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Canada

Information for Health Care Providers on Allergies and Anaphylaxis following administration of COVID-19 vaccines

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PROTECTING AND EMPOWERING CANADIANS
TO IMPROVE THEIR HEALTH

Conflicts of interest

- Bryna Warshawsky – no conflicts of interest to declare
- Catherine Dickson– no conflicts of interest to declare
- Joseline Zafack– no conflicts of interest to declare

Objectives

- To outline Canada's vaccine safety system
- To describe allergy related contraindications or precautions to COVID-19 vaccination
- To describe the features and management of anaphylaxis and other acute events following administration of COVID-19 vaccines

Outline

- Overview of safety monitoring infrastructure in Canada
- Anaphylaxis: definition and mechanism
- Experience with mRNA COVID-19 vaccines in Canada
- Experience with mRNA COVID-19 vaccines in the US
- Possible allergens in mRNA COVID-19 vaccines
- Patients screening and management of history of allergy
- Management of anaphylaxis, fainting and local hives

Overview

Safety is a central consideration for any health product.

- Canada's rigorous regulatory system ensures that vaccines are safe, effective and of high quality before they are approved, based on clinical trial results and other data submitted to Health Canada.
- No health product is completely risk-free – post-market vaccine surveillance is required to tell us how vaccines are behaving in the entire population and their real-world impact.

Canada's well-established vaccine surveillance system is a FPT collaboration (e.g., Canadian Immunization Committee, Vaccine Vigilance Working Group) with Health Canada's regulator, vaccine manufacturers, health care providers, researchers, and the public. It monitors:

(1) **Safety –** Does the vaccine cause new, higher frequency or more serious than expected side effects?

(2) **Effectiveness –** How well does the vaccine perform in preventing disease transmission and in reducing illness and death?

(3) **Coverage –** How many people have been vaccinated and what determines the uptake rate (e.g. vaccine hesitancy, cultural and ethnicity considerations)?

Vaccine safety surveillance

rapid detection and action on safety signals

Health Canada – regulator for quality, safety and efficacy; surveillance; legislative and regulatory tools for compliance and enforcement

Public Health Agency of Canada – surveillance; P/T coordination; NACI secretariat

P/Ts – vaccine program delivery, data collection and reporting adverse events following immunization to PHAC

Manufacturers – submit evidence of safety (also efficacy and quality) to support authorization, monitor product safety post-authorization, report serious adverse events to HC within 15 days and summary safety reports on request, notify HC of any changes to product benefit/risk profile

Canada's Vaccine Safety Monitoring System

A system built to detect safety signals, alert public health, investigate thoroughly and respond rapidly.

Adverse events following immunization (AEFI)

Adverse reactions are identified during clinical trials and are expected during immunization campaigns, noting new adverse reactions may only be detected when a vaccine is used in real world conditions.

- Vaccine clinical trials may not include groups with different types or higher risk for adverse reactions than the volunteers studied during clinical trials (e.g. people with chronic medical problems).

Types of Adverse Events

Range from minor reactions (e.g. muscle aches, bruising, mild headache, etc) to **very rare but serious** adverse events (e.g. paralysis, nerve damage).

- An adverse event is a health problem that occurs after vaccination that may or may not be caused by the vaccine – in-depth investigations assess causality.

Post-Market Vaccine Safety Monitoring

HC and PHAC have a well established system to monitor post-market vaccine safety and respond to safety signals in collaboration with provincial and territorial public health authorities.

AEFI – any unfavorable or unintended medical occurrence following immunization, that may or may not have been caused by the vaccine

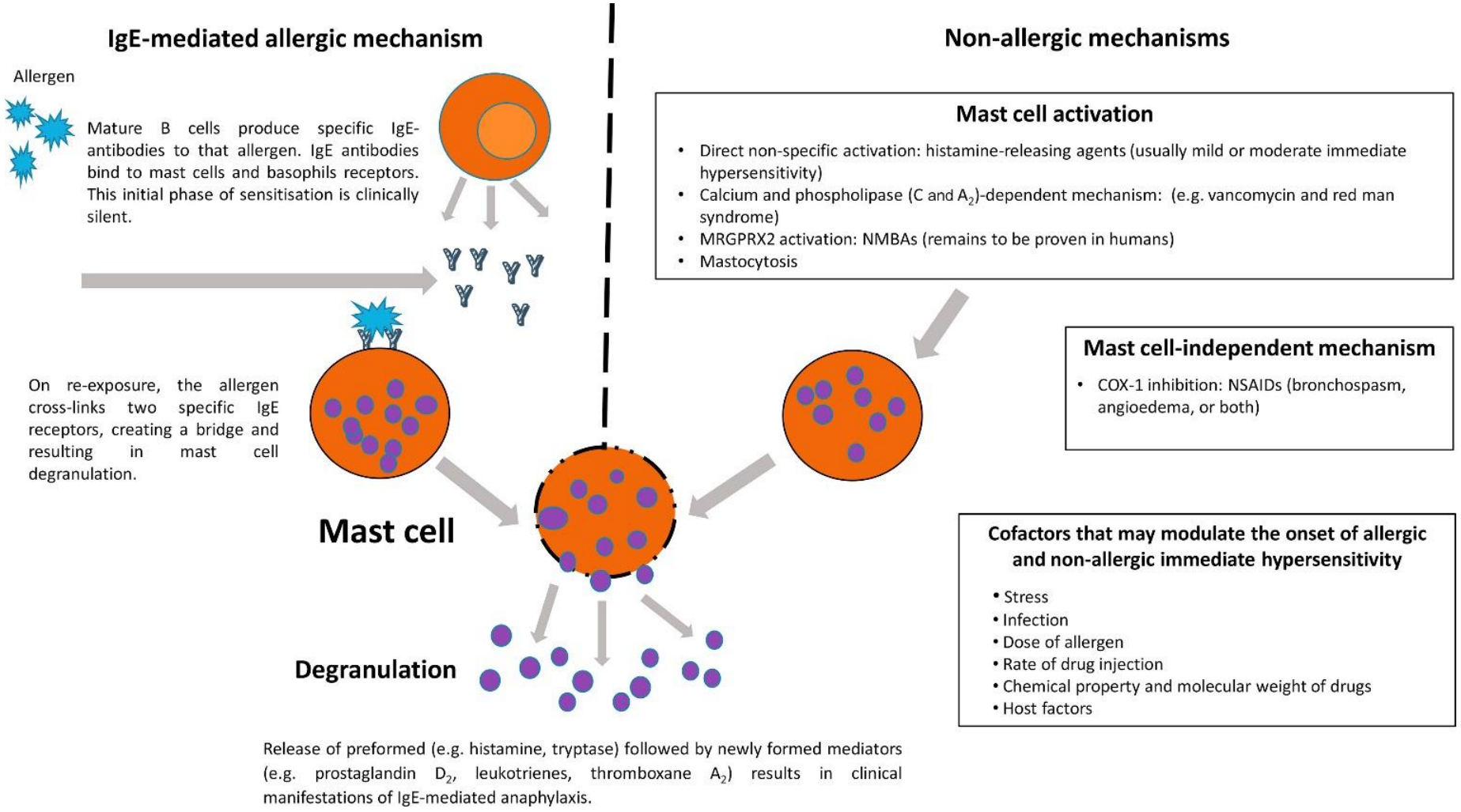
During pandemic H1N1

12.5 million people vaccinated in Canada

5500 AEFIs reported
460 (8%) serious

Transparent vaccine safety monitoring supports public confidence in immunization programs

Mechanisms of anaphylaxis



BJA Education 2019 19313-320DOI: (10.1016/j.bjae.2019.06.002)

Signs and symptoms of anaphylaxis

- Sudden onset
- Rapid progression
- ≥ 2 body systems involved

System	Signs and symptoms
General/CNS	Fussiness, irritability, drowsiness, lethargy, reduced level of consciousness, somnolence
Skin	Urticaria, pruritus, angioedema, flushing
Upper airway	Stridor, hoarseness, oropharyngeal or laryngeal edema, uvular edema, swollen lips/tongue, sneezing, rhinorrhea, upper airway obstruction
Lower airway	Coughing, dyspnea, bronchospasm, tachypnea, respiratory arrest
Cardiovascular	Tachycardia, hypotension, dizziness, syncope, arrhythmias, diaphoresis, pallor, cyanosis, cardiac arrest
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal pain

Reproduced with permission from: Cheng A; Canadian Paediatric Society, Acute Care Committee. Emergency treatment of anaphylaxis in infants and children. Paediatr Child Health 2011;16(1):35-40. Reaffirmed February 2018.

Assessment of anaphylaxis cases

- Anaphylaxis cases that are reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) undergo medical case review and the diagnostic certainty is assessed using the Brighton Collaboration case definition.

ANAPHYLAXIS *(Vaccine 2007; 25:5675-84)*

Table 1	A. COURSE OF ILLNESS ☐ SUDDEN ONSET OF SIGNS AND SYMPTOMS ☐ RAPID PROGRESSION OF SIGNS AND SYMPTOMS	
	B. MAJOR CRITERIA	**C. MINOR CRITERIA**
SKIN	☐ Generalized urticaria (hives) ☐ Generalized erythema ☐ *Angioedema (general or localized) ☐ Generalized pruritus WITH skin rash	☐ Injection site urticaria ☐ Red AND itchy eyes ☐ Generalized prickle sensation ☐ Generalized pruritus WITHOUT skin rash
RESP	☐ Bilateral wheeze (by stethoscope) ☐ Stridor ☐ ≥ 2 indicators of respiratory distress: ○ Tachypnea ○ Cyanosis ○ Grunting ○ Chest wall retractions ○ ↑ use of accessory muscles	☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat closure ☐ Sneezing OR rhinorrhea ☐ Difficulty breathing WITHOUT wheeze or stridor
CV	☐ Documented hypotension ☐ ≥3 signs of uncompensated shock ○ Tachycardia ○ Capillary refill >3 seconds ○ Reduced central pulse volume ○ ↓ level or loss of consciousness ☐ Documented MD diagnosis of shock	☐ ≥2 signs of reduced peripheral circulation ○ Tachycardia ○ Capillary refill >3 seconds ○ ↓ level or loss of consciousness
GI		☐ Nausea ☐ Vomiting ☐ Abdominal pain ☐ Diarrhea
LAB		☐ Elevated mast cell tryptase

Other terms:
☐Bilateral red eyes
☐Sore throat
☐Difficulty swallowing
☐Chest tightness
☐Rash -generalized
☐Rash – localized at non-injection site
☐Pallor
☐Dizzy
☐Metallic taste
☐Other (specify)

Other relevant info: Medical History: ☐ Chronic disease ☐ Allergy ☐ Concomitant med(s)
Treatment at immunization clinic: ☐ Epinephrine ☐ Benadryl ☐ Other _____
Emergency room: Yes No If yes: ☐ Epinephrine ☐ Benadryl ☐ Other _____
Hospitalized: Yes No **Outcome:** ☐ Fully Recovered ☐ Not yet recovered ☐ Fatal

Assessment of anaphylaxis cases

- Levels I to III are considered anaphylaxis cases.
- Levels IV and V are not considered cases of anaphylaxis

Levelling Tool: Check all that apply; level=highest row in table with all boxes checked

Level	≥1 SKIN	≥1 RESP	≥1 CV	Additional Criteria needed to Meet Level II or III
I	☐ MAJOR	☐ MAJOR	☐ MAJOR	
	☐ MAJOR	☐ MAJOR		
	☐ MAJOR		☐ MAJOR	
II		☐ MAJOR	☐ MAJOR	
		☐ MAJOR		☐ ≥1 minor from skin, cardiovascular, gastrointestinal or lab
			☐ MAJOR	☐ ≥ 1 minor skin, respiratory, gastrointestinal or lab
	☐ MAJOR	☐ Minor		
	☐ MAJOR		☐ Minor	
III		☐ Minor		☐ ≥ 1 minor criterion from at least 2 different systems __skin* cardiovascular gastrointestinal lab
			☐ Minor	☐ ≥ 1 minor criterion from at least 2 different systems __skin* respiratory gastrointestinal lab
IV	**Reported anaphylaxis with insufficient evidence to meet case definition levels 1,2or3**			
V	**Not a case of anaphylaxis**			

- For level III, a skin MAJOR can count as a minor criterion

Anaphylaxis AEFI reports

- As of January 28, 2021 there were 45 AEFI reports of anaphylaxis submitted to CAEFISS and 915,231 doses administered. This represents a reporting rate of 4.92 per 100,000 doses administered.

- Background rate for anaphylaxis in Canada excluding Quebec, is 8.4 cases per 100,000 people; 95% CI: 8.07-8.74

Data source: Discharge Abstract Database and National Ambulatory Care Reporting System, Canadian Institute for Health Information, fiscal years 2018-2019

Disclaimer for background rate calculations:

- Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.
- The numerator data is from the Discharge Abstract Database (DAD) (acute and non-acute) and the National Ambulatory Care Reporting System (NACRS) with the population estimates from Statistics Canada as the denominator. These rates also allow one individual to contribute more than one event per year.
- Does not include data from Quebec
- Cases of anaphylaxis were identified using **all ICD-10CA codes related to anaphylaxis**

Anaphylaxis following Pfizer-BioNTech COVID-19 vaccine

- One case of anaphylaxis in clinical trials
- US: 50 cases of anaphylaxis (5.0 per million doses administered)*
- Interval between vaccination and onset of symptoms*:
  - 74% within 15 minutes
  - 16% within 15 to 30 minutes
  - 10% after 30 minutes
- 80% had a documented history of allergies; (24%) had previous anaphylaxis*
- Follow-up (based on 21 patients)**
  - 19% hospitalized
  - 81% treated in emergency department
  - Of 20 with known outcome, all recovered

*https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf
**https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm

Anaphylaxis following Moderna COVID-19 vaccine

- No anaphylaxis in clinical trials
- US: 21 cases of anaphylaxis (2.8 per million doses administered)*
- Interval between vaccination and onset of symptoms*:
  - 86% within 15 minutes
  - 4% within 15 to 30 minutes
  - 10% after 30 minutes
- 86% had a documented history of allergy; 24% had previous history of anaphylaxis*
- Follow-up information (based on 10 patients)**
  - 60% hospitalized (5 ICU, 4 intubated)
  - 40% treated in emergency department
  - Of 8 with known outcome, all recovered

*https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf
**https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm

Authorized COVID-19 vaccines

Pfizer-BioNTech	Moderna
• nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	• nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
• 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide • 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) • cholesterol • ALC-0315 • potassium chloride • monobasic potassium phosphate • sodium chloride • dibasic sodium phosphate dehydrate • sucrose	• polyethylene glycol (PEG) 2000 DMG • 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) • cholesterol • lipid SM-102 • tromethamine • tromethamine hydrochloride • acetic acid • sodium acetate • sucrose

Authorized COVID-19 vaccines

Pfizer-BioNTech	Moderna
• nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	• nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
• 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide • 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) • cholesterol • ALC-0315 • potassium chloride • monobasic potassium phosphate • sodium chloride • dibasic sodium phosphate dehydrate • sucrose	• polyethylene glycol (PEG) 2000 DMG • 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) • cholesterol • lipid SM-102 • tromethamine • tromethamine hydrochloride • acetic acid • sodium acetate • sucrose

Polyethylene glycol (PEG)

- Component in several products
  - mRNA COVID-19 vaccines (Pfizer-BioNTech, Moderna)
  - Osmotic laxatives and oral bowel preparations for colonoscopy procedures
  - Excipient in medications
- Rare cause of IgE-mediated reactions
  - patients who have undergone treatment with PEGylated therapeutics can develop antiPEG antibodies
  - PEG-associated anaphylaxis during colonoscopy preparation or laxative use: ~ 4 cases per year in the US
- Potential cross-reactive hypersensitivity between PEG and polysorbates

Stone CA, et al., DOI:10.1016/j.jaip.2018.12.003
Zhou et al, doi: 10.1016/j.jaip.2020.11.011

Tromethamine (trometamol or tris)

- Component in several products
  - Vaccines (e.g. Moderna COVID-19 vaccine, Act-HiB, Nimenrix)
  - Contrast agents, oral/parenteral medications
- Rare cause of IgE-mediated reactions
  - One case report of anaphylaxis to trometamol (in gadolinium based contrast agents, GBCA)

CIG, Contents of Immunizing Agents Available for Use in Canada
Lukwaska et al, DOI: 10.1016/j.jaip.2018.08.035

Pre-vaccination screening (contraindications)

An authorized COVID-19 vaccines should not be offered routinely to:

- Individuals with a history of severe allergic reaction (e.g. anaphylaxis) after previous administration of either of the authorized COVID-19 vaccines.

- Individuals with a proven severe allergic reaction (e.g. anaphylaxis) to any component of the specific COVID-19 vaccine or its container. For a comprehensive list of components in each authorized COVID-19 vaccine and its container, please consult the corresponding product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database.

Subject to change

Pre-vaccination screening (precautions)

- Individuals with mild to moderate immediate allergic reactions after a previous dose of either mRNA COVID-19 vaccines

  - assessment by a physician or a nurse with expertise in immunization may be warranted prior to re-vaccination
  - 30 minutes of observation post-vaccination, if re-vaccination is chosen

- Individuals with proven severe allergic reaction (e.g. anaphylaxis) to injectable therapy not related to a component of a COVID-19 vaccine

  - do not need to be assessed
  - 30 minutes of observation post-vaccination

Subject to change

Not a contraindication nor a precaution

- Individuals with a history of allergy not related to a component of a COVID-19 vaccine or other injectable therapy (e.g. foods, drugs, insect venom or environmental allergens)
  - can receive the COVID-19 vaccines without any special precautions
  - 15 minutes of observation post-vaccination

- All patients should be instructed to seek medical care if they develop signs or symptoms of an allergic reaction after their observation period ends and they have left the immunization clinic/venue

Subject to change

Had a serious or allergic reaction to a previous dose of COVID-19 vaccine	• A **known severe allergic reaction (e.g., anaphylaxis)** to a past dose of mRNA COVID-19 vaccine is a contraindication to another dose of either mRNA COVID-19 vaccines. • Health care provider assessment, with referral as appropriate, is recommended for individuals with **less severe allergic reactions** that occurred within 4 hours following a previous dose of mRNA COVID-19 vaccine. If the vaccine is given, the individual should be observed for 30 minutes after vaccination.
Allergic to polyethylene glycol (PEG)	• A **known severe allergy (e.g., anaphylaxis) to PEG** is a contraindication to mRNA COVID-19 vaccination. • Health care provider assessment, with referral as appropriate, is recommended for individuals with **less severe PEG allergy.** If the vaccine is given, the individual should be observed for 30 minutes after vaccination.
Allergic to tromethamine (trometamol, Tris)	People who are **allergic to tromethamine** can be given the Pfizer-BioNTech vaccine which does not contain tromethamine.
Past allergic reaction to another (non-COVID-19) vaccine or other medication given by injection or intravenously	Individuals with **past allergic reactions to vaccines or medications given by injection or intravenously** (other than as referred to above) should be observed for 30 minutes after receiving an mRNA COVID-19 vaccination.
Past allergy but NOT RELATED to any of the above	Individuals with **past allergic reactions NOT RELATED to mRNA COVID-19 vaccines or its components or other injectable vaccines or therapies** (e.g., allergic to foods, oral drugs without PEG or tromethamine, insect venom, pets or environmental allergens) can receive the mRNA COVID-19 vaccines without any special precautions. Individuals should be observed for a minimum of 15 minutes following vaccination.

Distinguishing anaphylaxis and other events

- Vasovagal syncope (fainting)
- Breath-holding, hyperventilation

Clinical features	Anaphylaxis	Vasovagal syncope
Onset from time of immunization	Within minutes up to 4 hours after injection; most within 2 hours	During or within minutes of injection
Skin	Urticaria, angioedema, pruritus, erythema	Generalized pallor, cold clammy skin
Respiratory	Cough, wheeze, stridor, respiratory distress, rhinorrhea, sneezing	Normal respiration – may be shallow but not laboured
Cardiac	Tachycardia	Bradycardia
Neurologic	Sense of severe anxiety and distress; loss of consciousness – no improvement once supine or in head down position	Sense of light-headedness; loss of consciousness – improves once supine or in head down position; may be transient jerking of the limbs and eye-rolling

Adapted with permission from: Immunisation Section, South Australian Department for Health and Wellbeing.

Fainting

- **Cause:**
  - Anxiety, stress or pain leads to low pulse and blood pressure and subsequent lack of blood flow to the brain
- **Prevention:**
  - Ask clients if they have ever fainted during or after a vaccine or medical procedure
  - Observe for signs of being overly anxious, pale or sweating
  - If any of the above, vaccinate lying down
- **Management:**
  - Lie down on back, turn on side if going to vomit or if pregnant (left side)
  - Raise legs
  - Will come around within a minute or two
  - Continue to monitor until feeling much improved
    - Can offer juice and/or food when better
    - Have someone drive them home

Management of anaphylaxis (kit)

Recommended items	Essential	Optional
Laminated documents	• Clear, concise summary of emergency management protocol • EPINEPHrine dosage by weight and age	N/A
Drugs	EPINEPHrine three vials - 1:1000 (1 mg/mL) solution for IM injection	N/A
Injection supplies	• Two 1 cc syringes with attached 25 gauge needle (one - 1 inch; one 5/8 inch) • Three extra 25 gauge needles of each different size: 5/8 inch, 1 or 1.25 inch, 1.5 inch	EPINEPHrine autoinjectors labelled by age and weight
Other	• Scissors • Alcohol swabs • Tongue depressors • Pocket mask • Wristwatch with second hand (for heart rate) • Ready access to a phone to call emergency services • Flashlight	• 1 nasopharyngeal, 1 oropharyngeal airway for each age range anticipated in the clinic • Oxygen and related equipment • IV lines, fluids and related equipment • Stethoscope • Sphygmomanometer

CIG, Anaphylaxis and other Acute Reactions following Vaccination.

Management of anaphylaxis in a community setting

1. **Direct someone to call 911** (where available) **or emergency medical services**.
2. **Assess** airway, breathing, circulation, mental status, skin, and body weight (mass).
3. **Place** individual on his/her back (supine) and elevate lower extremities.
   Exceptions to the supine position:
   - if in respiratory distress, place in a position of comfort (elevate head and chest)
   - if vomiting or unconscious, place lying on his/her side
   - if pregnant, place lying on their left side
4. **Inject EPINEPHrine**:
   - Dose: 0.01 mg/kg body weight of 1:1000 (1 mg/mL) solution, MAX 0.5 mg (see CIG, Table 4 for dosage by age or weight)
   - Route: IM in mid-anterolateral thigh (*vastus lateralis* muscle)
   - Repeat every 5 minutes if symptoms persist (most patients improve in 1-2 doses)
   - Record the time of each dose
5. **Stabilize and monitor** patient
6. **Transfer to hospital** for observation

Management of hives at the injection site

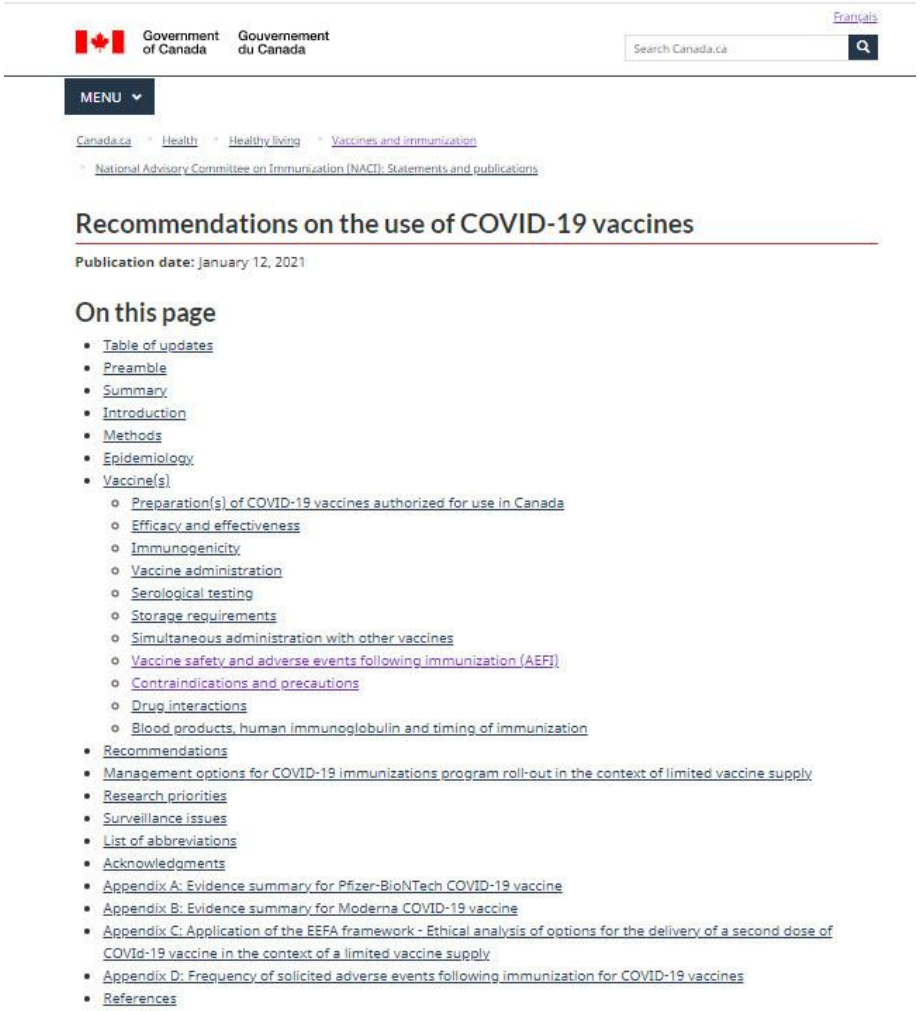
- Itchy, swollen bumps at the injection site
- Observe for 30 minutes to ensure the hives remain localized
- Can apply ice to the injection site
- If hives disappear and no evidence of spread to other parts of the body and no other symptoms within 30 minutes of vaccination, no further observation needed
- Manage as anaphylaxis if:
  - Any other symptoms arise, even if mild (e.g., sneezing, nasal congestion, tearing, coughing, facial flushing); OR
  - Progression of hives or swelling of the body

Key messages

- Anaphylaxis following mRNA COVID-19 vaccines appears to be more frequent than with other vaccines but is still rare
- Most anaphylactic reactions occur within 15 minutes to 30 minutes after vaccination
- Cause of allergic reaction is not clear; asking about possible allergens can support client management
- Anaphylaxis is a manageable medical emergency
  - Equipment, protocols and training help to ensure good outcomes

NACI Statement on COVID-19 Vaccines

- Refer to NACI recommendations on the use of COVID-19 vaccines for guidance on COVID-19 vaccines.



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> National Advisory Committee on Immunization (NACI): Statements and publications

Recommendations on the use of COVID-19 vaccines

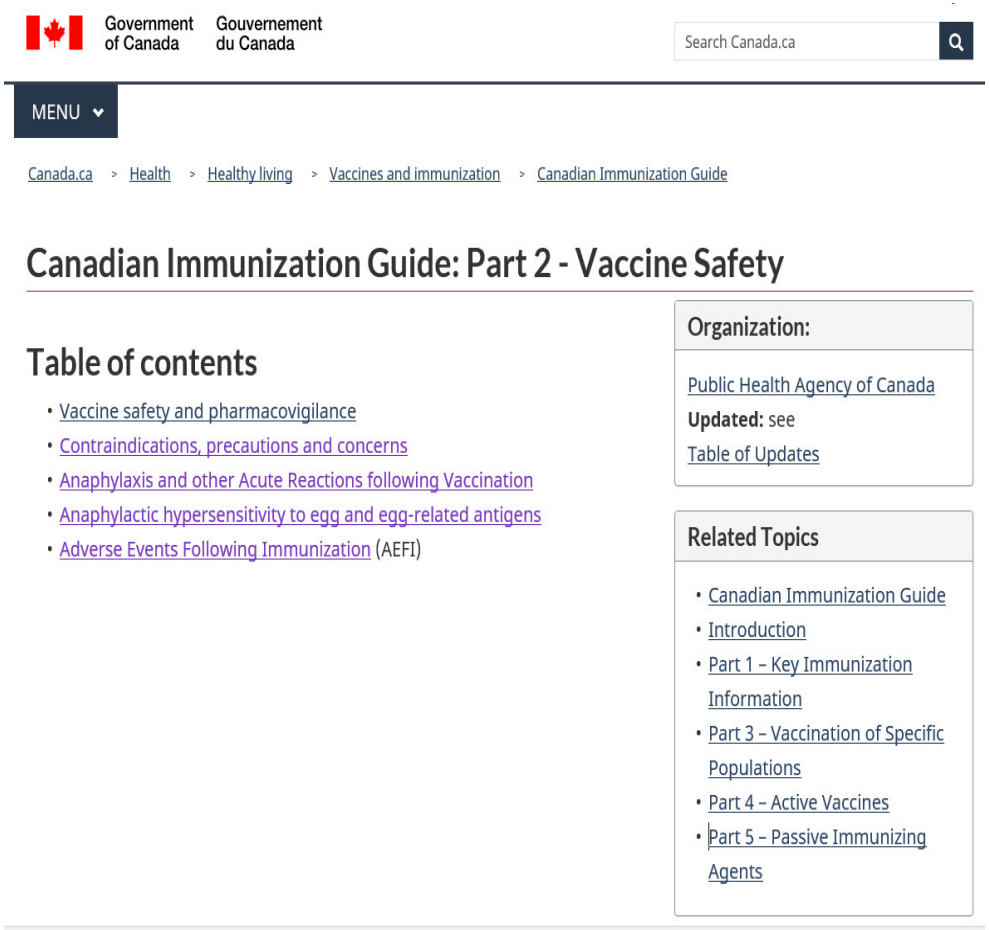
Publication date: January 12, 2021

On this page

Canadian Immunization Guide

- Refer to Part 2 - Vaccine Safety in the Canadian Immunization Guide (CIG) for definitions of AEFIs and additional general information.

- Guidance on anaphylaxis can be found in the chapter Anaphylaxis and other Acute Reactions following Vaccination.



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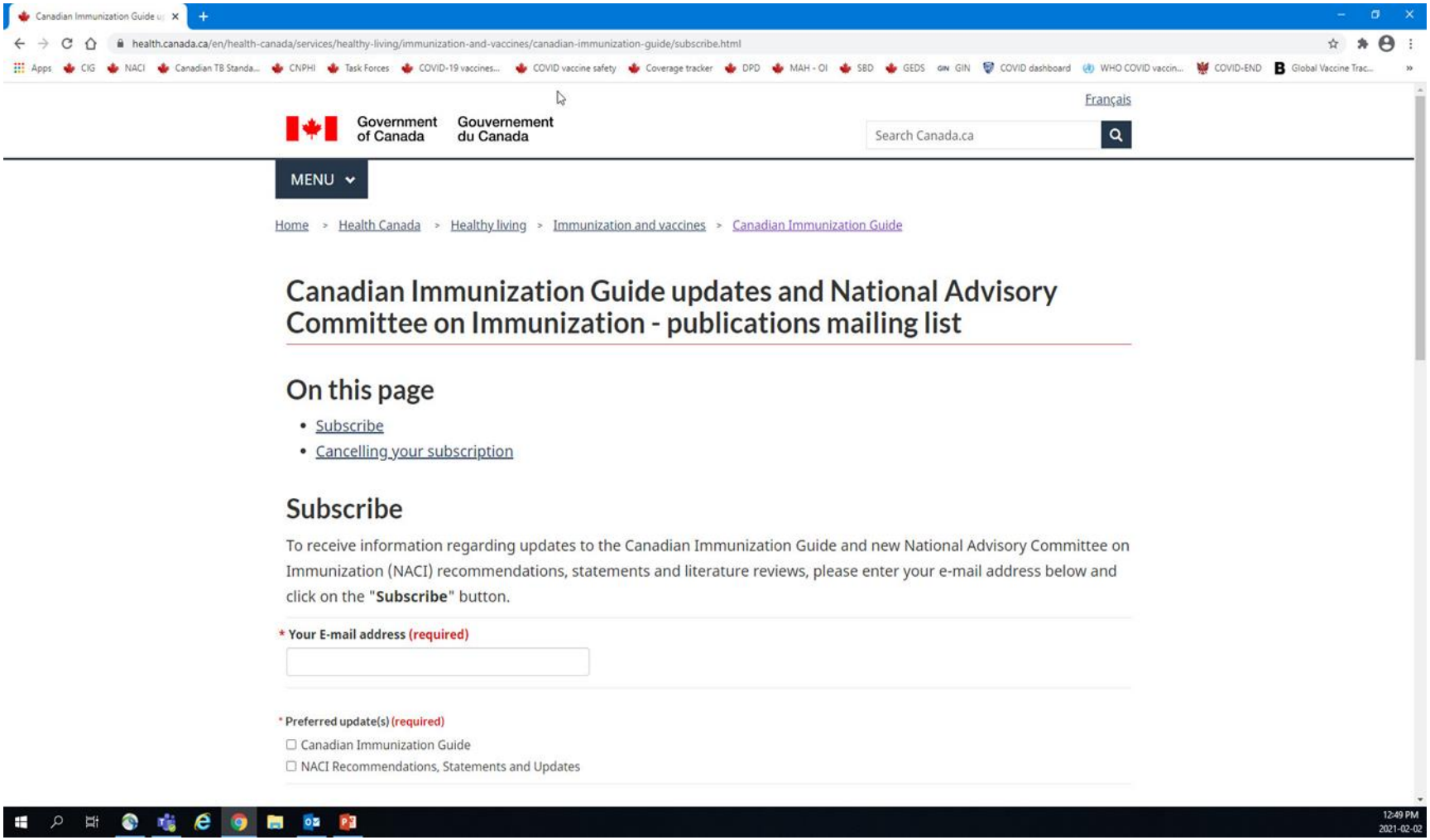

Additional resources

- How to report an AEFI: Reporting Adverse Events Following Immunization (AEFI) in Canada
- Submission of AEFI reports: User guide to completion and submission of the AEFI reports

Acknowledgements

- PHAC Vaccine Safety Section
- National Advisory Committee on Immunization (NACI)
- NACI Vaccine Safety Working Group

Supplementary slides

How AEFIs are detected

Safety signal detection – a shared responsibility between Health Canada, the Public Health Agency of Canada, vaccine manufacturers and the provinces and territories who administer vaccination programs

Safety signal sources

- Signal notification from a province or territory
- HC's Canada Vigilance Database (**CVD**) and PHAC's Canadian Adverse Events Following Immunization Surveillance System (**CAEFISS**) (weekly)
- International safety notification
- Safety notification from other regulatory agencies
- Safety notification from manufacturer
- Safety summary report from manufacturer
- Published literature review (weekly)
- Media reports

Ongoing review by Health Canada and Public Health Agency

What we look for

- New, unusual, or rare adverse events following immunization (AEFI)
- increase in AEFI reporting for special events of interest, known and potential AEFIs
- Potential issues with specific vaccine lots
- Potential risk factors related to vaccines
- Potential interactions with other treatments or vaccines
- Unexpected or unusual patterns in the AEFIs reported

How AEFIs are investigated