

## A Prospective Validation of a Diagnostic Algorithm for Hypersensitivity Reactions to COVID-19 Vaccines

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The devastating impact of COVID-19 pandemic has prompted the creation of effective and safe vaccines with new technologies, which have represented a challenge for allergists around the world [1]. By the end of 2020, the first mRNA vaccines against SARS-COV-2 developed by Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) were authorized [2]. Reports of diverse allergic reactions, including anaphylaxis, have led to concern that the new mRNA vaccine technology has the potential to cause these reactions at a greater rate than other vaccines [2,3].

Excipients were presumed as potential agents of anaphylaxis, as most vaccine allergic reactions are caused by them, rather than by their main compounds [4, 5, 6]. Both Pfizer-BioNTech and Moderna vaccines contain Polyethylene glycol (PEG), which is a known allergen widely used in several industries. In addition, Moderna contains Trometamol, also known as Tromethamine [1]. Otherwise, other developed vaccines available in Europe, such as AstraZeneca (AZD1222) and Janssen (Ad26.CoV2.S), which use viral-vector technologies, contain Polysorbate [4, 7].

We aimed to study the vaccine reaction patterns of healthcare workers (HCWs) who were referred to the Allergy Department in our hospital and therefore validate a protocol to identify and stratify the individual risk so that they could receive another dose or an alternative, evaluating the tolerance of every single HWC [3,8].

As the vaccination campaign started at our center, Ramón y Cajal University Hospital (Madrid, Spain), in January 2021, we recruited 485 HCWs until September 3rd 2021 out of 7.088 vaccinated workers (6.659 with 2 doses), who reported any adverse effect after the 1st or 2nd dose of any COVID-19 vaccine, or unvaccinated workers who had a previous history of allergy to any excipient of these vaccines [8]. All of them were referred to our Allergy Department from different departments, such as Occupational Risk Prevention and Preventive Medicine. We followed up those who had previous reactions with COVID-19 vaccines and evaluated their tolerance to a 3rd dose [9].

We recorded sex, age, type of vaccine received, reaction characteristics, latency period and need of medication [8,10].

HCW with allergic reactions to COVID-19 vaccines and unvaccinated workers with previous history of allergic reactions to excipients underwent skin prick testing (SPT) with Polyethylene glycol (PEG-2000, PEG-3350 and PEG-4000), Polysorbate-80, Trometamol, as well as intradermal tests with Polyethylene glycol (PEG-3350), Polysorbate-80 and Trometamol [3,7]. We also performed patch tests with Polysorbate-80 and Polyethylene glycol (PEG-400) for delayed reactions and performed basophil activation tests with the administered mRNA vaccine in two anaphylactic cases [8, 10] (Figure 1).

After performing a structured and detailed clinical history to the 485-recruited HCW, 219 were ruled out because they did not meet the criteria for allergic reactions considering the classic concept of hypersensitivity and its classification stated by Gell-Coombs [11]. 139 reported an allergic reaction to the vaccine, of whom 131 occurred with the 1st dose (group 1) and 8 reported it after the 2nd dose (group 2). The rest, 127 unvaccinated HCWs (group 3), were evaluated because of history of previous reaction to any of the excipients.

Of the 131 HCWs of group 1, 65% were women with a mean age of 55 years. 51% of them had local reactions (immediate: 22.4%, delayed: 77.6%) and 49% systemic ones (immediate: 62%, delayed: 38%). 82% of group 1 tolerated the 2nd dose without incidents, 12% showed mild symptoms (94% referred local reactions (immediate: 27%, delayed: 73%) and 6% systemic ones (immediate: 0%, delayed: 100%)). 6% of them refused to be vaccinated again. Patients of group 2 were all women with a mean age of 54 years, of whom 87% assured they had tolerated the 1st dose without incidents. 25% experienced local reactions (immediate: 50%, delayed: 50%) and 75% systemic ones (immediate: 75%, delayed: 25%).

Skin tests were negative in all cases, except for one patch test with Polyethylene glycol, which resulted positive after 96-hours reading. It belonged to a 60-year-old woman who experienced a local reaction 96 hours after the 1st dose and 72 hours after the 2nd dose of BNT162b2 vaccine, tolerating a 3<sup>rd</sup> dose. Skin tests were performed particularly on her as long as she was one of the first studied cases and the nature of COVID-19 vaccine's reactions was initially unknown. After observing its lack diagnostic value, the algorithm was adjusted. Basophil activation tests were negative, as well as tryptase levels remained unchanged compared to baseline in both anaphylactic cases.

Out of the 12% of group 1 patients who presented mild symptoms with the 2<sup>nd</sup> dose, one of them showed a delayed urticarial rash despite negative skin tests. Concerning group 3, 5 patients developed delayed urticarial rash after receiving the 2<sup>nd</sup> dose, despite not having reported any reaction to the 1<sup>st</sup> dose (Supplementary figure 1).

After COVID-19 vaccine booster shots approval, we followed up by phone-call both groups 1 (n=131) and 2 (n=8). Concerning group 1, from 131 HCW, 68 have not received the 3<sup>rd</sup> dose at that time, 54 received it uneventfully and 9 presented reactions; of whom

78% were women with a mean age of 57 years, experiencing delayed local skin reactions in 6 of them. The other 3 HCW experienced immediate systemic reactions (urticarial rash). All of them have had previous skin reactions with the 2nd dose.

In this group, 44% received all three doses of mRNA-1273 but 56% had previously received BNT162b2 in their two first doses and mRNA-1273 at their 3<sup>rd</sup> dose. All HCWs of group 2 received a 3<sup>rd</sup> dose, 4 of them, all women, experienced delayed local skin reactions with a mRNA-1273 3<sup>rd</sup> dose. One of them had always received mRNA-1273 and the other 3 HCWs received BNT162b2 in their two first doses (Supplementary figure 1).

This single-center experience shows that most reactions occurred in young women with a previous history of allergy, presenting delayed skin reactions. It suggests that most HCWs who have had mild immediate reactions to 1st doses of mRNA vaccines have received 2nd and 3rd doses uneventfully or with only mild recurrent reactions. Otherwise, our data suggest that there tend to be reactions in greater proportion after two doses, showing that it seems that both vaccine doses are needed for cell-mediated immunity development, although our group 2 sample size is too small [12,13]. We have observed that reaction incidence is higher when different mRNA vaccines are administered in a single individual. Although this difference was statistically not significant, it could be useful to propose the use of a single vaccine type in patients with previous mRNA vaccine reactions, although a greater sample size should be followed up. Further studies shall shed light in this regard.

A prior allergological evaluation is necessary in patients with a previous history of severe reactions to some of the excipients contained in these vaccines in order to stratify the individual risk to receive it under surveillance or an adequate alternative [8,1].

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## Conflicts of Interest

None

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Figure 1. COVID-19 vaccination assessment during January-September 2021 in Ramon y Cajal University Hospital.

