

# SARS-CoV-2 Vaccine Testing & Administration Guidance for Allergists/Immunologists from the CSACI

**Current as of April 10, 2021 and based on available evidence to date**

Safe and effective vaccines provide the first hope for mitigating the devastating health and economic impacts resulting from COVID-19 and related public health orders. Two mRNA vaccines (Pfizer-BioNTech, Moderna), and two adenovirus vector vaccines (AstraZeneca/COVISHIELD, Janssen) are currently approved in Canada, with further vaccines likely becoming available in the coming months.<sup>1</sup> A high rate of vaccine uptake across all sectors of Canadian society is a priority public health goal.

Reports of reactions to SARS-CoV-2 vaccines have raised questions about their safety for use in individuals with allergies and those who are immunocompromised. In this document, we aim to address these concerns and provide guidance for CSACI members.

## A. Suggested approach to vaccination in individuals with confirmed or suspected allergic conditions.

- **Assessment by an allergist prior to vaccination for SARS-CoV-2 is NOT required for individuals with a history of unrelated allergies:**
  - **foods**
  - **insect venom**
  - **environmental allergens**
  - **unrelated oral/injected medications**
  - **radiocontrast media (RCM)**
  - **unrelated vaccines**

In these individuals, the available SARS-CoV-2 vaccines can be administered without any special precautions. As for the routine administration of all vaccines, the SARS-CoV-2 vaccine should be administered in a healthcare setting capable of managing anaphylaxis, and individuals should be observed for a minimum of 15-30 minutes following vaccination.

- **Assessment by an allergist prior to vaccination for SARS-CoV-2 is warranted for any individual with a suspected allergy to the vaccine or any of its components.** This includes anyone who has experienced a suspected allergic reaction after receiving the first dose of a SARS-CoV-2 vaccine, or someone with a suspected or confirmed allergy to a component of the vaccine. Proper assessment will help to clarify whether and how a SARS-CoV-2 vaccine can be (re)administered and, if necessary, can help in the selection of an alternative SARS-CoV-2 vaccine.
- These recommendations will be updated as evidence evolves to reflect ongoing best practice.

## Summary:

1. There is a low risk for allergic reactions associated with vaccines. Non-allergic reactions to vaccines are much more frequent than allergic reactions.
2. The nature and cause of the reported allergic reactions to SARS-CoV-2 vaccines remain unclear, including what component of the vaccine those individuals may have reacted to.
3. The feasibility of allergy testing for SARS-CoV-2 vaccines is not yet known.
4. Polyethylene glycol (PEG), polysorbate and tromethamine have been identified as potentially allergenic, but it is not yet known whether allergy to these excipients is responsible for the reported adverse reactions to these vaccines.
5. It is unknown whether allergy testing for excipients will be relevant to the investigation of possible allergy to SARS-CoV-2 vaccines.
6. In someone with a suspected or confirmed allergy to a SARS-CoV-2 vaccine or one of its components for whom an additional dose is required, choices include deferral of the second vaccine dose, selection of an alternative vaccine with a different platform and excipients, and the administration of the same vaccine using a graded vaccine administration protocol.

### **1. There is a low risk for allergic reactions associated with vaccines. Non-allergic reactions to vaccines are much more frequent than allergic reactions.**

Vaccines activate the immune system, which will commonly result in minor local and systemic side effects, including fever and local inflammatory reactions (redness, swelling, pain and warmth) at the site of the injection.<sup>2</sup> A recent case series highlights this possibility after receiving Moderna's SARS-CoV-2 vaccine (the so-called "Moderna arm").<sup>3</sup> These reactions are not a contraindication to receiving the same vaccine in the future, as they do not pose a risk for future allergic reactions to the vaccine.

Other exposures should also be considered as a possible source of adverse reactions during vaccination with these vaccines. Localized irritation and contact reactions have been described to compounds used to prepare the injection site. More specifically chlorhexidine, which may be used to sterilize vaccine injection sites, may elicit allergic reactions. Skin testing for chlorhexidine allergy may be used to make a diagnosis but is not standardized.<sup>4,5</sup>

Non-allergic reactions to vaccines also include anxiety-related adverse events that can mimic allergic reactions, and may include breath-holding, hyperventilation, and vasovagal syncope (fainting) (see Table 1 in the Canadian Immunization Guide: Anaphylaxis and other Acute Reactions following Vaccination).<sup>6</sup>

Acute localized allergic reactions at the site of the injection, consisting of urticaria and angioedema, are also possible, but the risk of systemic allergic reactions, including anaphylaxis, is considered extremely rare. Studies suggest that the estimated annual rate of anaphylaxis in Canada is approximately 0.4 to 1.8 cases per 1,000,000 doses of vaccine administration.<sup>6-8</sup>

To date, there have been almost 135 million reported cases of COVID-19 worldwide, with over 1 million cases and 23,236 deaths in Canada due to COVID-19, representing a fatality rate of over 600 deaths per million persons in Canada.<sup>9-11</sup> By comparison, 16 of 27 reported deaths following SARS-CoV-2 vaccination in Canada have been determined not to be caused by a SARS-CoV-2 vaccine. While the cause of death for the remaining 11 remains under investigation, no death in Canada has been attributed to an allergic reaction after vaccination for SARS-CoV-2 to date.<sup>10</sup>

**2. The nature and cause of the reported allergic reactions to SARS-CoV-2 vaccines remain unclear, including what component of the vaccine those individuals may have reacted to.**

A recent publication suggests that “the rate of anaphylaxis associated with the Pfizer SARS-CoV-2 mRNA vaccine appears to be approximately 10 times as high as the incidence reported with all previous vaccines” and as of April 2, 2021, the Public Health Agency of Canada (PHAC) reveals that of almost 6 million vaccinations for SARS-CoV-2 administered in Canada, there have been 60 reported episodes of anaphylaxis (0.001% or 10 per 1,000,000 vaccinations) based on Brighton Collaboration criteria (BCC).<sup>10,12,13</sup> However, we must be cautious not to repeat history. Previous experience with the pandemic H1N1 (pH1N1) vaccine has educated us that although the pH1N1 vaccine was initially reported to have caused a “rate of anaphylaxis 20 times greater than the historical average”, subsequent careful investigation revealed that a striking 96% of those initially reported to have experienced anaphylaxis after receiving the vaccine had no evidence of allergy to that vaccine.<sup>14</sup>

Millions of doses of SARS-CoV-2 vaccines have been safely administered around the world, with over 754 million vaccinated worldwide for SARS-CoV-2 to date.<sup>13</sup> The nature and cause of the reported allergic reactions to these vaccines remain unclear, including what component of the vaccine those individuals may have reacted to. This remains under investigation.

**3. The feasibility of allergy testing for SARS-CoV-2 vaccines is not yet known.**

Epicutaneous and intradermal testing to SARS-CoV-2 vaccines is not recommended for use as routine screening before vaccination for SARS-CoV-2. Although non-irritant concentrations for skin testing to the Pfizer-BioNTech vaccine have recently been published, the authors of that manuscript acknowledge that the validity of such testing has not yet been established.<sup>15</sup> In addition, a consistent source of SARS-CoV-2 vaccines for the purpose of skin testing is not yet available.

**4. Polyethylene glycol (PEG), polysorbate and tromethamine have been identified as potentially allergenic, but it is not yet known whether allergy to these excipients is responsible for the reported adverse reactions to these vaccines.**

Allergic reactions to vaccines can be elicited by the active vaccine component, or more commonly, by one of the other components.<sup>6-8</sup>

Polyethylene glycol, commonly known as PEG, has been identified as the most likely potentially allergenic component of both Pfizer-BioNTech and Moderna SARS-CoV-2 vaccines, and polysorbate80 in the AstraZeneca/COVISHIELD and Janssen vaccines.<sup>16-24</sup> Tromethamine

(trometamol or Tris) in the Moderna SARS-CoV-2 vaccine has also been identified as a potentially allergenic excipient.<sup>16,20</sup>

It is not yet known whether these excipients are responsible for the reactions that have been reported to date. The other components of these vaccines, including the active components of the vaccines available in Canada, are unlikely to be allergenic.

##### **5. It is unknown whether allergy testing for excipients will be relevant to the investigation of possible allergy to SARS-CoV-2 vaccines.**

Allergy to PEG has previously been reported. PEG compounds have a range of molecular weights, and allergic sensitization to PEG has mainly been documented for PEG with higher molecular weight and when present in higher concentration.<sup>25-30</sup> However, PEG is ubiquitous and found in multiple products that are tolerated safely on a daily basis by many individuals in Canada, including bowel preparation products for surgical procedures, certain laxatives and other medications, certain skin care products and cosmetics, and some food and drinks.

A recent publication has suggested a possible role for allergy testing to PEG within the context of evaluation of allergy to these vaccines,<sup>31</sup> though an accompanying editorial challenged this approach.<sup>32</sup> Although both epicutaneous and intradermal skin testing for PEG has been described within the context of case reports and research,<sup>26,28,29</sup> such testing has not been standardized and its validity is not established.<sup>32</sup> In addition, systemic reactions, including anaphylaxis, has been described as a result of both epicutaneous and intradermal testing to PEG.<sup>27,29</sup> Furthermore, although cross-reactivity between different types of PEG has been suggested,<sup>26,27,30</sup> the Pfizer-BioNTech and Moderna SARS-CoV-2 vaccines contain different forms of PEG, and the degree of cross-reactivity between these PEG molecules has not yet been established.

Polysorbate 80 may cross-react with PEG, but the clinical implications of this are also unknown.<sup>31,33</sup> A recent World Allergy Organization statement explains that polysorbate is tolerated by most individuals with PEG allergy, including in vaccines. They further explain that influenza vaccines contain as much or more polysorbate than the Oxford-AstraZeneca SARS-CoV-2 vaccine and the rate of allergic reactions to influenza vaccines is no higher than with other vaccines in the general population.<sup>33</sup>

The Moderna vaccine also contains tromethamine.<sup>19,20</sup> Millions of individuals are exposed daily to tromethamine in medical and consumer products, including topical emollients, adhesives, coatings, polishes, and drugs such as gadolinium radiocontrast media (RCM) and ketorolac.<sup>34</sup> A single case report describes an individual experiencing a systemic reaction to RCM in whom an IgE-mediated allergy to tromethamine was the presumed trigger.<sup>34</sup> Another case report describes someone reacting to ketorolac and no other NSAIDs, opening the possibility that tromethamine was responsible.<sup>35</sup> However, the risk of anaphylaxis to ketorolac is rare, with only intermittent case reports in the literature.<sup>35-38</sup> Although at least one group suggests prescreening and testing for tromethamine,<sup>39</sup> the risk of adverse systemic reactions to this compound is extremely low. Therefore, those with a suspected history of adverse reactions to tromethamine, including those with a suspected history of systemic allergic reactions to RCM and ketorolac, may receive vaccines containing tromethamine.

6. **In someone with a suspected or confirmed allergy to a SARS-CoV-2 vaccine or one of its components for whom an additional dose is required, choices include deferral of the second vaccine dose, selection of an alternative vaccine with a different platform and excipients, and the administration of the same vaccine using a graded vaccine administration protocol.**

In summary, for a higher-risk patient with a suspected or confirmed severe allergic reaction to a SARS-CoV-2 vaccine or any of its components for whom an additional dose is required, allergy testing to the vaccine or its components is not currently recommended. Reasonable and safe options for consideration as part of shared decision-making include deferral of the second vaccine dose, selection of an alternative vaccine with a different platform and excipients, and the administration of the same vaccine using a graded vaccine administration protocol. For higher-risk patients who are hesitant to proceed with graded vaccine administration, allergy testing remains an option after education that the predictive value of such testing is unknown. Allergy testing for lower-risk patients is NOT recommended and may unnecessarily delay administration of SARS-CoV-2 vaccines. While serologic testing for SARS-CoV-2 antibody titres may become an option in the future as a method to determine whether an individual requires vaccination for SARS-CoV-2, this is not currently recommended, as the best methods and validity of such testing has not yet been established.<sup>40</sup>

Guidance for the cautious graded administration of a vaccine in someone with a confirmed IgE-mediated allergy to that vaccine or one of its components has previously been published: administer 0.05 mL 1:10 dilution, 10%, 20%, 30%, and 40% of the full dose incrementally in alternate arms at 15-minute intervals, followed by a minimum 30-minute observation period [see Table V in the referenced document].<sup>41</sup> Graded administration for adverse vaccine reactions determined not to be due to IgE-mediated allergy to the vaccine or one of its excipients may require an adjustment of this protocol as determined by the responsible physician.

## B. Suggested approach to vaccination in immunocompromised individuals.

- **SARS-CoV-2 vaccines should be offered to immunocompromised patients if the benefit is deemed to outweigh any potential risks of vaccination.**

Immunocompromised individuals are at high risk for severe COVID-19 and should be considered a priority group for intervention that will reduce their risk of this disease.

The Pfizer-BioNTech and Moderna SARS-CoV-2 vaccines are mRNA vaccines, and the AstraZeneca/COVISHIELD and Jansen vaccines are non-replicating adenovirus vector vaccines, and as such are safe for administration in immunocompromised individuals. However, it is not yet known how immunocompromised individuals will tolerate or respond to the SARS-CoV-2 vaccines, as there are no data yet available in these groups.

The CSACI suggests that SARS-CoV-2 vaccines should be offered to immunocompromised patients following a careful risk assessment using a shared decision-making approach if the benefit is deemed to outweigh any potential risks of vaccination. Canada's National Advisory Committee on Immunization (NACI) now also recommends this approach.<sup>16</sup> This may also include prioritizing household contacts of immune compromised individuals for vaccination against SARS-COV-2. This discussion will include considering the best timing of vaccination as

it relates to therapy a patient may be receiving to treat, contribute to, and/or manage their immunocompromised state, such as immunoglobulin administration, biologics and other medications.

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