Memorial Sloan Kettering Cancer Center

MSK COVID-19 VACCINE INTERIM GUIDELINES FOR CANCER PATIENTS

Last Update 10/8/2021

1. SCOPE OF THE DOCUMENT

The MSK COVID-19 vaccine interim guidelines are intended to provide clinicians with practical recommendations on using the emergency use authorized (EUA) COVID-19 vaccines for patients with active and treated cancer.

- There is currently a lack of vaccine efficacy and immunogenicity data, specifically in the cancer population.
- The vaccines are safe for use in cancer patients. None of the three EUA vaccines contain live virus. Specifically, Ad26.COV2.S (Janssen/J&J) contains a replication incompetent viral vector (Human adenovirus 26).**
- Published clinical trials of the authorized vaccines in the general population and existing approaches to other vaccines in cancer patients inform this document's recommendations for using COVID-19 vaccines in cancer patients.
- The vaccine taskforce constituted by oncology and infectious disease experts has carefully considered potential therapy-related interference with COVID-19 vaccine responses and make practical recommendations to guide clinicians until specific data are available.
- Recent studies suggest that patients treated for solid tumors mount good serological response to vaccines, However, humoral responses are subdued in certain hematologic cancers especially within 6-12 months after treatment with B-cell depleting therapies and HCT.
- Please review the FAQs under section 7 for topic specific special considerations.

The FDA has currently granted emergency use authorization to three vaccines with the following age and dosing interval parameters.

Manufacturer	Technology	Age Recommendation	Interval between doses	Grace Period for 2nd dose*
Pfizer	mRNA	≥ 12 years	21 days	17-21 days
Moderna	mRNA	≥ 18 years	28 days	24-28 days
Janssen/J&J**	Vector vaccine (Human adenovirus 26)	≥ 18 years	Single dose	Not applicable

*dose can be administered after the grace period if patient is unable to receive the 2nd dose in the recommended timeframe

Other vaccines that have completed Phase 3 clinical trials but are **not** currently authorized for use in the United States include:

Manufacturer	Technology	Safety concerns in immunocompromised hosts	# of Doses
AstraZeneca	Vector vaccine (simian adenovirus)	Replication deficient	Two
Novavax	Protein subunit (adjuvanted)	None	Two

2. PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Authors: *Tobias Hohl, Santosh Vardhana, David Knorr, Alex Lesokhin*

Background and Rationale

The rationale to vaccinate MSK patients with hematologic malignancies is to reduce the risk of COVID-19 morbidity and mortality. COVID-19 vaccination will enable receipt of disease-specific therapy and avoid delays in cancer care.

In ideal circumstances, when planning is possible and community rates are low, patients with hematologic disease, particularly patients on B-cell depleting therapies, should undergo shared decision making with their oncologist for recommendations related to optimal timing of vaccination, with the considerations below.

However, when rates of community transmission of SARS-CoV-2 are high, as they are <u>currently</u>, and if the vaccine is offered to them, it is reasonable for patients to proceed with vaccination, even if they are likely to have a blunted immune response.

General considerations for vaccination in hematologic disease

The following considerations should guide eligibility and timing of vaccination:

1. Ability to mount a cellular and humoral immune response is paramount [1,2]. Proceed with vaccination in the following patients at the earliest opportunity:

- Patients that have not yet started lymphocyte-depleting therapies and can complete 2-dose schedule 14 days prior to initiation of lymphocyte-depleting therapy.
- Patients that have completed therapy (see below for lymphocyte-depleting therapies).
- Patients with stable lymphocyte counts while on therapy. We define stable lymphocyte counts as an ALC ≥ to 1.0 (normal range: 1.3 - 4.0 x 10^3 cells/microliter) or B cell counts ≥ 50 cells per microliter. *

For patients that have received lymphocyte-depleting therapy (I.e., rituximab, blinatumomab, anti-thymocyte globulin, alemtuzumab, etc.), it is reasonable to consider deferring vaccination until six months after completion of therapy or until there is evidence of lymphocyte reconstitution (ALC ≥ 1.0 and/or B cell counts ≥ 50) *. This is because patients with B cell aplasia will in all likelihood not mount a humoral immune response. However, given that COVID vaccination generates T-cell memory that may offer at least partial protection, it is reasonable to offer vaccination during times of high community transmission even to patients unlikely to mount a B-cell response. ** Limited data to suggest use of ALC and/or B cell count as a predictive biomarker, can consider use to guide clinical decision making.*

2. Therapy- and Disease-specific recommendations for vaccination (in setting of adequate and steady vaccine supply and low community transmission rates) [3,4]

Lymphoid Malignancies

CLL (special consideration of rituximab, venetoclax, ibrutinib)

- If patients are asymptomatic from a CLL standpoint, we would recommend holding B-cell depleting therapy until one month after completion of vaccination (both doses for mRNA vaccination).
- For small molecule therapy in symptomatic patients, we would recommend holding vaccination until 1 month after completion of treatment, once there is evidence of B-cell recovery (ALC ≥ 1.0, B-cell count ≥ 50 cells/ lymph by flow cytometry). When chronic therapy for symptomatic patients is required, vaccination should be considered, as it may still generate T-cell memory responses in the absence of B-cell recovery.

B- or T-ALL (Induction/maintenance therapy)

- Induction therapy for newly diagnosed disease should not be delayed for vaccination.
- Vaccine should be given during the maintenance phase at a time patient displays evidence of hematopoietic count recovery. It can also be considered during induction with less intense regimens (e.g. steroids + TKI)

DLBCL and other aggressive B-cell lymphoma

- Systemic induction therapy, including anti-CD20 antibodies, for newly diagnosed disease should in general not be delayed for vaccination.
- Vaccine should be given after completion of therapy, assuming patient is in remission and no further treatment is planned, once there is evidence of B-cell recovery from anti-CD20 depletion (ALC ≥ 1.0, B-cell count ≥ 50 cells/microliter lymph by flow cytometry). During times of high community transmission, vaccination should be considered, as it may still generate T-cell memory responses in the absence of B-cell recovery.

Indolent lymphomas

- If patients are asymptomatic, we would recommend holding on B-cell depleting therapy until 1 month after completion of vaccination series
- If patients are in need of systemic therapy, we would recommend treating with induction but without maintenance therapy, and vaccinating following completion of therapy, assuming no further immediate treatment is planned and there is evidence of B-cell recovery from anti-CD20 depletion (ALC ≥ 1.0, B-cell count ≥ 50 cells/microliter lymph by flow cytometry). During times of high community

transmission, vaccination should be considered, as it may still generate T-cell memory responses in the absence of B-cell recovery.

T cell lymphomas

- Therapy for newly diagnosed and progressive disease should not be delayed for vaccination purposes.
- Vaccine can be given during induction therapy, preferably following count recovery.

Lymphoma patients with relapsed or refractory disease

- In the context of disease recurrence or progression, systemic therapy with the potential for therapeutic benefit should not be delayed for vaccination purposes.
- For patients having received B-cell depleting agents, similar considerations apply, as outlined above

Myeloma

- With the exceptions of lymphodepleting therapy administration there are no specific disease or treatment related contraindications for vaccination in patients with myeloma.
- Patients treated with lymphodepletion (e.g., high-dose Melphalan with SCT, Cytoxan/Fludarabine or anti-CD52 mAb conditioning for cellular therapy) vaccination can be attempted once lymphocyte recovery is observed, as aligned with HSCT and cellular therapy guidelines.

Myeloid Malignancies

- **AML** (induction/consolidation therapy): Induction therapy for newly diagnosed disease should not be delayed for vaccination purposes. Vaccine should not be given during the induction remission phase but should be considered during consolidation therapy. Patients with relapsed disease may be considered for vaccination.
- **MDS**: Patients with MDS on observation or active therapy with HMA should be considered for vaccination.
- **MPNs**: Patients with ET, PV, or MF on observation or active therapy should be considered for vaccination.
- **CML**: Patients receiving TKIs (with or without remission) should be considered for vaccination.

Therapy specific recommendations

- **Steroids**: Patients treated with corticosteroids may have diminished responses to vaccination. Corticosteroids are detrimental to patients with mild COVID-19 yet

appear beneficial to patients with severe COVID-19[5]. It is recommended that patients treated with corticosteroids are vaccinated prior to therapy, if feasible.

- **IVIG**: COVID-19 vaccines may be administered to patients receiving plasma therapy not specific to COVID-19 (e.g., IVIG), as these are unlikely to substantially impair development of protective antibody responses.
- **Rituximab**: Patients treated with rituximab clearly have diminished humoral responses to vaccination. Patients treated with rituximab and naturally infected with SARS-CoV-2 appear to be one of the highest risk groups for COVID-19 morbidity and mortality. It is recommended that patients are vaccinated prior to initiation of therapy (e.g., both doses completed ≥ two weeks prior to initiation of B-cell directed therapy), when feasible. If it is not feasible to delay Rituximab-based therapy, it is still reasonable to consider vaccination during times of high community transmission given that vaccination can generate T-cell memory responses even in the absence of humoral immunity.

Post-vaccination follow-up

At this time, post-vaccine serologies are not recommended in the general population or in patients with hematologic malignancies. Development of and patient enrollment in clinical studies to measure humoral and cell-mediated immunity to COVID-19 vaccination is recommended.

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3. HEMATOPOIETIC STEM CELL TRANSPLANT AND CELLULAR THERAPY RECIPIENTS

Authors: *Miguel Perales and Zenia Papanicolaou*

Timing of vaccine administration [1,2]

Autologous HCT

- Vaccination may be initiated 2- 3 months after HCT

For patients receiving tandem auto HCT (i.e. GCT) vaccination should be initiated after last planned stem cell infusion

Allogeneic HCT

Conventional, no severe GVHD, no anti-CD20 antibodies

- Vaccination may be initiated as early as 3 months post HCT (time frame 3-6 months based on local vaccine availability, and rate transmission in the community). COVID19 vaccination should take priority over the regular vaccination schedules.

Ex-vivo T-cell depleted and post Cy HCT

- Vaccination may be initiated around 6 months post HCT with confirmed presence of B cells (>50) and CD4+ T-cells (>100).

CART cell therapy and receipt of antiCD20 antibodies

- Vaccination may be initiated as early as 3 months if demonstrated IVIG independence and B-Cell count ≥50.

HSCT patients with GVHD

- Studies with other vaccines with good immunogenicity potential have shown efficacy also in patients with ongoing moderately severe GVHD without obvious risks to result in worsening of the GHVD. These patients should therefore receive the vaccine.
- Although side effects are expected as with any vaccine, there is no example that side effects of non-live vaccines be more frequent or more severe in HCT than in the healthy population of the same age range. So far, there is no data suggesting immune activation of underlying conditions making the likelihood that COVID-19 vaccines will exacerbate GVHD low.

Reasonable criteria to postpone vaccination with our current knowledge are:

- Severe, uncontrolled acute GVHD grades III – IV.
- Recipients, who have received anti-CD20 antibodies during the last six months and absolute B-cell count <50.
- CAR T cell patients with B-cell aplasia (absolute B-cell count <50)
- Recent therapy with ATG or alemtuzumab.
- With limited vaccine supply, donor vaccination for passive immunity to HCT recipient is not advised at this time.
- Caregivers are not eligible to receive the vaccine unless they are already in a priority group.

References

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4. IMMUNE CHECKPOINT INHIBITORS (ICIs)

Authors: *Mini Kamboj and Jedd Wolchok*

Background and Rationale

- Patients on ICI therapy, particularly lung cancer, are at a higher risk for severe COVID-19. Existing data is mixed but suggests that these findings may be driven by non-therapy related risks and co-existing medical conditions [1-4].
- Patients with lung cancer who have other risk factors for severe COVID-19 infection are also more likely to be treated with ICI. If vaccine supplies are constrained, ICI treated patients with lung cancer should be prioritized to receive the vaccine among other high-risk cancer patients (age>74, multiple co-morbid conditions, hematologic malignancy, active treatment, and metastatic disease) [3,4].
- There is no published data on mRNA vaccines' immunogenicity in cancer patients, including those on ICI.
- Humoral and cell-mediated immune responses to the influenza (flu) vaccine are more robust in patients treated with ICI than those treated with cytotoxic chemotherapy [5-6].
- There is no data to suggest that patients receiving immune checkpoint inhibitors experience complications or exaggerated immune-related adverse (irAE) events from any viral vaccine.
- Multiple studies have demonstrated influenza vaccine safety during ICI treatment without any signal of exaggerated irAE's [7-9].
- COVID-19 outcomes are not specifically worse among those with recent immunotherapy treatment. Although vaccine interaction with ICI is not studied, this finding, and the flu vaccine safety in recently treated patients, inform the recommendation for vaccination regardless of when ICI therapy is initiated.

Recommendations

1. **Patients on ICI therapy should receive the COVID-19 vaccine. Clinicians should not pause ICI therapy for vaccination.**
2. No specific timing is recommended relative to recent vs. continued therapy.
3. Systemic side effects with the COVID-19 vaccine tend to occur within 2-3 days of the vaccine and may be more pronounced with the second dose. Side effects are also more frequent in those <55 years of age. If possible, avoid scheduling ICI therapy when vaccine side effects are expected [10].

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5. PATIENTS WITH SOLID TUMORS

Authors: *Monika Shah and Diane Lagunes-Reidy*

Overview

Patients with solid tumor cancers should be offered the vaccine if components of the vaccine are not contraindicated. The rationale for COVID-19 vaccination in patients with solid tumor malignancies is to reduce the risk of COVID-19 morbidity and mortality. COVID-19 vaccination will also enable ongoing receipt of disease-specific therapy and avoid delays in cancer care.

General Background

- Patients with active cancer have a higher risk of morbidity and mortality from COVID-19. [1]
- Data from other vaccine preventable illnesses such as influenza, pneumococcal disease and herpes zoster suggest a protective effect of vaccination in cancer patients. [2]
- For example, influenza vaccination offers protection to cancer patients by reducing influenza-related hospitalizations, interruption of chemotherapy cycles, and risk of death. [3]
- Antibody responses to vaccines are generally lower in patients receiving cytotoxic chemotherapy compared with healthy individuals or cancer patients who are not actively receiving treatment. Several small studies have yielded conflicting results related to generation of immune responses stratified by timing of influenza vaccination in relation to chemotherapy and the nadir/cytopenic period. [4] Recent reports suggest this timing does not seem to matter. [5,6] Precise immune correlates are unknown.
- Given the paucity of data, optimal timing of vaccination in relation to cytotoxic chemotherapy or other cancer directed therapy has not been established. When there is opportunity to choose, vaccination at the furthest possible time point away from the cytotoxic treatment effect (i.e. nadir) during a given cycle is recommended.
- The impact to the humoral and cellular immune responses is variable across solid tumor types and treatment paradigms.

Additional considerations related to mRNA vaccination in patients with solid tumors

- The dosing schedule recommended for the mRNA vaccines is a two-dose series either 21 days apart (Pfizer) or 28 days apart (Moderna). There are no data to support significant deviations from the recommended vaccine schedule. Given this, precision timing of the 2-dose series is likely not feasible.
- There is no contraindication to receipt of COVID-19 vaccine across the broad range of therapies that patients with solid tumors may receive, inclusive of:

- Cytotoxic chemotherapy
- Radiation therapy
- Hormonal therapy
- Targeted therapies
- Immunotherapy
- Corticosteroids
- Surgical management

Recommendations for use

1. **Patients with solid tumors should receive the COVID-19 vaccine, as stratified by factors such as age. There are no additional stratification recommendations related to cancer type or stage of disease at this time.**

2. Clinicians should not hold or pause cancer directed therapy for vaccination.

3. **No specific timing is recommended relative to cancer directed medical or radiation therapy**. Some circumstances to consider are listed below. Vaccination should be offered when made available to the patient.

    a. If feasible, for patients planned for but not yet on immunosuppressive cancer directed therapy, time first dose of vaccine to be given ≥ 2 weeks prior to initiation of therapy.

    b. If feasible, for patients already on cytotoxic chemotherapy, time first dose of vaccine in between chemotherapy cycles, and away from nadir period.

    c. If feasible, for patients completing cytotoxic therapy, time first dose of vaccine to be given after therapy complete and nadir period resolved.

    d. For patients on other cancer directed therapies, including those that may confer additive immunosuppression (i.e. corticosteroids), there is no recommendation related to timing.

4. Immunotherapy related considerations discussed separately (section 4, page 9-10).

5. Systemic side effects with the COVID-19 vaccine tend to occur within 2-3 days of the vaccine and may be more pronounced with the second dose. Side effects are also more frequent in those <55 years of age. If possible, avoid scheduling immunotherapy or other chemotherapeutic infusions when vaccine side effects are expected.

6. **For patients undergoing cancer related surgery**, no specific timing is recommended relative to surgery from a vaccine efficacy standpoint.

    However, given that in the peri-operative period it may be difficult to appropriately attribute symptoms (i.e. fever) to a vaccine side effect or to a post-surgical complication, a separation

of vaccine with major surgery* by a few days or a week or two may be desirable. In the post-surgical period, this timing should be considered as appropriate to the circumstance, i.e. the recovery course for the specific type of major surgery.

For patients undergoing elective splenectomy as a part of cancer treatment, first dose of vaccination should occur ≥ 2 weeks prior to splenectomy or in the post-surgical period, after recovery [7].

**major surgery is any invasive operative procedure in which a more extensive resection is performed, i.e. a body cavity is entered, organs are removed, or normal anatomy is altered*

References

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6. PEDIATRIC CANCERS

Authors: *Farid Boulad and Gil Redelman-Sidi*

Background

1. Currently FDA-approved COVID-19 vaccines include mRNA-1273 (Moderna) and BNT162b2 (BioNTech and Pfizer) and Ad26. COV2.S (Janssen)
2. Initial phase III clinical trials supporting the approval of these vaccines excluded young children. mRNA-1273 was tested in individuals who were 18 years or older [1], and BNT162b2 in individuals who were 16 years or older [2]. Clinical trials of COVID-19 vaccines including younger individuals are ongoing and effective May 10, 2021 FDA EUA authorization for the BNT162b2 (BioNTech and Pfizer) vaccine was extended to adolescents age 12-15 years old [3].
3. COVID-19 is generally mild in children [4,5], including in children with cancer [6-8].
4. COVID-19–Associated Multisystem Inflammatory Syndrome (MIS-C) is a severe manifestation of COVID-19 that has been described in children. The pathogenesis of this syndrome appears to be immune-mediated and there are theoretical concerns that COVID-19 vaccination could elicit a similar syndrome [9].

Recommendations

Based on the considerations listed above, and pending additional data on the safety of COVID-19 vaccines in the pediatric population, we recommend the following:

1. **Limit vaccination to the age ranges approved under the current EUAs, specifically ≥12 years of age for BNT162b2 (Pfizer) and ≥18 years of age for mRNA-1273 (Moderna) and Ad26. COV2.S (Janssen), with prioritization and limitations of patient cohorts harmonized to federal guidance for use, institutional guidelines and phased distribution plans.**
2. For guidelines for COVID-19 vaccination by specific disease and treatment please see sections 2-5.
3. Decrease in the lower age limits after safety and efficacy data are available from current clinical trials of vaccine in pediatric participants.

References

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7. SPECIAL CONSIDERATIONS AND FREQUENTLY ASKED QUESTIONS

Authors: *Mini Kamboj, Monika Shah, and Elizabeth Robilotti*

General Considerations

1. **Should patients who have recovered from cancer be prioritized to receive the COVID-19 vaccine?**

   Yes, patients who have recovered from cancer should receive the vaccine. Patients with active disease, especially hematologic, thoracic malignancies, and metastatic disease, are at a higher risk for severe disease. Although it is unclear if past cancer treatment similarly increases the risk of adverse outcomes, the COVID-19 vaccine should be offered to these patients.

2. **Can COVID-19 vaccine be administered to patients enrolled in clinical trials at MSK?**

   There are no specific limitations for patients enrolled on clinical studies unless otherwise stated in the protocol inclusion/exclusion criteria. If so, the provider should discuss with the study PI and/or sponsor.

3. **Should patients receive additional doses of mRNA vaccine if their second dose was after the recommended time interval?**

   No, third doses are not recommended. Patients should adhere to the recommended dosing interval (see table on page 1).

4. **Should cancer patients get revaccinated if the vaccine was administered during a period of immunosuppression?**

   No, revaccination is not recommended at this time.

5. **Will booster doses of vaccine be needed in the future?**

   The need for and timing of booster doses for COVID-19 vaccines has not been established. No additional doses beyond the two-dose primary series are recommended at this time for the m RNA vaccine. Two doses of Janssen vaccine are being evaluated in an ongoing clinical trial but the vaccine is authorized for use as a single dose immunization currently.

Patients with a history of COVID-19

6. **Should patients with a previous history of COVID-19 infection be vaccinated?**

Yes, patients who have recovered from COVID-19 infection should also be offered vaccination. Approximately 2.2 % of patients with prior COVID-19 disease were included in the clinical trials evaluating mRNA vaccines, and 9.7 % participants in the Janssen trial had serological evidence of previous SARS CoV-2 infection. These patients were able to mount an appropriate response without any evidence of ADE. Reinfection with SARS COV-2 is uncommon in the first 90 days after infection. CDC does not recommend a minimum interval between infection and vaccination in recovered individuals. MSK vaccine clinic staff should follow the CIS indicator for appropriate transmission-based precautions for recent COVID positive patients. Guidance can be followed here.

7. **If a patient tests (newly) positive for COVID after the first dose of the mRNA vaccine, but before receipt on the second dose, can the patient proceed to the second dose?**

Yes, if the patient has recovered from acute COVID illness prior to the scheduled second dose. Clinical recovery is defined as resolution of fever for at least 24 hours, without the use of fever-reducing medications, and with improvement of other symptoms. If the patient has not yet recovered, vaccination may be scheduled for administration up to 6 weeks (42 days) after the first dose, for both the Pfizer and Moderna COVID-19 vaccines (CDC link). There are currently limited data on efficacy of mRNA COVID-19 vaccines administered beyond this window. If the second dose is administered beyond these intervals, there is no need to restart the series. MSK vaccine clinic staff should follow the CIS indicator for appropriate transmission-based precautions for recent COVID positive patients. Guidance can be followed here.

8. **Should vaccine be given to patients with positive COVID-19 antibodies?**

Yes, it is safe for patients with a positive COVID-19 antibody test to be vaccinated. There is not enough experience to correlate antibodies with future protection against COVID-19 infection and immunity duration is not clearly established. Routine serological testing (COVID-19 antibody) before vaccination is not recommended. Serological testing should not be used to guide the timing of vaccination.

Safety of vaccine in patients with a history of allergy (see section 8 for allergy management)

9. **Should patients with a history of severe allergies, including anaphylaxis, be offered the vaccination against COVID-19?**

The risk of anaphylaxis with the mRNA vaccine is estimated to be 2.5-4.7 cases per million doses. Patients with a wide variety of common allergies are eligible to get COVID-19 vaccines. This is also true for patients with cancer and an allergy history. The only patients with allergies who should not get the vaccine are those

who have a history of anaphylaxis specifically to one of the vaccine components. For example, individuals with a known history of allergy to PEG (polyethylene glycol) should not receive the currently available mRNA products and individuals with a known history of polysorbate allergy should not receive the Janssen vaccine. Patients with anaphylaxis to other injectable medications should undergo a longer observation period of 30 minutes following receipt of vaccination against COVID-19. Patients with allergies to foods, nuts, animals, latex, or environmental triggers are also eligible to receive an mRNA-based COVID-19 vaccine. Please refer to this resource for additional guidance.

10. Can individuals with an allergic reaction to the first dose of the mRNA vaccine receive the Janssen/J&J vaccine?*

Yes, if no other contraindications exist, Janssen/J&J vaccine may be administered at least 28 days after the initial mRNA vaccine dose.

Adverse effects

11. What are the common side effects of the COVID-19 vaccines?

The most common side effects of the mRNA vaccines include injection site pain. Other common side effects include fatigue, tiredness, muscle pain, chills, joint pain, and fevers.

These side effects were more commonly reported in younger vaccine recipients and following the second shot of the 2-dose series. Side effects typically resolved after one to two days. At times, patients report swelling of the axillary or supraclavicular lymph nodes on the side on which they received the shot. This side-effect can be associated with a sensation of axillary fullness and is self-resolving.

For Janssen/J&J vaccine, local and systemic side effects were less frequently reported than in the mRNA vaccines, among all the clinical trial recipients. Up to half of vaccine recipients had side effects that were mostly mild (Gr 1-2) and resolved in 1-2 days. A small numeric imbalance in the vaccine arm was observed for tinnitus and VTE, with plans for ongoing monitoring through VAERS at the time of the EUA approval.

12. Should cancer patients pre-medicate before the vaccine to reduce side-effects?

Premedication is generally not advised. For patients with a history of allergy, premedication may mask early symptoms of life-threatening hypersensitivity and is therefore not routinely recommended.

13. Is the vaccine safe for patients with a history of Guillain-Barre Syndrome (GBS)?

There is no epidemiological link between SARS-CoV-2 infection as a trigger for GBS (Keddie, Brain 2020). No cases of GBS were reported in clinical trials of both mRNA vaccines. A slightly higher risk of GBS with the Janssen vaccine was recently discovered with reports of 100 cases among 12.8 million J&J doses administered. The symptoms of GBS appeared within 6 weeks after the vaccine, and most of the affected are male, with many over age 50 years. m RNA vaccines have not been associated with an elevated risk of GBS.

14. Is the vaccine safe for patients with a history of Bell's palsy?

In the m RNA vaccine clinical trials, a numerical difference was observed in the number of Bell's palsy cases between the vaccine and placebo arm. A causal link between Bell's palsy and the vaccine has not been established. Patients with a history of Bell's palsy may receive the vaccine.

15. What clotting side effects have been reported with the COVID-19 vaccines?

Thrombosis with thrombocytopenia syndrome (TTS) has rarely been reported following adenoviral derived COVID-19 vaccines (Janssen/J&J and AstraZeneca). Rare cases of thrombosis (predominantly cerebral venous sinus thrombosis, but in other veins and arteries as well) with thrombocytopenia, have been reported in 15 women between March 19 and April 21, 2021 in the US, among 8 million doses administered. The clinical features of this rare syndrome appear to be similar to reports from the European Union following receipt of the AstraZeneca vaccine, and the clinical presentation resembles autoimmune heparin induced thrombocytopenia. There is specific evaluation and management guidance for patients suspected of TTS following recent receipt of the J&J COVID-19 vaccine. Please see section 9 of this document for details. TTS has not been reported following mRNA vaccines (Pfizer and Moderna).

16. My patient was recently vaccinated with the Janssen/J&J vaccine. What should they look out for?

At present, the CDC advises that people who have received the vaccine and who develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination should contact their health care provider for assessment. Health care providers are asked to report adverse events to the Vaccine Adverse Event Reporting System at https://vaers.hhs.gov/reportevent.html.

Co-administration of COVID-19 vaccine with other anti-viral therapeutics and vaccines

17. Can vaccine be given to COVID-19 recovered patients who received the monoclonal antibodies or convalescent plasma (CP)?

CDC guidelines recommend postponing the vaccine for 90 days after receipt of monoclonal antibody or CP to treat COVID-19 to avoid any interference with vaccine mediated immunity. If antibody therapy is administered between vaccine doses, clinicians should postpone the second dose.

18. Can COVID-19 specific monoclonal antibodies and other therapeutics be given after mRNA COVID-19 -vaccine?

For patients with SARS-CoV-2 infection, vaccine status should not alter the decision or timing for the use of monoclonal antibodies, convalescent plasma, corticosteroids, or antivirals.

19. Is it safe to receive other vaccines with the COVID-19 vaccine?

Previously, and out of an abundance of caution, it was recommended to space COVID-19 vaccination at least 14 from other vaccines. Given the amassed data on the safety of EUA COVID-19 vaccines currently authorized by FDA it is reasonable to consider co-administration. Both the safety profile of COVID-19 vaccine and extensive 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. Physicians should balance co-administration concerns on vaccine-reactogenicity with an individual patient's risk for acquiring a vaccine-preventable disease and outcome from severe disease.

Infection Control Considerations

20. Should vaccine be routinely offered to patients after household, community, or hospital-based exposure to SARS CoV-2?

The vaccine is unlikely to provide clinical protection after exposure to SARS COV-2. The earliest evidence of partial clinical protection is around 12 days after the first dose of the vaccine, which is much longer than the average incubation period for COVID-19 (5-7 days). Routine post-exposure vaccination is not recommended.

21. When is it safe for patients to receive the vaccine after a significant exposure (for example, COVID-19 in a household contact)?

Patients may receive the vaccine if they remain asymptomatic and have completed the recommended quarantine period.

22. Should vaccinated patients follow the current MSK testing protocol for asymptomatic patients?

Yes, the vaccine's effectiveness in cancer patients is unclear at this time and there is insufficient post-authorization experience in general. Patients should follow testing protocols regardless of the vaccine status. Encourage patients to continue all safety measures, including masking, social distancing and hand hygiene.

23. Do vaccinated patients pose a transmission risk to others in the household?

No, none of the three authorized vaccines contain live virus and do not pose a transmission risk to others. No special precautions need to be taken around other household members after vaccination.

Serological Tests

24. How should positive serological assays for SARS CoV-2 be interpreted in vaccinated individuals?

	Anti-Nucleocapsid	Anti-Spike antibody
Prior infection with or without vaccine	+	+
Vaccine response only	-	+

Two assays are available at MSK. The Anti-Nucleocapsid assay is a qualitative test and does not measure vaccine response. The Anti-Spike antibody is a semi-quantitative test and would measure either prior infection and/or vaccine response, although the utility of doing measuring this has limited clinical applicability.

Clinicians should be familiar with the limitations of serological testing for SARS-CoV-2. An antibody test should not be used alone to definitively diagnose or exclude SARS CoV-2 infection.

The durability of immunity and the precise immune correlates of clinical protection is unclear, from both natural infection and from vaccination. Some recent reports suggest that humoral immune responses after SARS CoV-2 infection persist for up to 6-8 months and may correlate with clinical protection. Further, cell-mediated immune responses are not measured in these reports.

25. My patient was vaccinated. Should I check for a serological response?

No, antibody testing to assess for vaccine response has limited clinical applicability, as there is no current information about the precise immune correlates that determine protection from infection. Furthermore, a negative result, even in a fully vaccinated individual, is not an approved indication for additional doses of vaccine. The CDC recommends serological assays to determine vaccine response be performed only in the context of a research study.

26. Should I avoid receiving mRNA vaccine due to reports of myocarditis and pericarditis?

A small number of cases of myocarditis and pericarditis of varying severity have been reported, predominantly among adolescent and young adult males ≥ 16 years of age following receipt of either Pfizer-BioNTech or Moderna vaccination. This was more common following the second dose and typically occurred within days of receiving dose two. Presenting symptoms included chest pain, shortness of breath and/or irregular heartbeat. Patients who have developed post-vaccine myocarditis have recovered with supportive care. [Refs doi:10.1001/jamacardio.2021.2833; DOI: 10.1542/peds.2021-052478]

27. If my patient was vaccinated outside of the US can they be re-vaccinated at MSK?

Yes. If your patient received a non-FDA EUA approved vaccine outside of the US they are eligible for re-vaccination through the MSK patient vaccine program. An up-to-date list of WHO approved vaccines can be found here. The minimum interval between the last dose of a non-FDA authorized vaccine or a WHO-listed vaccine and an FDA-authorized COVID-19 vaccine is 28 days

	Received all recommended doses	**Did not receive all recommended doses**
WHO authorized vaccine	No action required, considered fully vaccinated	Vaccinate with US authorized vaccine (
Not a WHO authorized vaccine	Vaccinate with US authorized vaccine	Vaccinate with US authorized vaccine

28. Is there an association between receipt of Ad26.COV2.S COVID-19 (Janssen/J&J) Vaccine and development of Guillain-Barré Syndrome (GBS)?

Data from the Vaccine Adverse Event Reporting System (VAERS) database was reviewed in one study which identified 130 cases of presumptive GBS. A majority of presumptive cases were identified in males and those <65 years of age (median age, 56 years; IQR, 45-62 years). These findings suggest a potential small safety concern for GBS following receipt of the Ad26.COV2.S vaccine. This study was limited by reliance on passive surveillance data and lack of conformation of definitive diagnosis from medical records review and should be considered preliminary. [Ref: JAMA. doi:10.1001/jama.2021.16496].

8. MANAGEMENT OF HYPERSENSITIVITY TO VACCINES

Authors: *Sejal Morjaria, Deborah Korenstein, Mini Kamboj, Monika Shah*

Background

- While rare, anaphylactic reactions have been reported following vaccination with mRNA vaccines. Most reactions have occurred within 15 minutes of vaccination. [1]
- People with history of an immediate allergic reaction to any ingredient in the COVID-19 vaccine should not receive that vaccine. [2]
- The ingredient in both mRNA vaccines which is believed to be the allergenic culprit is polyethylene glycol (PEG). For individuals with PEG allergy, Janssen vaccine can be administered after risk assessment and with 30-minute observation.
- Polysorbate is an ingredient in the Janssen vaccine but not the m RNA vaccines. For individuals with a **known** polysorbate allergy, m RNA vaccine can be given with a 30-minute observation period due to the potential for cross-reactivity between PEG and Polysorbate.
- Both PEG and polysorbate are found (as one component) in many injectable cancer therapeutics (appendix table) as well as other injectables [3,4]
- Persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is PEG and/or polysorbate, but in whom it is unknown which component elicited the immediate allergic reaction, may proceed with vaccination with extended post-vaccination monitoring period [2, see Appendix Figure].
- **Patients with a history of any type of allergic reaction to food, pets, venom, latex, other drugs (including injectables or other vaccines) may proceed with vaccination**; the post-vaccination monitoring period in clinic varies according to spectrum of allergy (anaphylaxis/immediate allergic reaction vs. non-anaphylaxis/immediate allergic reaction) [See Appendix Figure]
- Immediate allergic reactions to vaccination are defined as any hypersensitivity-related signs or symptoms such as hives, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within four hours following administration.

Contraindication to either mRNA vaccine*

- Known severe allergic reaction (e.g., anaphylaxis) or immediate allergic reaction after a previous dose or any ingredient of the mRNA COVID-19 vaccine
- Diagnosed immediate allergic reaction of any severity to PEG*

**may consider allergist consultation. For patients who require facilitated referral to an allergist, process to do so with MSK consultants and external partners is available.*

Contraindication to Janssen/J&J vaccine**

- Known severe allergic reaction (e.g., anaphylaxis) or immediate allergic reaction to an ingredient of the Janssen vaccine
- Diagnosed immediate allergic reaction of any severity to polysorbate**.

***May consider mRNA vaccines or allergist consultation to clarify allergy. For patients who require facilitated referral to an allergist, process to do so with MSK consultants and external partners is available.*

References:

1. *Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States*, December 14–23, 2020 *Early Release* / January 6, 2021 / 70
2. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html, (accessed Feb 10, 2021)
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4. Mishra P, Nayak B, Dey RK. *PEGylation in anti-cancer therapy: An overview.* Asian Journ Pharm Sciences 2016; 11:337-348.
5. https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf

APPENDIX (separate documents, posted in same subsection as this document)

1. Figure: MSK Allergy Screening Algorithm and Allergist Referral Process
2. Table: MSK Formulary Injectable Medications that contain PEG and/or Polysorbate.

9. Diagnosis and Management of Thrombosis with Thrombocytopenia Syndrome (TTS) after Janssen /J&J COVID-19 vaccine

Authors: Jodi Mones, MD and Mini Kamboj, MD

Background and Incidence

The Janssen / J & J COVID-19 vaccine (made with a replication incompetent human adenovirus 26 vector) was approved for emergency use authorization in the United States on Feb 27, 2021, and vaccine administration began on March 2, 2021. Beginning in March 2021, the US has identified 28 cases of Thrombosis with Thrombocytopenia Syndrome (TTS), also known as vaccine -induced thrombosis and thrombocytopenia (VITT) among ~ 8 million doses A majority of cases occurred in young (<50yo)females. Further review by the FDA determined this to be a rare event and use of the J&J product was resumed under EUA guidance after a brief pause. The symptom onset was within 1-2 weeks after the vaccine and clinical presentation resembles autoimmune heparin induced thrombocytopenia (HIT). The clinical features of TTS are as follows:

- Thrombosis of the large veins with thrombocytopenia (commonly severe < 50,000 /mm^3)
- Most common involved site is cerebral venous sinuses (n=12). Thrombosis of other large veins in the abdomen, lung, neck, and extremities were also noted.
- Other identified risk factors were oral contraceptive use (2), Obesity (7), Hypertension (2) and Hypothyroidism (2).
- The syndrome is *not* associated with current or past COVID-19 infection.

Diagnostic Considerations

Cerebral venous sinus thrombosis (CVST), which can be a specific manifestation of TTS, can and does occur albeit rarely without an antecedent COVID-19 vaccine at annual incidence of 10-15 per million. [1, 2]. CVST is not typically associated with thrombocytopenia and thus the vaccine associated CVST is unique in presentation and can be challenging to treat

A high index of suspicion is important to promptly identify patients. Patients with symptoms suggestive of CVST (including severe headache, visual changes, new-onset shortness of breath, petechiae, or easy bruising) or other thrombotic events should be asked about COVID-19 vaccine history. Those who received the Johnson & Johnson/Janssen COVID-19 vaccine within the preceding three weeks should be evaluated promptly and treated in accordance with current recommendations from the American Society of Hematology. ***Patients with suspected TTS after Johnson & Johnson/Janssen COVID-19 vaccination should be tested for platelet factor 4 (heparin-induced thrombocytopenia, [HIT]) antibodies and should not be treated with heparin unless HIT testing is negative.***

Diagnosis of TTS (must meet all four criteria)

1. COVID vaccine within three weeks (among the US authorized vaccines Johnson & Johnson is the only vaccine associated with TTS*)
2. Venous or arterial thrombosis (often cerebral or abdominal)
3. Thrombocytopenia
4. Positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA

*A similar syndrome has been described in individuals vaccinated with the Astra Zeneca CHaDOx1 nCov-19 AstraZeneca (AZ) vaccine outside the United States. This is also a replication deficient adenoviral vector vaccine.

In a patient presenting with an atypical thrombosis (CVST or splanchnic) and thrombocytopenia it is important to ask about COVID-19 vaccine status and history. Please note that the only vaccines associated with the TTS are Janssen (US) and Astra Zeneca* (outside the US). **TTS has not been associated with the two authorized mRNA vaccines (Moderna and Pfizer).**

If there is a high index of suspicion for vaccine related TTS, order the following tests:

1) CBC and platelet count with peripheral smear
2) Symptom directed imaging (e.g. head CT or MRI venogram for headaches, abdominal imaging for abdominal pain)
3) Heparin/PF4 IgG ELISA
4) Fibrinogen (often low in TTS, < 150)
5) D-Dimer

Treatment Considerations

Suspected TTS: The following treatment algorithm applies for suspected cases:

1) Do not wait for PF4 ELISA to result before starting the following if there is high clinical suspicion of TTS
2) Consult the Benign Hematology Service
3) Avoid heparin
4) Try to avoid platelet transfusions (exceptions apply – please discuss with Benign Hematology)
5) Start a non-heparin containing anticoagulant (argatroban, rivaroxaban, apixaban, fondaparinux)
6) Give IVIG early 1-2 g/kg divided doses (associated with platelet recovery in TTS)

Proven TTS: Continue non-heparin anticoagulant for a provoked VTE – 3 months

References

1.Coutinho, J.M., et al., *The incidence of cerebral venous thrombosis: a cross-sectional study.* Stroke, 2012. **43**(12): p. 3375-7.

2.Ferro, J.M., et al., *Cerebral vein and dural sinus thrombosis in Portugal: 1980-1998.* Cerebrovasc Dis, 2001. **11**(3): p. 177-82.

3. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattør TH, Tjønnfjord GE, Holme PA. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Apr 9. doi: 10.1056/NEJMoa2104882

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5. ACIP/CDC https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html

6. ASH https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

10. Third Vaccine Dose and Booster dose update

The third dose and booster dose are not the same. Please review the indications for each below.

Third Dose of mRNA COVID-19 vaccine

The CDC had previously authorized a third vaccine dose for select patients with moderately to severely weakened immune systems on August 13, 2021.

A **third dose** of the mRNA COVID-19 vaccines (Pfizer or Moderna) is identical to the first two doses. It is considered to be part of the primary vaccine series for a select group of patients with moderate-to-severe immunosuppression who are expected to have an insufficient immune response to the first two doses of one of the mRNA vaccines. A **third dose** can be given 28 days after the second mRNA dose and should be the same brand as the first two doses. We are continuing to offer patients who are moderately to severely immunocompromised a **third dose** of the Pfizer or Moderna vaccine, which they should receive instead of a booster. For clinical guidance on the **third dose**, see this link with more information about who is eligible.

Please see responses to commonly asked questions on booster dose eligibility and administration for patients at MSK.

Booster Doses of mRNA COVID-19 vaccine

On September 24, 2021 the CDC authorized a booster dose of the Comirnaty (Pfizer-BioNTech) COVID-19 vaccine for several groups, including:

- Adults age 65 and older
- Residents of long-term care facilities
- Adults age 18-64 with underlying medical conditions, including cancer
- Adults working in healthcare or other occupations putting them at high risk of contracting COVID-19

A **booster shot** is an additional dose of the Pfizer vaccine that is identical to the first two doses. It is given after the protection provided by the primary two-dose vaccine series has begun to decrease over time. A **booster shot** is given 6 months after the primary series. A **booster dose** is approved for Pfizer-vaccinated adults age 65 years and older, healthcare workers, residents of long-term care facilities, and Pfizer-vaccinated adults 18-64 years old with underlying medical conditions, including patients with cancer. Given this, we consider all adult MSK patients to have underlying conditions and therefore to be eligible for a **booster shot**, if they don't also meet eligibility criteria below for the third dose.

Please see responses to commonly asked questions on **booster dose** eligibility and administration for patients at MSK.

1. Which MSK patients can receive the booster Pfizer-BioNTech vaccine dose?

The booster dose of the COVID-19 Pfizer-BioNTech vaccine is recommended for the following groups:

- Adults age 65 and older
- Residents of long-term care facilities
- Adults age 18-64 with underlying medical conditions, including cancer
- Adults working in healthcare or other occupations putting them at high risk of contracting COVID-19

Because of the above guidelines, we're considering our patients currently or previously treated for cancer eligible to receive the booster dose.

2. Are pediatric patients eligible to receive the booster vaccine dose?

No, even though the Pfizer vaccine is also approved for 12- to 17-year-olds, the Pfizer booster dose EUA is for 18 and older only.

3. Which patients are not eligible for a booster dose at this time?

- Patients who received 2 doses of the Moderna vaccine or 1 dose of the Johnson & Johnson/Janssen vaccine are not eligible for a booster dose at this time. We are closely following FDA and CDC guidance for these vaccines and will communicate any changes in the future.
- Patients who have already received three doses of the Pfizer vaccine should not receive the booster.
- Patients less than 18 years of age should not receive the booster.

4. How are we communicating with patients about scheduling a booster dose?

MSK sent an email to our patients that explained the booster guidelines. It also stated that in the coming weeks, we will email patients a link to schedule the booster or third dose online.

When they receive that link, patients will have to attest that they meet the guidelines before scheduling a booster or third dose.

We are also encouraging our patients to look for vaccine availability at other clinics, due to our limited vaccination supply and available appointments.

5. ***Do providers need to place an order for a patient to receive the booster or the third dose?***

Booster Dose (Provider Orders are Not Required)

Patients with solid tumors who had 2 doses of the Pfizer vaccine and do not meet the criteria for the third dose should receive a booster. MSK will contact patients via email on a rolling basis with a link to self-schedule their appointment. Provider orders are not required.

Patients with hematologic malignancies who had 2 doses of the Pfizer vaccine and do not meet the criteria for the third dose should receive a booster. This includes patients in remission, patients under observation only, or patients who are more than two years past their stem cell transplant or CAR-T treatment. MSK will contact patients via email on a rolling basis with a link to self-schedule their appointment. Provider orders are not required.

Patients over 65 with no history of cancer but with underlying medical conditions can also self-schedule their booster dose appointment.

Third Dose (Provider Orders are Required for Patients with Hematologic Malignancy Only)

Patients with solid tumors receiving chemotherapy or immunotherapy and who are eligible to receive the third dose will be able to self-schedule their appointments. MSK will contact patients via email on a rolling basis, with a link to self-schedule their appointment. Provider orders are not required.

Patients under active treatment for a hematologic malignancy (currently or within the past year) or recent stem cell transplant/CAR-T treatment (within two years) who qualify for a third dose as part of their primary series should continue to reach out to their provider‘s office to schedule the third dose. Providers can transcribe these orders. Office practice nurses and care coordinators have received the instructions to support the effort.

6. ***When and where will MSK begin administering the additional doses?***

Patients may begin scheduling the booster dose on Wednesday, September 29 at:

- The David H. Koch Center for Cancer Care at Memorial Sloan Kettering Cancer Center, located at 530 E. 74 Street
- MSK Westchester, located at 500 Westchester Avenue in West Harrison, New York
- MSK Nassau, located at 1101 Hempstead Turnpike in Uniondale, New York
- MSK Bergen, located at 225 Summit Avenue in Montvale, New Jersey

Booster vaccine clinic hours at each location will be available on OneMSK.

7. ***What is the minimum dosing interval between the second and booster dose for eligible patients?***

The Pfizer booster dose should be administered at least 6 months after the second Pfizer dose.

8. ***Are patients who received monoclonal antibody (mAb) therapy for post-exposure prophylaxis eligible to receive the vaccine?***

Yes, but a minimum of 90 days should have elapsed after the mAb treatment.