Review of: "Evolution of new variants of SARS-CoV-2 during the pandemic: mutation-limited or selection-limited?"

Fortunato Vesce[1]

1 University of Ferrara

Potential competing interests: No potential competing interests to declare.

The article is an attempt to investigate the role of mutation-limited and selection-limited immunity-evading variants of SARS-CoV2, and the decline of immunity as a cause of new waves of infection.

The Authors premise that the new waves of infection are generally believed to derive from variants evading both natural and vaccine immunity, but the role of these variants has not been adequately evaluated. They also report that the study models that divide the population into two groups, susceptible and immune, are inadequate, because immunity is not a binary process, but is constantly evolving. There are also models that consider three groups: S = susceptible (i.e. not immune and therefore capable of being infected, thus becoming ill and infecting others?); I = infectious (i.e. positive to the viral test and therefore able to infect others?); R = 'recovered', (i.e. healed, and therefore immune, unable to infect others?).

Furthermore, the Authors report that the new variants appear during the acute phase of the pandemic, when viral shedding is highest. In this circumstance the new variant gradually replaces the one for which the immune system already produced the antibodies. But it is also possible that a new variant is produced independently of the immune response against the previous virus, without a selection process, with a completely unknown mechanism. A decline of immunity independent of the new variants is also hypothesized among the causes of a new infectious wave.

The Authors recognize that the immune response is largely unknown. However it seems that they refer this statement solely to the production of antibodics, i.e. to humoral immunity. Furthermore, they seem not to make any difference between natural and vaccine triggered immune response, both being directed against several viral epitopes, and both cross-reacting to different variants. However, since the mutations do not concern all the epitopes, they consider the consequent evasion from the antibody protection to be only partial.

Furthermore, the Authors argue that both natural infection and vaccination produce 'immunity' (i.e. antibodies?) above the minimum level below which there would be no protection. They also include the density and behavior of the population, the temperature and humidity of the atmospfere, plus other unspecified factors, among the causes of a decline of the immune response. They also report that unknown factors favor the emergence of new variants, however eventually unrelated to the genesis of new infectious waves.

The Authors analyzed country-specific data derived from public databases that report the number of the cases

and deaths on a daily basis. They performed a simulation in which S, I and R respectively represent fractions of susceptible, infectious and immune subjects of the study sample.

No project of clinical value is adopted in the selection of the subjects in the study population, neither in relation to true number of positive cases nor to their real health condition.

They provide a definition of the following concepts: ‘data segment’, ‘origin of a variant’, ‘invasion by a variant’, ‘wave’, and finally ‘data interval for correlation analysis’.

Furthermore, the Authors report a number of limitations of the study, regarding the number of the variants, the low number of case sequencing, the lack of randomization of the sequenced cases and the variable accuracy of data recording across countries.

Additional doubts can be raised regarding the moment of appearance of a viral mutation. Their number, indeed, must be considered infinite, and their ptoduction unpredictable and endless. Accordingly, the discovery of a mutation may not correspond to the moment of its appearance, because, being unknown, it had not been sought before, and therefore could have been there for a long time.

Even greater doubts can be raised regarding the number of viral tests. Indeed, waves of tests were triggered by the fear generated by the mass media in the population. Moreover, everyone knows that the positivity of the test was favored by an incongrous setting of the polymerase chain reaction, which leads to a high number of clinically false positive cases. In fact the great majority of positive subjects were nothing more than healthy or paucisymptomatic carriers. True and false positivity and negativity, without any correlation with clinical criteria heavily influenced the registered number of deaths. For example, during the pandemic, in countries such as Italy, the classification of the causes of deaths was no longer performed on the basis of incontrovertible clinical and pathological criteria: autopsies were prohibited, or strongly hindered, and a positive viral test was sufficient to increase the number of COVID-deaths! Not to mention the deaths caused by the vaccine itself, several thousand, a largely underestimated number.

Further criticism must also be raised to the definition of infectious subjects. To simplify a topic that deserves a complex approach, it must be said that a negative individual, just like a recovered one, transmit the virus in the same way as other carriers: the former because he can become positive after the test, the latter because recovery prevents him from falling ill again, but not from encountering and transmitting the virus to others.

Finally, vaccine immunity cannot be placed at the same level of the natural one. Indeed, following the entry of the virus through the respiratory tract or other natural pathways, the immune response is produced by the contact of the entire immune system with the entire set of viral epitopes. In these cases the efficacy of the immune response is high, and its duration is very long, potentially unlimited. None of this applies to injection of the mRNA vaccine, which within a few seconds spreads to all organs and tissues, triggering an inflammatory reaction, and giving rise to an immune response of weak efficacy and short duration in terms of antibody

production. Indeed, by 'efficacy' of a vaccine we must mean its ability to prevent a disease: it is a clinical effect, not simply a biological one. The mere production of antibodies is not enough: it must be of adequate duration and intensity to prevent a disease.

The striking difference, only partially mentioned here, between the immune response to the natural infection and that produced by the anti-COVID vaccination should alarm every health worker involved in the mass vaccination business. It is good to recall that the worldwide experimental administration of mMRA vaccines against COVID19 was authorized only under emergency conditions. It is a unique experiment in the history of medicine, still ongoing after more than three years, and there are still no clinical studies able to demonstrate the efficacy and the safety of these vaccines.

Despite all above limitations and criticism, the Authors come to the conclusion that the hypothesis of immunity decline as a common cause for the rise of new waves and the selection of the variants is 'more promising' than that of new waves caused by mutation of the previous virus. If true, such results would support a widely held opinion, namely that mRNA vaccines against COVID19 are not capable of triggering a clinically effective antibody production.

This interesting conclusion should be confirmed through randomized, double-blind controlled clinical trials, with careful selection of the study population on the basis of the features of the immune system of each subject, and by comparison with a control population with similar demographic and clinical characteristics.

Overall, the topic is relevant, and the article reads well. Beyond its limitations, it has the merit of bringing Science back to its natural and eternal home, i.e. that of critical analysis, far from the hasty acceptance of statistics.