Interim phase 3 report suggests BBV152 COVID-19 vaccine is safe and protects against disease

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Interim data from a phase 3 trial of BBV152, a COVID-19 vaccine developed in India, reports that two doses offer 77.8% protection against symptomatic COVID-19.

The findings, published in *The Lancet*, indicate that BBV152 induces a robust antibody response. No severe vaccine-related adverse events or deaths were reported among the trial participants. The majority of the adverse events, including headache, fatigue, fever, and pain at the injection site, were mild and occurred within seven days of vaccination.

BBV152, a Vero cell derived, inactivated whole virion vaccine developed by Bharat Biotech in India, recently received emergency use approval from the World Health Organization (WHO) for people aged 18 and older. The vaccine is formulated with a novel adjuvant and administered in a two-dose regimen, 28 days apart. The vaccine can be stored and transported between 2-8°C with a 28-day multi-dose open vial policy.

The trial, which took place from 16 Nov 2020-17 May 2021, included 25,798 participants, of whom 24,419 adults aged 18 and older were randomly assigned to receive two doses of the vaccine (12,221) or a placebo (12,198). Participants considered to be at risk of acquiring COVID-19 were prioritized, with a total of 2,750 participants above 60 years of age and 5,724 participants who reported at least one pre-existing medical condition, such as cardiovascular disease, diabetes, or obesity, across ages. This study was conducted with participants from diverse geographic locations across 25 hospitals in India. The primary outcome was a laboratory-confirmed (RT-PCR positive) symptomatic COVID-19, with onset at least 14 days after the second dose.

The researchers conducted an efficacy analysis based on 130 laboratory-confirmed (RT-PCR positive) participants symptomatic for COVID-19 among 16,973 initially seronegative participants. These cases were recorded at least two weeks after participants had received a second dose. Researchers recorded 24 positive cases among 8,471 people in the vaccine group and 106 positive cases among 8,502 people in the placebo group, suggesting an overall vaccine efficacy of 77.8%.

Among the efficacy analysis population, there were a total of 16 cases of severe symptomatic COVID-19 disease—defined as severe systemic illness, respiratory failure, evidence of shock, significant acute renal, hepatic, or neurologic dysfunction, admission to an intensive care unit, or death—among trial participants; one case (out of 8,471 people) in the vaccine group and 15 cases (out of 8,502 people) in placebo recipients. However, the authors note this data is preliminary and more research with a larger sample size is needed to determine efficacy against severe disease and hospitalization.

BBV152 was well-tolerated among all trial participants, with 12% of vaccine and placebo groups reporting an adverse event, with no clinically or statistically significant differences in the distributions of solicited, unsolicited, or serious adverse events between groups, and no cases of anaphylaxis or vaccine-related deaths. Long-term safety monitoring will continue for one year after the administration of the first dose of BBV152.

Analysis of immune responses induced by the vaccine showed that BBV152 produced a strong neutralizing antibody response measured by the concentration of neutralizing antibodies at day 56 (one month after receiving the second dose). Similar to the phase 1/2 studies [2], BBV152-induced antibodies showed no significant decrease in neutralization activity against the alpha (B.1.1.7) variant but demonstrated marginal reductions in neutralization activity against other variants of concern, including the delta and gamma variants.

Researchers conducted a preliminary analysis of efficacy against the delta variant and found BBV152 to be 65% effective against symptomatic COVID-19 infection from the delta variant but note that this data should be presented as preliminary and further observations are necessary to confirm clinical efficacy against delta and other variants.

The study found no significant differences in immune responses across the broad age groups of under- and over-60-year-olds. The oldest trial participant was 97 years of age.

This study has several limitations. Due to the low number of cases reported between the first and second vaccine doses, the researchers could not calculate vaccine efficacy after a single dose. This report contains a median safety follow-up of 146 days from the first dose for all participants, and long-term safety follow-up of BBV152 is required and is currently underway. The data presented on efficacy against variants other than alpha and delta must be considered preliminary as the numbers reported are small. Furthermore, this study population was limited to India and therefore lacked ethnic and racial diversity, underscoring the importance of evaluating the efficacy of BBV152 in other populations. Finally, some groups, including pregnant women, those living with HIV or with severe co-morbidities, were specifically excluded by the study inclusion/exclusion criteria. Further investigations will be required to support the use of the vaccine in such groups.

Although the study was designed to vaccinate and follow participants for one year after the second dose, given the nature of the pandemic in India and the emergency use authorization for BBV152, after meeting the pre-defined efficacy success criteria, the data and safety monitoring board (DSMB) and the research team decided to un-blind those placebo participants who were eligible to receive an approved COVID-19 vaccine.

Writing in a linked comment, Jing-Xin Li and Feng-Cai Zhu of the Jiangsu Provincial Center for Disease Control and Prevention (China), who were not involved with the study, say, "The roll-out of BBV152 might ease the ultra-cold chain requirements of other SARS-CoV-2 vaccine platforms, increase the finite global manufacturing capacity, and improve insufficient supply of vaccines which disproportionately affects

low-income and middle-income countries. The next step for studies of BBV152 should be a focus on monitoring for epidemiological variations in SARS-CoV-2 and the long-term vaccine efficacy against symptomatic COVID-19 and asymptomatic infection to identify whether the vaccine provides ongoing protection when any VOC replacement (other than by the VOCs investigated in this study) has occurred."

More information: Raches Ella et al, Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial, *The Lancet* (2021). DOI: 10.1016/ S0140-6736(21)02000-6

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