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BCG to Protect against Covid-19 in Health Care Workers. Reply

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KRAS-mutant and wild-type tumors, respectively. After the publication of the results of our trial, we conducted a post hoc analysis to explore the effect of FTD-TPI plus bevacizumab in patients with or without KRAS G12 mutations. To date, we have found no evidence to suggest that the addition of bevacizumab to FTD-TPI was less effective in any particular molecular KRAS subgroup.

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Since publication of their article, the authors report no further potential conflict of interest.

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BCG to Protect against Covid-19 in Health Care Workers

TO THE EDITOR: Pittet et al. (April 27 issue)¹ report the results of the BCG Vaccination to Reduce the Impact of Covid-19 in Healthcare Workers (BRACE) clinical trial, which assessed the protective effect of bacille Calmette–Guérin (BCG) vaccine against Covid-19. Early in the pandemic, many articles and preprints were published suggesting this association. Although some of these studies directly examined the biologic properties of the BCG vaccine, many other analyses^{2,3} used incomplete data sets and occasionally lacked methodologic rigor, resulting in misleading connections between BCG and SARS-CoV-2.⁴ Three years after the world came to a standstill and an unprecedented number of studies have been published (including more than 400 addressing the possible role of BCG in preventing Covid-19 infection, with more than 100 of those published in the first 8 months of the pandemic), it has become clear that we need to apply more rigorous methods to prevent cluttering the literature with dubious results. In the current context in which artificial intelligence (AI) is used to screen and analyze a massive amount of information, it is of paramount importance that we ensure the quality of the information available and prevent “infocination.”⁵

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Randomized, controlled trials (RCTs) have shown that BCG reduces nontargeted morbidity and mortality among infants.¹ Immunologic studies have shown potential pathways for such effects.² Because of these nonspecific effects, many groups began testing BCG against Covid-19 infection in RCTs when the pandemic started in 2020. As in the BRACE trial, most trials have not shown that a single dose of BCG protects against Covid-19 infection. We performed an analysis of the eight recent trials that compared BCG with placebo with respect to protection against Covid-19 infection and respiratory infections among health care workers or older adults.³⁻⁵ Although there was variability across trials, we found that the BCG groups had a total of 26 deaths and the placebo groups had a total of 44 deaths, corresponding to a 39% (95% confidence interval, 3 to 62) lower mortality among BCG recipients than among placebo recipients.³ This post hoc observation should be examined further; modification of the effect of BCG according to sex, previous BCG vaccination, and coadministration with other vaccines should be investigated.¹

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THE AUTHORS REPLY: Lopez-Campos and Valvano correctly highlight the danger posed by flawed studies that reduce the signal-to-noise ratio in the medical literature and the consequent effect on information harvested by ChatGPT and other AI language models.¹ We agree that the many retrospective and ecologic studies on the ability of BCG vaccination to protect against Covid-19 published early in the pandemic were highly prone to bias and contributed to infoxication.² We also strongly agree that proposed interventions, including repurposed vaccines, need robust evaluation in RCTs.³ The BRACE trial highlights that this can be achieved even in the context of a global pandemic.

With respect to the BRACE trial results, it is important to understand that, in retrospect, the threshold for meeting the trial definition of severe Covid-19 was too low, and consequently mainly moderate disease episodes were captured (i.e., nonhospitalized participants who felt too unwell to go to work). Due to the low number of Covid-19–related hospitalizations (10) and deaths (1) in the first 6 months in the BRACE trial, we could not determine the effect of BCG vaccination on the current definition of severe disease.

As a result, we were unable to test the hypothesis that BCG-induced modulation of the immune response to SARS-CoV-2,⁴ while increasing symptomatic disease, may reduce viral load and subsequent severe disease, as defined by hospitalization or death.

We therefore welcome Benn and colleagues' analysis of eight trials of BCG vaccination against respiratory infections, including Covid-19, that suggest a beneficial effect on all-cause mortality among adults. This finding underlines the complexities in interpreting the outcomes of trials of the off-target effects of vaccines and, in particular, the importance of outcome measures: the beneficial effects of BCG appear to be most clinically relevant in high-risk populations and for severe disease.⁵ In the BRACE trial, secondary outcomes included the effect of BCG vaccination on a number of non-Covid-19 infections and conditions, including hospitalization and death from febrile and respiratory illnesses; the results for these additional secondary outcomes have not yet been reported. We agree with Benn and colleagues on the importance of considering the effect of modifying factors such as sex, BCG strain and dose, and other vaccines.

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Since publication of their article, the authors report no further potential conflict of interest.

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