody titres and the *a priori* defined superiority criteria were met. Four weeks after the first XBB.1.5 booster, the neutralising antibody titres were more than twice those in the arm that received the ancestral strain vaccine as a booster. Two weeks after a second booster this differential was nearly three times showing meaningful superiority of the updated XBB.1.5 subunit vaccine over the Ancestral strain RBD subunit vaccine. Secondary immunogenicity endpoints included calculating the GMFR of neutralising antibodies and anti-XBB.1.5

IgGs as well as the rate of seroconversion by neutralising antibody titre assessments. More than 89% of the participants who received the updated vaccine demonstrated detectable nAb titres by Day 42, which is two weeks after the second booster. These neutralising antibodies are of particular importance given that they are likely correlates of protection against SARS-CoV-2 infection.[22,23] The GMFR of neutralising antibodies was nearly 8 in the XBB.1.5 arm at Day 28 and more than 17 on Day 42. In comparison, in the ancestral strain arm, the GMFR was about 3 on Day 28 and a little less than 5 on Day 42. Anti-XBB.1.5 IgG GMFRs in the two arms were comparable while being slightly higher after the updated subunit vaccine. Importantly, a *post hoc* analysis showed that participants in this study vaccinated with the XBB.1.5 RBD subunit vaccine also produced neutralising antibodies against the JN.1 SARS-CoV-2 strain. The test vaccine produced a near two-fold rise in post-boost to pre-boost neutralising antibodies on Day 42 suggesting robust cross protection against JN.1. These immunogenicity data when taken together support the robust immunogenic response to the XBB.1.5 strain by the updated XBB.1.5 RBD subunit vaccine administered as two booster doses.

Safety-wise, the XBB.1.5 RBD subunit vaccine was found to have a comparable safety profile to CORBEVAX™ which in turn has gone through an extensive clinical development program with nearly 85,000,000 doses having been administered.[11–13] The safety profile of the ancestral strain vaccine was found to be consistent with other protein subunit vaccines. Overall, the new XBB.1.5 RBD subunit vaccine was found to have an acceptable safety profile when administered in a two-dose series across multiple age groups.

Multiple biopharmaceutical companies have developed or are developing monovalent vaccines targeting the XBB.1.5 strain. Presently, the only vaccine targeting the XBB.1.5 strain with Emergency Use Listing from the WHO is NUVAXOVID™ Omicron XBB.1.5 developed by Novavax.[24] This vaccine, and two other mRNA vaccines from Pfizer and Moderna have received emergency use authorisation from the FDA (USA).[25] Pfizer conducted a phase 2/3 study to assess the safety and immunogenicity of their XBB.1.5 vaccine in participants aged ≥12 years who had received three or more doses of an mRNA vaccine with the most recent one being against the BA.4/BA.5-adapted bivalent one. This study showed strong neutralising antibody response to the omicron XBB.1.5 strain and the authors concluded that the vaccine had a favourable risk-benefit profile.[26] Another study showed that after a XBB.1.5 Moderna mRNA booster, the neutralising antibody titre GMFR against JN.1 was 27 suggesting that vaccines that target XBB.1.5 may also protect against the JN.1 sub-lineage.[27] A recent preprint supports this notion by showing that nursing home residents in the USA had robust neutralising antibody

Parameter	XBB.1.5-RBD vaccine	CORBEVAX™ ancestral strain vaccine	GMT ratio (95% CI)
PSVNT geometric mean titres (95% confidence interval) N = Number of participants			
Day 0	31.72 (26.49–37.98) N = 240	38.12 (30.56–47.56) N = 120	–
Day 28	242.0 (204.3–286.5) N = 239	116.4 (92.85–146.0) N = 118	**2.08** (**1.64**–2.63)
Day 42	539.1 (468.6–620.3) N = 239	185.2 (152.1–226.5) N = 118	**2.91** (**2.38**–3.56)

Bolded values represent those that meet the pre-specified endpoint and/or represent statistically significant results highlighted for easy reading.

Table 2: **Anti-XBB.1.5 geometric mean neutralising antibody titre (GMT) ratios of XBB.1.5 arm: CORBEVAX™ at different time points.**

GMFR (95% CI)	XBB.1.5 subunit test vaccine	CORBEVAX™ control vaccine
Neutralising antibodies (PSVNT)		
Day 28	7.637 (6.090–9.578)	3.033 (2.340–3.932)
Day 42	**17.02** (13.79–21.01)	**4.824** (3.731–6.236)
Anti-XBB.1.5 IgG antibodies by ELISA		
Day 28	3.772 (3.208–4.434)	4.047 (3.284–4.986)
Day 42	8.130 (6.975–9.476)	6.575 (5.356–8.070)

Bolded values represent those that meet the pre-specified endpoint and/or represent statistically significant results highlighted for easy reading.

Table 3: **Geometric mean fold rise (GMFR) of neutralising antibody and anti-XBB.1.5 IgG titres in the two arms at different time points.**

Percentage (n)	XBB.1.5 RBD subunit test vaccine	CORBEVAX™ control vaccine
Neutralising antibodies (PSVNT)		
Day 28		
Seroconverted[a]	79.1% (189)	58.5% (69)
≥2-fold rise	80.3% (192)	62.7% (74)
≥4-fold rise	64.8% (155)	38.1% (45)
Day 42		
Seroconverted[a]	**89.1%** (213)	68.6% (81)
≥2-fold rise	**89.5%** (214)	69.5% (82)
≥4-fold rise	**81.2%** (194)	54.2% (64)
Anti-XBB.1.5 IgG antibodies by ELISA		
Day 28		
Seroconverted[a]	64.8% (155)	71.2% (84)
≥2-fold rise	71.1% (170)	73.7% (87)
≥4-fold rise	48.9% (117)	53.4% (63)
Day 42		
Seroconverted[a]	84.5% (202)	89.0% (105)
≥2-fold rise	87.8% (210)	89.0% (105)
≥4-fold rise	81.2% (194)	77.1% (91)

Bolded values represent those that meet the pre-specified endpoint and/or represent statistically significant results highlighted for easy reading. [a]**Seroconversion definition:** For participants with Pseudo-Virus Neutralization Titer50 (PSVNT) below detection level (assigned titre of 5) at Day-0; the participant was considered seroconverted if the fold rise in PSVNT or IgG Concentration was ≥4.0. For participants with detected PSVNT at Day-0 (PSVNT ≥ 10.0); the participant was considered seroconverted if the fold rise in PSVNT or IgG concentration was ≥2.0.

Table 4: **Percentage of participants that were seroprotected, with a ≥2-fold rise, and ≥4-fold rise in neutralising antibodies after the test and control vaccine on Day 28 and Day 42.**

Parameter	XBB.1.5-RBD vaccine	CORBEVAX™ ancestral strain vaccine	GMT ratio (95% CI)
Day 42 PSVNT against JN.1	171.0 (149.2–196.0) N = 239	90.1 (74.44–109.0) N = 118	**1.90 (1.56–2.31)**

Bolded values represent those that meet the pre-specified endpoint and/or represent statistically significant results highlighted for easy reading.

Table 5: **Anti-JN.1 geometric mean neutralising antibody titre (GMT) ratio of XBB.1.5 arm: CORBEVAX™ at Day 42 (Post hoc analysis).**

Parameter/visit N1 (%) (95% CI) n	XBB.1.5 Covid-19 vaccine (Group 1) (N = 240)	CORBEVAX vaccine (Group 2) (N = 120)
Number (%) of participants with at least one AE	54 (22.50%) (17.38, 28.31), 59	27 (22.50%) (15.38, 31.02), 27
Number (%) of participants with at least one AE reported during 60 min post-vaccination	17 (7.08%) (4.18, 11.10), 18	4 (3.33%) (0.92, 8.31), 4
Number (%) of participants with at least one AE reported during 60 min post 1st dose vaccination	14 (5.83%) (3.23, 9.59), 14	3 (2.50%) (0.52, 7.13), 3
Number (%) of participants with at least one AE reported during 60 min post 2nd dose vaccination	4 (1.67%) (0.46, 4.21), 4	1 (0.83%) (0.02, 4.56), 1
Number (%) of participants with at least one AE reported during 7-day diary period	47 (19.58%) (14.76, 25.18), 51	22 (18.33%) (11.86, 26.43), 22
Number (%) of participants with at least one AE reported during 7-day diary period post 1st dose of vaccination	39 (16.25%) (11.82, 21.54), 40	13 (10.83%) (5.90, 17.81), 13
Number (%) of participants with at least one AE reported during 7-day diary period post 2nd dose of vaccination	11 (4.58%) (2.31, 8.05), 11	9 (7.50%) (3.49, 13.76), 9
Number (%) of participants with at least one AE reported during Day 0–Day 28.	40 (16.67%) (12.18, 22.00), 41	14 (11.67%) (6.53, 18.80), 14
Number (%) of participants with at least one AE reported during Day 28–Day 42	16 (6.67%) (3.86, 10.60), 16	12 (10.00%) (5.27, 16.82), 12
Number (%) of participants with at least one AE reported during Day 42–Day 56	2 (0.83%) (0.10, 2.98), 2	1 (0.83%) (0.02, 4.56), 1
Number (%) of participants with at least one AE reported during Day 28–Day 56	17 (7.08%) (4.18, 11.10), 18	13 (10.83%) (5.90, 17.81), 13
Number (%) of participants with at least one solicited AE	47 (19.58%) (14.76, 25.18),51	22 (18.33%) (11.86, 26.43), 22
Number (%) of participants with at least one unsolicited AE	7 (2.92%) (1.18, 5.92), 8	5 (4.17%) (1.37, 9.46), 5
Number (%) of participants with at least one local AE	29 (12.08%) (8.24, 16.89), 32	17 (14.17%) (8.47, 21.71), 17
Number (%) of participants with at least one systemic AE	26 (10.83%) (7.20, 15.47), 27	10 (8.33%) (4.07, 14.79), 10
Number (%) of participants with at least one serious AE	0 (0.00%) (0.00, 0.00), 0	0 (0.00%) (0.00, 0.00), 0
Number (%) of participants with at least one medically attended AE	1 (0.42%) (0.01, 2.30), 1	1 (0.83%) (0.02, 4.56), 1
Number (%) of participants with at least one AESI	0 (0.00%) (0.00, 0.00), 0	0 (0.00%) (0.00, 0.00), 0
Number (%) of participants with severity grading		
Mild	51 (21.25%) (16.25, 26.97), 56	26 (21.67%) (14.67, 30.11), 26
Moderate	3 (1.25%) (0.26, 3.61), 3	1 (0.83%) (0.02, 4.56), 1
Severe	0 (0.00%) (0.00, 0.00), 0	0 (0.00%) (0.00, 0.00), 0
Number (%) of participants with causality grading		
Related	54 (22.50%) (17.38, 28.31), 58	25 (20.83%) (13.96, 29.20), 25
Unrelated	1 (0.42%) (0.01, 2.30), 1	2 (1.67%) (0.20, 5.89), 2

N = No. of participants per arm, N1 = Participant count, % = Percentage of participants, n = Event count.

Table 6: **Summary of adverse events (AEs) in the safety population.**

GMFRs against both XBB.1.5 and JN.1 strains[28] after being vaccinated with a monovalent XBB.1.5 vaccine. Recent observational data also show that the clinical severity of those vaccinated with a XBB.1.5 COVID-19 vaccine; and then infected with the JN.1 strain, was not worse than those who acquired the XBB.1.5 strain.[29] Although this was not a head-to-head study, the GMFR values observed with our vaccine (GMFR of 7.6 at Day 28) are comparable to published data from XBB.1.5 mRNA and protein-based boosters. In a Pfizer phase 2/3 clinical trial of a monovalent XBB.1.5 mRNA vaccine, GMFR post vaccination was 6.9 against XBB.1.5 in participants aged 18–55 years.[24] Similarly, participants who received Novavax's protein subunit XBB.1.5 booster had a GMFR of about 7.5 post-vaccination.[30] In Moderna's Study 205J, participants that received a monovalent XBB.1.5 mRNA booster as their 5th COVID vaccination had a GMFR of 17.5,[31] similar to the Day 42 GMFR of 17 we report where participants had received either 4 or 5 COVID vaccine doses in total.

This phase 3 study of a new XBB.1.5 subunit vaccine is limited as it did not include efficacy assessments of the updated booster series. Immunogenicity assessments for this study were conducted in about 360 participants putting the level of evidence generated lower than large efficacy phase 3 trials that enrol thousands of participants. While the *a priori* defined superiority objective was met, it remains to be seen if the vaccine reduces the incidence of symptomatic COVID-19, hospitalisations, and deaths due to the new strain. Large real-world studies of other XBB.1.5 vaccines have shown a reduction in COVID-19-associated hospitalisations and deaths, supporting the widespread use of this updated vaccine.[32] Another important limitation is that participants in this phase 3 study were followed up for only 42 days for this study. It is therefore unclear how long these protective neutralising antibody titres remain for. Our study excluded key risk groups—including individuals with confirmed or suspected immunosuppressive or immunodeficient conditions. These groups are a major focus of COVID-19 vaccination strategies in 2025, which prioritise the prevention of severe disease in immunocompromised individuals. This exclusion limits the generalisability of our findings to certain high-risk populations and warrants explicit mention. A common limitation to all strain-specific booster vaccines and their trials is the ever-evolving nature of the SARS-CoV-2 virus. At the time this study was conducted, JN.1 became the predominant strain in India.[33] We demonstrated that our vaccine elicited robust cross-protection against the JN.1 strain.

While there is evidence that XBB.1.5-specific vaccines, like ours, also protect against JN.1, it remains to be seen if these vaccines also provide protection against the later NB.1.8.1 and LF.7 strains. An administrative disadvantage of our XBB.1.5 RBD subunit vaccine was that it was tested as a two-dose booster series compared to other single-dose boosters. However, we demonstrate significant neutralising antibodies after the first booster dose itself. As of writing this manuscript, Biological E is developing a monovalent variant-specific vaccine against the JN.1 strain as recommended by the WHO (The Strategic Advisory Group of Experts [SAGE] committee recommendation on Dec 23, 2024, and reaffirmed in March 2025). For the clinical development of this vaccine, it will be tested as a single-dose booster likely improving uptake of boosters. This strategy aligns with WHO SAGE's stratified approach to booster vaccination, which prioritises single-dose boosting in high-risk groups—including older adults, individuals with underlying comorbidities, immunocompromised persons, pregnant individuals, and frontline health workers—while permitting flexible, context-dependent use in healthy adults and children. The focus remains on optimising booster coverage in populations at highest risk for severe outcomes,

SOC/preferred term N1 (%) (95% CI) n	Overall	
	XBB.1.5 Covid-19 vaccine (Group 1) (N = 240)	CORBEVAX vaccine (Group 2) (N = 120)
Number of participants with at least one AE	54 (22.50%) (17.38, 28.31), 59	27 (22.50%) (15.38, 31.02), 27
Gastrointestinal disorders	2 (0.83%) (0.10, 2.98), 2	0 (0.00%) (0.00, 0.00), 0
Abdominal pain (Upper)	1 (0.42%) (0.01, 2.30), 1	0 (0.00%) (0.00, 0.00), 0
Nausea	1 (0.42%) (0.01, 2.30), 1	0 (0.00%) (0.00, 0.00), 0
General disorders and administration site condition	43 (17.92%) (13.28, 23.36), 46	23 (19.17%) (12.56, 27.36), 23
Fatigue	1 (0.42%) (0.01, 2.30), 1	1 (0.83%) (0.02, 4.56), 1
Injection site–erythema	2 (0.83%) (0.10, 2.98), 2	3 (2.50%) (0.52, 7.13), 3
Injection site–pain	27 (11.25%) (7.55, 15.94), 30	14 (11.67%) (6.53, 18.80), 14
Pyrexia	13 (5.42%) (2.92, 9.08), 13	5 (4.17%) (1.37, 9.46), 5
Nervous system disorder	9 (3.75%) (1.73, 7.00), 9	3 (2.50%) (0.52, 7.13), 3
Headache	9 (3.75%) (1.73, 7.00), 9	3 (2.50%) (0.52, 7.13), 3
Respiratory, thoracic, and mediastinal	2 (0.83%) (0.10, 2.98), 2	0 (0.00%) (0.00, 0.00), 0
Cough	1 (0.42%) (0.01, 2.30), 1	0 (0.00%) (0.00, 0.00), 0
Rhinorrhoea	1 (0.42%) (0.01, 2.30), 1	0 (0.00%) (0.00, 0.00), 0
Skin and subcutaneous tissue disorder	0 (0.00%) (0.00, 0.00), 0	1 (0.83%) (0.02, 4.56), 1
Miliaria	0 (0.00%) (0.00, 0.00), 0	1 (0.83%) (0.02, 4.56), 1

N = No. of participants per arm, N1 = Participant count, % = Percentage of participants, n = Event count.

Table 7: **Summary of adverse events (AEs) by system-organ-class (SOC) and preferred term in the safety population.**

without mandating repeated dosing in low-risk groups. The JN.1 formulation is being pursued based on available immunogenicity and neutralisation data, in line with WHO guidance to select vaccine composition based on prevailing immune escape and variant dominance, particularly in the XBB/JN.1 lineage cluster such as NB.1.8.1 and LF.7.

In conclusion, we provide strong evidence to suggest a favourable risk-benefit profile for the use of Biological E's updated XBB.1.5 RBD subunit vaccine as a two-dose booster for individuals aged 5–80 years. Based on these data, the vaccine was approved for use in individuals aged 12 years and above by the Central Drug Standard Control Organization, the Indian national regulatory agency. This vaccine, if approved for use by the WHO, will be particularly useful for low- and middle-income countries, given its lower cost and easier cold-chain management than existing mRNA vaccines. Post-approval real-world and phase 4 studies may provide additional evidence about the continued safety and efficacy of this vaccine.

Contributors

ST designed the study. SG oversaw the conduct. VP, RRM, VY, SN, and CD were involved in data management, data analysis, and medical monitoring. CSG, MN, SSK, and AVR were principal investigators on the study. MP executed the neutralising antibody titre testing (assay design, assay development/validation, sample testing) which formed the primary end-point analysis for the trial. CD wrote the first draft of the manuscript and created data visualisations. All authors edited and approved the final draft of the manuscript.

Data sharing statement

Access to raw or de-identified participant-level data will be granted to researchers on reasonable request made to the corresponding author and subject to institutional review.

Declaration of interests

ST, VP, SG, RRM, VY, SN, CD, and MP are all employed by Biological E Limited and receive no stock options. CD received consulting fees from InterVenn Biosciences and owns stocks of InterVenn Biosciences, Pfizer, and Vaxcyte. CSG, MN, SSK, and AVR were principal investigators on the study and received funding for the same from Biological E Limited. We declare no other competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2025.100642.

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