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Vaccinating against COVID-19 in Allergic Patients

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Abstract:

It is over a year since the outbreak of coronavirus (COVID-19) and we are still facing an ongoing pandemic. Whilst the number of infected patients and death rates are increasing everyday, newly developed vaccines are the main hope for humanity to end this misery. From December 2020, emergency authorized vaccines had been distributed to many parts of the world. Studies of the vaccine have confirmed effectiveness with only very rare severe adverse reactions. There are no absolute contraindications for use of the vaccines in people with a history of allergy and preexisting allergic diseases. However, risk assessment and stratification are crucial to ensure ongoing safety for vaccine injection services. The precautions in place for use of the COVID-19 vaccines within high-risk populations include patients with a history of anaphylaxis to previous vaccinations, severe/uncontrolled asthma, and underlying mast cell disorders. These patients should have their vaccine injections under healthcare provider supervision. A consultation with an expert will provide deeper evaluation and shared decision-making for use of the appropriate vaccine. The observation period for the patients with risks of allergic reactions should be at least 15-30 minutes. If anaphylaxis occurs, prompt treatment improves the survival outcomes. Anaphylaxis is a treatable condition without long-term effects. Taking all of this into account, we encourage everybody to join the immunization campaign. Do not let the fear of the reactions outweigh the advantages of being vaccinated.

Keywords: COVID-19, Vaccine, Anaphylaxis, Allergy

Introduction

Since the outbreak of coronavirus (COVID-19) and emerging of SARS-CoV-2 variants, over 170 million confirmed cases and 3.5 million deaths have been reported globally, according to the World Health Organization (WHO) as of June 2021[1]. The disease has affected people differently, from asymptomatic or mild illness cases, to critical respiratory failure and shock[2, 3]. For over a year, people around the world are now living in a "New Normal" lifestyle, under strict social restrictions, to prevent viral transmission. Despite this a rising number of cases and death rates are still occurring everyday. To end this ongoing

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pandemic, vaccination is an effective intervention to provide protective immunity against the virus and significantly reduce morbidity and mortality among large populations[4-6]. From December 2020, more than 1.5 billion doses of vaccines have been administered, with good efficacy and low rates of serious adverse events[7]. In Thailand, 3.7 million doses of vaccines have already been given and currently a plan on mass distribution of vaccines is due to start on June 7, 2021. Although the vast majority of people are willing to get vaccinated, some people may refuse to join the immunization program due to multiple factors. Concerns about unknown future effects and misinformation are known to lead to vaccine hesitancy. This situation might delay success in the control of the pandemic[8,9]. This article aims to review adverse events following COVID-19 immunization, in which the author will focus on allergic reactions to vaccines and immunization in allergic patients. The aim is to encourage and build confidence in vaccination among the general population and healthcare providers.

Adverse event following immunizations (AEFIs)

An adverse event following immunization (AEFI) is "…Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine…"[10]. The adverse events can be any unintentionally noxious signs and symptoms or abnormal laboratory results. The reactions may range from minor or local reactions to severe reactions. Minor reactions are mild unfavorable symptoms such as pain and swelling at the site of injection or a systemic reaction, such as fever. Minor reactions resolved spontaneously after a short period. The severe reaction may cause patients disability for a definite of time but not results in long-term morbidities, such as seizure or allergic reactions to vaccines. Rarely, a severe reaction results in death. Subjects with underlying conditions are likely to have severe adverse events after vaccination[11]. To monitor medication safety, authorities in each country have set up surveillance systems of suspected adverse events on vaccines, such as the Vaccine Adverse Event System (VAERS) in the United States [VAERS - Report an Adverse Event (hhs.gov)], the European medicines agency (EMA) in Europe [European Medicines Agency (europa.eu)], (MHRA) in the UK and the Active surveillance system for COVID-19 Vaccine (App-Based Monitoring or Hospital-Based Safety Monitoring) at https://co-vaccine.moph.go.th in Thailand.

The causality assessment or determination of a relationship between the two events is a tool for healthcare providers to find potential causes of AEFI, based on evidence studies to avoid bias and confounders. Several factors may precipitate unwanted events. However, if the link to the vaccines is suspected, the events must occur only after the injections. Other considerations that could alternate the causes of the events including, preexisting diseases, and newly acquired illness, exposure to drugs or toxins, and infections preceding the vaccinations.[12] Classification of AEFIs, definitions and examples are shown in table 1.

Table 1 Classifications, definitions, examples and cluster characteristics of AEFIs (Adapted from World Health Organization. (2014). Global manual on surveillance of adverse events following immunization, 2016 update. Available from https://apps.who.int/iris/handle/10665/206144)[13]

Classification of AEFI	Definition	Example	Cluster characteristics
• Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product	- Biological plausibility of the vaccine products - Individual's reactions to the properties of vaccines such as allergic reactions to vaccines, aseptic meningitis following mumps vaccine	- Cases received the same vaccine or lot - No similar cases in the community - Increased frequency reported from multiple settings to known vaccine reactions
• Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.	- Insufficient inactivation of wild-type vaccine agent - Contamination during manufacturing process	
• Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature	- Error in vaccine preparation by health care workers - Contamination during preparation, transportation, or storage - Defect in vaccine storage and transportation - Error in administration techniques - Identification error	- Cases received vaccines from the same healthcare worker or facility and there are no other cases

Classification of AEFI	Definition	Example	Cluster characteristics
• Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization	- Not related to properties of the vaccines - Individual's psychological reactions - Top four frequent reactions (faint, hyperventilation, vomiting, convulsions)	- Cases of symptoms after immunization are well-recognized as anxiety-related reactions during immunization programs targeting adolescent girls
• Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety	- Not related to properties of the vaccines - Inevitable events could occur especially during the mass campaign - Example: death of the infant following days after DTP vaccination (could be from the vaccine or a coincidental death at a normal death rate of the infancy period)	- Cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated from the same area in the same age group - Calculating the expected rate of an adverse event may be helpful for investigators.

Cases selection for causality assessment is crucial. Serious AEFIs that result in death, hospitalization, significant disability or congenital anomaly, the events that happened at an unusual rate or severity and clusters that largely impacted public health policy are the main focus for causality assessment.[12]

Assessing reactions to vaccines

Currently (June 2021), there are seven vaccines in use worldwide, of these five are verified for use by WHO and available for use in Thailand. These emergency authorized COVID-19 vaccines, the recommended schedules of administration, and frequent reported adverse reactions, are shown in table 2. The majority of the cases report only mild symptoms, usually self-limited and not requiring additional treatment.

Table 2 Authorized COVID-19 vaccines, recommended schedules of administration, and frequent adverse reactions.[14-20]

Platform	Developer/ Vaccine name	Dose schedule and administration	Common side effects
RNA-based vaccine	BioNTech–Pfizer (BNT162b2)	Two doses (day 0, day 21) Intramuscular	Injection site: pain, swelling, redness Systemic: fatigue, headache, muscle pain, chills, fever, joint pain
	Moderna (mRNA-1273)	Two doses (day 0, day 28) Intramuscular	Injection site: pain, swelling, redness Systemic: fatigue, headache, muscle pain, chills, fever, nausea, joint pain
Adenovirus vector (Nonreplicating)	AstraZeneca and University of Oxford (AZD1222)	One (day 0) or two (day 0, day 28 or 8-12 weeks) doses Intramuscular	Injection site: pain Systemic: fatigue, headache, muscle pain, nausea, fever, joint pain
	Janssen (Johnson & Johnson)	One (day 0) or two (day 0, day 56) doses Intramuscular	Injection site: pain, redness, swelling Systemic: fatigue, headache, muscle pain, nausea, fever
Inactivated	BBIBP-CorV (Sinopharm)	Two doses (day 0, day 21-28) Intramuscular	Injection site: pain, swelling Systemic: fatigue, headache, muscle pain, nausea, fever, diarrhea
	CoronaVac (Sinovac)	Two doses (day 0, day 14-28) intramuscular	Injection site: pain, redness, swelling Systemic: fatigue, headache, muscle pain, nausea, fever, diarrhea

Hypersensitivity reactions to COVID-19 vaccines

Despite safety profiles of vaccine phase 3 trials, hypersensitivity reaction is the issue that raises the public fear of vaccination. Nevertheless, at the date of the VAERS report, confirmed anaphylaxis occurred at a rate of 11.1 per million doses of BioNTech–Pfizer vaccines, 71% of the onsets were within 15 minutes after injection, over 95% have been discharged home without any deaths.[21] Clinical recognition of anaphylaxis is very important to ensure provision of early essential initial treatments, before taking

of a thorough history, physical exam, and other investigations. Mechanisms of immediate reactions are divided into three main categories, Immunoglobulin E (IgE) mediated reaction, Non-IgE mediated reaction, and non-immune reaction (vasovagal reaction). For IgE-mediated reaction, the symptoms can be mild, such as urticaria and pruritus, to presenting with a severe multi-systemic reaction, known as anaphylaxis. The previously used term "Anaphylactoid" represents reactions that resemble anaphylaxis without evidence of IgE. These clinical features may result from direct mast cell and basophil activation, activation of complement pathways, and many other pathways. In this case, serum for tryptase will be of benefit to distinguish between the two conditions.[22] Comparison of anaphylaxis and vasovagal features are shown in table 3.

Table 3 Comparison of anaphylaxis and vasovagal features (Adapted from Banerji et al)[23]

Characteristics	Anaphylaxis	Vasovagal reactions
Onset after vaccination	15-30 minutes	Within 15 minutes
Signs and symptoms		
Consciousness	Anxiety, may progress to unconsciousness	Fainting sensation, dizziness, loss of consciousness in some cases
Pulse	Rapid, weak, and irregular	Slow, weak but regular
Blood pressure	Hypotension (SBP<90) In children: SBP <70 mmHg +2 x age (year) in 1-10 years old	Variable; may have hypotension, or bradycardia during syncope event
Respiratory	Difficulty breathing; coughing, sneezing, wheezing, stridor	Variable; if accompanied by anxiety, may have an elevated respiratory rate
Cutaneous	- Warm skin, progressing to clammy and pallor - pruritus urticaria in >90% of cases - angioedema	- pallor, diaphoresis, clammy skin sensation, facial warmth
Gastrointestinal	Nausea, vomiting, abdominal pain, diarrhea	Nausea, vomiting

Patients at risk for COVID-19 vaccines anaphylaxis

For newly developed vaccines, it is always a challenging question of who is at risk of anaphylaxis. Ongoing research is needed to identify specific risk factors. A detailed history, including allergy to vaccine components, previous drug allergy, atopic history (especially asthma), and drugs or substance use/ activities before vaccination must be obtained. Currently, proposed risk factors for COVID-19 vaccines anaphylaxis are as followed [24]

- Patients with previous anaphylactic episode to vaccines
- Patients with mastocytosis and other mast cell disorders
- Patients with severe/uncontrolled asthma.

Investigation of the culprit agents responsible for the patient's reaction, allergic testing (skin prick test, intradermal skin test, and blood testing), and allergist consultation are crucial to lowering the risks of future vaccination.

Table 4 Current emergency approved COVID-19 vaccines and excipients[27]

Vaccines	Excipients
BioNTech–Pfizer (BNT162b2)	(4-hydroxybutyl) azanediyl) bis (hexane-6,1-diyl) bis (2-hexyldecanoate)] (ALC-0315), **2-[(polyethylene glycol)-2000]**-N,N ditetradecylacetamide (ALC-0159),1,2-distearoyl-sn-glycero-3-phosphocholine cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, water for injection
Moderna (mRNA-1273)	Lipids (SM-102, 1,2-dimyristoyl-rac-glycero3-**methoxy-polyethylene glycol-2000 [PEG2000-DMG],** cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose
AstraZeneca and University of Oxford (AZD1222)	L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, **polysorbate 80**, Ethanol, Sucrose, Sodium chloride, Disodium edetate dihydrate, Water for injection
Janssen (Johnson & Johnson)	Sodium chloride, citric acid monohydrate, **polysorbate 80**, 2 hydroxypropyl-B-cyclodextrin (HBCD), ethanol (absolute), sodium hydroxide
BBIBP-CorV (Sinopharm)	**Aluminum hydroxide**, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, sodium hydroxide, sodium bicarbonate, M199
CoronaVac (Sinovac)	**Aluminum hydroxide**, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride

Frequently, the immediate allergic reaction is due to excipients components (Inactive ingredients in the vaccine that helps formulate the product, to increase stability, efficacy, and sterility, such as egg protein, gelatin, formaldehyde, thiomersal, etc.)[25,26] A list of excipients in the vaccine is shown in table 4

For the mRNA vaccines, Polyethylene glycol (PEG, also known as macrogol) and polysorbate, the additives used to improve water solubility in the vaccines, are the

key components that contribute to IgE-mediated reactions.[28] PEG is contained in many household and cosmetic products, such as toothpaste and skin creams. A variety of medications e.g., laxative agent for bowel preparation in colonoscopy, Methylprednisolone acetate (Depo-Medrol), Medroxyprogesterone acetate (Depo-Provera) contain PEG 3350. Hence, this specific formulation of PEG in the mRNA vaccine is designed to stabilize the liposome portion, and is in use for the first time for vaccination purposes. Polysorbates, on the other hand, are extensively used in common injectable medications and vaccines, including influenza vaccine (Fluarix quad, Flulaval Quad), DTaP (Infanrix), and Rotavirus (RotaTeq). Polysorbate 80 is used in AstraZeneca and Johnson & Johnson. These two chemicals have potential cross-reactivity due to their structural similarity. Though allergies to the substances are rare, sensitization in the prior exposure to polysorbate 80 had been reported before the first dose of vaccination [23,28,29]

Aluminum is a strong adjuvant that enhances immunogenicity in classical inactivated vaccines. Several vaccines, for instance, Diphtheria and Tetanus vaccines, within controlled injectable limits, have used this adsorbed compound, with a good safety profile, for decades. The aluminum itself can cause local reactions, such as granuloma formation and skin rash, and anaphylaxis can occur.[30,31] In phase 3 and phase1/2 study of inactivated COVID-19 vaccines, no anaphylaxis had been observed.[19,32] Though all of these reactions are rare, to date (June 2021), in the real world, 17 per million anaphylaxis episodes were reported in Chile and Thailand.[33,34] Further research and monitoring of the reactions are ongoing.

COVID-19 Vaccination in patients with preceding allergic diseases[35]

The allergy, asthma and immunology Association of Thailand (AAIAT) recommend that there is no absolute contraindication for COVID-19 vaccine in patients with preceding allergic diseases. The details for each allergic disorders are as followed,

Patients with asthma

Patients with asthma can be vaccinated with COVID-19 vaccines. Patients with controlled asthma should continue their controller medications even on the day of vaccination. For uncontrolled asthma and severe asthma patients, however, there are precautions for these groups, especially those who are using the systemic steroid for controlling symptoms at the time of vaccination. Patients who are not well-controlled asthma should consult with their physician before getting vaccinated. For the patients who currently receiving biologic therapy, such as omalizumab, benralizumab, or dupilumab, at least 7 days intervals after the last dose of biologic medication is recommended before vaccination.

Patients with food allergy

Patients with any food allergy can go on vaccinating with covid-19 vaccine without special precautions.

Patients with drug allergy

Patients with a history of drug allergy including antibiotics (i.e. penicillin, sulfa), Non-steroidal anti-inflammatory drugs (i.e. ibuprofen, naproxen, aspirin), anti-convulsants, gout treatment, and radiocontrast media allergy can be vaccinated with COVID-19 vaccine. However, a 30-minute observation period under health care provider supervision is recommended.

Patient with history of vaccine allergy

Patients who previously had severe allergic reactions to other vaccines and who previously had severe reactions or urticarial rash after the first dose of COVID-19 vaccine should consult their physician before getting COVID-19 vaccines.

Vaccination safety measures and precautions

According to the CDC, "…people should get vaccinated even if they have a history of severe allergic reactions not related to vaccines or injectable medications…." Since the benefits of COVID-19 vaccinations greatly exceed the risks of allergy, everyone should be encouraged to join the campaign.

The first dose of COVID-19 vaccination

Before the first dose of COVID-19 vaccination, The European Academy of Allergy and Clinical Immunology (EAACI) and The American College of Allergy, Asthma, and Immunology (ACAAI) recommend a list of questions for physicians and other providers to ask patients, to screen for the risks of allergic reactions. The example of the questions are as following,

- Do you have a history of severe allergic reaction to an injectable medication?
- Do you have a history of severe allergic reaction to a previous vaccine?
- Do you have a history of a severe allergic reaction to polyethylene glycol (PEG), a polysorbate, or polyoxyl 35 castor oil (e.g., paclitaxel)?
- Do you suffer from allergies or allergy-like diseases? (e.g., mast cell disorder)

These questions triage the patient whether to proceed with the vaccination, referral for further evaluations, or using other alternative vaccines. In addition, people with higher risks should be monitored for a longer period. Schematic for screening question and risk stratification is shown in figure 1.[27,36,37]

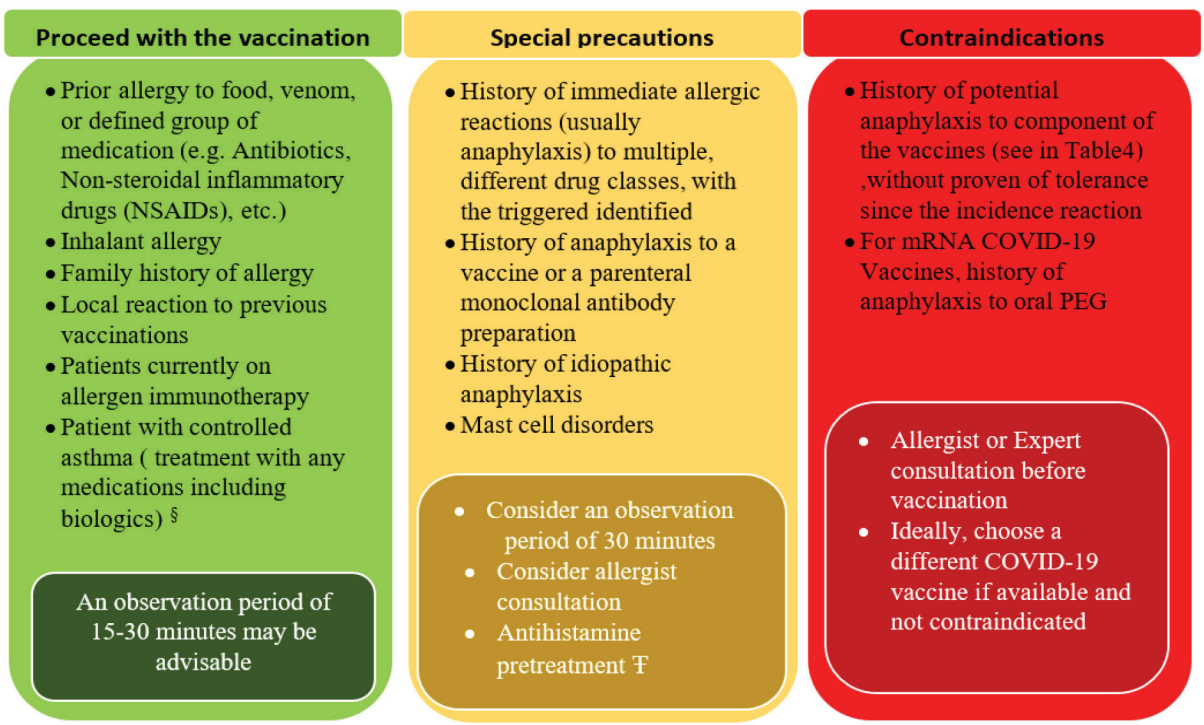

Figure 1 Schematic for screening question and risk stratification. (Adapted from *Turner P et al.*) [27]

(Detailed in red box is newly arranged)
§ British Thoracic Society (BTS) and Global initiative for asthma (GINA) recommend that Patients with asthma who currently on biological therapy should not receive COVID-19 vaccine on the same day, a 7- day interval is advisable (recommendation as of Mar 2021)[38, 39]
Ŧ No clear evidence on pretreatment of antihistamine with COVID-19 vaccine, the medication may mask initial symptoms or reactions

In figure 1, the green box, yellow box and red box represent the low, medium and high risk for severe allergic reactions following the first dose of COVID-19 vaccination, respectively. Patient with previous allergies, mild or local reaction to previous other vaccines, patients currently on immunotherapy and patients with controlled asthma can proceed to COVID-19 vaccination safely. A routine 15- to 30- minute observation is generally recommended. Patients with a history of anaphylaxis to multiple drugs or previous vaccination are at medium risk. These patients may need detailed evaluation before getting vaccinated. A premedication with antihistamine (e.g. cetirizine, fexofenadine) may reduce mild discomforting symptoms such as mild rash or itching. However, this may delay early signs of anaphylaxis and may delay treatments, which could lead to morbidity and mortality. Since the anaphylaxis episodes usually occur at 15 to 30 minutes after injection, therefore at least 30 minutes of observation after vaccination is needed. Health care providers should consult expert or allergist before giving the vaccines to the high risk patients who had history of anaphylaxis to any component of COVID-19 vaccines. For mRNA vaccine, skin test with polysorbate 20 and 80 is important to confirm diagnosis of PEG allergy. If possible, patients with positive skin test should be injected with other alternative types of COVID-19 vaccines. This risk stratification ensure safety for all patients for current and future vaccination.

During the observation period, healthcare providers should obtain the patient's vital signs and look for any abnormal clinical symptoms. Emergency Supplies and medications should be readily prepared. In the case of anaphylaxis, early recognition and appropriate initial management improve the outcomes. In some situations, patients might not fulfill all the diagnostic criteria. However, from the expert panel discussion, whenever severe allergic features are in doubt, epinephrine is the treatment of choice[40]. For all patients with suspected allergic reactions, a detailed history, physical examination, and initial blood sampling (e.g., tryptase) is recommended. Consider referral for allergist for further evaluation.

For local reactions, a self-treatment by cold compression at the side of injection, exercising the arms, over-the-counter pain-reliever medications, and drinking plenty of water can reduce the symptomatic discomfort. Some people might experience delayed localized hypersensitivity reactions. Magaret et al. reported a case series of 16 patients who received mRNA vaccine (Moderna) with erythematous rash, pruritus, induration, and tenderness at the site of injection, in which the median onset was 7 days after the first dose and 5 days after the second dose. The lesions may persist for up to 21 days. All the skin lesions resolved spontaneously and so are not considered as contraindications for the second dose of the vaccine [41].

Second dose of COVID-19 vaccination

It is crucial to follow up on patients' clinical symptoms after the first dose of vaccinations. According to the CDC recommendation as of Mar 2021[42], "...if a person

has received the first dose uneventfully, then they can proceed to the second dose in the same manner..."

If the patients experience mild allergic reactions, likewise, only pruritus or urticaria, a second dose can be given with precautions. Pretreatment with fexofenadine or cetirizine 1-2 hours before the injection might reduce the discomforting symptoms. A 30-minute observation period is required to ensure patient safety. However, once a person has severe allergic reactions, healthcare providers should consider further evaluation and shared decision-making, related to the risks and benefits of receiving the vaccine, with the patient and an allergist. Even though the non-irritating concentration of the vaccine's component had not been standardized, skin testing may be utilized to identify the potential component-related symptoms. For re-challenging of the COVID-19 vaccines, there is a lack of evidence of efficacy of this[23]. Also the American Academy of Allergy Asthma& Immunology COVID-19 response task force states that in the present situation, with often limited vaccine resource, it would be more beneficial for the vaccine to be used for vaccination rather than for evaluation of the reactions.[43]

Conclusion

In the battle against COVID-19, vaccination is the prime key to success. There are no absolute contraindications for COVID-19 vaccine use in any patients with pre-existing allergic conditions and diseases. While the benefits of vaccination are clear and the risks of severe adverse events are rare, fear of adverse reactions must be addressed. Healthcare providers have a role in promoting the COVID-19 immunizing campaign. Well-prepared and prompt treatment of any emergency conditions, at the time of vaccination, helps improve the outcomes and will ensure patient's safety, and vaccine confidence, as part of the vaccination service.

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