COVID VACCINE IN IMMUNOCOMPROMISED PATIENTS

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When considering vaccinating people on immunosuppressive therapy, it is important to review the:

- **Mechanism** of the effect of the medicine or other treatments on the immune system,
- consequence of using **combination therapies —** for example, corticosteroids and other immunosuppressive therapies such as DMARDs (disease-modifying anti-rheumatic drugs), which can contribute to the nature, extent and length of the immunocompromising condition.
- anticipated **duration of the person's immunocompromised** state, whether due to the therapy or the underlying disease.

Vaccine Antigens

- **B Cell/Antibody Targets:**
- Protection induced by currently available vaccines against viruses is primarily based on **virus-neutralizing antibodies**. Such antibodies usually block the interaction of the virus with its cellular receptor or prevent conformational changes required for fusion of the virus with the cell membrane.
- **T Cell Targets:**
- Preventive anti-viral vaccines are successful because they induce antibodies that neutralize viral particles in the extracellular space, immediately after body entry and before viruses infect the host's cells. Importantly, B cell responses and antibody production are strongly promoted by **CD4 T helper cells**. **Therefore, vaccines should simultaneously induce both B cells and T cells.**

- Compared to people without immunocompromise, **antibody levels have been lower** among individuals with higher degree of immunosuppression, such as SOT, individuals with haematological malignancies, and those receiving B-cell depleting therapy.

- **Few studies have evaluated T-cell responses among IC** individuals, with some indicating relatively preserved cellular immunity, whereas other studies found blunted responses in line with decreased antibody response.

- **Data with influenza vaccines have suggested that cellular immune response and recall responsiveness can remain at high levels despite the lack of an antibody response after vaccination**.

Immunocompromised people and SARS-CoV-2 infection

- More likely to get **severely ill** from COVID-19
- **Prolonged** SARS-CoV-2 infection and **shedding**
- **Low antibody/neutralization** titers to SARS-CoV-2 variants
- More likely to **transmit SARS-CoV-2** to household contacts
- More likely to have **breakthrough infection**:

  - **44% of hospitalized breakthrough cases are immunocompromised people in US study and 40% in Israeli study**

The humoral or cellular immune response to various COVID-19 vaccines

- Of **SOT recipients**: 10% to 54%; antibody responses after mRNA vaccine.
- In another study: detectable antibody response ;(17%) with an **adenovirus-based COVID-19** vaccine ;compared to 59% with an **mRNA vaccine.**

- In patients receiving cytotoxic chemotherapy for treatment of solid tumors : 80%; neutralising antibody response to the mRNA vaccine

- In rheumatic or musculoskeletal disease **(RMD):** more favorable; 65% to 100% antibody responses with an mRNA or inactivated virus vaccines; (though antibody titers were lower than controls).

COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials

MAY 2021

COVID-19 Vaccination in patients with cancer

nature reviews clinical oncology

- patients with cancer have an increased risk of complications and mortality from COVID-19, including 30- day mortality of 30% in hospitalized patients with COVID-19 and cancer compared with **21%** in those without cancer.

- Given the greater severity of the disease and higher risk of death, **patients with cancer are considered a high- priority subgroup for COVID-19 vaccination.**

- Vaccination is recommended in all patients with cancer, **whenever a vaccine is available** including those receiving active therapy with the Exception of some conditions.

- Allow **at least 3 days** of spacing if possible and avoid vaccination on the same day as a **regular infusion** (e.g., immunoglobulin, immunosuppressant infusion), or an **investigational agent** to avoid incorrect attribution of vaccine-related adverse events to the infusion treatment or vice versa.

Haematological malignancies

- **Preferably complete vaccination 2 weeks before receiving immunosuppressive drugs.**

- For patients receiving cytotoxic chemotherapy, given the lack of data on the optimal timing of vaccination (in several studies , the suggested time is 3 months after the end of chemotherapy).

In neutropenic patients

- **Intensive cytotoxic** chemotherapies expected to result in profound and prolonged immunosuppression (e.g. anthracycline- based and/or cytarabine- based induction regimens):

✓ Delay until absolute neutrophil count recovery (ANC >1000)

[This is to avoid fever, which may result in additional investigations being required to rule out other differential diagnoses (such as sepsis].

- In **chronic neutropenia** duo to marrow failure expected to have no recovery (like A.A): vaccination whenever a vaccine is available.

In patients with thrombocytopenia

- Consider temporary deferral of vaccination or use additional precautions during periods of severe thrombocytopenia (e.g., plt count < 50 x109 /L).

- **After vaccination**, the injection site should not be rubbed, and firm pressure should be applied for 5-10 minutes.

Solid tumours

- **Cytotoxic chemotherapies**:

2 weeks before or 1–2 weeks after drug dose, when possible, to increase the potential for the immune system to mount a response.

On vaccine availability

- **Hormone therapy** (e.g. anti- androgens or anti-estrogen therapy or HRT)
- **Epigenetic therapy**
- **Targeted therapy**:

✓ **TKIs** (imatinib ،nilotinib ،sunitinib ....)

✓ **PARP inhs. (olaparib,…)**

✓ **CDK4/6 inhs. (ribociclib ،palbociclib,…)**

- **Immunotherapy** with **checkpoint inhibitors** (nivolumab, ipilimumab, pembrolizomab)
- **Intra bladder injection** (BCG ،mitomycin ، jemcitabin ،epirubicin…)
- **Capecitabine , Temozolomide**

Radiation oncology

- On vaccine availability

- the exception is total body radiation, after which vaccination might need to be delayed to provide time for immune reconstitution.

elective surgery,

- **For patients undergoing elective surgery:**
  - Administer at discharge after recovery from post- operative complications, or
  - 1 week before surgery, whichever is most feasible

- **In the case of urgent or emergent surgery:** patients can be vaccinated postoperatively, **after patient recovery**.

breast cancer screening

- For participants in breast cancer screening, consideration should be given to the fact that COVID-19 vaccination can cause **transient lymphadenopathy.**

- Therefore, if possible and if patient management will not be unjustifiably interrupted, screening examinations should be conducted either before the first dose of a COVID-19 vaccine or 4–6 weeks after the second dose.

COVID-19 Vaccination in Solid Organ Transplant Recipients

Timing of vaccination

- **Ideally, vaccinating should be completed at least two weeks before transplantation .**

- Risk of acquiring COVID-19 must be balanced with the potential benefits of waiting longer to vaccinate after transplantation in an effort to optimize vaccine response.

- When possible, we delay vaccination for at least one month from the time of transplantation

- For patients who are **transplanted between vaccine doses**, we **delay the second dose until at least one month after transplantation** (if induction did not include a T or B cell-depleting agent).
- and for **at least three months** (Ideally 6 months) after use of T cell-depleting agents (eg, anti-thymocyte globulin) or specific B cell-depletion agents (eg, Rituximab), for rejection or induction therapy

Induction therapy

- **The ideal timing** for vaccination in SOT recipients who receive standard induction immunosuppression is **unknown.**

For induction:

- **Baziliximab**: **On vaccine availability**

- **Anti-thymocyte globulin**
- **Alemtazamab**
  - **Delay vaccination for at least 3 months (Ideally 6 months)**

maintenance therapy

- **The optimal approach** to managing immunosuppression around the time of vaccination is **not known**.

- For transplant recipients outside of the early posttransplantation period, there are insufficient data to guide modifications of immunosuppression for vaccination, and society guidelines do not recommend routine modification of immunosuppression .

Back bone regimen for maintenance therapy:

- **Calcineurin inhibitors** : (cyclosporine or tacrolimus)
- **Antimetabolite agents** (Azathioprine or Mycophenolic acid)
- **+- Corticosteroids**
- **mTOR inhibitors**: (sirolimus, everolimus):

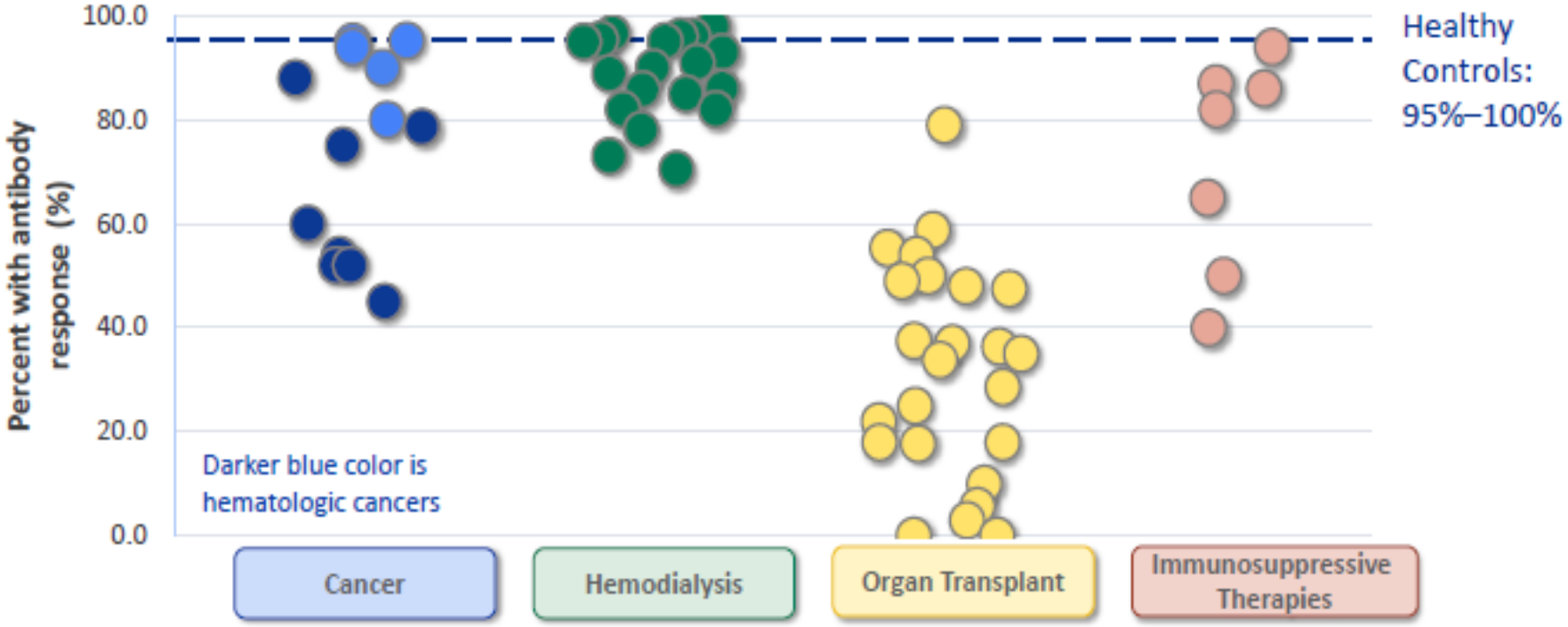
  An altenative to the CNIs
- **Co-stimulation blocking agents**: (blatacept)

Breakthrough infections

- Breakthrough infections among vaccinated solid organ transplant patients, including cases requiring hospitalization and mechanical ventilation, have been reported .

- Although the overall incidence of breakthrough infections among vaccinated transplant patients is low, **it appears to be greater than that among vaccinated individuals in the general population**.

Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63)



- Studies that compared response after 1st and 2nd dose demonstrated poor response to dose 1
- Antibody measurement and threshold levels vary by study protocol

- **Poor antibody response** to vaccine in both solid organ transplant and RMD patients receiving mycophenolate , sometimes as low as 27%.

- Rheumatology guidelines recommend holding mycophenolate for one week after each vaccine dose when possible.

- **(This is specific for CID/RMD),** as temporarily holding mycophenolate **may not be recommended in transplant recipients.???**

EBMT

COVID-19 vaccines. Version 5.0, February 21, 2021

COVID-19 Vaccination Haematopoietic stem cell transplantation

ASH-ASTCT COVID-19 Vaccination for HCT and CAR T Cell Recipients: Frequently Asked Questions

(Version 4.0; last updated September 29, 2021)

HSCT

- HCT recipients are often immunosuppressed for months afterwards due to:
  - ✓ **Conditioning regimens,**
  - ✓ **Maintenance therapies,**
  - ✓ **Immunosuppressive drugs,**
  - ✓ **Hypogammaglobinemia,**
  - ✓ **or development of GVHD, (in allo-HCT)**

- These factors may lead to a blunted immune response and affect vaccine efficacy

Haematopoietic stem cell transplantation

- Preferably complete vaccination 1 month before transplantation.
- The best efficacy of the vaccine is 6 month after the transplantation

- **If vaccination before transplantation is not possible :**

✓ **In both autologous and allogenic HSCT:**

start vaccination **3 month** after the transplantation

Is it safe to combine routine post-transplant vaccines with SARS-CoV-2 vaccines?

- Previously, it was recommended that SARS-CoV-2 vaccines should be administered alone, and at least 14 days separate from routine post-transplant vaccines.

- However, **this restriction was recently lifted by the CDC and** 14 days wait time is no longer needed between vaccinations.

Should HCT recipient revaccinate regardless of whether they were partially or fully vaccinated prior to transplantation?

- If an HCT recipient has received COVID-19 vaccine before HCT, the procedures will most likely **wipe out all immune memory** as for other vaccines.

- So, it is recommended repeating the COVID-19 vaccination series at least three months after HCT **regardless of vaccination status prior to transplantation**.

GVHD & COVID vaccine

- 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 GVHD.
- Although side effects are expected as with any vaccine, there is no example of a non-live vaccine having **more frequent or more severe side effects** in HCT recipients 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 .**

GVHD

- **In Severe, uncontrolled acute GVHD grades III – IV:**

✓ delay Vaccine until therapy is reduced

✓ or be decided based on immunophenotyping of T-cell and B-cell immunity .

Adoptive cell therapies

- Adoptive cell therapies for example, CAR T cells **(Chimetric Ag Receptor T-cells)**:

✓ postpone COVID-19 vaccination >3 months after treatment.

Human intravenous immunoglobulins

- IVIG are often given to patients with hypogammaglobinemia due to poor B-cell function.
- As SARS-CoV-2 becomes more widespread, IGs to SARS-CoV-2 may be detectable in pooled IVIG.

- Theoretically, the Igs would mask the antigens and dampen the immune response to the vaccines and cross react with serologic testing;
- **However, based on available data no delay in vaccination is recommended for patients who are receiving IVIGs**

Vaccinaton of the donor

- It is likely that stem cell donors will have been vaccinated prior to donation.
- **There is no risk to vaccinate donors** and such individuals can donate as long as they are feeling well .

- For non-replicating vaccines , it might be reasonable to wait a few days (3-7) after vaccination before starting G-CSF for stem cell mobilization to avoid overlapping toxicities or before collection.

- **The transplant donation should not be delayed** due to vaccination of the donor in case the transplant is urgent.

Should stem cell donors receive the COVID-19 vaccination to prevent disease in transplant recipients?

- Vaccinating stem cell donors prior to stem cell harvesting has not been shown to benefit HCT recipients in prior .
- **Stem cell donors should not be offered the COVID-19 vaccine for the sole purpose of benefiting the HCT recipient** unless under a research protocol.
- However, if the donor has been vaccinated, it may be desirable to wait at least two weeks after the second vaccine dose before stem cell donation (if possible) as **it may provide some protective effect to the recipient.**

When should HCT recipients receive their second dose of the COVD-19 vaccine if they become infected with COVID between doses?

- Based on data from patients previously infected with COVID-19 prior to mRNA vaccination series, HCT recipients, could be offered the second dose of their respective vaccines once symptoms have resolved and isolation precautions are discontinued, as there is no indication so far of vaccine-associated enhanced disease (VAED) or other serious adverse events.

Vaccination after monoclonal antibodies or convalescent plasma

- It is recommended delaying COVID-19 vaccination for 90 days in HCT recipients if they received either SARS-CoV-2 monoclonal antibodies or COVID-19 convalescent plasma, as part of their COVID-19 treatment;

(based on the half-life of the COVID-19–specific antibodies and based on the evidence that reinfection after natural infection is uncommon within three months ?)

COVID-19 Vaccine Clinical Guidance Summary
for Patients with Rheumatic and Musculoskeletal Diseases

August 19, 2021.

COVID-19 Vaccination in Rheumatic and Musculoskeletal Disease

American College of Rheumatology
Empowering Rheumatology Professionals

General Considerations

- autoimmune and inflammatory rheumatic disease **(AIIRD)** patients are **at higher risk for hospitalized COVID-19 and worse outcomes** compared to the general population.
- Beyond known allergies to vaccine components, **there are no known additional contraindications** to COVID-19 vaccination for AIIRD patients.

- The expected response to COVID-19 vaccination for many AIIRD patients on systemic immunomodulatory therapies is blunted in its magnitude and duration compared to the general population.

- COVID vaccination should occur as soon as possible for, irrespective of disease activity and severity, except for those patients with life-threatening illness (e.g., in the ICU for any reason).

- **A theoretical risk exists for AIIRD flare or disease worsening following COVID-19 vaccination**. However, the benefit of COVID-19 vaccination for RMD patients outweighs the potential risk for new onset autoimmunity.

No modifications to either immunomodulatory therapy or vaccination timing

- Hydroxychloroquine;
- IVIG;
- Sulfasalazine;
- Leflunomide;
- Azathioprine;
- apremilast
- TNFi (infliximab, adalimumab, etanercept);
- IL-6R (sarilumab; tocilizumab);
- IL-1(anakinra, canakinumab) ;
- IL-17(ixekizumab, secukinumab) ;
- IL-12/23 (ustekinumab);
- IL-23 (*guselkumab, rizankizumab);* Belimumab)

Corticosteroids

- Corticosteroids interfere with normal immune function in a variety of mechanisms.
- Systemic corticosteroids are subject to dose- and duration-dependency regarding their immunosuppressant effects.
- Corticosteroid doses equivalent to > 2 mg/kg or 20 mg/day of prednisone administered for ≥ 2 weeks are generally considered sufficiently immunosuppressive to warrant concern about coadministered vaccines.

- Corticosteroid use (particularly higher-dose) has been associated with impaired antibody response to COVID-19 vaccination in several studies of post-transplant patients as well as in patients with RMD.

Glucocorticoids

- glucocorticoids, prednisone-equivalent dose **<20mg/day**: **no modifications to vaccination timing**
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- There is no Consensus for vaccination timing in patients receiving prednisone-equivalent doses **≥ 20mg/day**
- (if feasible, **hold glucocorticoids 1 week prior to and 1-2 weeks after each vaccination**
- For **pulse therapy**: **no modifications** to vaccination timing

oral calcineurin inhibitors

- Assuming that disease is stable, hold for 1 week following each vaccination?
- No modification to vaccination timing

Janus Kinase Inhibitors

- (JAK) inhibitors: (**baricitinib, tofacitinib, Ruxolitinib, upadacitinib)**
- There is limited data about the impact of JAK inhibitors on COVID-19 vaccine response
- Assuming that disease is stable, hold for 1 week following each vaccination .

Cyclophosphamide

- Specific data regarding concurrent use of the COVID-19 vaccine are not available.
- Rheumatology guidelines recommend timing (IV) cyclophosphamide administration for **at least one week after each vaccine dose when possible.**

- For orally administered cyclophosphamide **no modifications** to the timing of cyclophosphamide or the vaccine are required.

These recommendations are specific for RMD and do not apply to treat cancer or for other indications.

Methotrexate

- At **higher doses MTX** inhibits the formation folates, leading to inhibition of purine synthesis and interference with DNA synthesis and repair.
- However, the mechanism by which MTX works at **the lower doses** typically used for rheumatoid arthritis and is uncertain, but some impact on immune function is likely.

- In patients with CID/RMD, lower antibody response following the mRNA vaccine was observed in patients treated with methotrexate compared to other immunosuppresants .
- In contrast, methotrexate use was not associated with poor vaccine response in several other studies.
- .

Methotrexate

- COVID vaccination Guidelines recommend holding MTX(specifically for RMD) for one week after each vaccine dose when possible.
- **One publication also recommends** holding the MTX dose scheduled prior to the vaccine.
- **No specific recommendations are available for higher, anti-cancer doses of MTX.**

Abatacept

- **For the first COVID-19 vaccine dose (only)**
- Hold **SQ abatacept** both one week prior to and one week after the first vaccination
- **Abatacept IV** : administration of the first vaccine dose will occur 4 weeks after abatacept infusion (i.e., the entire dosing interval), and postpone the subsequent abatacept infusion by one week (i.e., **a 5-week gap in total)**

- No medication adjustment for the second vaccine dose

rituximab

- In small studies of patients who received rituximab for rheumatologic disease, **only 20% to 33% had an antibody response** to the mRNA vaccine.

- Patients with a **serologic response** tended to have a greater time since last rituximab dose (median 704.5 days versus 98 days, respectively) and a greater degree of B-lymphocyte reconstitution.

rituximab

- If disease activity allows : at least 4 weeks between initiation of the vaccine series and the next rituximab dose after vaccination, as well as delaying rituximab for 2-4 weeks following the final vaccine dose if disease severity allows.

- **For patients currently receiving rituximab**: vaccinating at least 3-6 months after rituximab treatment.

- Can measure **CD19 B cells** as a tool with which to time the booster and subsequent rituximab dosing. or
- Provide **the booster 2-4 weeks before next anticipated rituximab** dose (e.g., at month 5.0 or 5.5 for patients on an every 6 month rituximab dosing schedule)

other anti-CD20 medications

- Whether other anti-CD20 medications (**obinutuzumab, ocrelizumab, ofatumumab, ibritumomab tiuxetin**), or other agents that can decrease circulating B-lymphocyte populations would have a similar effect as rituximab is unclear.

- Similarly, **the optimal timing** for COVID-19 vaccination relative to these agents **is not known.**

Acetaminophen, NSAIDs, ASA

- Assuming that disease is stable, hold for 24 hours prior to vaccination
- (no restrictions on use post vaccination to treat symptoms)

What is the appropriate timing of serologic testing for COVID-19 after COVID-19 vaccination?

- Neutralizing antibodies against the receptor binding domain (RBD) of the spike protein are considered protective against reinfection, in contrast to antibodies against the nucleocapsid, (N) which are not thought to be protective.

- **As the role of serologic testing post-vaccination is not clear, It is not recommend routine testing with serology unless done under a research protocol.**

- If serologic testing is desired by the patient or health care providers, it is recommend testing for antibodies against the spike protein anytime between 30 and 90 days after the second dose of the vaccine.
- Some of the commercially available serology assays test for antibodies against the (N) protein, which are markers of prior natural infection **and not an indication of immune response** to COVID-19 vaccines.

- Additionally, pooled immunoglobulin (IgG) may contain antibodies against SARS-CoV-2 spike and nucleocapsid proteins; thus, if serologic testing is desired, **it is not recommended testing for SARS-CoV-2 antibodies within 4 weeks of IVIG infusion due to possible false-positive results**.

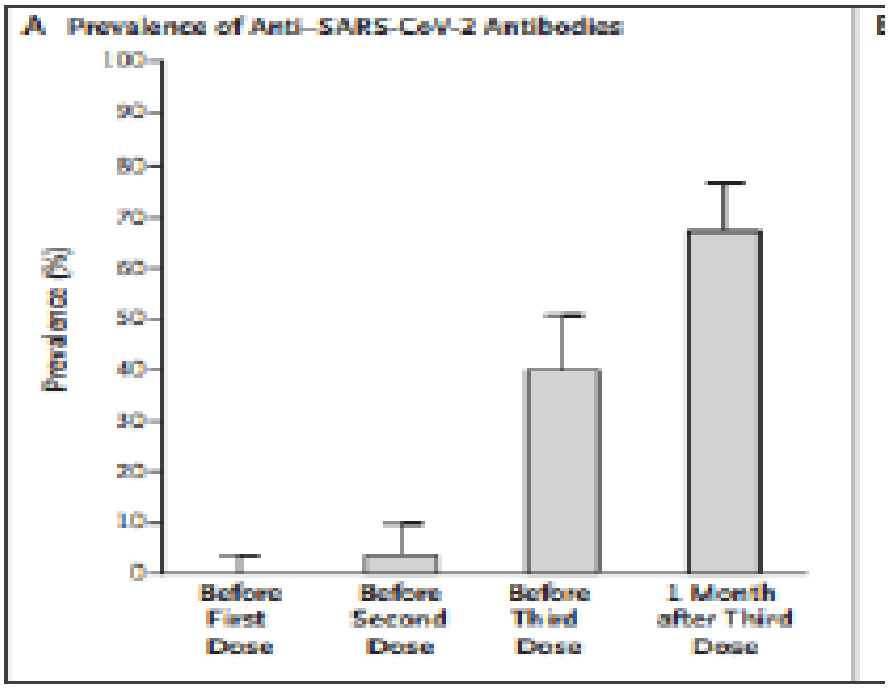
Comparing evidence 3rd mRNA COVID-19 vaccine dose in immunosuppressed people with seropositive response

Study	Patient Population	2nd Dose			3rd Dose Seronegative after 2nd dose		
		Sample Size	Seronegative N (%)	Seropositive N (%)	Sample Size	Seronegative N (%)	Seropositive N (%)
Kamar et al.	Recipients of solid-organ transplant	99	59 (60)	40 (40)	59	33 (56)	26 (44)
Werbel et al.*	Recipients of solid-organ transplant	30	24 (80)	6 (20)	24	16 (67)	8 (33)
Longlune et al.	Patients on hemodialysis	82	13 (16)	69 (84)	12	7 (58)	5 (42)
Maxime et al.	Patients on hemodialysis	106	66 (62)	40 (38)	12	6 (50)	6 (50)

- Among those who had **no detectable antibody response to an initial mRNA vaccine series,**
- **33-50%developed an antibody response to an additional dose**

Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients

No serious adverse events were reported after administration of the 3rd dose, and no acute rejection episodes occurred (n=99)



- Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)

Are there data to support mixed-dose series in immunocompromised people

- Studies from Europe have assessed heterologous primary series (AstraZeneca and Pfizer-BioNTech) in the general adult population and found immunogenicity to be **at least equivalent to homologous** series
- Large UK trial (Com-COV) found that one dose of AstraZeneca + one dose of Pfizer-BioNTechresulted in **superior immunogenicity compared with two doses of AstraZeneca vaccine** but lower antibodies than 2 doses of Pfizer-BioNTech; increase in systemic reactogenicity observed with heterologous schedules

- Evidence is needed regarding the safety and immunogenicity of using a mixed-dose approach for Janssen +mRNA vaccine in immunocompromised people

Pre-exposure prophylaxis

- Data from randomized trials indicate that Hydroxychloroquine is not effective in preventing infection and the WHO specifically recommends **against using hydroxychloroquine to prevent COVID-19.**
- Ivermectin has also been proposed as a potential prophylactic agent, but it has only been evaluated in low-quality unpublished studies and **clinical evidence supporting its use is lacking.**
- Using monoclonal antibodies for pre-exposure prophylaxis is **not recommended at the present time** outside clinical trials.

- **Recommendations are against using agents for prophylaxis outside a clinical trial.**

post-exposure prophylaxis

- The panel also noted the Emergency Use Authorization (EUA) by the FDA for use of post-exposure prophylaxis using combination therapy with casirivimab and imdevimab (REGEN-COV) for prevention of COVID-19 in patients who are **at high risk for progression to severe COVID-19:**

✓ individuals who are **not fully vaccinated** or who **are not expected to mount an adequate immune response** to complete COVID vaccination:

✓ includes those receiving immunosuppressive or immunomodulatory therapy other than hydroxychloroquine.

Thanks for your attention!