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Letter to the Editor

"Original antigenic sin": A potential threat beyond the development of booster vaccination against novel SARS-CoV-2 variants

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To the Editor—Recently, concern has increased over the emergence of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, which are spreading rapidly across the globe. These variants of concern (B.1.1.7, B.1.351, P.1, and B.1.427/429) have been initially reported in the United Kingdom, South Africa, Brazil, and California, respectively.[1] All of the currently available vaccines that have received emergency use authorization, such as Johnson & Johnson, Moderna, and Pfizer/BioNTech, are based on the Wuhan-originated virus. Regarding the novel variants, the accumulation of multiple mutations in the spike protein, which is the target for neutralizing antibodies, has challenged the efficacy of these vaccines. Several previous laboratory-based studies have reported that the neutralizing activity of sera obtained from individuals who were vaccinated is lower against novel SARS-CoV-2 variants,[2–5] highlighting the need for developing a booster vaccination containing new mutations of the virus.

A phenomenon called "original antigenic sin" (OAS) was firstly proposed by Francis[6] in 1960. This phenomenon occurs in the second exposure of the immune system to a similar pathogen to which it has previously been exposed. In this situation, the immune system progresses to the memory response, generating cross-reactive antibodies that may not be effective against the new pathogen.[7] In addition, it has been speculated that overproduction of memory B cells could compromise the activation of naïve B cells capable of producing efficient and novel antibodies.[8] In this way, OAS can trigger immune evasion of the emerging variants in those who had been affected by or vaccinated against former versions of the pathogen. In the context of coronaviruses, cross-neutralization is a rare event, but cross-reactivity in antibody binding to spike protein is common in SARS-CoV-2 and SARS-CoV.[9] Furthermore, some degrees of cross-reactivity have also been demonstrated between seasonal coronaviruses and SARS-CoV-2.[10] Aydillo et al[11] reported a strong back-boosting of antibodies in SARS-CoV-2–infected patients previously infected with human β-coronaviruses. Interestingly, a negative correlation was observed between pre-exposure to human β-coronaviruses and induction of antibodies against SARS-CoV-2, mentioning the reduction of de novo humoral immune response and occurrence of OAS in patients with pre-existing immunity against related coronaviruses.[11]

The impact of OAS in developing vaccines is of paramount interest. The hypothesis of antigenic distance was proposed to explain how the efficacy of vaccines could be influenced by the difference or relatedness of prior vaccinations. This hypothesis is substantially evident in the case of dengue fever-related vaccine research. Once an individual is immunized against a dengue virus variant, the booster shot for the second variant is unlikely to be successful because it triggers only the original neutralizing antibodies rather than effective antibodies for the new variant.[12] This scenario also applied to the human papillomavirus Gardasil 9 vaccine. The vaccine contained 4 antigens presented in the original Gardasil in addition to 5 novel antigens. Individuals who had been vaccinated previously by original Gardasil exhibited lower levels of antibodies against 5 new antigens compared with those who had been never vaccinated for human papillomavirus.[13] In the context of influenza infection, Choi et al[14] noticed that following the vaccination program against the 2009 pandemic H1N1 influenza, individuals who had already been given a seasonal influenza virus vaccination developed lower antibody response than those who had never been vaccinated against influenza virus. Therefore, OAS can leave individuals with limited and imprinted memory immune response, and booster vaccination containing novel versions of the pathogen may not provide as much protection.

Given the cross-reactivity feature of antibodies against SARS-CoV-2 and other β coronaviruses,[10] the occurrence of OAS for initial and subsequent variants of SARS-CoV-2 would not be unexpected. On the other hand, when it comes to the incidence of ongoing mutations, booster immunization may become a necessary countermeasure for combating the novel resistant variants to current vaccines. If OAS is feasible in the case of SARS-CoV-2 and its emerging variants, the effectiveness of the booster dose will somehow be questioned. Clinical trial NCT04785144 is recruiting to assess the immunogenicity of the mRNA-1273.351 vaccine, which has recently manufactured for immunization toward the novel South African variant of SARS-CoV-2. To evaluate the efficacy of this booster dose on those who have received 2 vaccinations of mRNA-1273, the trial has been designed in 2 arms. The first arm evaluates the administration of a booster dose containing mRNA-1273.351 solely, whereas the

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second arm contains both mRNA-1273.351 and mRNA-1273 in equal proportions.[15] The consequences of this trial could shed light on how OAS may alter the effectiveness of booster vaccination for novel SARS-CoV-2 variants. Eventually, further well-designed animal or human studies on a different type of vaccines are required to evaluate the efficacy of booster immunization over the potential threat of OAS in SARS-CoV-2 vaccines.

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