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

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The devastating impact of the COVID-19 pandemic has prompted the creation of effective and safe vaccines based on new technologies. These 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, raised concerns 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 to be potential agents of anaphylaxis, as most vaccine allergic reactions are caused by them, rather than by the main compounds [4-6]. Both the Pfizer-BioNTech and Moderna vaccines contain polyethylene glycol (PEG), which is a known allergen that is widely used in several industries. In addition, Moderna contains trometamol, also known as tromethamine [1]. Other 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 health care workers (HCWs) who were referred to the allergy department of our hospital in order to validate a protocol to identify and stratify the individual risk so that patients could receive another dose or an alternative agent. We evaluated the tolerance of all HCWs who experienced an adverse effect [3,8].

The vaccination campaign started at our center (Ramón y Cajal University Hospital, Madrid, Spain) in January 2021. Therefore, until September 3, 2021, we recruited 485 HCWs out of 7088 vaccinated workers (6659 with 2 doses) who reported any adverse effects after the first or second dose of COVID-19 vaccine and unvaccinated workers who had a previous history of allergy to any excipient of these vaccines [8]. All the HCWs were referred to the Allergy Department from other 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 third dose [9].

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

HCWs with allergic reactions to COVID-19 vaccines and unvaccinated workers with a previous history of allergic reactions to excipients underwent skin prick testing (SPT) with PEG (PEG-2000, PEG-3350, and PEG-4000), polysorbate-80, and trometamol, as well as intradermal tests with PEG (PEG-3350), polysorbate-80, and trometamol [3,7]. We also performed patch tests with polysorbate-80 and PEG (PEG-400) for delayed reactions and basophil activation tests with the administered mRNA vaccine in 2 cases of anaphylaxis [8,10] (Figure).

After taking a structured and detailed clinical history for the 485 HCWs recruited, 219 were ruled out because they did not meet the criteria for allergic reactions as per the classic concept of hypersensitivity and its classification according to Gell and Coombs [11]. An allergic reaction to the vaccine was reported by 139 HCWs, of whom 131 reacted to the first dose (group 1) and 8 reacted to the second dose (group 2). The remaining 127 unvaccinated HCWs (group 3) were evaluated because of a history of reactions to any of the excipients.

Of the 131 HCWs in group 1, 65% were women with a mean age of 55 years. Of these, 51% had local reactions (immediate, 22.4%; delayed, 77.6%) and 49% systemic reactions (immediate, 62%; delayed, 38%). In group 1, 82% tolerated the second dose without incident, 12% experienced mild symptoms (94% reported local reactions [immediate, 27%; delayed, 73%] and 6% systemic reactions [immediate, 0%; delayed, 100%]). Six percent of the HCWs refused to be vaccinated again. The patients in group 2 were all women, with a mean age of 54 years; of these, 87% reported tolerating the first dose without incidents. Local reactions were recorded in 25% (immediate, 50%; delayed, 50%) and systemic reactions in 75% (immediate, 75%; delayed, 25%).

Skin tests were negative in all cases, except for 1 patch test with PEG, which was positive after the 96-hour reading. The patient was a 60-year-old woman who experienced a local reaction 96 hours after the first dose and 72 hours after the second dose of BNT162b2. She tolerated the third dose. The patient underwent skin testing, since she was one of the first cases studied and the nature of reactions to the COVID-19 vaccine was initially unknown. Given its lack of diagnostic value, the algorithm was adjusted. Basophil activation test

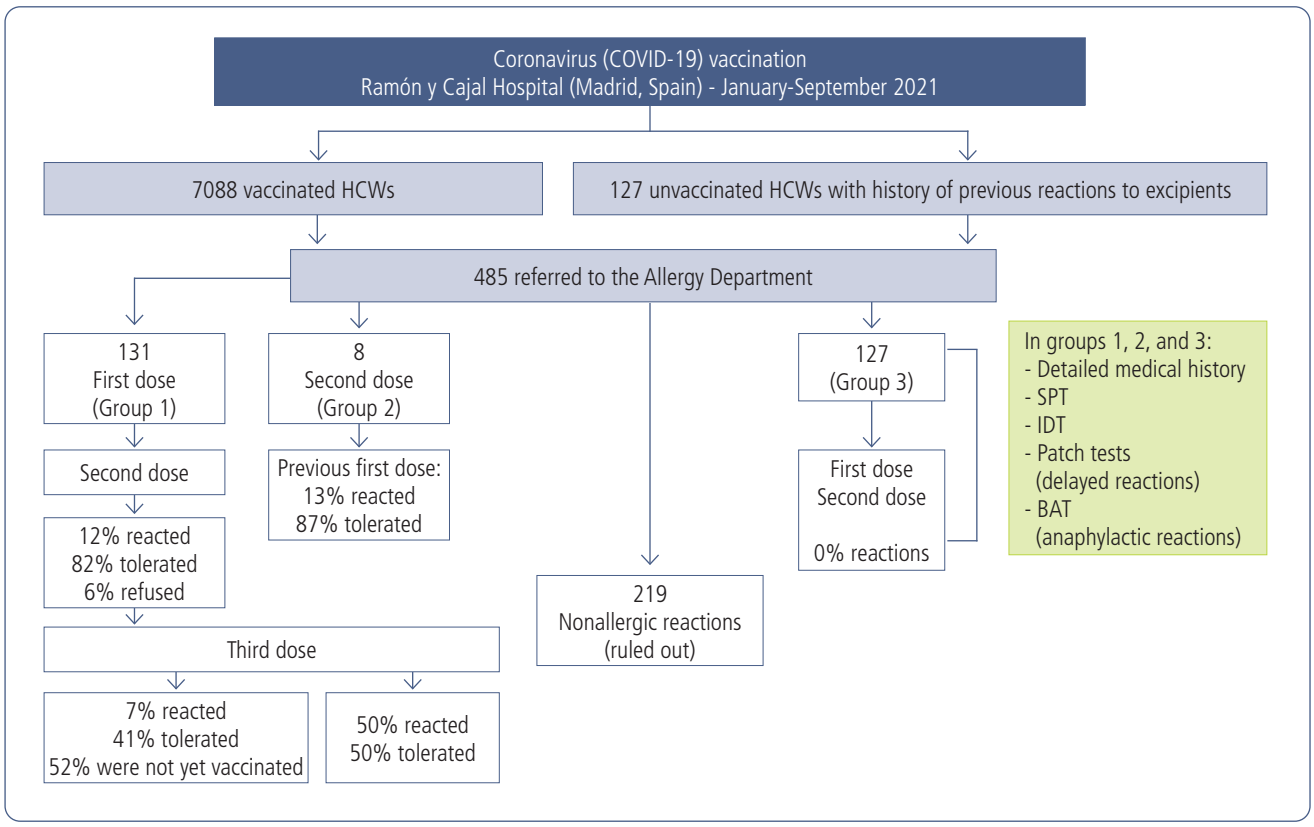

Figure. COVID-19 vaccination at Ramon y Cajal University Hospital during January-September 2021. HCW indicates health care worker; SPT, skin prick test; IDT, intradermal test; BAT, basophil activation test.

results were negative, and tryptase levels remained unchanged compared to baseline in both cases of anaphylaxis.

Out of the 12% of group 1 patients who presented mild symptoms with the second dose, 1 developed a delayed urticarial rash despite negative skin tests results. Five patients in group 3 developed delayed urticarial rash after receiving the second dose, despite not having reported any reaction to the first dose (Supplementary figure 1).

After approval of the COVID-19 vaccine booster shots, we telephoned the HCWs in groups 1 (n=131) and 2 (n=8). In group 1, 68 of the 131 HCWs had not received the third dose at the time, 54 had received it without complications, and 9 developed reactions. Women accounted for 78%, the mean age was 57 years, and the reactions were delayed local skin reactions in 6 cases. The other 3 HCWs experienced immediate systemic reactions (urticarial rash). All of them have had previously experienced skin reactions with the second dose.

In this group, 44% received all 3 doses of mRNA-1273, although 56% had previously received BNT162b2 in their first 2 doses and mRNA-1273 in their third dose. All HCWs in group 2 received a third dose. Of these, 4, all women, experienced delayed local skin reactions with their third dose of mRNA-1273. One of them had always received mRNA-1273 and the other 3 had received BNT162b2 for their first 2 doses (Supplementary figure 1).

This single-center experience shows that most reactions were delayed skin reactions in young women with a previous history of allergy. Furthermore, it seems that most HCWs who had mild immediate reactions to their first doses of mRNA vaccines received their second and third doses uneventfully or with only mild recurrent reactions. Otherwise, our data suggest that there tend to be more reactions after 2 doses and that both vaccine doses are needed for development of cell-mediated immunity, although our group 2 sample size is too small to draw firm conclusions [12,13]. We found the incidence of reaction to be higher when different mRNA vaccines were administered in a single individual. Although this difference was not statistically significant, it could be useful to propose the use of a single vaccine type in patients with previous reactions to mRNA vaccine. Studies with larger samples are necessary.

A prior allergology work-up is necessary in patients with a previous history of severe reactions to the excipients contained in these vaccines in order to stratify the individual risk and receive the drug under surveillance or to provide an adequate alternative [1,8].

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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