BRACE Trial Primary and Secondary Outcomes at 6 months

Background

Shortly after the start of the COVID-19 pandemic, it was proposed that the BCG vaccine could be repurposed to reduce the impact of COVID-19. It was hypothesised that the immunomodulatory 'off-target' effects of BCG vaccine could enhance the immune response to SARS-CoV-2 to provide some protection against the disease.

The potential use of BCG vaccine to bridge the gap until specific vaccines became available for COVID-19 was outlined in the *Lancet* by the Director General of the WHO, Tedros Ghebreyesus, together with the Chief Principal Investigator of the BRACE trial, Prof Nigel Curtis.

The BRACE trial is recognised internationally as the definitive trial of BCG for COVID-19 as a result of its robust design, large size, precise outcome measures, active and thorough follow up of participants, extensive testing for COVID-19, almost 100% retention rate and detailed analysis.

The BRACE trial

- BRACE (BCG vaccination to Reduce the impAct of COVID-19 in hEalthcare workers) is an international, multi-site, randomised controlled trial (ClinicalTrials.gov NCT04327206).
- The trial was started in record time in March 2020, recruitment starting within 3 weeks of its conception and design, having completed all ethics, governance and other regulatory requirements.
- The trial was led by the Murdoch Children's Research Institute; over 400 researchers and staff in five countries worldwide have worked on the trial.
- *Participants*: Between March 2020 and April 2021, nearly 7000 healthcare workers were recruited in 36 sites in Australia, the Netherlands, Spain, UK and Brazil.
- The trial comprised two stages. COVID-19 outcomes were analysed in the second stage only as the first stage exclusively included participants in Australia during the time when there was negligible COVID-19 exposure.
- *Intervention & Control*: Stage 2 was double-blinded and placebo-controlled. Participants were randomised in a 1:1 ratio to receive BCG-Denmark vaccine or a placebo saline vaccine, regardless of previous BCG vaccination status.
- *Outcomes*: The primary outcomes of the trial were the incidence of *Symptomatic* COVID-19 and the incidence of *Severe* COVID-19 during the 6 months after randomisation.
- The trial's definition of *Severe* COVID-19 included those 'non-ambulant or unable to work for 3 or more consecutive days'. This definition differs to that more widely used in COVID-19 studies, which commonly includes only hospitalisations and deaths.
- The primary outcomes were assessed in each participant for the period before they received any COVID-19-specific vaccine. Sensitivity analyses included one ignoring COVID-19 vaccinations.

- Participants were followed up intensively for 12 months. Participants were asked to provide detailed information on all illnesses during the 12-month trial follow-up period and to respiratory swab test using PCR and/or rapid antigen test for COVID-19 with each episode of illness. In addition, participants completed 3-monthly questionnaires to capture any missing data.

- Blood samples were collected from participants at the start of the trial and every 3 months to test for antibodies to SARS-CoV-2. In addition to plasma, multiple other sample types (including PBMC and RNA) were stored to establish an extensive biobank.

- The trial protocol was published in BMJ Open and the statistical analysis plan (SAP) published online.

- The trial was overseen by a Trial Steering Committee and an independent Data Safety Monitoring Board.

- The trial was funded by the Bill & Melinda Gates Foundation, the Minderoo Foundation and various other philanthropic donors and government bodies (see below).

BRACE trial main findings

The results of the trial, based on the nearly 4000 participants in Stage 2, showed that **BCG vaccination did not reduce, and possibly increased, the incidence of COVID-19**.

- Of the 3988 healthcare workers randomised, 74% were female. The median age was 42 years, 20% had at least one comorbidity and 77% had previously received a BCG vaccination.

- The main analyses were done on a modified intention-to-treat population that excluded the 15% participants who had immunological or microbiological evidence of previous exposure to SARS-CoV-2. The retention rate in the trial was 98%.

- In the first 6 months after randomisation, 242 of the 3988 participants had an episode of COVID-19. A higher proportion of the participants randomised to BCG had an episode of COVID-19 compared to those randomised to placebo (adjusted hazard ratio 1.23; 95% CI, 0.96 to 1.59).

- The estimated 6-month risk of *Symptomatic* COVID-19 was higher in the BCG group (14.7%) than in the placebo group (12.3%; difference, 2.4%; 95% CI -0.7% to 5.5%; p=0.13).

- The 6-month risk of *Severe* COVID-19, as defined in this trial, was also higher in the BCG group (7.6%) than the placebo group (6.5%; difference, 1.1%; 95% CI, -1.2% to 3.5%; p=0.34). Participants in the *Severe* COVID-19 category comprised mainly participants reporting relatively moderate disease (i.e., being too unwell to go to work for 3 or more consecutive days).

- The effect of BCG on *Severe* COVID-19 as more commonly defined by hospitalisation or death could not be assessed due to too few of these events occurring in trial participants (10 hospitalisations, including 1 death in the placebo group).

- The difference between the BCG and placebo groups was not 'statistically significant' for either the incidence of *Symptomatic* COVID-19 or for the trial's definition of *Severe* COVID-19.

- **The results suggest the possibility that BCG vaccination increased the risk of symptomatic COVID-19** as, in the main analysis, as well as in pre-defined subgroup, sensitivity and other supplementary analyses, the risk of a COVID-19 episode was consistently higher in BCG-vaccinated participants compared to placebo-vaccinated participants.

- The earlier-than-expected availability of COVID-19-specific vaccines led to **recruitment to the trial being stopped prematurely, before the planned sample size was reached**. This also reduced the follow-up time (as participants were censored at COVID-19 vaccination) and therefore the number of COVID-19 episodes. The consequent reduction in power of the trial means that the lack of statistical significance in the difference between the groups in the trial outcomes might be attributable to type 2 error.

- In participants over 60 years of age, the **duration of COVID-19 episodes** was shorter in the BCG group. In those who received BCG, episodes were longer in those with a comorbidity and shorter in those without.

- The incidence of **asymptomatic SARS-CoV-2 infection** was too low (1.3% overall) to enable a meaningful assessment of the effect of BCG on this secondary outcome.

- Subgroup analyses did not find a substantial effect of sex or previous BCG vaccination.

- Expected local adverse events (AE) of BCG occurred in 70 (3.5%) participants, including 14 instances of injection site abscesses. A serious adverse event (SAE) occurred in 29 participants, all unrelated to the intervention, bar one participant who was briefly hospitalised with a BCG injection site abscess.

Background and context to the trial's findings

The BRACE trial underlines the power and critical importance of randomised controlled trials (RCTs) to evaluate novel interventions

- Previous observational studies and small trials of BCG for COVID-19 reported inconsistent and contradictory results.

- Despite this, early in the pandemic, prior to assessment of its effectiveness, there was 'panic-use' of BCG vaccination to protect against COVID-19. To prevent an impending shortage of BCG for preventing tuberculosis in infants, WHO highlighted that BCG should not be used to protect against COVID-19 outside of clinical trials, a message reiterated by Prof Curtis in the media during the trial.

- The findings of the BRACE trial highlight the need for rigorous evaluation of novel or repurposed interventions by RCTs prior to implementation, even for emergency use during a pandemic.

The BRACE trial was unable to test the effect of BCG vaccination on severe COVID-19 defined by hospitalisation or death

- It is possible that the observed increased risk of symptomatic COVID-19 in the first 6 months in the BCG-vaccinated participants reflects an enhanced immune response to SARS-CoV-2 (as symptoms reflect the immune response to the virus). The trial was unable to assess whether this led to more efficient clearance of the virus and protection against life-threatening COVID-19 (as characterised by hospitalisation or death), or whether an enhanced immune response was associated with improved protection against subsequent reinfection. The shorter duration of episodes in participants over 60 years of age in the BCG group is consistent with the possibility of enhanced viral clearance.

The off-target effects of BCG are influenced by many factors

- Results from trials highlight that the off-target effects of BCG vaccine are influenced by setting and other factors, including age and comorbidities of participants, target disease, BCG strain and number of doses, and the interval between vaccination and exposure to the pathogen.

- The BRACE trial findings should not be extrapolated beyond the effect of BCG-Denmark on COVID-19 in adults. Recent reports confirm the beneficial 'off-target' effects of BCG in other settings, particularly infants in high-mortality settings, and ongoing research is unravelling the underlying immunological mechanisms.

What next?

Further analyses of data from the BRACE trial are ongoing, including the effect of BCG vaccination on other outcomes measured in the trial, including:

- COVID-19 episodes over 12 months, including breakthrough infections
- Immune response to COVID-19-specific vaccines
- Fever and respiratory illnesses
- Herpes simplex virus recurrences (cold sores)
- Safety of BCG vaccination and revaccination

In addition, a number of laboratory projects are ongoing, including investigating:

- The specific and heterologous immune response to BCG vaccination
- Biomarkers for COVID-19 risk
- Factors influencing COVID-19-specific vaccine responses

BRACE trial funding

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Prof Nigel Curtis