# Review of: "Factors influencing variable symptoms of COVID-19 patients and proposed revision of public policy for COVID-19 vaccination"

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Unfortunately, this manuscript adds no specific information nor provides any original perspective on current knowledge on SARS-CoV-2 infection and immunity. Furthermore, its oversimplistic approach based on weak or no evidence to support the author's statements is dangerously misleading. This is particularly true in the context of a very sensitive subject, such as vaccination and more generally trust in Science, which has been massively targeted by misinformation and non-scientific theories in recent years, possibly prompting to the need for even higher-standard information for a wide public. Finally, several reported data or considerations are out of date.

More specifically,

1) The manuscript appears to be aimed at discussing factors affecting clinical variability among patients with COVID-19 and at proposing revisions in public policies for anti-SARS-CoV-2 vaccination. However, there is no systematic description of COVID-19 clinical spectrum nor precise data on evolving clinical phenotypes during the pandemic, while data on (anti-SARS-CoV-2 or anti-other microbial agents) vaccines are not reported nor discussed at all. In parallel, only a handful of basic immunological concepts are discussed without any referenced or supposed correlation with clinical variability, besides potential misleading concepts (see below). The statement that "everybody should be vaccinated" reported in the conclusions is obviously true, or, more precisely, was true in 2021 when anti-SARS-CoV-2 vaccination began, and still is valid today, although most people have indeed received at least some vaccine doses. However, discussed data in support of this statement are very scarce and this is not because of limited evidence in the scientific literature (there is plenty of evidence available to this regard), but because the review analysis in this manuscript has major limitations.

2) As anticipated, discussion on immunological mechanisms of general antiviral and anti-SARS-CoV-2 immunity is deeply oversimplistic. First, there is no mention of innate immune mechanisms, especially with regard to interferon responses, which play a major role in COVID-19 pathophysiology. The topic of timing of deployment of the immune response (which is strongly linked to interferon responsiveness) is also not covered, preventing any correlation with symptoms. Second, besides the T-B and cytotoxic-helper T cell dichotomies, there is no description of the multifaceted aspects of T cell polarization and differentiation nor of B cell, macrophage and dendritic cell subpopulation in general and during viral infection. There is also no description of tissue-specific factors affecting host susceptibility. Third, the statement about the main approaches employed for anti-viral vaccines seems to imply that only humoral responses are induced and that

antibodies only or mainly are responsible for anti-SARS-CoV-2 protection. Fourth, there is no mention of mechanisms affecting affinity maturation of BCR and TCR, nor about the role of immune phenomena such as TCR promiscuity/heterologous immunity in shaping the immune response in subjects who had been already exposed to antigens with molecular similarities to SARS-CoV-2 components. Fifth, consequently, questions like "if the virus evades immunity, why it does not evade everybody? Why do not all vaccinated people become infected?", labelled as mysteries, are difficult to understand.

3) In the paragraph "Perspective to explain various symptoms after viral exposure", the author suggests the existence of a clinical-pathophysiological classification based on patient expression of viral receptors and "compatible" MHC class I and II and showing symmetric correlations with clinical features. This classification is totally arbitrary and, again, unfortunately potentially misleading, especially in the setting of SARS-CoV-2. First, it is not clear whether the author refers to SARS-CoV-2 or other viral infections. While lack of virus target receptor(s) is a known mechanism of innate non-susceptibility or reduced susceptibility to infection (e.g. for HIV), this is not necessarily true for all viruses and all receptors and does not guarantee an asymptomatic course. No evidence is provided regarding SARS-CoV-2 to this regard. Second, discussion on which specific HLA-I and/or HLA-II variants might be involved in enhanced or reduced susceptibility to COVID-19 or other infectious disorders is entirely not developed. Third, consequently, inferences on the likelihood of developing effective antibody responses and suitability to vaccination (further mentioned in the following paragraph) are entirely devoid of supporting evidence.

4) There is no updated discussion on current pandemic situation nor about SARS-CoV-2 phylogenic evolution, which just a rough mention on "variants".