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Mini Review

COVID19 Vaccine's Delta Paradox and Dangers of Further Viral Evolution

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Abstract

Despite the rapid deployment of effective COVID19 vaccines that were designed against the original Wuhan strain of SARS-CoV-2, viral mutations that led to the Delta and other variants are now fueling another round of global pandemic. As the world seeks to find an exit scenario from the pandemic, better understanding on the viral evolution that shaped the Delta variant and its possible future course would be invaluable. Of particular significance, vaccinated individuals have been reported to mainly experience milder or asymptomatic infection by the Delta variant with paradoxically high viral titers at similar level to those without vaccination. Analysis on this paradox of symptomatic reduction without viral neutralization raises worrisome possibilities of its future evolution into becoming a chronic macrophage-inhabiting pathogen in the likes of HIV. Careful considerations are required in adopting endemic or with-COVID approaches, as the infection case number is the driver of the viral evolution, and since the measures remove the initial contact barrier to the public in the event of another lethal variant emergence. Anti-pandemic measures need to focus more on the case number reduction for preventing further pandemic risks.

Keywords: *COVID19; Macrophage; Endemic; Vaccine; Immunity; Delta with-COVID*

Introduction

Over the course of the viral evolution from Wuhan original strain to Delta variant, COVID19 became the deadliest pandemic that continues today with over 4.8 million deaths and counting [1]. The current shape of the pandemic we face is a culminated result of a series of underestimation on the evolutionary capacity by the SARS-CoV-2 virus, which quickly and repeatedly overcame all the containment [2], treatment [3] and vaccination [4] measures around the world. With the economic distress from the prolonged pandemic forcing many larger nations into considering the "endemic" or "with-COVID" policies that propose to resume normal activities bearing the circulating SARS-CoV-2, possibilities of further SARS-CoV-2 evolution must be considered to prevent another critical misstep.

Intra-host evolution promoting anti-viral resistance - The case of remdesivir

A cornerstone idea enabling the endemic strategy is the availability of an effective treatment against lethal COVID19 infection. While the recent news of the nucleotide analogue molnupiravir's Phase III clinical success of 50% reduction in death among mild or moderate COVID19 patients [5] holds promise in the regard, the case of remdesivir must be revisited. On 22 October 2020, FDA issued Emergency Use Approval (EUA) on remdesivir for treatment of COVID19 requiring hospitalization, supported by numerous clinical evidence that demonstrated significant clinical improvement and death risk reduction during the early pandemic period in the first half of 2020 [6-8]. However, later multicenter global clinical investigations, most namely the SOLIDARITY study by WHO, showed that remdesivir did not

show clinical benefits in reducing overall mortality, initiation of ventilation, or the duration of hospital stay [9], despite the *in vitro* studies that indicated its continued effectiveness versus the variants as-of-the date [10,11]. The ambiguous clinical benefits of remdesivir were explained in a later study published in November 2020, which showed intra-host evolution that led to enhanced viral compartmentalization into lungs in response to remdesivir treatment as the cause of its clinical loss of efficacy [3]. As the study reported the observation of the intra-host viral evolution in four of the nine patients studied (4/9 patients) independent of their immunocompetent/compromised status, wide use of molnupiravir in COVID19 treatment may initially require careful attention in isolation for preventing the emergence of potential molnupiravir-resistant SARS-CoV-2 variants.

Vaccines selecting the virus toward immune evasive evolution

Another cornerstone idea enabling the endemic strategy is the availability of at least one vaccine that can reduce hospitalization and death. In response to the June 2020 WHO and US FDA guidelines that suggested at least 50% reduction in the laboratory-confirmed COVID19 cases as the primary end-point for placebo-controlled clinical studies [12], several effective COVID19 vaccines based on the original Wuhan sequences were developed and deployed, some with prevention efficacies upwards of 94% (BNT162b2 and mRNA-1273) during multicenter Phase 3 studies that were conducted in 2020 [13,14]. Their global roll-out starting December 2020, however, was challenged with successive emergence of numerous variants that eroded the vaccine benefits. Most notably with the Delta variant, Israel Ministry of Health reported on 22 July, 2021 that the BNT162b2 vaccine protection efficacy against infection was reduced to 39% versus the Delta variant while the efficacy against hospitalization was held at 88% [15]. Similar result was also reported by Mayo Clinic in the US, whereby the Delta variant was reported to cause a drop in the protection efficacy of the same vaccine to 42% [16]. While some believe that the dramatic drop in the protective efficacies of the once-highly effective BNT162b2 vaccine is due to waning immunity within 6 months of the inoculation - thus argument for booster jabs [17], reported formation of persistent B-cell memory in the germinal centers post BNT162b2 vaccination paints contradicting picture of lasting immunity post the vaccination [18]. The drop in the protection against infection was markedly less with mRNA-1273 in both studies [15,16], with the mRNA-1273 offering twice the protection against breakthrough infection over BNT162b2 (IRR = 0.50, 95% CI: 0.39 - 0.64) [16]. This indicates that the reported drop in the BNT162b2's protective efficacy is product-specific and ungeneralizable as the result of immunity waning.

An answer to this contradiction may be found in the recent result of a University of California San Francisco (UCSF) study thatx investigated the whole-genome sequence of the SARS-CoV-2 viruses in the fully-vaccinated, partially vaccinated, and in the non-vaccinated patients in San Francisco Bay Area, California [4]. The study data demonstrated that the vaccine breakthrough infections were more likely to be caused by immunity-evading variants such as the Delta variant, which also indicated selective evolutionary pressure for immune-resistant variants among vaccinated population in the region [4]. As the Delta and other immune-resistant variants harbor convergent mutations that emerged in different corners of the world with high infection rates, this finding is consistent with the hypothesis that these variants may be adaptation products to natural immunity through serial re-infections.

Another important finding of the study was, consistent with the earlier study in Massachusetts [19], that it showed reduced hospitalization and death among the vaccinated versus the non-vaccinated patients despite the lack of difference in the RNA viral load in vaccine breakthrough patients versus the unvaccinated infections ($p = 0.99$) [4]. These repeated observations of paradoxical reduction in COVID19 hospitalization and death without virus neutralization among the vaccinated patients may provide important clues toward the ongoing SARS-CoV-2 evolution.

COVID19 vaccine's delta paradox - Is it becoming the next HIV?

Although the observed effectiveness of the leading COVID19 vaccines in reducing the hospitalization and death was received as a positive news, no explanation has been offered on how the vaccine benefit arose in the absence of the clinical virus neutralization in the breakthrough patients during the period of Delta pandemic (as noted by the high viral load near to the level of the unvaccinated infec-

tion [4,19]). This is a clear pharmacological paradox, as the intended benefit of the vaccine should be afforded by the virus-neutralizing immune activity against the Delta variant. One possible explanation for the paradox may be that the immune complex between the Delta-variant and the vaccine-induced antibodies exert immune suppression against the infected monocyte/macrophages - the center of lethal cytokine storm in severe COVID19 cases [20]. This hypothesis is supported by previous studies that demonstrated monocyte/macrophage modulatory activities by the antibody-virus immune complexes infecting the immune cells [21-24]. In this light, possible disease-promoting effects by the SARS-CoV-2 reprogrammed macrophages have been voiced with regards to rheumatoid arthritis [25] and cancer [26,27]. Another concerning possibility on the pathological evolution of SARS-CoV-2 is its evolution into a macrophage-inhabiting chronic virus in the likes of HIV, wherein the monocyte/macrophages serve as the viral reservoir and as the mediator of chronic tissue infection. Given the literatures that showed the infected alveolar macrophage as the facilitator of the viral lung tissue infection [22] and as the potential short-term reservoir for SARS-CoV-2 [28], the pandemic virus may be only a few adaptations away from becoming the next HIV - a chronic viral infection causing immune disruptions.

Conclusion - Actionable solutions to prevent SARS-CoV-2 evolution and ending the pandemic

An undeniable conclusion from the pandemic developments-to-date is that the virus demonstrated its capacity to evolve past treatments, immunity, and vaccination as exemplified by the Delta variant, and that its herd immunity is improbable as exemplified by the recent big surges in Singapore and South Korea with respectively over 80% and 70% full vaccination rates. Going into winter and left uncontrolled, the appearance of another detrimental variant that will fully nullify the hard-won vaccines will only be a matter of short time, not of if.

As countless experts have pointed out, the solution to preventing the next detrimental SARS-CoV-2 variant is simple - cut the infection case numbers that fuel the viral mutation rate. In this regard, the "endemic" or "with-COVID" policy in discussion by some leading nations is in direct conflict with current vaccination efforts, as well as the idea of preventing further SARS-CoV-2 evolution. Another detrimental consequence of "with-COVID" policy would be the marginalized opportunity to quarantine the next deadly pandemic variant, as the large number of background cases would make its early detection infeasible. This secondary consequence of the "with-COVID" policy would bring severe complications to border re-opening, considering the different progress and localized SARS-CoV-2 viral evolutions in different countries with varying capacities to survey and report local viral genomes.

Herein the following actionable solutions for curbing the COVID19 evolution and case numbers are proposed as overlays to the conventional measures:

1. Mandatory use of N95/VFE99/KF94 masks in public - no more cloth or surgical masks.
2. Mandatory use of nasal [29] and oral [30] products containing broad anti-viral actives such as carrageenan, Povidone Iodine, or chlorhexidine in public transportation, buildings, and in restaurants, in conjunction with masks.
3. Development of multi-epitope/multi-valence vaccines against currently dominant SARS-CoV-2 variants with immune evasive features.
4. Isolation of COVID19 patients undergoing mAb or molnupravir until negative PCR results on fecal or anal swab sample is obtained.

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Conflicts of Interest

JFC owns shares of Xylonix PTE. LTD. and Moderna Inc.

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