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BRIEF REPORT

Immunogenicity of the BA.1 and BA.4/BA.5 Severe Acute Respiratory Syndrome Coronavirus 2 Bivalent Boosts: Preliminary Results From the COVAIL Randomized Clinical Trial

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In a randomized clinical trial, we compare early neutralizing antibody responses after boosting with bivalent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccines based on either BA.1 or BA.4/BA.5 Omicron spike protein combined with wild-type spike. Responses against SARS-CoV-2 variants exhibited the greatest reduction in titers against currently circulating Omicron subvariants for both bivalent vaccines.

Keywords. SARS-CoV-2; variant; vaccine.

The emergence of Omicron subvariants and waning immunity led to the authorization in various countries of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) bivalent vaccines that combine wildtype (ancestral) spike and either Omicron BA.1 or BA.4/BA.5 spike [1, 2]. Currently, the predominant circulating Omicron subvariants contain key mutations in the spike protein receptor binding domain (eg, R346T) that enhance viral escape from neutralizing antibodies. The Coronavirus Variant Immunologic Landscape Trial (COVAIL) is an adaptive phase 2, open-label, randomized clinical trial assessing the immunogenicity of variant-containing SARS-CoV-2 vaccines, from different platforms, in previously vaccinated adults. Here we describe results from stage 4, where participants were randomized to a second boost with either the bivalent Pfizer/BioNTech BNT162b2 Wildtype/Omicron BA.1 vaccine or Wildtype/Omicron BA.4/BA.5 vaccine to determine their ability to produce antibodies that neutralize past and contemporaneous variants.

METHODS

Study Design and Eligibility Criteria

The study was performed at US sites (Supplementary Table 1), enrolling participants in October 2022. Eligible persons were healthy adults between the ages of 18 and 49 years of age (with or without prior SARS-CoV-2 infection) who had received a primary series and a single boost with an approved or emergency use authorized wild-type coronavirus disease 2019 (COVID-19) vaccine (Supplementary Table 2) confirmed by a review of their vaccination card. The most recent vaccination and prior infection, if applicable, must have occurred at least 16 weeks prior to randomization. Full eligibility criteria are described at clinicaltrials.gov (NCT 05289037).

After providing written informed consent, participants underwent screening, including medical history, a targeted physical examination, and a urine pregnancy test (if indicated). Eligible participants were randomly assigned to 1 of 2 vaccines in a 1:1 ratio, and immunogenicity samples were collected prevaccination (day 1) and after vaccination on days 15 and 29,

and 3, 6, 9, and 12 months. Intercurrent SARS-CoV-2 infections were collected by passive surveillance. The trial was reviewed and approved by a central institutional review board and overseen by an independent Data and Safety Monitoring Board. The trial was sponsored and funded by the National Institutes of Health.

Trial Vaccine

The bivalent Pfizer/BioNTech BNT162b2 Wildtype/Omicron BA.1 and Wildtype/Omicron BA.4/BA.5 vaccines were provided by Pfizer BioNTech (total amount of 30 mcg messenger RNA [mRNA] per vaccine; 15 mcg for each strain). The vaccine candidates are manufactured similarly to their corresponding authorized/approved vaccines.

Study Outcomes

The primary objective was to evaluate humoral immune responses of candidate SARS-CoV-2 variant vaccines. The secondary objective was to evaluate the safety of these vaccines assessed by solicited injection site and systemic adverse events (AEs), which were collected for 7 days after vaccination; unsolicited AEs through day 29; and serious adverse events (SAEs), new-onset chronic medical conditions (NOCMCs), adverse events of special interest (AESIs), AEs leading to withdrawal, and medically attended adverse events (MAAEs) through the duration of the trial. Safety and immnologic data are currently available through days 29 and 91.

Immunogenicity Assays

SARS-CoV-2 neutralization titers, expressed as the serum inhibitory dilution required for 50% neutralization (ID_{50}), were assessed at baseline and at days 15, 29 and 91, as described previously, using pseudotyped lentiviruses [3, 4] presenting SARS-CoV-2 spike mutations for different strains. All samples (101 per vaccine arm) were tested in a commercial lab (Monogram Biosciences, California, USA) for the following variants: the D614G (Wuhan-1 containing a single D614G spike mutation), B.1.617.2, B.1.351, B.1.1.529 (Omicron BA.1) and Omicron BA.4/BA.5. Omicron BQ.1.1 and Omicron XBB.1 neutralization titers were assessed on a random subset of 25 samples per vaccine arm, distributed roughly equally between previously infected and uninfected participants in the Montefiori Lab at Duke University. Electrochemiluminescence immunoassays (ELECSYS) were used for the detection of anti-nucleocapsid (N) (N-ELECSYS; Elecsys Anti-SARS-CoV-2 N, Roche, Indianapolis, Indiana, USA) at baseline [5].

Statistical Analysis of Immunogenicity Endpoints

The primary objective of this study is to evaluate the magnitude, breadth, and durability of SARS-CoV-2 specific immune responses measured by geometric mean antibody titers (GMT) with associated 95% confidence intervals (CI). No formal hypothesis tests were planned. The geometric mean fold rise (GMFR) is calculated as the geometric mean of titers at a timepoint divided by titers at day 1. The geometric mean ratio to D614G (GMR_{D614G}) is the ratio of the GMTs for a variant of concern to titers against D614G. The GMFD was calculated by dividing the result at Day 29 by the result of D91 and then calculating the geometric mean. Seropositivity rate is calculated as the proportion of participants with titers above the lower limit of detection (LLOD). The 95% CI for GMT, GMFR, and GMR_{D614G} are calculated using the Student *t*-distribution, and the 95% CI is calculated using the Clopper-Pearson binomial method. For analysis, participants were defined as previously infected by self-report of a confirmed positive antigen or polymerase chain reaction (PCR) test or by a positive anti-nucleocapsid (N) antibody test at enrollment. Participants with COVID-19 occurring between vaccination and a pre-specified immunogenicity timepoint were excluded from the immunogenicity analyses at all timepoints post infection.

RESULTS

Study Population

Previously vaccinated and boosted participants were enrolled between 4 and 28 October 2022 and received either the bivalent Pfizer/BioNTech BNT162b2 Wildtype/Omicron BA.1 (n = 101) or Wildtype/Omicron BA.4/BA.5 vaccines (n = 101). Baseline characteristics were similar between the 2 study arms (Supplementary Table 3). Median age was 31 years (range: 18–49). The majority of participants (93% per arm) had received an mRNA-based primary series and boost vaccine. At enrollment, 77% were defined as previously infected by anti-N antibody seropositivity at baseline and/or by self-reported positive SARS-CoV-2 testing (Supplementary Table 3). Median duration (range) between study vaccination and the last previous vaccination or infection was 293 (112–585) days.

Safety

Solicited local and systemic AEs after vaccination were similar to other booster trials [6] and did not differ between arms (94% for the Wildtype/Omicron BA.1 arm and 92% for the Wildtype/Omicron BA.4/BA.5 arm). The most frequently reported solicited local AE was injection-site pain (80%). The most common solicited systemic AEs were fatigue (68%) and myalgia (53%). Most solicited AEs were mild to moderate; only 1% of local AEs (induration/swelling), and 3% of systemic AEs (predominantly headache and fatigue in addition to fever, arthralgia, myalgia) in 7 participants were graded as severe. There were no AESI, SAEs, or AEs leading to withdrawal from the study at the time of interim analysis (Supplementary Figures 1 and 2 and Supplementary Tables 10–12).

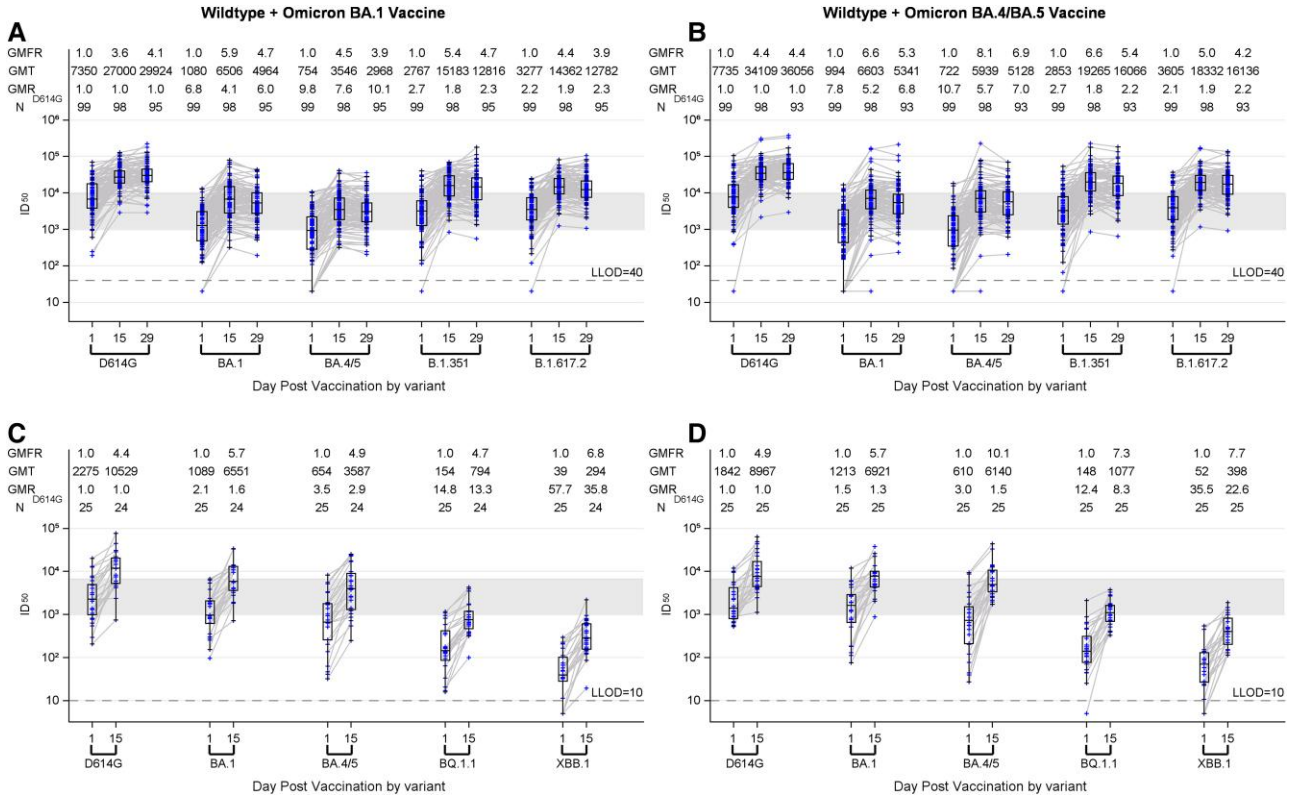

Figure 1. Pseudovirus neutralization ID_{50} titers by timepoint (baseline, day 15, and day 29) and variant before and after vaccination with 30 mcg of Pfizer/BioNTech BNT162b2 Wildtype/Omicron BA.1 (*A* and *C*) or 30 mcg Pfizer/BioNTech BNT162b2 Wildtype/Omicron BA.4/BA.5 (*B* and *D*). Panels *A* and *B* show results from the Monogram lab for each vaccine candidate against D614G, Omicron BA.1 [B.1.1.529], BA.4/BA.5, B1.351 [Beta], B.1.617.2 [Delta] at baseline, days 15 and 29 post vaccination. Panels *C* and *D* show results from the Duke University Montefiori lab for each vaccine candidate against D614G, Omicron BA.1 [B.1.1.529], BA.4/BA.5, BQ.1.1, and XBB.1 at baseline and day 15 post-vaccination. Boxes with horizontal bars denote interquartile range (IQR) and median ID_{50}, respectively. Whisker denotes 95% confidence interval. Abbreviations: GMFR, geometric mean fold rise from baseline; GMT, geometric mean titer; ID_{50}, 50% neutralization; LLOD, lower limit of detection of the assay.

Neutralizing Antibody Responses

All participants were seropositive against all variants after the boost, with titers peaking at Day 15 for all variants except D614G, which peaked at Day 29 (Figure 1). At day 15, ID_{50} GMTs in the Wildtype/Omicron BA.1 arm were numerically similar (with overlapping confidence intervals) to corresponding titers in the Wildtype/Omicron BA.4/BA.5 arm for D614G (ID_{50} 27 000 vs 34 109), BA.1 (ID_{50} 6506 vs 6603), B.1.351 (ID_{50} 15 183 vs 19 265) and B.1.617.2 (ID_{50} 14 362 vs 18 332). However, day 15 titers against Omicron BA.4/BA.5 were >1.5 higher with the Wildtype/Omicron BA.4/BA.5 ($GMT_{BA.4/BA.5} = 5939$) compared to titers after vaccination with the Wildtype/Omicron BA.1 vaccine ($GMT_{BA.4/BA.5} = 3546$) (Figure 1, Supplementary Tables 4–7). Similar findings were observed at Day 29. The geometric mean fold drop in titers at Day 91 was similar for both the Wildtype/Omicron BA.1 and Wildtype/Omicron BA.4/BA.5 vaccines, and lowest against Omicron BA.1 (1.3,1.4) and BA.4/BA.5 (1.5,1.4) when compared to D614G, B.1.351 and B.1.617.2 (Supplementary Tables 4 and 5), though numerically higher against BA.4/BA.5 for the Wildtype/Omicron BA.4/BA.5 vaccine (GMT 2067 vs 3842) (Supplementary Tables 4 and 5). Titers from participants without a history of prior infection were lower at all timepoints (Supplementary Tables 6 and 7) than those with hybrid immunity (Supplementary Tables 4 and 5).

Titers against all Omicron subvariants were lower than against D614G; the lowest titers were observed against XBB.1 (Figure 1). Notably, titers against BQ.1.1 and XBB.1 were similar between the two arms (with overlapping confidence intervals). Titers against BQ.1.1 and XBB.1 were 8–22 times and 13–35 times lower than against BA.1 and D614G, respectively, with the Wildtype/Omicron BA.1 vaccine. Titers against BQ.1.1 and XBB.1 were 4–12 times and 8–22 times lower than against BA.4/BA.5 and D614G, respectively, with the Wildtype/Omicron BA.4/BA.5 vaccine (Figure 1, Supplementary Tables 8 and 9).

DISCUSSION

Our study is the only randomized trial to date to report results from a head-to-head comparison of the 2 mRNA Wildtype/Omicron (BA.1 or BA.4/BA.5) bivalent vaccines currently authorized worldwide as a boost in individuals previously immunized with a first generation COVID-19 vaccine series. Our

early immunogenicity results demonstrate better neutralization against BA.4/BA.5 with the Wildtype/Omicron BA.4/BA.5 vaccine. However, there was increasing neutralization escape with the late 2022 Omicron subvariants (BQ.1.1 and XBB.1). This escape is similar between the two bivalent vaccines as demonstrated by numerically similar GMTs with overlapping confidence intervals, even though BA.1 and BA.4/BA.5 spike sequences are known to have different mutations in the receptor binding domain [7].

Although modest serologic advantages to Omicron BA.1 and BA.4/BA.5 have been previously reported with bivalent compared to wildtype vaccines [8], we do not currently have precise immune correlates of protection for emerging variants. Moreover, we did not evaluate the immunogenicity of the wildtype vaccine because this vaccine is no longer recommended as a boost in the United States. We conducted passive surveillance for SARS-CoV-2 intercurrent infections, and some cases could have been missed that could confound our immunogenicity results. These early preliminary results also do not address durability beyond 3 months and the conclusions about protection are limited by the small sample size. Finally, serologic data from timepoints up to 1 year after vaccination, and cellular responses, which are known to influence disease severity, are also pending.

However, our findings highlight ongoing concern that the breadth of antibody response from current updated vaccines is not optimal for the pace of virus evolution. Consequently, although early vaccine effectiveness (VE) data with bivalent vaccines have emerged [9, 10], continuous surveillance is crucial to assess for potential VE waning.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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