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LETTER TO THE EDITOR

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Cross-immunity and trained immunity in explaining variable COVID-19 mortality—Guidance for future pandemics

Dear Editor,

The variable spread and infection mortality of COVID-19 in different countries need careful examination (Figures 1 and 2). Although at present the major focus is on the detection and containment of COVID-19, including the development of vaccines, it appears that a better understanding of the host's response to SARS-CoV-2 invasion may provide us clues to explain the epidemiology of this pandemic in different countries and formulate nation-specific management plans.[1,2]

Published reports in peer-reviewed journals and major live-data websites reveal that the majority of COVID-19 patients remain asymptomatic or mildly symptomatic, and mostly a vulnerable group of subjects succumb to the illness through acute respiratory distress syndrome or coagulopathy.[3] One of the possible factors that may be responsible for the mild course of COVID-19 in many patients could be the existence of cross-immunity in the population as a result of exposure to endemic coronaviruses like HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1. While discussing the Indian COVID-19 scenario, we hypothesized as early as April 2020 that this cross-immunity mediated by primed T cells and neutralizing antibodies developed as a result of prior exposure to endemic coronaviruses would result in very low infection mortality and a slow spread of this disease in India, which has been proved to be true subsequently (Figures 1 and 2).[1,2] Meanwhile experimental studies have demonstrated the existence of memory CD4+ T cells responsive to SARS-CoV-2 spike and nonspike protein epitopes in subjects never exposed to the virus.[4] Moreover, circulating neutralizing antibodies and memory B cells developed against one type of coronavirus have been shown to cross-react with other members of the coronavirus family.[2] The importance of this cross-immunity in modifying the spread of COVID-19 in a population and the development of herd immunity has been discussed by us as well as by other authors in a recent review with several theoretical models.[5]

Apart from cross-immunity mediated by the adaptive immune system, the innate immune system exhibits "trained immunity" and "immune tolerance" which could be important factors modifying the clinical spectrum and infection mortality in COVID-19. The importance of "trained immunity" in the COVID-19 pandemic has been argued by some researchers, but the significance of innate "immune tolerance" has not been expanded in this context.[6] The innate immune system after exposure to invading organisms or vaccines (BCG, measles

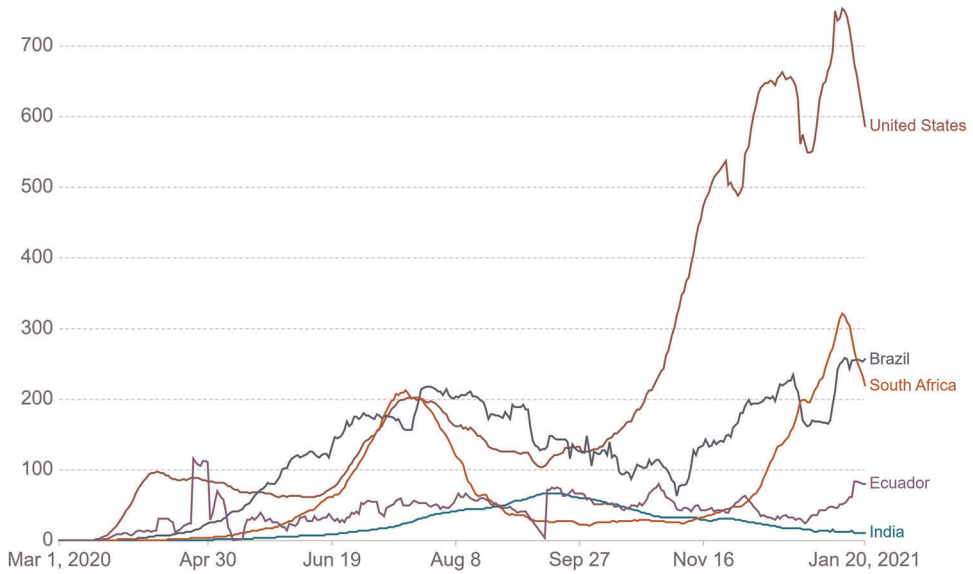

FIGURE 1 Daily new confirmed COVID-19 cases per million people. The *x*-axis shows a timeline from March 1, 2020 to January 20, 2021. The *y*-axis shows the number of COVID-19 cases per million population in a specific country. Countries are represented by differently shaded lines. A rolling 7-day average is taken for the number of cases. *Source*: Figure obtained from https://ourworldindata.org/coronavirus

FIGURE 2 Daily new confirmed COVID-19 deaths. The *x*-axis shows the timeline since 5 daily deaths first reported. The *y*-axis shows the number of COVID-19 deaths per day in a specific country (log-scale). Countries are represented by differently shaded lines. A rolling 7-day average is taken for the number of deaths. *Source*: Figure obtained from https://ourworldindata.org/coronavirus

vaccine, etc.) or complex biomolecules derived from bacteria or fungi (lipopolysaccharides, β-glucan, etc.) undergoes metabolic readjustment or epigenetic modifications which enables it to show a heightened response following a subsequent challenge by the first trigger or diverse unrelated organisms or molecules.[7–9] This nonspecific "trained immunity" is different from the classical epitope-dependent memory of adaptive immunity mediated by lymphocytes. In contrast to "trained immunity," the innate immune cells may also attain a state of "immune tolerance" or a "hyporesponsiveness" to heterologous secondary challenge, typically exhibiting a decreased production of proinflammatory mediators.[7–9] The evidence in favor of "trained immunity" as well as "immune tolerance" has been accrued from epidemiological studies, especially with BCG vaccines, in vitro studies with isolated human or murine peripheral blood mononuclear cells exposed to LPS, β-glucan, flagellin, poly (I:C), and so on, and also in vivo models.[7–9] In fact, the development of a tolerogenic state in animals by repeated administration of LPS was well-studied for many years, and in vitro experiments with monocytes and macrophages have elucidated the molecular pathways of "immune tolerance" to some extent.[8–10] What determines the innate immune system to exhibit either of these two phenomena is not clearly known, but the high dose and prolonged duration of the primary trigger could be an important factor.[9,10] Interestingly, "the immune tolerance" inhibits the production of proinflammatory cytokines by innate immune cells, but some nontolerizeable genes responsible for antimicrobial functions are not downregulated.[8] At present the details of the pathways, the cellular components involved and the duration of the "trained immunity" and "immune tolerance" are under active study. Although most initial studies on "trained immunity" and "immune tolerance" focused on circulating mononuclear cells with a short lifespan, it is becoming evident that different progenitor and stem cells of the bone marrow and epithelial cells and resident tissue macrophages with long lifespan could be similarly trained.[7,8] This will obviously produce a long-lasting effect on the host's innate immune response to different pathogens.

In the context of COVID-19, "trained immunity" and "immune tolerance" may have important implications. We hypothesize, that in countries like India huge sections of the population, living in crowded, and unsatisfactory hygienic conditions, are subjected to repeated infections by viruses, bacteria, and eukaryotic parasites, and this probably leads to a state of "immune tolerance" in them against a novel organism like SARS-CoV-2. This, in turn, will prevent the development of a hyperinflammatory state, that is, the "cytokine storm" initiated by the innate immune system which is generally held responsible for the eventual fatality of COVID-19. This had been one of the pathological reasons for our April hypothesis, in addition to cross-immunity. On the other hand, the absence of such a state of "immune tolerance" in populations of advanced countries unexposed to diverse microorganisms during their lifetime may partially explain the increased vulnerability of such populations to novel organisms like SARS-CoV-2.

The epidemiological data of COVID-19 in India and other developing countries vis-à-vis that of more advanced countries should be analyzed in light of this interplay of cross-immunity, trained immunity, and immune tolerance and this will help individual nations to develop effective strategies to combat future pandemics of this nature.

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