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The Imperative of Early Treatment for Children With COVID-19 Infection

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is uncommon in children [1], with greater morbidity and mortality in adults and elderly. A number of hypotheses may explain the low susceptibility of children to COVID-19 virus [2] *viz,* (*i*) immaturity and limited function of angiotensin-converting enzyme 2 (ACE2) receptors in children, as undifferentiated cells that express low levels of ACE2 are not readily infected by SARS-CoV; (*ii*) the immature innate immune system in young children results in less inflammation and consequently fewer symptoms; and, (*iii*) possible cross-reactivity of antibodies against other viruses (influenza, adenovirus, respiratory syncytial virus *etc*.) with the SARS-CoV-2, which could provide partial protection.

As COVID-19 infection is not universally mild in children [3], it is important that they are protected as a vulnerable population, as still there is limited data on the risk factors for severe infection in children.

The long-term effects on the lungs of COVID-19 in children are not known, even for those with moderate symptoms. In patients hospitalized in French pediatric units in recent weeks, the chest computed tomography (CT) scans have often been pathological, even in children with limited respiratory sign with associated decline in lung function (unpublished data). In light of this, should not all children with moderate to severe respiratory symptoms be treated, irrespective of their comorbidity? Why do pediatricians appear to be unwilling to consider employing the COVID-19 treatments that are available, e.g., hydroxychloroquine and azithromycin [4]? These drugs (which are already widely used in pediatrics in other indications) certainly have side effects that are of concern, but their use in a hospital environment shall allow these side effects to be monitored and ensure greater safety for the patient [5].

In the absence of specific antiviral treatments, pediatricians need more virological, epidemiological, and clinical data to better treat and manage COVID-19 infections. It should be kept in mind that children, even when asymptomatic, may be a potential cause of spread and transmission of the disease in their communities [6]. In light of this, barrier precaution needs to be rigorously applied within families in order to protect the elderly.

Funding: None; *Competing interest*: None stated.
Published online: April 30, 2020; *PII:* S097475591600169

NARCISSE ELENGA
Pediatric Medicine and Surgery,
Centre Hospitalier Andrée Rosemon, Rue des flamboyants,
BP 6006, 97306, Cayenne Cedex, French Guiana.
elengafr@yahoo.fr

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Demystifying BCG Vaccine and COVID-19 Relationship

Efforts for developing vaccines for novel coronavirus disease (COVID-19) are ongoing, but it is unlikely to be available in the immediate future [1]. In the absence of specific therapy, the researchers are exploring other potential preventive and therapeutic options. Recently, there has been a buzz about the protective effect of Bacille Calmette-Guérin (BCG) vaccine in COVID-19. Based on epidemiological correlations, many unpublished preprints hypothesized that the BCG vaccine may offer protection against COVID-19. It gained so much popularity that within 20 days three randomized controlled trials (RCTs) got registered, and many more are in the pipeline [2]. To make an informed decision, we must understand the mechanism of action of BCG, and appraise the robustness of the evidence.

The basis of the possible use of the BCG vaccine against COVID-19 lies in its non-specific effects (NSEs) over the immune system [3]. The NSEs of BCG are mainly mediated by potentiating innate immune response through epigenetic mechanisms.These epigenetic changes within the innate cells act as *de novo* enhancers to boost the immune response against a secondary challenge [3-5]. This enhancing response is popularly known as 'trained immunity' and is very characteristic of BCG. This trained immunity also offers protection against a variety of pathogens (Salmonella, Shigella, malaria, respiratory viruses, *etc*.) other than *Mycobacterium tuberculosis,* and forms the basis of its use in bladder cancer, melanoma *etc.* However, this non-specific effect is mostly short-lived and wanes soon after the primary BCG stimulus is cleared from the body. By virtue of the NSEs, BCG vaccine has shown to decrease all-cause mortality in children. Though a few observational studies suggest that the NSEs may last till adulthood, but the overall evidence is still inadequate and is of low quality [3,6,7].

On critical appraisal of the non-peer reviewed pre-print evidence, at the relationship between BCG and COVID-19 is being proven by looking at correlation/ association among two data set (BCG vaccine coverage and COVID-19), without acknowledging the confounders. The variables like the difference in testing strategies, reporting bias, demographics, nation's ability to respond to the pandemic, prevalence of co-morbidities, and different stages of the pandemic across various countries might have a significant impact on these associations/correlations and must be interpreted carefully. Therefore, at this stage, this association should be considered as a hypothesis only and should be tested through appropriately designed studies.

Though the epidemiological association between BCG and COVID-19 is striking, it does not prove causal relationship unless tested in well-designed clinical trials. Also, we should not forget that the NSEs of the BCG vaccine has not been well-studied in human beings and their clinical relevance is unknown [2,3]. Therefore, in the absence of evidence, the BCG vaccination for the prevention of COVID-19 cannot be recommended. The results of the ongoing RCTs shall guide us further.

Funding: Alone, *Competing interest:* None Stated.
Published online: April 30, 2020; *PII:* S097475591600168

JOGENDER KUMAR[1]* AND JITENDRA MEENA[2]
Departments of Pediatrics,
[1]Post Graduate Institute of Medical Education and Research, Chandigarh; and [2]All India Institute of Medical Sciences, New Delhi; India.
**Jogendrayadv@gmail.com*

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