Ontario Health
Cancer Care Ontario

The COVID-19 Vaccine and Cancer: FREQUENTLY ASKED QUESTIONS

The following are frequently asked questions about the COVID-19 vaccine and adult cancer patients. The information is:

- related to the Pfizer (Comirnaty™)and the Moderna (Spikevax™) COVID-19 vaccines that use mRNA technology
- related to the AstraZeneca COVID-19* (Vaxzevria™) vaccine that uses non-replicating viral vectors (adenovirus)
- current as of August 8, 2022

The information below may not be appropriate for all patients. Prescribers must determine whether adopting suggested COVID-19 vaccine information is clinically appropriate for individual patients through a risk-benefit assessment. Consult appropriate clinical prescribing guidelines and local institutional guidance for patient prioritization to inform treatment and vaccination decisions.

Everyone should receive a COVID-19 vaccination, when available, unless contraindicated. See question 2 "What are the contraindications to the COVID-19 vaccines?" for more information. There are limitations to the current knowledge around the use of COVID-19 vaccines in the cancer population. The advice below is based on the best available evidence at this time. Guidance will be updated as more evidence becomes available.

Patients should continue to practice recommended public health measures for prevention of COVID-19 infection regardless of vaccination status.

** Note that COVISHIELD (manufactured by Serum Institute of India) and the AstraZeneca COVID-19 vaccine (manufactured by AstraZeneca) are ChAdOx1-S recombinant vaccines developed by AstraZeneca and the University of Oxford. Health Canada has reviewed the manufacturing information for these vaccines and found them to be comparable.*

1. Are COVID-19 vaccines safe for cancer patients?

COVID-19 vaccines use either conventional or novel mechanisms of action to safely elicit immune responses. Conventional platforms include recombinant viral proteins, live attenuated vaccines and inactivated vaccines, while novel methods include viral vector-based vaccines and mRNA-based vaccines.[8]

The COVID-19 vaccine is safe for use in cancer patients. Studies demonstrate the safety profile of mRNA vaccines in the immunocompromised population, including patients with cancer, are comparable to what has been observed in the general population, with no unexpected or serious safety signals to date.[17, 20] Additionally, prior experience with other protein-based or inactivated vaccines have not reported unique or major side effects in immunocompromised patients.[7] The most frequently reported side effects of COVID-19 vaccine candidates were usually mild or moderate and include pain at the site of injection, fatigue, headache, myalgias and fever (see question 9 below). Live attenuated vaccines carry the risk of disease caused by vaccine strains and are not recommended during and after immunosuppressive therapy (such as chemotherapy).[3]

Currently, these are the vaccines available* for use in Ontario for active immunizations to prevent COVID-19:

- Pfizer COVID-19 mRNA vaccine (BNT162b2 or Comirnaty™)
- Moderna COVID-19 mRNA vaccine (mRNA-1273 SARS-CoV-2 or Spikevax™)
- AstraZeneca COVID-19 non-replicating adenovirus vaccine (AZD1222 or ChAdOx1-S recombinant or Vaxzevria™)

* Other vaccines (e.g. Janssen, Novavax, Medicago) may also be available in limited supplies. Refer to the latest Ministry of Health guidance for the most up to date information as new vaccines become available.

The Pfizer, Modena and AstraZeneca vaccines are administered intramuscularly as a series of two doses. The recommended immunization schedules of the 2-dose COVID-19 vaccines are listed in Table 1.
Additional dose(s) of an authorized mRNA COVID-19 vaccine are recommended in certain populations. [18,19]

For details on a three-dose primary series of COVID-19 vaccine and booster doses, see question 7: Should additional doses of COVID-19 vaccine be considered in patients with cancer?

Table 1: Recommended Immunization Schedule of 2-dose COVID-19 Vaccines[1,4,5,6,12]

Vaccine product (manufacturer)	Clinical trial interval	Minimum interval	Manufacturer authorized interval[a]
Pfizer COVID-19	19-23 days	19 days	21 days
Moderna COVID-19	21-42 days	21 days	28 days
AstraZeneca COVID-19	3-26 weeks	4 weeks	4 to 12 weeks[b]

[a]While efforts should be made to vaccinate according to the authorized schedules as per individual vaccine product monographs or local public health guidelines, extended vaccination intervals may not be appropriate in certain patient populations, as described below.[13, 15]
[b]A 12-week interval is preferred for the AstraZeneca COVID-19 vaccine based on available ad hoc analyses of the vaccine clinical trial interval data; efficacy may be lower if interval is less than 12 weeks, in the general population.

The following patient groups should receive the COVID-19 vaccine at the dose interval recommended by the manufacturers:[15]

- Transplant recipients (including solid organ transplants and hematopoietic stem cell transplants).
- Patients receiving active treatment (chemotherapy, targeted therapies, immunotherapy, excluding individuals receiving solely hormonal therapy or radiation therapy) with:
    - Malignant hematologic disorders
    - Non-hematologic malignant solid tumors

Refer to the latest NACI and Ministry of Health recommendations on the use, dosing interval and interchangeability of approved COVID-19 vaccines.

Both the Moderna and Pfizer vaccines use COVID-19's genetic code in the vaccine, exploiting the host cell to translate the code and make the target spike protein, eliciting both neutralizing antibody and cellular immune responses.[4] The AstraZeneca COVID-19 vaccine uses replication deficient adenovirus vectors, to

deliver the COVID-19 spike protein genetic sequence into the host cell, locally stimulating neutralizing antibody and cellular immune responses.[11,12, 14] As there is no whole, live or replicating virus involved, the vaccines cannot cause disease and, therefore, may be administered to cancer patients after a risk-benefit assessment by the cancer health care team. It is important to note that immunocompromised persons, including individuals receiving immunosuppressant therapy, may not produce a full antibody response and should therefore continue to follow Public Health guidance to avoid exposure, unless otherwise advised by their health care team.[10]

Please see Appendix for a complete list of references.

2. What are the contraindications to the COVID-19 vaccines?

The Pfizer, Moderna and AstraZeneca COVID-19 vaccines are contraindicated in individuals who are hypersensitive to the active substance or to any ingredient in the formulation.[1,2,3,4]

The AstraZeneca vaccine is contraindicated in patients who have experienced major venous and/or arterial thrombosis with thrombocytopenia after vaccination with AstraZeneca COVID-19 vaccine. It is also contraindicated in those who have previously experienced episodes of capillary leak syndrome (CLS) as some fatal cases have been observed very rarely following administration of the AstraZeneca vaccine.[3]

Refer to the product monographs for the complete description of contraindications.

Please see Appendix for a complete list of references.

3. Which patient factors require further consideration before giving a COVID-19 vaccine?

Patients with a history of severe allergy (e.g., anaphylaxis) to the COVID-19 vaccine or any of its components, including PEG, polysorbate or tromethamine should be referred to an allergist, other appropriate physician or nurse practitioner to determine if and how the vaccine can be safely administered.[1,5] See question 10: "Can a cancer patient receive the COVID-19 vaccine if they have allergies?" for more information.

Patients who have experienced a previous cerebral venous sinus thrombosis (CVST) with thrombocytopenia or heparin induced thrombocytopenia (HIT) should only receive the adenovirus-based vaccine if the potential benefits outweigh the potential risks. [2,3] A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with adenovirus-based vaccines. In patients with a history of immune thrombocytopenia (ITP), the risks of developing low platelet levels should be considered before vaccination with adenovirus-based vaccines.[2, 3] See question 9: "What are possible side effects of the vaccination?" for more information.

Patients who have experienced major venous and/or arterial thrombosis with thrombocytopenia following vaccination with the AstraZeneca COVID-19 vaccine should not receive a second dose of the AstraZeneca COVID-19 vaccine. [2, 4]

Please see Appendix for a complete list of references.

4. Which cancer patients are at a higher risk of becoming infected with COVID-19 and/or having severe complications with COVID-19?

Cancer patients have a higher risk of contracting COVID-19 and some cancer patients are at higher risk for poorer outcomes with the infection. The following patients are at a higher risk:

- Patients with **hematological cancers**
- Patients with **lung cancer**
- Patients who were **diagnosed with cancer within the last year**
- **Patients who have had a stem cell transplant within the last 6 months**
- Patients with **active cancer**, defined as:
    - **metastatic disease** and/or
    - receiving or recently completed cancer-directed **systemic treatment, radiation therapy**, or **surgical resection**

Also consider the following patient factors when determining risk:

1. **Time since diagnosis:**
   Patients with a recent diagnosis (within the last year) especially those with a hematologic malignancy have an increased risk of mortality with COVID-19 compared to those with a less recent diagnosis. Patients with a diagnosis 1 to 5 years prior have a higher risk of mortality than patients with a diagnosis beyond 5 years. Patients with hematologic malignancy or following allogeneic stem cell transplant may remain at high risk of infection and mortality even beyond 5 years, as they are often on a prolonged course of treatment or have ongoing significant immunosuppression.

2. **Cancer type:**
   In general, patients with hematologic cancers who are at any stage of treatment (especially those ≥ 60 years of age) and patients with lung cancer have a higher risk of mortality compared to patients with other cancer diagnoses.

3. **Treatment type:**
   There is some evidence to suggest that patients who are currently or recently (within the last 6 months) treated with immune checkpoint inhibitors are at a higher risk of mortality; however, the population-based data are likely to be influenced by a number of confounding factors. A retrospective study of adult patients with lymphoma identified an association with prolonged hospitalization due to symptoms and a higher risk of death from COVID-19 in patients who were recently treated (within 12 months) with anti-CD20 therapy. Other studies were unable to demonstrate whether systemic treatment types (such as chemotherapy and targeted therapy) increase the risk of mortality from COVID-19. In a population-based study, however, patients with active cancer, particularly those on active treatment, were associated with higher rates of hospitalization, ICU admission, and 30-day mortality. In addition, patients on active treatment may be at an increased risk of neutropenia and development of infections. Patients who have had a stem cell transplant within the last 6 months are also considered to be higher risk.

4. **Other factors:**
   (a) Older patients (≥ 65) are at higher risk of mortality compared with younger patients.
   (b) Patients who have recently had neutropenia (within 90 days) and patients with lymphopenia at time of COVID-19 diagnosis are at a higher risk of mortality.

(c) Patients who smoke or have other comorbidities, including obesity, may be at risk for increased hospitalizations and mortality. Follow local public health advice to determine risk based on non-cancer related factors.
(d) Consideration of COVID-19 vaccination should be given to household or close contacts of cancer patients at higher risk of infection/mortality (based on public health guidance) to reduce the risk of exposure to the virus.

Rationale:

Current available data suggest that COVID-19 mortality is higher in patients with cancer than in the general population.[1,2,3,4,5,14,15] A pooled analysis of 18,650 found the probability of death to be 25.6% in patients with both a COVID-19 and cancer diagnosis.[3] A multivariate analysis of over 10,000 COVID-19 deaths from the UK found that, relative to patients without cancer, patients with nonhematologic malignancy diagnosed within one year prior to a COVID-19 diagnosis had a 1.8-fold higher risk of death, and a hematologic malignancy carried a fourfold higher risk.[5] The risks were lower for patients diagnosed with cancer 1 to 4.9 years prior to COVID-19 when compared those diagnosed within the preceding year; however, risk was still elevated compared with people without cancer. Beyond five years, risks for death remained elevated for those with hematologic but not for those with nonhematologic malignancies.[5]

Most studies show a higher risk of mortality among patients with hematologic and lung cancers.[1,6,7,16] A small Chinese study suggested that lung cancer, metastatic disease, and hematologic malignancy may be associated with higher rates of COVID-19–related death and intensive care unit (ICU) admission.[6] A larger study of 309 cancer patients with a diagnosis of COVID-19 found that hematologic malignancies were associated with increased COVID-19 severity and patients with lung cancer demonstrated higher rates of severe or critical COVID-19 events.[1]
Adults with hematologic cancers are reported to be at high risk for progression to severe disease and death from COVID-19, with an estimated mortality of 36% or greater.[19]

An analysis of 536 Italian patients with hematologic malignancy and COVID-19 found that mortality was significantly higher than in the general Italian population with COVID-19, regardless of age.[7] A large meta-analysis found the risk of death among adults with hematologic malignancies (n = 3240) was 34 percent, and patients ≥60 years of age had a significantly greater risk of dying than did younger patients (relative risk [RR] 1.82, 95% CI 1.45-2.27).[8]

A multi-institutional international registry study including 400 patients with thoracic cancer also diagnosed with COVID-19 showed that many patients were hospitalized (78%), and 36 percent of patients died.[9,10] Patients who had received chemotherapy within three months had a higher risk of dying from COVID versus patients who did not (hazard ratio 1.7, 95% CI 1.1-2.6); however, in univariate analysis, there were no factors that were identified, including active cancer treatment, as being associated with mortality.[10]

Recent active oncologic therapy did not appear to increase the risk of mortality from COVID-19 in some studies. Jee et al reported that cytotoxic chemotherapy was not significantly associated with a severe or critical COVID-19 event and a systemic review indicated that there was no association between receipt of a particular type of oncologic therapy and mortality.[4] Patients on active immunosuppressive therapy (such as chemotherapy) are, however, more likely to be neutropenic and are at a high risk of developing infection.[12] Robilotti et al analysed 423 patients with cancer and COVID-19 and found that age older than 65 years and treatment with immune checkpoint inhibitors (ICIs) were predictors for hospitalization and severe disease, whereas receipt of chemotherapy and major surgery were not. In this study, treatment with ICI predicted

both hospitalization and severe disease, although there was considerable heterogeneity in ICI-treated tumor types, and disease-specific factors could not be individually addressed.[11] A more recent retrospective study looked at adult lymphoma patients (n=111) who were admitted to hospital for COVID-19. The median length of admission was 14 days (range,1–235) and the 6-month overall survival was 69%. In multivariable analyses, recent administration of anti-CD20 therapy (within 12 months) was associated with prolonged hospitalization (sub-distribution hazard ratio 2.26, 95% confidence interval 1.42–3.6, p < 0.001) and higher risk of death (hazard ratio 2.17, 95% confidence interval 1.04–4.52, p = 0.039). An age ≥70 years and relapsed/refractory lymphoma were also associated with prolonged hospitalization and decreased overall survival.[21]

Garassino reviewed evidence around ICIs and COVID outcomes, which included further analysis of the Robilotti data. It was concluded that there is insufficient evidence at this time to suggest that ICIs worsen complications from COVID-19 and that the population-based registries reporting on the incidence of COVID-19 in patients with cancer receiving ICI therapy compared with patients with cancer not receiving ICI or individuals without cancer, are likely to be plagued by multiple confounding factors.

A recent population-based study with 323 patients enrolled prior to the pandemic (n=67 cancer patients; n= 256 non-cancer patients) compared COVID-19 outcomes. After adjusting for demographics, smoking status, and comorbidities, a diagnosis of cancer was independently associated with higher odds of hospitalization (odds ratio = 2.16, 95% confidence interval = 1.12 to 4.18) and 30-day mortality (odds ratio = 5.67, 95% confidence interval = 1.49 to 21.59). Notably, older age, Black race, and number of comorbidities were statistically significantly associated with increased odds of hospitalization and ICU admission (all P<.05). In addition, exploratory subgroup analyses were performed to investigate these associations among patients with active cancer (defined as having metastatic disease and/or receiving cancer-directed systemic therapy, radiation therapy, or surgical resection in the 2 months before COVID-19 diagnosis) compared with noncancer patients, as well as those with cancer in remission compared with noncancer patients. The analyses showed that adjusted associations with hospitalization, ICU admission, and 30-day mortality were strongest in the active cancer patient group. The authors concluded that patients with cancer, particularly those receiving active treatment, should be among groups specifically targeted for COVID-19 mitigation and prevention strategies such as vaccination.[14]

Lymphopenia at COVID-19 diagnosis was associated with higher rates of severe critical illness.[1] Patients with baseline neutropenia 14-90 days before a COVID-19 diagnosis had worse outcomes.[1] In addition, current literature suggests that the likelihood of a severe illness and death from COVID-19 is higher among adult patients with cancer who have other comorbidities, including obesity.[2]

Please see Appendix for a complete list of references.

5. When will cancer patients receive immunity (mount an immune response) after the COVID-19 vaccine?

In the general population, individuals may not receive optimal protection until after the vaccine series is completed. [1,2,7,8,9,10,12] Immunocompromised individuals were initially excluded from the earlier Phase 2/3 vaccine clinical trials.[1,2] More recently, studies have indicated that after a full vaccine series, patients with solid tumours demonstrate high rates of immune response; though, immune response may be diminished compared to the general public.[11,14,15,16,17,26,27, 33]

Evidence suggests that patients with hematologic malignancies mount blunted, less durable and highly variable antibody responses after completing two doses of the primary COVID-19 vaccine series.[15-21,28-30, 32] This is a result of both their underlying condition and treatments affecting the efficacy of COVID-19 vaccines. In addition to active treatment within the last 6-12 months with BTKIs (Bruton tyrosine kinase inhibitors) and anti-CD19/CD20/CD38 antibody therapies, BCMA directed therapies, PI3-K inhibitors (e.g., alpelisib), JAK2 inhibitors (e.g., ruxolitinib) and venetoclax treatments also negatively affected antibody response, rendering these patients sub-optimally protected from COVID-19.[18-21, 30, 34] Patients on immunomodulators, proteosome inhibitors (or both) mount poorer antibody responses than do untreated patients with hematological malignancies.[21] Other treatments, including hematopoietic stem cell transplantation, may result in a reduced antibody response.[25, 31]Although immune response may be sub-optimal, COVID-19 vaccinations still offer some protection, and some protection is better than none.[6]

Observational studies in multiple myeloma patients have reported that older age, impaired renal function, low lymphocyte counts, patients who have had more than 2 lines of systemic treatment and those not in complete remission were associated with lower antibody levels.[32]

To optimize immune response, individuals on active treatment for malignant hematologic disorders and non-hematologic malignant solid tumors (excluding individuals receiving solely hormonal therapy or radiation therapy) should receive the COVID-19 vaccine at the dose interval indicated in the product monograph.[13] For **moderately to severely** immunocompromised patients, an additional dose may be required.[25] For details on a three-dose primary series of COVID-19 vaccine and booster doses , refer to question 7: Should additional doses of COVID-19 vaccine be considered in patients with cancer?

Patients should continue to follow Public Health guidance to avoid exposure to COVID-19, unless otherwise advised by their health care team.[1,2] To protect those who are immunocompromised, it also is strongly recommended that all people that come into close contact (e.g., family, friends, caregivers) with these individuals are fully vaccinated according to public health guidelines. [4,24]

Please see Appendix for a complete list of references.

6. When is the optimal time for cancer patients to receive the COVID-19 vaccine?

Ideally, vaccination should occur at a time when patients are least likely to be immunocompromised as efficacy will depend on patients' ability to mount a response to the vaccine.[26,30] Based on real-world evidence with COVID-19 vaccines and extensive experience with the flu vaccine, response rates can be highly variable. The effectiveness of the vaccine will depend on underlying disease as well as the type and timing of treatment that could hinder a patient's ability to mount an immune response.[17,18]

The following guidance on the timing of the COVID-19 vaccine administration, in relation to treatment for cancer patients has been adapted from information pertaining to the inactivated influenza vaccine and is updated as new evidence emerges.

General guidelines:

- Clinical judgement should be exercised around administration of the complete series of the vaccine prior to initiation of systemic treatment (chemotherapy or immunotherapy). Prioritization of systemic treatment over vaccination, or vice versa, should be determined via risk assessment, considering factors such as patient's age, comorbidities, treatment intent, type of treatment, etc.

- When feasible, vaccines should be administered at least 2 weeks before initiation of systemic treatment to optimize immunogenicity.[1,2,4,20]
- For COVID-19 vaccines given as a 2-dose series:
    - If the complete series of the vaccine cannot be administered 2 weeks before the start of treatment, the first dose of the vaccine should be administered at least 2 weeks before initiation of systemic treatment, and the second dose within a few days prior to administration of systemic treatment. Although evidence around timing with systemic treatment varies, this can minimize uncertainty around the cause of flu-like symptoms or infusion-related reactions if vaccine is administered around the day of systemic treatment.[5,6,20,21]
    - If the second dose cannot be administered within a few days of systemic treatment administration, a risk assessment should be conducted around prioritization of either the treatment schedule or vaccination schedule, with consideration for factors such as patient's age, comorbidities, treatment intent, type of treatment, etc.
    - If administration of the second dose of the vaccine is delayed, it should be administered as soon as possible.[19]
- Patients receiving vaccine during treatment may have an attenuated or absent response to the vaccine and should continue to exercise precautions when possible (wearing a mask when unable to maintain social distance etc.).[1,2,4,20] An additional dose of COVID-19 vaccine may be required.[33]
- Patients who are not on active treatment may receive the vaccine after an appropriate time has passed since their last treatment was completed, depending on the agents used.

Cytotoxic Chemotherapy

- If feasible, allow at least two weeks to pass after the second vaccine dose before starting cytotoxic therapies to allow for memory T cell formation. [22]
- During active chemotherapy treatment, all doses of the vaccine should be administered, at minimum, within a few days prior to next chemotherapy cycle, if feasible (i.e. when immunosuppressive effects of cytotoxic chemotherapy are at their lowest and not on the same day of chemotherapy).[5,6,20]
- Immunization in patients receiving chemotherapy when blood counts are low is discouraged.[13,14]
- Induction Chemotherapy for Leukemia:
    - Vaccine should be given at least 2 weeks prior to the start of immunosuppressive therapy or when effects of immunosuppressive therapy are at the lowest level.[2]
    - If the vaccine cannot be given prior to start of induction treatment in acute leukemia, it may be given upon blood count recovery, prior to the start of consolidation treatment.

Targeted therapy

- Vaccines may be administered at any time during treatment for most targeted therapies. Consideration for timing should be taken for targeted treatments that may cause neutropenia or lymphopenias.[3,20]

Immunotherapy

- Monoclonal antibodies:
    - If feasible, allow at least two weeks to pass after the second vaccine dose before starting B-cell depleting therapies to allow for memory T cell formation. [22]
    - Patients receiving maintenance rituximab may receive vaccine at any time during treatment; although there may be a reduced response, evidence suggests it is unlikely to cause harm.[7,20]

- Immune checkpoint inhibitors (ICI):
    - Many trials using ICI do not allow vaccinations due to a concern of increased autoimmune events. However, evidence with inactivated influenza vaccine suggests that patients receiving ICI therapy may not experience an increase in immune-related adverse events when they receive the vaccine within 2 months of treatment.[9,10] Recent research with mRNA vaccines supports this. Cancer patients treated with ICI who received mRNA vaccine were not likely to develop new immune-related side effects or exacerbation of existing immune-related side effects in the short-term.[31]
    - For patients receiving a combination of ICI, the risk of increased autoimmune events is uncertain and should be weighed against the definite risk of a patient potentially contracting COVID-19. Experience with vaccinations in this population is mostly with the influenza vaccine and more data will need to be collected before any further recommendations can be made.

Radiation Therapy

- Patients who are receiving radiation therapy alone (not in combination with chemotherapy) may receive vaccine at any time during treatment.[20]

Stem cell transplant

- If feasible, both doses of the vaccine should be administered at least 2 weeks before initiation of a transplant conditioning regimen, and at least 2 weeks prior to stem cell collection for donors.[2]
- Post-transplant, the vaccine may be administered as early as 3 months after transplant.[12,18,22,24]

CAR T-Cell Therapy

- If feasible, both doses of the vaccine should be administered at least 2 weeks before CAR T-cell therapy.[18]
- Vaccines should not be administered until at least 3 months after completion of therapy.[22,25]

Corticosteroids

- If feasible, the vaccine should be administered after corticosteroid treatment has been completed or reduced to ≤ 10 mg/day of prednisone or equivalent, due to the immunosuppressive nature of corticosteroids.[32]

Surgery

- Essential urgent surgery should take place, irrespective of vaccination status. Non-urgent elective surgery can also take place soon after vaccination. There is some rationale for separating the date of surgery from vaccination by a few days (at most 1 week) so that any symptoms such as fever might be correctly attributed to the consequences of either vaccination or the operation itself.[23] For surgeries inducing immunosuppression (e.g. splenectomy), a wider window (e.g. 2 weeks) may be recommended.[27]

Cancer Screening

- Since lymphadenopathy is a potential COVID-19 vaccine side effect, screening exams should be conducted before the first dose of a COVID-19 vaccine or 4–6 weeks after the second dose of a COVID-19 vaccine if feasible, and when it does not unjustifiably interrupt management.[28,29]

See question 7: “Should a additional doses of COVID-19 vaccine be considered in patients with cancer?” for information around timing of third doses.

Please see Appendix for a complete list of references.

7. Should additional doses of COVID-19 vaccine be considered in patients with cancer?

Three-dose Primary Series for Immunocompromised Patients

Studies have shown decreased immunogenicity in some immunocompromised adults, including patients with malignancy (solid tumour and hematological), when compared to healthy vaccine recipients[1,3, 5, 13] Emerging data suggest that an additional COVID-19 vaccine dose in immunocompromised patients enhances antibody response and increases the proportion of patients who respond.[7,8,13]

NACI recommends that a third dose of an authorized mRNA COVID-19 vaccine should be offered to **moderately to severely** immunocompromised patients in the authorized age groups.[13]

A third dose of a viral vector vaccine should only be considered when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent for an additional dose of viral vector vaccine should include discussion about its lack of evidence as an additional dose in this population, and the increased risk of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), Capillary Leak Syndrome (CLS), and Guillain-Barre syndrome (GBS) following viral vector COVID-19 vaccines.[13, 14]

Moderately to severely immunocompromised cancer patients include those who:[12, 13, 14]

- Are on active treatment for solid tumour or hematologic malignancies that can cause moderate to severe immunosuppression.
    - Active treatment is defined as chemotherapy, targeted therapies, immunotherapy, and excludes individuals receiving therapy that does not suppress the immune system, e.g. solely hormonal therapy or radiation therapy
    - Active treatment includes patients who have completed treatment within 3 months, or within 12 months for patients receiving B-cell depleting therapy.
- Are on active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22, e.g., blinatumomab, rituximab, obinutuzumab, inotuzumab ozogamicin), high-dose systemic corticosteroids (prednisone equivalent of ≥ 20 mg/day)**,** alkylating agents (e.g. bendamustine, cyclophosphamide), antimetabolites (e.g. 5-fluorouracil, methotrexate), or tumour-necrosis factor (TNF) inhibitors (e.g. infliximab) and other biologic agents that are significantly immunosuppressive.
- Are recipients of chimeric antigen receptor **(CAR)-T-cell therapy** or **hematopoietic stem cell transplant (HSCT)** (within 2 years of transplantation or taking immunosuppression therapy).
    - The timing of vaccination depends on many factors and should be considered on a case-by-case basis.
    - Cell Therapy Transplant Canada recommends[17]:
        - Patients in the first 3-6 months following allogeneic stem cell transplant, autologous cell transplant, CAR-T therapy, or on active immunosuppression, should receive a full course of mRNA vaccine post-transplant/therapy, independent of prior COVID-19

vaccination, and should include booster doses at the appropriate times (e.g., dose 1, 2 and 3 at 3 months, 4 months and 6 months post transplant respectively).
- Re-vaccination should start 3-6 months after transplant, according to institutional guidelines. A more potent immune response will be obtained if the first vaccine dose is administered closer to the 6-month mark.
- Patients may end up receiving up to 5 or 6 vaccination doses, depending on whether they were vaccinated pre-transplant.

Refer to the latest NACI recommendations for definition of moderately to severely immunocompromised non-cancer populations.

Ontario guidelines recommend an interval of at least 2 months (8 weeks) between the last dose of the 2-dose series and the third dose. As per NACI, the minimum interval should be 28 days; an interval longer than the minimum 28 days between doses is likely to result in a better immune response. If a longer interval is being considered, then risk factors for exposure (including local epidemiology and circulation of variants of concern) and risk of severe disease should also considered.[13, 14]

Booster Doses[15]

Booster doses refer to additional COVID-19 vaccine doses after the primary series is completed.

Individuals with higher risk of severe disease from COVID-19 infection (e.g. moderately to severely immunocompromised, adults 60 years of age and older or living in long-term care homes, or First Nation, Inuit and Métis communities) are strongly recommended to receive booster doses of an authorized mRNA COVID-19 vaccine, as soon as they are eligible.

Booster doses should be administered at least 5 months (minimum 3 months) after completing the primary vaccination series. [14] Booster doses may be a fourth dose in the vaccine series, or more, depending on timing of previous COVID-19 vaccinations.

Please refer to the Ministry of Health - COVID-19 Vaccine Booster Recommendations or local public health units for specific eligibility criteria, dose and timing of COVID-19 vaccine booster doses.

Patients should continue to follow Public Health guidance to avoid exposure to COVID-19, unless otherwise advised by their health care team. To protect those who are immunocompromised, it also is strongly recommended that all people that come into close contact (e.g., family, friends, caregivers) with these individuals are fully vaccinated according to public health guidelines.

Please see Appendix for a complete list of references.

8. When should the COVID-19 vaccine be given in relation to other vaccinations?

Currently, it is recommended by Public Health that COVID-19 vaccines may be safely and effectively administered at the same visit, or any time before or after, non-COVID-19 vaccines (including live, non-live, adjuvanted, or unadjuvanted).[1,2,3] Though studies to assess the safety and immunogenicity of concomitant

administration of COVID-19 vaccines with other vaccines are ongoing, experience with non-COVID-19 vaccines has demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone.[1]

Although data is still limited in the immunocompromised setting, evidence does not suggest that concomitant administration of COVID-19 vaccines with other non-COVID-19 vaccines (e.g., the flu vaccine) would cause harm or affect efficacy of either vaccine. If more than one type of vaccine is administered at a single visit, they should be administered at different anatomical injection sites.[1,2,3]

Patients who are administered vaccines concomitantly should be counseled about the benefits and risks given the limited data available.

9. What are possible side effects of the vaccination?

Side effects of the COVID-19 vaccines were usually mild or moderate and generally resolved in a few days.[1,4,6,7,10,11,12] Local reactions for the vaccines included pain, rash, redness or swelling at the injection site.[2,7,11,12,16] Delayed local reactions have been reported.[15] Systemic side effects included fatigue, headache, muscle/joint pain, diarrhea, chills, fever and nausea/vomiting.[2,7,11,12, 16]

Frequencies of systemic effects for the mRNA COVID-19 vaccines were generally higher after the second dose, and in patients < 56 years of age for the Pfizer vaccine and between 18 to 64 years for the Moderna vaccine.[2,3,7,8]

Preliminary data demonstrate side effects after the 3rd dose of an mRNA vaccine were similar to that of the two-dose series: fatigue, headache, muscle/joint pain and pain at injection site were the most commonly reported side effects, and overall, most symptoms were mild to moderate.[30,31, 37] No worsening of underlying disease was reported after immunization. [33] No serious adverse events were deemed to be associated with the additional vaccine dose. The impact of additional doses on rare adverse events, including myocarditis/pericarditis, are unknown.[33]

For the AstraZeneca vaccine, fewer and milder adverse reactions were reported after the second dose and reactogenicity reduced with increasing age.[3, 10,11]

Patients should be educated to seek medical attention if the symptoms last longer than 48-72 hours, due to the similarity with symptoms of COVID-19 or other infections.

Cases of lymphadenopathy occurring in the arm and neck region [24.28] have been reported post all doses of the COVID-19 vaccination, which may mimic metastasis. Following the first and second COVID-19 vaccine doses, vaccine-related lymphadenopathy typically occurs within 7 days of vaccination and generally subsides by 12-14 days. However, vaccine-related lymphadenopathy may persist as far as 4-6 weeks after first and second COVID-19 vaccine administration.[17,21,22,23, 26,27] The peak of lymph node activity tends to be earlier after the second vaccination as compared to the first vaccination.[27] Data suggests high grade vaccine-related lymphadenopathy following the third dose has shorter duration (does not usually persists for weeks) and lower uptake intensity after the first 5 days from vaccination. It is unlikely for high grade vaccine-related lymphadenopathy to be observed 6 days from inoculation of the third vaccine dose, and is even less likely in older and obese patients to interfere with imaging interpretations.[38] Consider timing of vaccination and dose number in the vaccine series when assessing patients with new or worsening lymphadenopathy. [2,7,11,12, 13, 14, 23]

Very rare cases of moderate-to-severe thrombocytopenia and thrombotic complications at unusual sites (e.g., abdomen, splanchnic vein, sinus or cerebral vein), called vaccine-induced immune thrombotic thrombocytopenia (VITT), have been reported with the AstraZeneca COVID-19 vaccine (some emerging reports with Pfizer or Moderna vaccines in the United States).[3, 12, 23, 25, 34, 35] In some cases, these have been accompanied by bleeding.[12] VITT typically occurs within 3 weeks following AstraZeneca vaccine administration.[12] Fatalities have been reported. The exact mechanism is still under investigation but appears to be similar to heparin-induced thrombocytopenia (HIT). It is associated with platelet activating antibodies, which stimulate clot formation and thrombocytopenia. Patients should be advised to seek immediate medical attention if they develop symptoms of thromboembolism accompanied by thrombocytopenia, which becomes clinically apparent approximately 4-28 days after receiving a viral vector COVID-19 vaccine and should be monitored for symptoms up to 42 days.[3, 12, 18-20, 23,25] Close monitoring of patients with previous thrombocytopenia is highly recommended as VITT can develop earlier than the expected onset in patients with a history of thrombocytopenia and worsen pre-existing thrombocytopenia.[32]

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving the AstraZeneca vaccine, typically within the first 4 weeks after vaccination. There were very rare cases of low platelets (< 20 x 10^9/L) and/or bleeding events, including fatal cases. Some cases occurred in patients with a history of immune thrombocytopenia.[11]

Very rare cases of myocarditis and/or pericarditis following vaccination administration of mRNA vaccines have been reported.[2,3,7] The onset of symptoms (including chest pain, shortness of breath and palpitations) have typically occurred within one week after vaccination; cases have occurred more commonly after the second dose, in adolescents, young adults and male patients.[3, 36] Available short-term follow-up data suggest that the symptoms are generally mild and resolve in most individuals, but information on long-term sequelae is lacking. Patients receiving an mRNA vaccine should be informed about the very rare risk of myocarditis and/or pericarditis following immunization. Individuals who experienced this adverse effect within 6 weeks of receiving an mRNA vaccine should defer subsequent doses until they have discussed the risks and benefits with their healthcare provider. Cardiology consultation for management and follow up should be considered.[2,3, 39] Refer to the COVID-19 vaccine: Canadian Immunization Guide for more information regarding subsequent immunization in individuals who experienced myocarditis.

Bell's Palsy (typically temporary weakness or paralysis on one side of the face) has been reported very rarely after the use of mRNA COVID-19 vaccines. The exact cause is unknown, with symptoms appearing suddenly and generally starting to improve after a few weeks. It is believed to be due to swelling and inflammation of the nerve that controls muscles on one side of the face.[29]

Very rare events of demyelinating disorders, such as Guillain-Barré Syndrome, have been reported after vaccination with the AstraZeneca COVID-19 Vaccine.[12]

Please see Appendix for a complete list of references.

10. Can a cancer patient receive the COVID-19 vaccine if they have allergies?

Severe allergic reactions to the vaccine have been reported.[1,2,4, 12, 13]

Patients with a history of severe allergy (e.g., anaphylaxis) to any of the components of a COVID-19 vaccine, or patients that have had an allergic reaction within 4 hours of receiving a previous dose of a COVID-19 vaccine, should be referred to an allergist, other appropriate physician or nurse practitioner to determine how the vaccine can be safely administered.[15]

Polyethylene glycol (PEG), a water-soluble polymer used as a drug delivery vehicle, is a component of both Pfizer and Moderna vaccines and is known to cause mild to severe hypersensitivity reactions.[6,7] Cancer medications containing PEG include (but are not limited to) the following:

1. PEGaspargase (Oncaspar®)
2. Pegfilgrastim (e.g., Neulasta® and others)
3. Liposomal irinotecan (Onivyde®)
4. PEG-liposomal doxorubicin (Caelyx®)

Polysorbate, a surfactant and emulsifier used as an excipient in some drug formulations,[7] is structurally related and has the potential for cross-reactivity to PEG. It is also a component of the AstraZeneca vaccine.[12] Individuals who are allergic to polysorbates should be offered an mRNA vaccine.[16] Cancer medications containing polysorbate include (but are not limited to) the following:

1. Cabazitaxel
2. Docetaxel
3. Etoposide
4. Fosaprepitant (IV)
5. Rituximab (reactions with rituximab are typically a result of cytokine release syndrome and may not be related to polysorbate)
6. Paclitaxel (contains the excipient, Cremophor EL (polyethoxylated castor oil) which has the potential for cross-reactivity with polysorbate)[9]

Not all medications that contain PEG or polysorbate will cause allergic reactions and many drugs, including oral medications, may contain PEG or polysorbate in various concentrations, depending on the manufacturer.

Tromethamine is a component of the Moderna vaccine and may cause allergic reactions. It is also a component in contrast media and some oral and parenteral medications (e.g., ketorolac).[14] Individuals who are allergic to tromethamine should be offered the Pfizer-BioNTech COVID19 vaccine if 12 years or age or older.[16]

Clinicians should consult individual product monographs for a full list of non-medicinal ingredients if their patients have had a history of anaphylactic reactions to their cancer medications. Patients should be counseled about the risks of developing a severe allergic reaction against the benefits of vaccination.

Refer to Ministry of Health guidance on COVID-19 vaccines and allergies for more information.

Please see Appendix for a complete list of references.

11. When should Evusheld (Tixagevimab and Cilgavimab) be given in relation to the COVID-19 vaccine?

In individuals who have received a COVID-19 vaccine, Evusheld should be administered at least 2 weeks after vaccination.[1]

If a patient is currently eligible for a COVID-19 vaccine dose, they should receive the vaccine before receiving Evusheld. There are no data available regarding COVID-19 vaccination after Evusheld administration.

Refer to Information about Evusheld (Tixagevimab and Cilgavimab) for more information.

Please see Appendix for a complete list of references.

If you have any questions regarding the COVID-19 Vaccine and cancer, please email the Drug Formulary team at OH-CCO_DrugFormulary@ontariohealth.ca

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Revision Dates:

Date	Updates
August 8, 2022	• Booster doses (Q9) • Management of severe/immediate allergies to COVID-19 vaccines (Q10) • New question on timing of Evusheld with COVID-19 vaccines (Q11)
December 9, 2021	• Additional risk factors for patients with reduced response rates to COVID-19 vaccines (Q5) • Added information for CAR-T/transplant patients and updated booster dose information (Q7) • Updated side effects (lymphadenopathy with 3rd dose, ITP) (Q9)
November 3, 2021	• Concomitant administration of COVID-19 vaccines with non-COVID-19 vaccines (Q8) • Booster doses (Q7)
September 14, 2021	• Approved age group for Moderna vaccine (Q1) • Recommendations on additional dose of COVID vaccine after 2-dose series (Q1, Q5, Q6, Q7) • Side effects (3rd doses, VITT, Guillain Barre syndrome) (Q9)
August 19, 2021	• Added questions regarding contraindications and 3rd doses for COVID-19 vaccines • COVID-19 risk relating to anti-CD20 treatment (Q4) • Information on mounting an immune response to a COVID-19 vaccine (Q5) • Information on side effects (3rd doses, myocarditis and Bell's Palsy) (Q9) • Information on corticosteroids (Q6) • Removed information relating to Johnson & Johnson COVID-19 vaccine and COVID-19 trials in immunocompromised patients
June 14, 2021	• Authorized age for Pfizer vaccine (Q1) • VITT side effect information (Q7) • Allergy guidance (Q8) • Clinical trial information (Q9)
April 30, 2021	• Information on AstraZeneca and Johnson & Johnson vaccines adverse effects (VIPIT, hypersensitivity) (Q1, Q6, Q7) • Information regarding ICIs (Q4)
April 12, 2021	• Recommended Immunization Schedule (Q1) • Optimal timing for cytotoxic chemotherapy, surgery and cancer screening (Q4) • Information on adverse effects and rare adverse effect (VIPIT) (Q6) • Information on tromethamine (Q7) • Emerging trials in the cancer population (Q8)
March 8, 2021	• Information about AstraZeneca and Johnson & Johnson COVID-19 vaccines • Risk factors (Q2) • Adverse effects(Q6)
January 6th, 2021	• Information about Moderna vaccine

Updated By:

Annie Cheung, Senior Pharmacist, Systemic Treatment Program
Andrea Crespo, Senior Pharmacist, Systemic Treatment Program
Jessica Ng, Pharmacist, Systemic Treatment Program
Sarah Salama, Pharmacist, Systemic Treatment Program
Rob Rementilla, Pharmacist, Systemic Treatment Program

Reviewed By:

Dr. Leta Forbes, Provincial Head, Systemic Treatment Program
Daniela Gallo-Hershberg, Manager, Systemic Treatment Program
Colleen Fox, Director, Integrated Cancer Treatment Programs
Multiple disease site experts in oncology across Ontario

Approved By:

Dr. Jonathan Irish, Vice-President Clinical, Cancer Programs, Ontario Health, Cancer Care Ontario
Elaine Meertens, Vice-President, Cancer Programs, Ontario Health, Cancer Care Ontario

Prepared By:

Annie Cheung, Senior Pharmacist, Systemic Treatment Program
Andrea Crespo, Senior Pharmacist, Systemic Treatment Program
Jessica Ng, Pharmacist, Systemic Treatment Program
Rob Rementilla, Pharmacist, Systemic Treatment Program
Sarah Salama, Pharmacist, Systemic Treatment Program

Appendix

1. Are all COVID-19 vaccines safe for cancer patients?

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