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

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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, there are more than 100 million reported cases with the death toll exceeding 2 million. In the Philippines, we have gone beyond the 500,000 mark, leading to a major health and socio-economic crisis.

Scientists around the world have been working to develop, test and produce vaccines to address the spread and decrease the mortality and morbidity of COVID-19. Several vaccines have already been rolled out in some parts of the world. The Philippines has its own National COVID-19 Vaccination Program which is scheduled to roll out before the end of the first quarter of 2021.

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 vaccine, mixed with an adjuvant, an aluminum-based compound which further stimulates the immune system.

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 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

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 reaction is an IgE-mediated reaction which can manifest as urticaria, vomiting, abdominal cramps, rhinitis and asthma within 4 hours after exposure to the allergen. Anaphylaxis, which is a severe type I reaction, is rare with an estimated incidence of 11.1 per 1 million doses in mRNA COVID-19 vaccines. The incidence of anaphylaxis to other COVID-19 vaccines is currently unknown. Anaphylaxis is highly likely if 2 or more organs are involved and can manifest as: urticaria, pruritus, flushing, angioedema, dyspnea, wheezing, vomiting, abdominal cramps, syncope, hypotension and tachycardia that occur within 4 hours. However, hypotension or respiratory compromise can be the only manifestation of anaphylaxis after exposure to a known allergen.

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, although rare, 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 an allergist for more extensive evaluation and management.

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, whether mild (e. g. rashes) or severe (e. g. anaphylaxis) to COVID-19 vaccine after the first dose should not receive the second dose.

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) or to polysorbate (which can be found in vascular graft materials, surgical gels, PEGylated medications) should not receive the COVID-19 vaccines. Polyethylene glycol (PEG) 2000 is an ingredient of the mRNA vaccines, while polysorbate 80 can be found in non-replicating adenovirus vector vaccines and protein subunit vaccines. There is a potential allergenic cross-reactivity between PEG and polysorbate. However, there are no reliable diagnostic tests to confirm allergic reactions to PEG or polysorbate.

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

Those who need further evaluation:

Patients who have experienced an immediate allergic reaction, such as urticaria, angioedema, difficulty of breathing, regardless of severity, to any OTHER vaccine or injected therapy must be evaluated by an allergist to assess possible allergic reactions to PEG or polysorbate. All vaccinated patients should be observed for at least 30 minutes after vaccination.

Special Groups who can receive the vaccines:

1. Patients with allergic reactions (of any severity) to food, inhalant/environmental allergens, insects, latex, oral medications, not related to vaccines and their components, can receive COVID-19 vaccines.
2. 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.

3. Patients with well-controlled asthma and on inhaled corticosteroids, and those with allergic rhinitis on intranasal corticosteroids can receive the COVID-19 vaccine.

SUMMARY:

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

- COVID19 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, protein subunit or inactivated virus.

- 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. However, it should be recognized and managed promptly with EPINEPHRINE 0.3-0.5ml IM. It is therefore essential that all vaccinees should 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 an allergist prior to COVID-19 vaccination.

- Patients with allergic reactions to food, inhalant/environmental allergens, insects, latex, oral medications, not related to vaccines and their components, can receive COVID-19 vaccines.

- 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 with well-controlled asthma and on inhaled corticosteroids, and those with allergic rhinitis on intranasal corticosteroids 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.

REFERENCES:

- World Health Organization. What we know about COVID-19 vaccine development. Cited 26 January 2021. Available from: https://www.who.int/publications/m/item/what-we-know-aboutcovid-19-vaccine-development.
- The Global Alliance for Vaccines and Immunizations. There are four types of COVID-19 vaccines: here's how they work. Cited 25 January 2021. Available from: https://www.gavi.org/vaccineswork/there-are-four-types-covid-19-vaccines-heres-how-they-work.
- Callaway E. The race for coronavirus vaccines: a graphical guide. *Nature* 2020; 580(7805): 576-577. doi: 10.1038/d41586-020-01221-y.

- Liu Y, Massoud TF, Paulmurugan R. SARS-CoV-2 vaccine development: an overview and perspectives. *ACS Pharmacol Transl Sci*. 2020; 3(5): 844–858. doi: 10.1021/acsptsci.0c00109.
- Centers for Disease Control and Prevention. Understanding viral vector COVID-19 vaccines. Cited 26 January 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/viralvector.html.
- Krammer F. SARS-CoV-2 vaccines in development. *Nature* 2020; 586:(7830):516-527. doi: 10.1038/s41586-020-2798-3.
- Wellcome. What different types of Covid-19 vaccine are there? Cited 8 January 2021. Available from: https://wellcome.org/news/what-different-types-covid-19-vaccine-are-there.
- Plotkin SA, Offit PA, Orenstein WA. Vaccines. (6th edition). *Vaccines.* Elsevier 2013;16-34e7. Doi: https://www.sciencedirect.com/book/9781455700905/vaccines#book-info.
- Pardi N, Hogan MJ, Porter FW et al. mRNA Vaccines - a New Era in Vaccinology. *Nat Rev Drug Discov* 2018; 17(4): 261–279. doi:10.1038/nrd.2017.243.
- Centers for Disease Control and Prevention. Understanding and explaining mRNA COVID-19 vaccines. Cited 24 November 2020. Available from: https://www.cdc.gov/vaccines/covid-19/hcp/mrna-vaccine-basics.html.
- Centers for Disease Control and Prevention. Understanding mRNA COVID-19 Vaccines. Cited 18 December 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html.
- Abbas, AK, Lichtman, AH, Pillai S. (9th edition). *Cellular and Molecular Immunology.* PA (Philadelphia): Elsevier 2018; 437-457.
- World Health Organization. Vaccine Safety Basics Learning Manual. Cited 2013. Available from: https://www.who.int/vaccine_safety/initiative/tech_support/Part-2.pdf
- Li YD, Chi WY, Su JH, et al. Coronavirus vaccine development: from SARS and MERS to COVID-19. *Journal of Biomedical science*. 2020; 27:104. doi: https://doi.org/10.1186/s12929-020-00695-2
- Liu KW, Wang T. SARS-CoV-2 Vaccine Development: An Overview and Perspectives. *ACS Pharmacology & Translational Science* 2020; 3: 844-858. doi: 10.1021/acsptsci.0c00109
- Zhang Y, Zeng G et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomized, double-blind, placebo-controlled, phase ½ clinical trial. *The Lancet* 2020; 21: 181- 192. doi: https://doi.org/10.1016/S1473-3099(20)30843-4.
- Herve C, Laupeze B, Del Giudice G, et al. The how's and what's of vaccine reactogenicity. *NPJ Nature Partner Journals* 2019; 1-11. doi: https://doi.org/10.1038/s41541-019-0132-6.

- Public Health England. Patient Group Direction for COVID-19 mRNA vaccine BNT162b2 (Pfizer/BioNTech). Cited 5 January 21. Available from: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/12/C0956-PfizerBioNTechCOVID-19PGD-v02.00-updated-5-January-2021.pdf
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *The New England Journal of Medicine* 2020; 383 (27): 2603-15. doi: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2034577?articleTools=true.
- Klimek L, Jutel M, Akdis CA, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines: an EAACI-ARIA position paper. *Allergy*. 30 December 2020. doi: https://doi.org/10.1111/all.14726.
- Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *WAO Journal* 2011; 4:13–37. https://doi.org/10.1097/WOX.0b013e318211496c.
- The New England Journal of Medicine. Covid-19 Vaccine —Frequently Asked Questions. Available from: https://www.nejm.org/covid-vaccine/faq.
- Glover RE, 1 Urquhart R, Lukawska J, et al. Vaccinating against Covid-19 in people who report allergies. *BMJ* 2021; 372: n120. doi: 10.1136/bmj.n120.
- Dreskin SC, Halsey NA. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organization Journal* 2016; 9 (32): 1-21. doi: 10.1186/s40413-016-0120-5.
- Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *Allergy Clin Immunol Pract*. 2021. https://doi.org/10.1016/j.jaip.2020.12.047.
- Centers for Disease Control and Prevention. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer - BioNTech COVID-19 Vaccine — United States, December 14-23, 2020. Cited 15 January 2021. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm.
- Centers for Disease Control and Prevention. Benefits of getting a COVID-19 vaccine. Cited 5 January 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/vaccine-benefits.html.
- Centers for Disease Control and Prevention. COVID-19 vaccines and allergic reactions. Cited 22 January 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/allergic-reaction.html.
- Centers for Disease Control and Prevention. COVID-19 Vaccination. Cited 20 December 2020. Available from: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.
- American College of Allergy, Asthma and Immunology. ACAAI Guidance on risk of allergic reactions to mRNA COVID-19 vaccines. Cited 6 January 2021. Available from: https://acaai.org/news/acaai-provides-further-guidance-risk-allergic-reactions-mrna-covid-19-vaccines

- Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *The New England Journal of Medicine*. Cited 30 December 2020. https://www.nejm.org/doi/pdf/10.1056/NEJMra2035343?articleTools=true.
- Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis - Practice Parameter Update 2015. *Ann Allergy Asthma Immunol* 2015; 115: 324-384. http://dx.doi.org/10.1016/j.anai.2015.07.019