Position Statements of the Philippine Society of Allergy, Asthma, and Immunology on COVID-19 Vaccines and their Adverse Reactions

March 19, 2021

These statements were developed by the COVID-19 Vaccine Adverse Reaction Task Force of the Philippine Society of Allergy, Asthma, and Immunology (PSAAI).

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INTRODUCTION

The COVID-19 pandemic has been the biggest global health challenge the world has faced. Globally, to date, there are around 120 million reported cases with the death toll exceeding 2.6 million. In the Philippines, we have gone beyond the 600,000 mark, leading to a major health and socio-economic crisis.

Since this pandemic started, scientists around the world have been working to develop, test and produce vaccines to address the spread and decrease the morbidity and mortality of COVID-19. There are more than 200 vaccine candidates with different mechanisms and in various stages of development. The mRNA vaccines, Pfizer-BioNTech's Comirnaty vaccine and Moderna COVID-19 vaccine have already rolled out in the Western world. Because of the global demand for vaccines and lack of adequate supply, the Philippine National COVID-19 Vaccination Program started to roll out this 1st quarter of 2021 using Sinovac's Coronavac, a whole inactivated virus vaccine, and Oxford-Astra Zeneca COVID-19 Vaccine, a viral vector

vaccine using the modified chimpanzee adenovirus ChAdOx1 as a vector. These are the only vaccines with emergency use authority (EUA) that are available in the Philippines. We are still awaiting the arrival of the Pfizer vaccine which also has an EUA issued by the FDA.

This position paper was developed in response to the concerns of many healthcare workers and the lay regarding adverse reactions to COVID-19 vaccines, especially allergic reactions. These statements are based on current data and will be updated periodically.

VACCINE IMMUNOLOGY AND AVAILABLE COVID 19 VACCINES

The spike protein is the major virulent factor that is used by the SARS-CoV-2 virus to enter and infect human cells. Many of the COVID-19 vaccines use the spike protein to stimulate the immune system through different platforms: messenger RNA (mRNA), viral vectors, protein subunit or inactivated virus. Once the vaccine enters the body, it is taken up first by the antigen presenting cells (APC) in the tissues, then they migrate to lymph nodes to present the vaccine antigens to T helper cells. These T helper cells activate the B cells to proliferate and produce neutralizing antibodies specifically targeted against the spike proteins. Some vaccines may also activate cytotoxic T cells that can kill cells infected with SARS-CoV-2. Once natural infection occurs and the virus enters the body, the patrolling immune cells and the specific neutralizing antibodies will recognize the spike proteins and prevent the virus from entering and infecting the host's cells. It also starts a cascade of events that leads to activation, proliferation, and enhancement of function of many types of immune cells which results to a stronger response. Presently, there is insufficient data on how long this immunity will last.

VIRAL VECTOR VACCINES

In viral vector vaccines, the gene for COVID-19 spike protein is inserted in the genome of a different virus (the vector). A commonly used vector is the adenovirus, which is stripped off its essential genetic materials for replication, rendering it harmless. Once this vaccine is injected, the viral vector delivers the genetic code to the host cell and uses the cell's machinery to produce and express the spike protein, which triggers an immune response.

There are two types of viral vectors:

1. Non-replicating vector vaccines - the virus does not infect the cells nor make new viral particles, so only the spike protein is produced. All current COVID-19 vaccines undergoing phase 2/3 clinical trials are non-replicating viral vector vaccines.
2. Replicating vector vaccines - the virus produces new viral particles in the cells it infects, which can then infect new host cells that will also produce the vaccine antigen.

Advantage:

- The immune response triggered by the antigen involves both T cells and B cells.

Disadvantage:

- Viral vector vaccines are relatively complex to manufacture
- People who have been previously exposed to the human virus used as vector may have weaker immune response to the vaccine due to previous immunity to the vector

COVID-19 viral vector vaccines undergoing Phase IIb/III trials:

- Oxford-AstraZeneca (ChAdOx1 nCoV-19) - chimpanzee AdV
- CanSino Biologics (Ad5-nCoV)
- Gamaleya Research Institute (Gam-COVID-Vac) - Ad5/Ad26
- Janssen (Ad26.COV2-S) - AdV26

THE mRNA VACCINES

The mRNA vaccines are novel forms of nucleic acid vaccines. These vaccines contain the mRNA encoding the SARS CoV-2 spike proteins and use a lipid-based nanoparticle carrier system to allow penetration into the host cells. Once injected, the mRNA uses the human cell's own machinery to produce the spike proteins to stimulate an immune response. The mRNA is then degraded by the cell's own enzymes, and therefore no viral genetic material is being integrated into the host DNA.

Advantages

- Immune response involves B cells and T cells
- No live components, so no risk of the vaccine triggering disease
- Relatively easy to manufacture
- Modifiable immunogenicity, stable efficacy, absence of anti-vector immunity

Disadvantages:

- Never been licensed for use in humans
- The high immunogenicity of mRNA vaccines may also be responsible for increased reactogenicity leading to more reports of local and systemic vaccine reactions.
- Some RNA vaccines require ultra-cold storage

COVID-19 mRNA vaccines undergoing Phase IIb/III trials:

- Pfizer/BioNTech (BNT162b2/Tozinameran/Comirnaty)
- Moderna COVID-19 vaccine (mRNA-1273)

PROTEIN SUBUNIT VACCINES

COVID-19 protein subunit vaccines contain specific fragments of the spike protein of SARS-CoV-2, produced and harvested from non-human host cells. These vaccines are usually administered with an adjuvant (e.g. polysorbate, AS03 and Matrix-M). Once injected, the spike protein subunit triggers an immune response. No active viral infection occurs.

Advantages:

- Immune response involves B cells and T cells
- Well-established technology
- Suitable for people with compromised immune systems
- No live components, so no risk of the vaccine triggering the disease
- Relatively stable

Disadvantages:

- Relatively complex to manufacture
- Adjuvants and booster shots may be required
- Determining the best antigen combination takes time

COVID-19 Protein subunit vaccines undergoing Phase I to III trials:

- Sanofi Pasteur (Phase I/II)
- Novavax (Phase III)
- Clover-GSK (Phase I/II), Clover-Dynavax (Phase III)

WHOLE VIRUS

Conventionally, whole-virus vaccines can be classified as either live attenuated vaccines or inactivated vaccines. Live attenuated vaccines contain viruses with weakened virulence, while inactivated vaccines contain viruses whose genetic material has been destroyed to prevent replication. However, inactivated vaccines can still elicit an immune response. The Sinovac vaccine, Coronavac, is an inactivated whole virion vaccine, mixed with an adjuvant, an aluminum-based compound which further stimulates the immune system. Aluminum hydroxide is a known adjuvant found in many vaccines, drugs and some cosmetics.

Advantages:

- Well-established technology
- Strong immune response
- Immune response involves B cells and T cells
- Relatively simple to manufacture

Disadvantages:

- Unsuitable for people with compromised immune systems (live attenuated)
- Live attenuated vaccines may trigger disease in very rare cases
- Relatively temperature sensitive, so careful storage necessary

COVID-19 Inactivated vaccines undergoing Phase IIb/III trials:

- Sinovac (Coronavac)
- Sinopharm

Table 1. Different Vaccine Brands Granted EUA in the Philippines

Vaccine Brand	Vaccine Type	Excipients	Adverse Reaction
CoronaVac (Sinovac)	Inactivated virus	**Aluminum hydroxide**, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, sodium hydroxide and water	Injection site pain, pruritus, erythema, swelling and induration, chills, fever, fatigue, myalgia, diarrhea, nausea, headache, vomiting, lower abdominal pain, dizziness, cough, loss of appetite, increased blood pressure, hypersensitivity No anaphylaxis reported during phase 3 trials There are reports of anaphylaxis in the local setting, diagnosed and managed or referred to allergists, pending confirmation by the NAEFIC*
ChAdOx1 nCoV-19 - chimpanzee AdV (Oxford-AstraZeneca)	Viral vector	L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, **Polysorbate 80,** Ethanol, Sucrose, Sodium chloride, Disodium edetate dihydrate Note: non-latex vial stopper	Injection site tenderness and pain, headache, fatigue, myalgia, malaise, pyrexia, chills, arthralgia and nausea No anaphylaxis reported on clinical trials There are reports of anaphylaxis in the local setting, diagnosed and managed or referred to allergists, pending confirmation by the NAEFIC*
BNT162b2/ Tozinameran/ Comirnaty (Pfizer/BioNTech)	mRNA	Lipids ((4-hydroxybutyl) azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), **2 [(polyethylene glycol)-2000]-N**, N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3- phosphocholine, Cholesterol, Potassium chloride, Monobasic potassium phosphate, Sodium chloride, Dibasic sodium phosphate dihydrate, and Sucrose Note: non-latex vial stopper	Injection site pain, tiredness, headache, muscle pain, chills, joint pain, fever, injection site swelling and redness, nausea, feeling unwell, swollen lymph nodes, rash, itching, hives, swelling of the face no anaphylaxis reported during clinical trials, but reported **anaphylaxis 5:1,000,000 with routine use**

*NAEFIC National Adverse Events Following Immunization Committee

POSITION STATEMENTS REGARDING COVID-19 VACCINE ADVERSE REACTIONS

REACTOGENIC AND ALLERGIC REACTIONS

STATEMENT 1. Adverse reactions to vaccines may occur and can range from reactogenic reactions to allergic reactions. A REACTOGENIC REACTION is not the same as an ALLERGIC REACTION.

What is a reactogenic reaction?

A reactogenic reaction is an inflammatory response that occurs after vaccination.

When vaccine antigens enter the body, they are recognized as potential pathogens (via pathogen associated molecular patterns) by the pathogen recognition receptors that are found on peripheral immune cells. This results in the synthesis and release of pyrogenic cytokines (IL-6, TNF-a, & PGE2) in the tissues or bloodstream, mimicking the response to natural infection. When this happens, a series of events occur – phagocytosis, release of mediators, activation of complement and cellular recruitment. These same events lead to the development of local and systemic inflammatory reactions. The reactions may occur within the first three days of vaccination and resolve within 1-3 days of onset. These symptoms are observed to be more frequent following the second dose of the vaccine and among younger persons compared to older persons.

Majority of these reactions from COVID-19 vaccines are local reactions which include pain, swelling and tenderness on the injection site. Leaking of these mediators and products of inflammation into the circulation can also result in systemic side effects. Most systemic post-vaccination reactions are mild to moderate in severity, which include headache, fatigue, malaise, muscle pain, chills, fever and vomiting.

What is Allergy?

An allergy or hypersensitivity reaction is an exaggerated immune response to a usually harmless substance.

The reactions are categorized into four principal groups, types I-IV.

Type I or immediate reaction is an IgE-mediated reaction which can manifest as urticaria, flushing, vomiting, abdominal cramps, rhinitis and asthma usually within 6 hours after exposure to the allergen. Anaphylaxis, which is a severe type I reaction, is highly likely if 2 or more organ systems are involved and can manifest as: urticaria, pruritus, flushing, angioedema, dyspnea, wheezing, vomiting, abdominal cramps, syncope, hypotension in most cases (hypertension may occur in 12.9%) and tachycardia that usually occur within 6 hours. However, hypotension or respiratory compromise may be the only manifestation of anaphylaxis after exposure to a known allergen. Biphasic anaphylaxis may happen in 0.4-

15% of anaphylactic episodes, wherein symptoms may abate and recur usually 6 hours to as late as 72 hours after the resolution of the initial symptoms.

The diagnosis of anaphylaxis during the acute event is based on the clinical presentation and a history of a recent exposure to an offending agent. There are no laboratory tests available in an emergency department or clinic setting to confirm a diagnosis of anaphylaxis in real time. However, laboratory tests such as serum tryptase obtained during or shortly after the acute event can help to support the clinical diagnosis of anaphylaxis. Tryptase is a mast cell marker released during anaphylaxis.

In patients who present with symptoms that are not very characteristic, or those who do not completely fulfill the criteria for anaphylaxis after receiving the COVID-19 vaccine, elevated levels of total serum tryptase may be useful for distinguishing anaphylaxis from other conditions in the differential diagnosis, such as vasovagal reactions, myocardial shock, or benign flushing.

Tryptase is best taken between 30 to 90 minutes after the reaction and may remain elevated up to 6 hours. A second sample should be collected at least 24 hours after all signs and symptoms have resolved to serve as a baseline sample for comparison. A rise in total tryptase levels above baseline may be more sensitive than a single tryptase level. The minimal elevation of the acute total tryptase level that is considered to be clinically significant is suggested to be ≥(2 + 1.2 x baseline tryptase levels) in units of ng/mL or mcg/liter.

An elevated serum tryptase level supports the diagnosis, but a normal level cannot refute the diagnosis.

Specimen collection

In the Philippines, ImmunoCAP tryptase determination is available at the Fe Del Mundo Medical Center. Serum and plasma (EDTA or heparin) samples from venous blood can be used. Collect blood samples and prepare serum or plasma according to standard procedures. Keep specimens at 2 °C to 8 °C for up to one week, or else at –20 °C.

Anaphylaxis is rare in mRNA COVID-19 vaccines, with an estimated incidence of 2.5 per 1 million doses in Moderna vaccine and 5 per 1 million doses in Pfizer/BioNTech vaccine. Polyethylene glycol or PEG, an excipient in mRNA vaccines, is also found in medications and in some vaccines. It has been implicated as a rare cause of anaphylaxis and may cross react with polysorbate. Aluminum hydroxide is known to activate TH2 immunity and thus, is a potential allergenic excipient found in whole virion vaccines (Coronavac, Sinopharm). It has been implicated in local allergic contact dermatitis to vaccines; however, anaphylaxis to this component is even rarer. The incidence of anaphylaxis to other COVID-19 vaccines is currently unknown.

Type II reaction is an antibody mediated cytotoxic/cytolytic reaction wherein the antibodies (IgG/IgM) are directed against the individual's own cell. This leads to cytotoxic action by killer cells or activation of the complement system leading to cytolytic reactions. Examples are anemia and thrombocytopenia. Type III reaction is an immune complex-mediated

reaction wherein the IgG or IgM antibodies form complexes with the antigens which are deposited in the tissues and activate the complement system causing local or systemic damage. Examples are the Arthus reaction and serum sickness. Type IV reaction is a cell mediated reaction which can cause delayed type hypersensitivity reactions such as maculopapular eruptions. Theoretically, any vaccine can produce these allergic reactions; however, these are rare occurrences.

MANAGEMENT OF ADVERSE REACTIONS TO VACCINES

STATEMENT 2. Reactogenic reactions are managed with supportive care. Mild allergic reactions can be treated with antihistamines. Anaphylaxis should be recognized and managed promptly with EPINEPHRINE. Every patient should be observed for at least 30 minutes post-vaccination.

Adverse reactions to vaccines can occur anytime, thus, the health care facility should be fully equipped with emergency medications. Reactogenic reactions are often mild and can subside within a few days with supportive care (paracetamol, NSAIDs, cold compress). Mild allergic reactions such as urticaria and rhinitis can be managed with antihistamines. Anaphylaxis should be recognized and treated immediately with EPINEPHRINE (1mg/mL) 0.3-0.5 mL intramuscularly at the mid antero-lateral thigh. Anaphylaxis may increase the risk of mortality if not treated promptly.

Other types of vaccine hypersensitivity reactions are managed usually in the hospital setting and controlled by oral or intravenous steroids, or other systemic immunomodulators, depending on the severity of the reaction. Patients with these reactions must be referred to a qualified specialist for more extensive evaluation and management.

Vaccines containing natural rubber latex in their packaging, (vial stoppers, syringe plungers), must not be administered to patients with a history of anaphylaxis to latex. A non-latex containing alternative should be given instead.

Giving antihistamines and systemic corticosteroids as prophylaxis for vaccination is not consistently effective and often fails to prevent severe reactions and anaphylaxis. Moreover, these medications may mask the early signs and symptoms of anaphylaxis and delay the administration of epinephrine. Antipyretics and NSAIDs are likewise not recommended as prophylaxis for reactogenic reactions. There is lack of data to recommend pharmacologic prophylaxis before vaccination.

STATEMENT 3. The ONLY current contraindication to COVID-19 vaccination is an allergy to a previous dose of COVID-19 vaccine and any of its components.

Those who should NOT receive the COVID-19 Vaccines:

1. Patients who have experienced an immediate allergic reaction within 6 hours, whether mild (e. g. rashes, pruritus, hives, angioedema other than laryngeal edema,

flushing without urticaria, tingling or itching without urticaria) or severe (e.g. anaphylaxis) that is most likely due to the first dose of the COVID-19 vaccine, should not receive the second dose.

Giving another vaccine type as the second dose cannot be recommended at this time. Data are still lacking regarding the safety and efficacy of using mixed platforms, as well as cross reactivity of these available vaccines. Moreover, there are no current reliable diagnostic tests to confirm allergy to vaccine component/s.

2. Patients who have a history of allergic reaction or anaphylaxis to certain vaccine excipients such as polyethylene glycol (PEG) (which can also be found in colonoscopy preparation, or laxatives), to polysorbate (found in vascular graft materials, surgical gels, PEGylated medications), or to aluminum hydroxide (found in vaccines, certain drugs and cosmetics) should not receive the COVID-19 vaccines that contain these excipients. Polyethylene glycol (PEG) 2000 is an ingredient of the mRNA vaccines, while polysorbate 80 and polysorbate 20 can be found in non-replicating adenovirus vector vaccines and protein subunit vaccines. There is a potential allergenic cross-reactivity between PEG and polysorbate. Aluminum hydroxide is found in inactivated whole virion vaccines. However, there are no reliable diagnostic tests to confirm allergic reactions to PEG, polysorbate or aluminum hydroxide.

These patients may be referred to an allergist for further evaluation.

Those who need further evaluation:

1. Patients who have experienced an immediate allergic reaction within 6 hours such as urticaria, angioedema, difficulty of breathing, wheezing, regardless of severity, or anaphylaxis to any OTHER vaccine or injected therapy with components NOT found in COVID-19 vaccines, or to unrecalled vaccines or injectable medicines, should be referred to a qualified specialist for evaluation.

2. Patients who had anaphylaxis to oral medications, food, latex, environmental allergens, or insect venom, or to an unclear allergen or etiology should be referred to a qualified specialist for evaluation.

3. Patients with uncontrolled asthma should be referred to their attending physician for evaluation and discussion on adequate attack-free period.

4. Patients with mast cell disorder should be referred to a qualified specialist.

   All vaccinated patients should be observed for at least 30 minutes after vaccination in a setting fully equipped to manage anaphylaxis.

Special Groups who can receive the vaccines:

1. Patients with non-anaphylactic allergy to food, inhalant/environmental allergens, insects, oral medications, can receive COVID-19 vaccines. Patients with latex allergy should receive a vaccine with non-latex packaging.

2. Patients with delayed local or systemic (maculopapular exanthem) reactions, local or systemic reactogenic reactions to other vaccines may receive COVID-19 vaccines.

3. Patients with immunodeficiency and autoimmune disease (e.g. Guillain-Barre Syndrome, Bell's palsy) may also get vaccinated but they should be informed that there is still not enough data available to establish vaccine safety and efficacy in these conditions.

4. Patients with well-controlled asthma whether on inhaled corticosteroids or not, and those with allergic rhinitis whether on intranasal corticosteroids or not, and those with atopic dermatitis and chronic urticaria may receive COVID-19 vaccines.

   All vaccinated patients should be observed for at least 30 minutes after vaccination in a setting fully equipped to manage anaphylaxis.

SUMMARY:

- The COVID-19 pandemic has been the biggest global health challenge the world has faced.

- COVID-19 vaccination may provide protection and herd immunity which may be the solution to this global health problem.

- Several kinds of vaccines have been developed. With the spike protein being the major virulent factor used by the SARS-CoV-2 virus to enter and infect human cells, many of the COVID-19 vaccines use this to stimulate the immune system through different platforms: messenger RNA (mRNA), viral vectors or protein subunit. Inactivated whole virus vaccine is also available.

- Adverse reactions to vaccines may occur and can range from reactogenic reactions to allergic reactions. A REACTOGENIC REACTION is not the same as an ALLERGIC REACTION.

- Majority of COVID-19 vaccine adverse reactions are mild. Reactogenic reactions include pain, tenderness and swelling and can be managed with supportive care. Mild allergic reactions such as rashes can be managed with antihistamines.

- The risk of severe allergic reactions, such as anaphylaxis, is rare in mRNA vaccines. The incidence of anaphylaxis to other COVID-19 vaccines is currently unknown. However, it should be recognized and managed promptly with EPINEPHRINE 0.3-0.5ml intramuscularly at the mid antero-lateral thigh. It is therefore essential that all vaccinees be observed for at least 30 minutes post-vaccination at vaccination centers.

- Healthcare practitioners who will be vaccinating against COVID-19 must be sufficiently trained to properly recognize and manage anaphylaxis. Vaccination centers must be equipped with the proper medications necessary to manage immediate allergic reactions such as anaphylaxis.

- The ONLY current contraindication to COVID-19 vaccination is an immediate allergic reaction of any severity to a previous dose of COVID-19 vaccine and any of its components.

- Patients with allergic reactions to other types of vaccines and injectable medications should be evaluated by a qualified specialist prior to COVID-19 vaccination.

- Patients with non-anaphylactic reactions to food, inhalant/environmental allergens, insects, latex, oral medications not related to vaccines and their components, can receive COVID-19 vaccines. Patients with latex allergy should not receive a vaccine with latex in its packaging.

- Patients with immunodeficiency and autoimmune disease (e.g. Guillain-Barre Syndrome, Bell's palsy) may also get vaccinated but they should be informed that there is still not enough data available to establish vaccine safety and efficacy in these conditions.

- Patients well-controlled asthma, allergic rhinitis, atopic dermatitis and chronic urticaria whether on maintenance medications or not can receive COVID-19 vaccines.

- Based on current data, the benefits of these vaccines to the general public far outweigh the potential risks of adverse reaction to COVID-19 vaccines, as well as to the risk of developing severe COVID-19 and death.

ASSESSMENT OF RISK FOR ALLERGIC REACTION TO THE **FIRST DOSE** OF COVID 19 VACCINE
March 19, 2021

LOW RISK	**MODERATE RISK**	**HIGH RISK**
PROCEED WITH VACCINATION Observe for at least 30 minutes	**PRECAUTION TO VACCINATION** Refer to a **qualified specialist** Observe for at least 30 minutes in a hospital setting	**CONTRAINDICATION TO VACCINATION**
1. NON-ANAPHYLACTIC allergy to **oral medications**[1] (including the oral equivalent of an injectable medication) 2. NON-ANAPHYLACTIC allergy to **food, pet, insect venom, environmental, latex**, etc.[1,2] 3. DELAYED LOCAL reactions (eg, contact dermatitis) to **OTHER vaccines**[3] 4. **REACTOGENIC** reactions, LOCAL (eg, pain, redness, swelling on injection site) or SYSTEMIC (eg, fever, chills, headache, malaise) to **OTHER vaccines** 5. Well-controlled atopic dermatitis, allergic rhinitis, asthma, chronic urticaria, whether on maintenance medications or not 6. Primary or secondary immunodeficiency (after evaluation of clinical status and discussion of ideal vaccine platform with attending physician) 7. Autoimmune disease – (after discussing efficacy with attending physician) 8. Family history of allergies[1]	1. ANAPHYLAXIS to **oral medications, food, latex, environmental, or insect venom**[2] **or unclear allergen/etiology**[3] 2. Uncontrolled asthma (discuss with a qualified specialist adequate attack-free period*) 3. Mast cell disorder (discuss with a qualified specialist for evaluation)[4] 4. IMMEDIATE (within 6 hours) **ALLERGIC** reaction of **any severity** [urticaria, angioedema, respiratory distress (eg, wheezing, stridor), or ANAPHYLAXIS] a. to **UNRECALLED** vaccines or injectable therapies (only if evaluated by allergist), or b. to **OTHER vaccines** or injectable therapies **with components NOT found in COVID vaccines**	• IMMEDIATE (within 6 hours) **ALLERGIC** reaction of **any severity** [urticaria, angioedema, respiratory distress (eg, wheezing, stridor), or ANAPHYLAXIS] to **a component of the COVID-19 vaccine**[1] (eg, PEG in mRNA vaccine, polysorbate in Janssen and AstraZeneca, aluminum hydroxide in Coronavac/Sinovac)

** Global Initiative For Asthma (GINA) Guidelines at https://ginasthma.org/gina-reports/*

[1] *https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#Appendix-B*

[2] *https://education.aaaai.org/resources-for-a-i-clinicians/reactionguidance_COVID-19*

[3] *Worm M, et al. Practical recommendations for the allergological risk assessment of the COVID-19 vaccination - a harmonized statement of allergy centers in Germany. Allergol Select. 2021 Jan 26;5:72-76.*

[4] *Rama TA, et al. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. J Allergy Clin Immunol. 2021 Mar;147(3):877-878.*

ASSESSMENT OF RISK FOR ALLERGIC REACTION TO THE **SECOND DOSE** OF COVID VACCINE
March 19, 2021

SYMPTOMS/ SIGNS AFTER FIRST DOSE	RECOMMENDATION FOR SECOND DOSE
1. **No cutaneous or systemic symptoms** after the first dose	• Proceed with second dose at recommended interval
2. Red, itchy, swollen, or painful rash where they got the first COVID vaccine shot or "**COVID arm**"[a]	• May proceed with second dose at the opposite arm
3. Delayed-onset LOCAL reaction (eg, erythema, induration, pruritus) around the injection site a few days through the second week after the first dose[b,c]	• Proceed with second dose at recommended interval
4. Mild delayed cutaneous generalized reaction (eg, maculopapular exanthems, allergic contact dermatitis)	• Proceed with second dose at recommended interval
5. **REACTOGENIC reactions**[d] (vaccine side effects) a few hours up to 3 days after the first dose (eg, fever, chills, fatigue; pain, erythema, or swelling at injection site; lymphadenopathy in same arm as vaccination; headache, myalgia, arthralgia, vomiting, diarrhea)	• Proceed with second dose at recommended interval
6. **VASOVAGAL reactions**[d] occurring within 15 minutes after the first dose [eg, feeling warm or cold; pallor, diaphoresis, clammy skin, sensation of facial warmth; dizziness, lightheadedness, syncope (often after prodromal symptoms for a few seconds or minutes), transient hypotension with bradycardia, weakness, changes in vision (such as spots of flickering lights, tunnel vision), changes in hearing]	• Proceed with second dose at recommended interval
7. Hypertension alone within 6 hours after the first dose	• Refer to a qualified specialist for clearance prior to the second dose
8. **IMMEDIATE onset allergic symptoms within the first 6 hours** after first dose that are **SEVERE** (eg, respiratory distress, laryngeal edema, anaphylaxis)[a]	• **Should NOT proceed with second dose**
9. **IMMEDIATE onset allergic symptoms within the first 6 hours** after first dose that are **MILD** (eg, rash, hives, swelling other than laryngeal edema, flushing without urticaria, subjective symptoms such as tingling or itching without urticaria, etc.)	• **Should NOT proceed with second dose**
10. Other **SEVERE** adverse reactions, whether **IMMEDIATE** within 6 hours after first dose or **DELAYED** (eg, thrombosis, purpura, etc)	• Refer to appropriate qualified specialist for clearance prior to the second dose

[a] *https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/allergic-reaction.html*

[b] *https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#Contraindications*

[c] *Blumenthal KG, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. N Engl J Med. 2021 Mar 3.*

[d] *https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#Appendix-D*

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