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Short Essay **Open Access**

Unraveling the tapestry: Immune Imprinting amidst a spectrum of challenges for modRNA Covid-19 vaccines

Ronald Palacios Castrillo[1*]

[1]M.D., Ph.D., Kidney Institute and The Section of Immunology, Incor Health Clinic, Santa Cruz, Bolivia. E-mail: ronalin50@gmail.com

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Abstract

Immunological imprinting is another road block added to the many obstacles and side effects, including some very serious including deaths), concerning the effectiveness and safety of the modRNA based Covid-19 vaccines. Together, they make it highly unethical and difficult to support/promote the widespread vaccination of children and adults with these vaccines.

Keywords: *modRNA vaccines, Immunológical imprinting, Covid-19, SARSCoV-2 virus*

1. Introduction

The concept of "immunological imprinting," also known as "original antigenic sin," is not novel; it originated in the 1960s with research into immune responses to infection by divergent strains of influenza viruses. Scientists discovered that individuals exhibited stronger neutralizing antibody responses against influenza strains they had encountered in childhood. In contrast, exposure to more antigenically distinct strains resulted in less effective immune responses (Francis, 1960; Smith *et al.*, 2004). Mechanistically, when different strains of a pathogen infect the host cell, the immune system tends to prioritize remembering the immune effectors used during the original exposure rather than generating responses against new strains, leading to immune evasion (Smith *et al.*, 2004).

Immune imprinting can be induced through either of two mechanisms: one where the immune system favors a remembered response over a de novo one ("antigenic antiquity"), and the other where the de novo response is actively suppressed ("primary addiction").

Wang *et al.* (2023) demonstrate that immune imprinting alters neutralizing antibody titers for bivalent modRNA vaccination against Omicron subvariants of SARS-CoV-2. Imprinting from three doses of monovalent vaccine can be alleviated by a breakthrough infection of the BA.5 or BQ lineage, but not by a bivalent booster.

Evidence for both phenomena has been found in SARS-CoV-2 infection and vaccination. Antigenic antiquity is evident in vaccinated individuals infected with variants such as Alpha, Delta, or Omicron,

* *Corresponding author: Ronald Palacios Castrillo, M.D., Ph.D., Kidney Institute and The Section of Immunology, Incor Health Clinic, Santa Cruz, Bolivia. E-mail: ronalin50@gmail.com*

where the neutralizing antibody response remains biased towards the original type. Additionally, SARS-CoV-2 infection in unvaccinated individuals induces antibodies that cross-react with common cold betacoronaviruses HKU1 and OC43. Direct evidence of primary addiction comes from experiments tracking the induction of memory versus de novo responses of B cells upon stimulation with a BA.1 spike, resulting in the dramatic suppression of a de novo response in favor of a biased response towards the spike of the original strain. These findings underscore the strong influence of immune imprinting on the ability to generate effective responses against antigenically variable variants of SARS-CoV-2 (Evans and Liu, 2023; Schmidt *et al.*, 2022; He *et al.*, 2023).

One of the significant challenges during the Covid-19 pandemic is maintaining vaccine effectiveness as SARS-CoV-2 continues to evolve. The emergence of the Omicron BA.1 variant in late 2021, characterized by a significant leakage of neutralizing antibodies stimulated by two-dose monovalent modRNA vaccines, marked a critical point. The virus has since evolved into numerous Omicron subvariants, including the more recent XBB variants. Each variant exhibits increasing immune escape, necessitating the reformulation of modRNA vaccination measures. In September 2022, bivalent formulations of the Pfizer and Moderna mRNA vaccines, including the BA.4/5 spike in addition to the ancestral spike, became available to stimulate immune responses toward the Omicron subvariants.

While the inclusion of the BA.4/5 spike in the bivalent formulations has helped stimulate the immune response towards the Omicron subvariants, the neutralizing antibody titers are nowhere near those exhibited for the parental-type spike/D614G. All Omicron subvariants, including BA.4/5, still show dramatic reductions in neutralizing antibody titers, indicating immunological imprinting stimulated by the initial doses of monovalent vaccine. Since BA.4/5, more immunoevasive lineages, including BQ.1, BQ.1.1, BA.2.75, CH.1.1, and recombinant subvariants XBB.1.5, XBB.1.16, XBB.2.3, EG.5, and FLip, have emerged (Cao *et al.*, 2023; Evans *et al.*, 2022; Zhang *et al.*, 2023; Faraone *et al.*, 2023).

In Cell Reports Medicine, Wang *et al.* (2023) sought to corroborate the idea of immune imprinting by demonstrating the role of breakthrough infection with Omicron BA.5 or BQ variants in overcoming immune imprinting. Breakthrough infection represents another means of stimulating the immune response toward the pathogen, and breakthrough infection with SARS-CoV-2 has been shown to stimulate a neutralizing antibody response biased toward the infecting variant.

The data presented by Wang *et al*. underscore that immunological imprinting is a critical issue in the current course of vaccinations. Individuals who received three doses of monovalent vaccine with a bivalent booster containing BA.4/5 showed little increase in titer toward Omicron subvariants, especially XBB.1.5 and XBB.1.16, relative to those who received three doses of monovalent vaccine with a monovalent booster lacking BA.4/5. In contrast, individuals who received at least two doses of monovalent vaccine and experienced breakthrough infection with BQ or, to a lesser extent, BA.5 exhibited more notable increases in titer toward Omicron XBB subvariants. Antigenic mapping analysis revealed that breakthrough infection minimized the antigenic distances between D614G, BA.5, and BQ.1, confirming concerns about immune imprinting in the Covid-19 vaccine. Recent studies have also demonstrated altered neutralizing antibody responses against the newer XBB variants, EG.5.1, and FLip.

Together, these works are crucial for SARS-CoV-2 vaccination design and strategies and have led to the decision to launch a monovalent modRNA vaccine XBB.1.5 in the fall of 2023. According to studies by Wang *et al.* and others, it has become clear that excluding the spike from the original/ancestral strain of the Omicron lineage spike vaccine should help overcome the immune footprint caused by the previous vaccination cycle and better protect against the Omicron subvariants currently in circulation.

Despite these advances, surveillance and characterization of new SARS-CoV-2 variants remain essential. XBB is likely not the last SARS-CoV-2 variant we will face, making studies like the one presented by Wang et al. timely and important for maintaining control of the COVID-19 pandemic.

2. Conclusion

Before the work of Wang *et al.* (2023), we already knew that modRNA-based vaccines did not protect against SARSCoV-2 infection or reinfection. Now, it is clear that this type of vaccines based on modRNA that encodes

the spike proteins of the ancestral/original virus and/or its variants induces immunological imprinting and consequently, dramatically decreases the protective immune response against infections by new variants.

There is a growing tsunami of reports of serious side effects and deaths related/caused by modRNA vaccines (reviewed Palacios-Castrillo, 2023 a, b, c).

Taken together, it is inconceivable and irrational that the use of vaccines based on modRNA platforms continues to be recommended.

For those reinfected, it is essential to eliminate the virus or its variants as quickly and efficiently as possible to reduce the risks of contracting Long Covid or triggering reactivation of spike protein-induced thrombotic vasculitis caused by modRNA-based vaccines.

Here I present an excellent option:

If you test positive for Covid, know this and act:

The safest, most accessible and most efficient treatment available for acute Covid infection is La Tripleta (Nitazoxanide+Hydroxychloroquine+Zinc) x 10 days = 93.5% effective in eliminating the virus (Palacios-Castrillo, 2021). Of the 3 components, Nitazoxanide is the one that has high virucidal activity and is an essential part of La Tripleta (Palacios-Castrillo, 2021).

Thousands of patients have been successfully treated in Central and South America, Africa and Asia. La Tripleta is VIRUCIDAL (kills the virus). The side effects of La Tripleta are mild nausea and easily controlled diarrhea.

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