The Century of mRNA Vaccines: COVID-19 Vaccines and Allergy

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To the Editor:

On December 2, 2020, the COVID-19 mRNA BNT162b2 vaccine was approved by the Medicines and Healthcare products Regulatory Agency (MHRA). Six days later, the UK began mass vaccina-tion. Only 24 hours later, Dr June Raine, Chief Executive of the MHRA, issued updated guidance to COVID-19 vaccination centers about the management of anaphylaxis following 2 reports of ana-phylaxis and 1 report of a possible allergic reaction following immunization. The guidelines state verbatim "Any person with a history of anaphylaxis to a vaccine, medicine or food should not re-ceive the Pfizer/BioNTech vaccine. A second dose should not be given to anyone who has experi-enced anaphylaxis following administration of the first dose of this vaccine." [1]. The present letter is a response to the consternation caused by the first part of this sentence in the Spanish allergology community.

Basic and clinical research into mRNA vaccines has increased dramatically. Most of the early work in mRNA vaccines focused on cancer applications. Similarly, a number of recent reports demon-strated the potency and versatility of mRNA for protection against a wide variety of infectious pathogens, including parasites and, of interest today, coronavirus 2 (SARS-CoV-2) [2-4].

mRNA vaccines are safe because mRNA is a noninfectious, nonintegrating platform with no poten-tial risk of infection or insertional mutagenesis. The various modifications make mRNA more stable and highly translatable [5,6]. mRNA vaccines have the potential for rapid, inexpensive, and scalable manufacturing, mainly owing to the high yields of in vitro transcription reactions [2].

The COVID-19 mRNA vaccine BNT162b2 manufactured by Pfizer/BioNTech is a highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free in

Table. Recommendations for Administration of COVID-19 mRNA Vaccines to Allergic Patients[a]

	Proceed With Vaccination	Precautions for Vaccination	Contraindications to Vaccination
	– History of allergy to food, latex, insect venom, and aeroallergens – History of drug allergy – Mild allergic reactions to vaccines or other injectable medications (ie, no anaphylaxis) – Family history of anaphylaxis	– History of severe allergic reaction[b] to food, latex, insect venom, or aeroallergens. – History of severe drug allergy[b] – History of severe allergic reaction[b] to another vaccine (not including currently authorized mRNA vaccines) – History of mastocytosis, mast cell activation syndrome, idiopathic anaphylaxis. – Moderate/severe acute illness – Pregnancy and breastfeeding	– History of severe allergic reaction[b] to any component of the currently authorized COVID-19 mRNA vaccines
Actions	– 30-minute observation period	– Risk assessment – Additional counseling – Potential deferral of vaccination – 45-minute observation period if vaccinated	– Do not vaccinate

[a]Modified from Centers for Disease Control guidelines for vaccination of allergic patients.
The SARS-CoV2 vaccines should be administered in a health care setting, where anaphylaxis can be treated.
[b]Severe allergic reaction, eg, anaphylaxis.

vitro transcription from the corresponding DNA templates, which encode the viral spike protein of SARS-CoV-2. The excipients include polyethylene glycol/macrogol (PEG) as part of ALC-0159. The vaccine uses fat bubbles called lipid nanoparticles to deliver messenger RNA (mRNA) to cells. Once there, the mRNA directs cells to produce the virus spike protein, thus provoking an immune response to the foreign protein [3]. This same technology is used in the mRNA-1273 vaccine (manufactured by Moderna), as mRNA-1273 is encapsulated into lipid nanoparticles with "PEG-lipid" [4].

PEG is a polyether compound that is widely used as an additive in pharmaceuticals, cosmetics, and food because of its stabilizing properties [7]. Anaphylactic reactions to PEG are rare. Contact sensi-tivity to PEG is more frequent [8].

Both COVID-19 mRNA vaccines—the BNT162b2 vaccine manufactured by Pfizer/BioNTech and the mRNA-1273 vaccine manufactured by Moderna—have been reported to be safe in clinical tri-als. The most commonly reported adverse reactions were injection site reactions, fatigue, headache, muscle pain, chills, joint pain, and fever. Severe adverse reactions were more frequent after dose 2 than after dose 1, in similar proportions for both vaccines. The third vaccine that uses mRNA, CureVac, has taken a slightly different approach, in choosing to use the potency of untranslated regions to optimize the RNA rather than make chemical modifications. CureVac is on track to initi-ate phase 3 testing of their COVID-19 vaccine by the end of this year [9].

A list of potential allergens in currently available vaccines can be consulted on the Institute for Vaccine Safety website and listed in recently published reviews [4,8,10,11]. The advice of the MHRA to avoid administration of the BNT162b2 vaccine should not be generalized to all patients who have experienced severe reactions to drugs and/or foods. It is necessary to perform a more in-depth study of the adverse effects caused by the vaccine in the UK.

Immunization is highly effective in preventing infectious diseases. Allergic patients deserve access to the same publicly recommended vaccines as nonallergic patients unless the risks associated with vaccination outweigh the gains. Whereas the number of reported possible adverse reactions to vac-cines is high, confirmed vaccine-triggered allergic reactions are rare [12].

The BNT162b2 vaccine, Pfizer/BioNTech, has the same contraindications as any other vaccine with respect to allergic patients, namely, it is not recommended in patients who have previously experi-enced allergic reactions to its components. Only patients with a documented history of allergy to PEG or Tween 80 or previous reactions to vaccines that may contain them should avoid the Pfizer/BioNTech and Moderna vaccines against COVID-19, if we consider the contraindications strictly in terms of allergy.

The adverse events related to the BNT162b2 vaccine are explained in the drug data sheet. The number of persons reporting hypersensitivity-related adverse events was numerically higher in the vaccine group than in the placebo group (137 [0.63%] vs 111 [0.51%]), although the overall risk is relatively low [11]. An allergy study is mandatory in persons who report allergic reactions to SARS-CoV2 vaccines in order to identify the culprit substance. It is not necessary to carry out a systematic preventive study of allergy before administration of the vaccine to individuals who have experienced severe allergic reactions to drugs and/or foods.

Data related to risk in individuals with a history of allergic reactions to previous vaccinations are very limited and continue to evolve. A decision to receive the Pfizer-BioNTech COVID-19 vaccine should be undertaken by the patient with his/her physician, whose professional judgment will play a key role in balancing the associated benefits and risks.

The Pfizer-BioNTech COVID-19 and Moderna vaccines are not live virus vaccines and, therefore, can be administered to immunocompromised patients. At this time, we do not know whether people with a weakened immune system will respond to the vaccine and be protected from COVID-19 [13]. The Table summarizes the management of COVID-19 vaccination for allergic patients, as suggested by the recommendations of SEAIC. These recommendations are based on the best knowledge to date and follow the guidelines of the Centers for Disease Control with respect to vac-cination of allergic patients [14]. On the same day that the cases of anaphylactic reactions to the Pfizer/BioNTech COVID-19 vaccine were reported, the Spanish Society of Allergology and Clinical Immunology released an official statement. The purpose of this letter is to provide the scientific community with recommendations that enable vaccination of allergic patients to be as safe as possible.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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