

Bacille Calmette-Guérin (BCG) vaccine and the COVID-19 pandemic: responsible stewardship is needed

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Running head: BCG vaccine: responsible stewardship

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Dear Editor,

We believe that responsible stewardship of the bacille Calmette-Guérin (BCG) vaccine in the context of the COVID-19 epidemic is urgently needed. Live attenuated BCG is currently the only licensed vaccine to protect against tuberculosis (TB). Neonatal BCG vaccination has proven efficacy in protecting infants and young children against life-threatening disseminated forms of TB, including TB meningitis and miliary TB.¹⁻⁴ Global BCG supply shortages in

recent years (particularly between 2014 and 2017) have highlighted the critical need to sustain newborn BCG vaccination, especially in settings with high TB and HIV burden.^{5,6} The risk associated with low vaccination coverage is highlighted by the dramatic increase in the incidence of TB meningitis in young children reported in association with BCG stock-outs.⁷ Although manufacturer and supply chain issues are now largely resolved, supply remains fragile due to the limited number of production facilities available globally.⁸

BCG has potential non-specific effects including putative impact on COVID-19

In addition to protecting against TB (its intended target disease), BCG vaccination modulates the immune response to subsequent infections caused by other pathogens through the induction of innate immune memory and heterologous lymphocyte activation, resulting in enhanced cytokine production, macrophage activity, T-cell responses and antibody titres, leading to reduced morbidity and mortality.⁹ These non-specific immunological effects of BCG are used to treat bladder carcinoma in adults.¹⁰

A recent ecological study (yet to be peer-reviewed), has been widely disseminated in the general and social media, and claims a possible association between BCG vaccination and protection against severe disease and fatal outcome from SARS-CoV-2 infection (i.e., COVID-19).¹¹ This paper provides interesting circumstantial evidence but does not confirm causality. Limitations in this and similar ecological studies imply that claims suggesting potential protective effects of BCG against COVID-19 need to be interpreted with extreme caution. Potential bias in this ecological analysis includes the selection of countries and the failure to take into account the fact that different countries may be at different stages of the COVID-19 epidemic. The exclusion of countries that appear to contradict the authors' conclusions is unexplained. For example, BCG has not been used in Germany for the past 28 years, but currently has one of the lowest COVID-19-related mortality rates globally. Other high-income countries without universal BCG vaccination include Australia, which also has had a low COVID-19 mortality rate, which calls into question any association. Therefore, the suggestion that BCG protects against COVID-19 remains a hypothesis only, with no rigorous, peer-reviewed scientific evidence.

There is a need for research regarding the potential effects of BCG on COVID-19

Several trials are planned to investigate whether BCG may indeed offer protection against COVID-19, including in healthcare workers. Such trials have already started in the Netherlands (BCG-CORONA; NCT04328441); in Australia (the BRACE trial; NCT04327206), where BCG is not routinely given to newborns; and in South Africa (TASK-008-BCG-CORONA),

where BCG is routinely recommended for all newborns. Outcome measures differ across these trials.

In many high TB burden countries, BCG has routinely been administered to newborns since the 1970s. Therefore, healthcare workers under 50 years of age are likely to have received BCG at birth. In these countries, healthcare workers are also commonly infected with *Mycobacterium tuberculosis* (i.e., have TB infection).¹² Under these circumstances, BCG administration may lead to a strong local reaction at the injection site (similar to a strongly positive tuberculin skin test reaction). Unfortunately, as a consequence of the article by Miller et al,¹¹ some healthcare workers (and members of the general public) are now requesting revaccination as protection for themselves and vaccination of their non-BCG-vaccinated dependents, especially older children. This is understandable given the fear of COVID-19. In this context, it is essential that we provide clear recommendations on BCG vaccination. The use of BCG for an unproven indication is irresponsible and may deplete BCG stocks for young children, for whom it has been proven to be a lifesaving preventive tool against TB-related morbidity and mortality.

Recommendations for high TB burden settings are required

The World Health Organization (WHO) recently issued a scientific brief calling for BCG to be used for neonatal BCG vaccination only in high-risk settings and not for the prevention of COVID-19.¹³ Likewise, as the co-authors on this paper – who are paediatricians, public health experts and researchers with many years of experience in TB and BCG – we implore you to protect BCG supplies for young children, for whom the vaccine offers substantial proven benefits. Consequently, we provide a series of recommendations (summarized in the Table).

First, the priority remains for neonatal BCG vaccination to be given to all infants in high TB burden settings. No neonate (unless clinically indicated) should leave a birthing facility without BCG vaccination—this should be documented in the vaccination card or the child’s handheld health record. Fair allocation of scarce basic resources such as BCG is crucial, and it is an ethical imperative that the most vulnerable should receive the greatest benefit according to Rawls’ theory of justice.¹⁴ Second, infants under 1 year of age who have not yet received BCG, require a catch-up vaccination at any health facility where BCG is available (unless there is a clear contra-indication), even if they are the only infant to be vaccinated from a vial and there is risk of wastage.¹ Third, as the risk for TB meningitis and miliary TB is the highest in young children under 3 years of age, catch-up BCG, if missed at birth or thereafter, should be administered to this age group once TB infection has been excluded. This is important because of the severe morbidity and mortality associated with TB meningitis. Fourth, older children (>3

years) should not routinely receive BCG if missed at birth, although we acknowledge that different countries have different guidance regarding the upper age threshold, and the national level guidance should be followed. Fifth, BCG is ineffective as post-exposure prevention for TB. Following documented exposure to *Mycobacterium tuberculosis*, it is essential that TB preventive therapy is provided according to WHO and local TB guidelines. Finally, there is currently no compelling evidence, either for or against, that BCG protects individuals from COVID-19. Outside of a clinical trial, healthcare workers (or other individuals) should therefore not receive BCG vaccination for protection against COVID-19. Healthcare workers, many of whom are at high risk of COVID-19 disease, should consider enrolling in trials, including those where BCG is used as an intervention, if feasible. Their participation would generate much needed data regarding any potential benefit or risk of BCG vaccination in the context of COVID-19. Importantly, the BCG vaccines used for such trials should be sourced specifically for clinical research, and not from the limited supply available for children in low-income settings.

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Table Recommendations for BCG vaccination in high TB burden settings

Priority populations	Further recommendations
Neonatal BCG vaccination remains the priority	National guidelines regarding the upper age limit for catch-up vaccination should be followed
Unvaccinated infants should be prioritised for catch-up vaccination, irrespective of possible vaccine wastage	BCG vaccination should NOT be used for TB prevention following TB exposure
Children younger than 3 years who have not been vaccinated, should also be prioritised to receive catch-up vaccination once TB infection has been excluded	BCG vaccination should NOT be used for protection against COVID-19 outside of a clinical trial

TB = tuberculosis; BCG = bacille Calmette-Guérin.