Reply to the Letter to the Editor: "*Importance of nasal secretions in the evaluation of mucosal immunity elicited by mRNA BNT162b2 COVID-19 vaccine*" by Francavilla B et al.

Lack of a strong oral mucosal immune response: rethinking the route of COVID-19 vaccine boost administration?

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Dear Editor,

We thank Francavilla and colleagues for their letter regarding our paper entitled "Mucosal immune response in BNT162b2 COVID-19 vaccine recipients."[1,2]

However, we do not agree with the authors when they state that the results of our research differ from those of other reports.

Of note, the aim of our study was to describe the development of mucosal immunity in healthy subjects undergoing the first vaccination cycle by measuring the total anti-S1 protein IgG and IgA antibodies in the serum and saliva. In addition, we also recorded the neutralizing activity detectable at these sites.

Regarding the development of IgG and IgA antibodies, our results were consistent with those reported by other authors. As an example, we could detect the presence of salivary anti-S1 IgA antibodies in the saliva of 50% of vaccinated individuals, a result very similar to that reported by Ketas et al.[3]

However, we found that the salivary IgA antibodies correlated with the antibody titre measured in the serum, suggesting that they were mainly exuded from the blood and not directly produced at the mucosal level. This feature was more evident in those individuals who had not been previously exposed to SARS-CoV-2 infection (i.e., seronegative subjects, SN).

A different trend was observed in previously infected individuals (i.e., seropositive subjects, SP), in whom salivary IgA showed higher titres, indicating that in these subjects the mRNA vaccination elicited a partial reactivation of the mucosal immunity, that had been previously primed by the infection.

Consistently, we demonstrated that after the first cycle of vaccination, neutralizing antibodies (NAb) with high neutralizing activity (90%) were found in the serum of all the recruited subjects, but not in the oral cavity, where NAb were detected only in a small percentage of seronegative individuals (i.e., 18%) and were dependent mainly on the IgG antibodies, renowned from being exuded from the serum. In contrast, 60% of the previously infected subjects showed NAb in their saliva, represented by both IgG and IgA antibodies. Furthermore, the NAb detected in the oral cavity were strictly dependent on the presence of salivary IgA but not of serum IgA, indicating that a reactivation of the mucosal immunity took place in SP.

Our findings are consistent with those reported in the literature, as we were able to detect the development of salivary anti-S1 IgG antibodies in all the vaccinated individuals and anti-S1 IgA antibodies in a significant percentage of individuals. However, we also added original data about the development of the neutralizing activity at the oral level, which represents a true indication of how the intramuscular mRNA vaccination elicits protection against SARS-CoV-2 infection and viral transmission. These data were not a consequence of the absence of a clear negative threshold for anti-SARS-CoV-2 antibodies in the saliva samples, as stated by the authors, since the neutralizing activity is an objective evaluation of how NAb are able to bind RBD and block the interaction with ACE2, preventing the virus from entering the cells of the respiratory system. Moreover, as stated by the authors, the collection of the sample was different, because we did not collect sputum for our analysis, which is a respiratory secretion, but oral saliva by the general spitting method, a method that we also used to validate the use of saliva for the diagnosis of SARS-CoV-2 infection in 2020 and that is recognized by the European Centre for Disease Prevention and Control.[4]

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In conclusion, mucosal immunity has been one of the most neglected aspects of the scientific literature dealing with COVID-19 pandemic and the immune response after vaccination. The mucosal immune system represents the first-line defense against infectious pathogens; thus, its activation may lead to prevent SARS-CoV-2 from infecting the host.

The intramuscular BNT162b2 COVID-19 vaccination does not elicit a specific immune response at the level of oral mucosa able to neutralize the virus, and the antibodies found in the saliva are mainly exuded from the serum. Indeed, circulating antibodies contribute protection against the severe disease, hospitalization and intensive care units crowding, but do not protect effectively against the infection at the mucosal sites. The generation of a second line COVID-19 vaccines able to induce mucosal immunity, as for example nasal vaccines, and to be adopted as a reinforcement after systemic vaccination certainly represents a promising preventive strategy to be adopted as to counteract the pandemic and stop viral circulation.[5] For this purpose, scientific reports providing data about the role of mucosal immunity at different sites are necessary.

Contributors

All authors are responsible for writing and revision of the manuscript.

Declaration of interests

The authors declare no conflict of interest.

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