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SURVIVORSHIP SYMPOSIUM

COVID-19: What Transplant Patients Need to Know in 2022

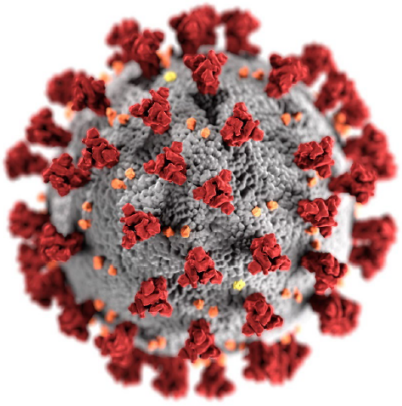
Celebrating a Second Chance at Life
Survivorship Symposium

April 30 - May 6, 2022

John Wingard MD
UF Health Cancer Center

COVID 19: What Transplant Survivors Need to Know

John R Wingard, MD
University of Florida



May 2, 2022

"I've lost count of how many patients I've lost to COVID-19. I've probably lost way more patients to COVID-19 than I have to actual cancer in the last two years."

- A hematologist in Colorado

Caution!

- HCT = hematopoietic cell transplant; aka, bone marrow or peripheral blood transplant, stem cell transplant
- COVID-19 = illness; SARS-CoV-2 = virus causing the COVID-19 illness
- This is a very rapidly changing field of knowledge
  - Some of the reports are in news releases, not peer-reviewed publications
  - Some of the reports are preliminary
  - Insights and recommendations are changing at a rapid pace

Learning Objectives

- How does COVID-19 differ from other viruses, like the annual flu
- Do HCT* recipients have a higher risk of developing a COVID-19 infection
- Do HCT recipients have a higher risk of developing a severe case of COVID-19 and/or death
- What precautions can a HCT recipient take to minimize the risk of a severe COVID-19 infection?
  - Who should be vaccinated and when?
  - Is one vaccine better for HCT recipients than another?
- What are the currently available treatments for COVID-19 and what's in the pipeline

*HCT = hematopoietic cell transplant; aka, bone marrow or peripheral blood transplant, stem cell transplant
COVID-19 = illness; SARS-CoV-2 = virus causing the COVID-19 illness

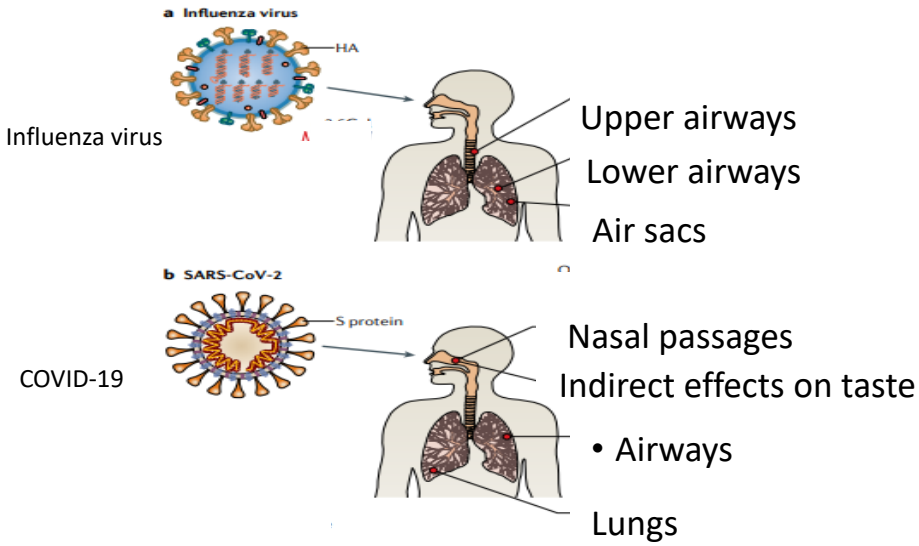
How does COVID-19 differ from other viruses, like the annual flu?

- The "flu" is not always the flu (influenza)
- There are nearly two dozen different respiratory viruses
  - Coronavirus is one of them
  - They infect animals as well as humans
- Genetic variations in the viruses occur naturally in all viruses
- Coronaviruses have been with us for a very long time
  - Most cause only mild illness
  - SARS-CoV-2 is one type of coronavirus

How does COVID-19 differ from other viruses, cont'd

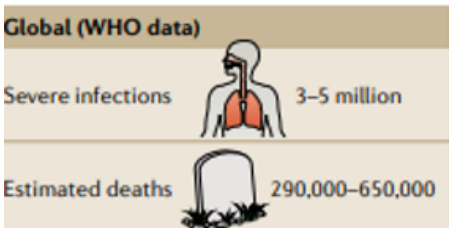
- SARS-CoV-2 virus causes COVID-19 infection
  - This is not the first variant to cause serious illness
    - SARS, MERS
- What makes SARS-CoV-2 nasty:
  - risk for deadly harm
  - highly contagious

How does COVID-19 differ from other viruses?



Global Impact

Influenza



Flerlage, Nature Reviews Microbiology, 4/2021

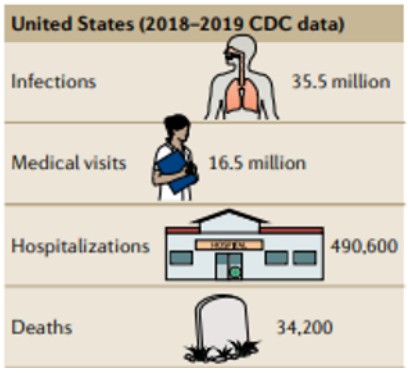
COVID-19

Cases	Deaths
458 million	6 million reported
	Daily deaths 3,547

As of March 19, 2022:

Impact of COVID-19 on U.S.

Influenza



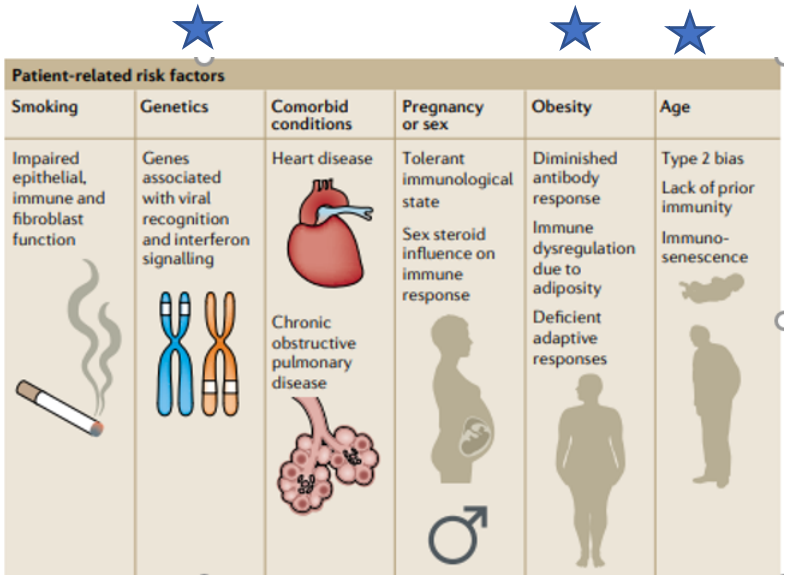
Flerlage, Nature Reviews Microbiology, 4/2021

COVID-19

Cases	Deaths
81.3 million	997,227

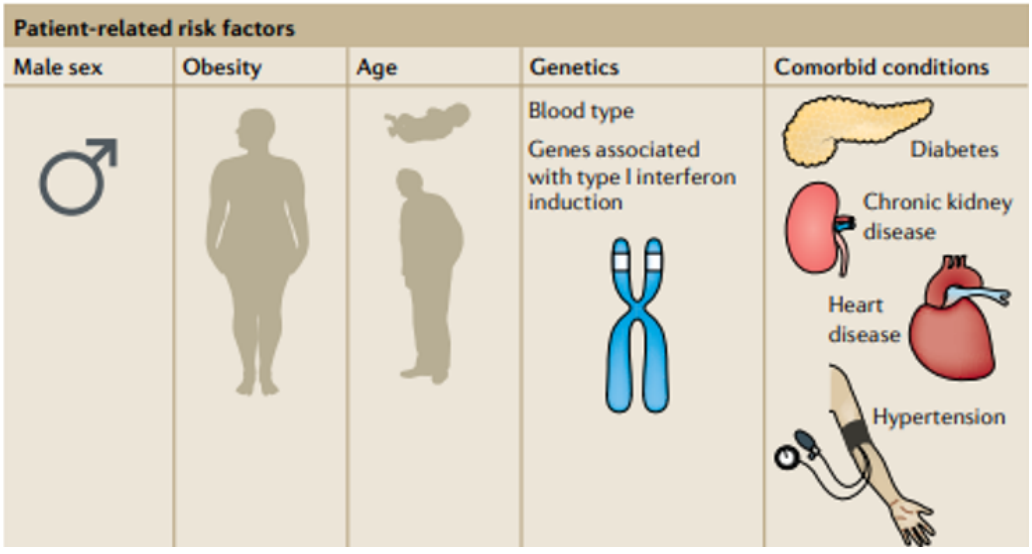
As of March 19, 2022

Risk factors - Influenza



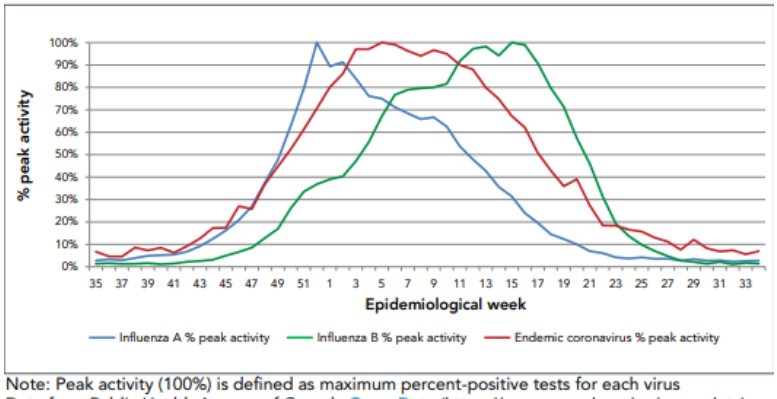
Flerlage, Nature Reviews Microbiology, 4/2021

Risk factors- COVID-19



Flerlage, Nature Reviews Microbiology, 4/2021

Most respiratory infections are seasonal

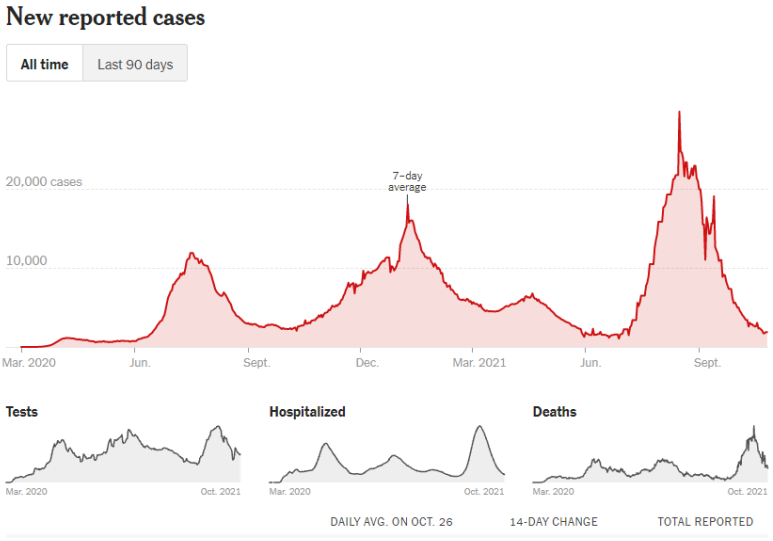


Note: Peak activity (100%) is defined as maximum percent-positive tests for each virus
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

Figure 3: The 10-year average activity of influenza A, influenza B and endemic coronaviruses by epidemiological week

In contrast, pandemic COVID-19 comes at us in waves

COVID-19 Infections, State of Florida, as of October 2021



Do HCT recipients have a higher risk of developing a COVID-19 infection?

Probably not

Do HCT recipients have a higher risk of developing a **severe case** of COVID-19 and/or **death**?

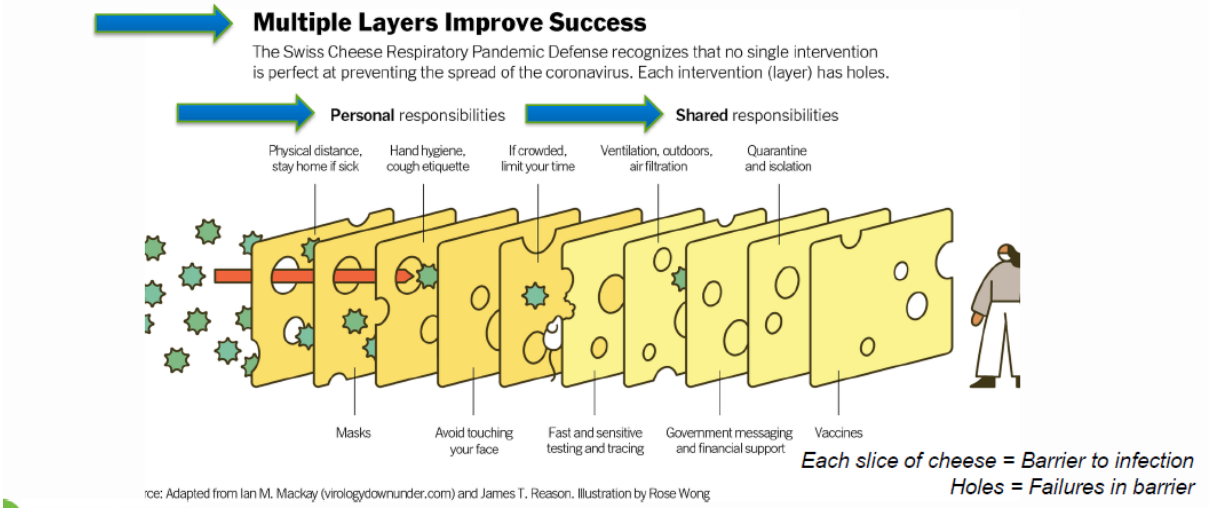
- **Yes**
- Death rate from COVID-19 in patients with blood cancers: 17%,
- Death rate from COVID-19 in general population in (U.S.): 1.2%
- Death rate from COVID-19 in HCT recipients
  - during first year: 22%
  - after first year: lower, but still higher than in general population
  - Autotransplants: higher than in general population
- Risk factors:
  - Recent HCT
  - use of immunosuppressive therapy
  - ?GVHD

ASH Research Collaborative COVID-19 Registry (Hicks, ASH annual meeting 2021, Abstr 3040; Johns Hopkins University (1/21/21)

What precautions can an HCT recipient take to minimize the risk of a severe COVID-19 infection?

How can we prevent exposure?

Swiss Cheese Respiratory Virus Pandemic Defense

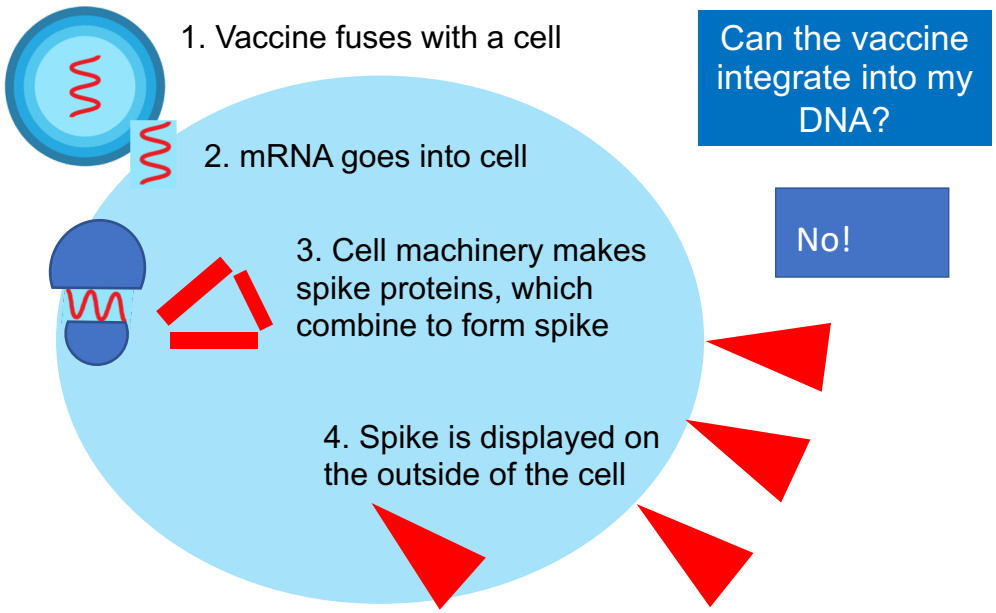


New York Times, 2020

Fast facts about the COVID-19 vaccines

- 3 approved vaccines in the US
  - Two are messenger RNA vaccines (Pfizer, Moderna)
  - One is an adenovirus (chimpanzee), that has been engineered (J and J vaccine)
- None of these are live vaccines
- All have side effects, which generally are mild
- All have enormous safety records in large and rigorous trials
  - J and J: rare clotting disorder

How do the mRNA vaccines work?



How good are the COVID-19 vaccines?

- **In the general population**, the mRNA vaccines provide >90% protection against serious illness
  - There are some breakthrough infections, but they tend to be asymptomatic or mild illness
  - BTW: this level of protection is better than provided by many of the influenza vaccines over the years
  - BTW: these vaccines are more effective than a number of other vaccines approved in other countries, notably in China
  - Vaccines offer added protection for individuals with prior natural infection
- The J and J vaccine has a lower rate of protection than the mRNA vaccines
- The vaccines may provide different amounts of protection against different variants
  - For now, this is not a big issue: the mRNA vaccines offer good protection against omnicron
- Over time, immunity wanes

How good are the COVID-19 vaccines **for HCT recipients**?

- For cancer patients, unfortunately, COVID-19 vaccines **responses are much lower**
  - One study showed 25% failed to mount antibody response after the second dose of an mRNA vaccine (Greenberger, Cancer Cell 39: 1031)
    - Especially those with B cell lymphoma, and CLL
    - Drugs such as ibrutinib and rituximab can block antibody responses
  - Small studies showed that 43% who failed to respond after 2 doses responded to a 3rd (Greenberger, ASH annual meeting, 2021, abstr 185)
- For HCT recipients: several studies in patients who were vaccinated more than one year after transplant showed reasonably good antibody responses
  - The reported data for early vaccination response is very small, but the data available suggests very low response rates

REVISED COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

February, 2022

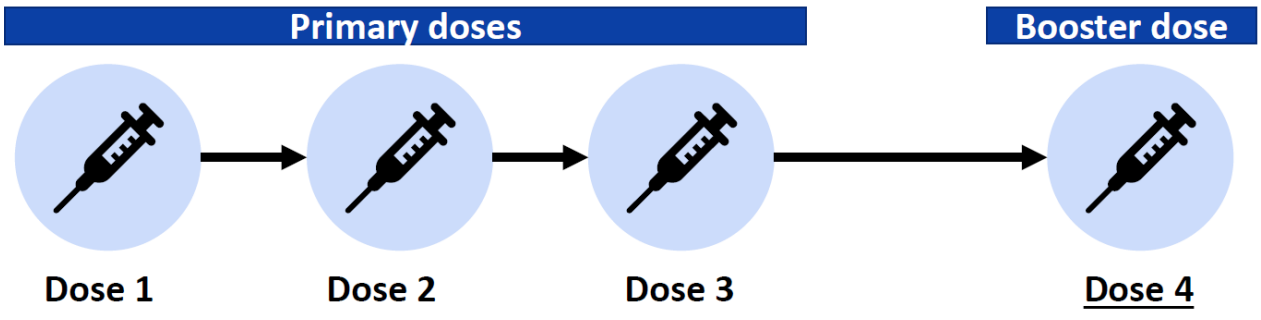
Vaccine	Vaccination Schedule				
Pfizer-BioNTech (ages 5 years and older)	1st dose	2nd dose (21 days after 1st dose)	3rd dose (at least 28 days after 2nd dose)		Booster dose* (at least 3 months after 3rd dose)
Moderna (ages 18 years and older)	1st dose	2nd dose (28 days after 1st dose)	3rd dose (at least 28 days after 2nd dose)		Booster dose* (at least 3 months after 3rd dose)
Janssen (ages 18 years and older)	1st dose	Additional dose† (at least 28 days after 1st dose)		Booster dose* (at least 2 months after additional dose)	

*Any COVID-19 vaccine can be used for the booster dose in people ages 18 years and older, though mRNA vaccines are preferred. For people ages 12–17 years, only Pfizer-BioNTech can be used. People ages 5–11 years should not receive a booster dose.
†Only Pfizer-BioNTech or Moderna COVID-19 Vaccine should be used

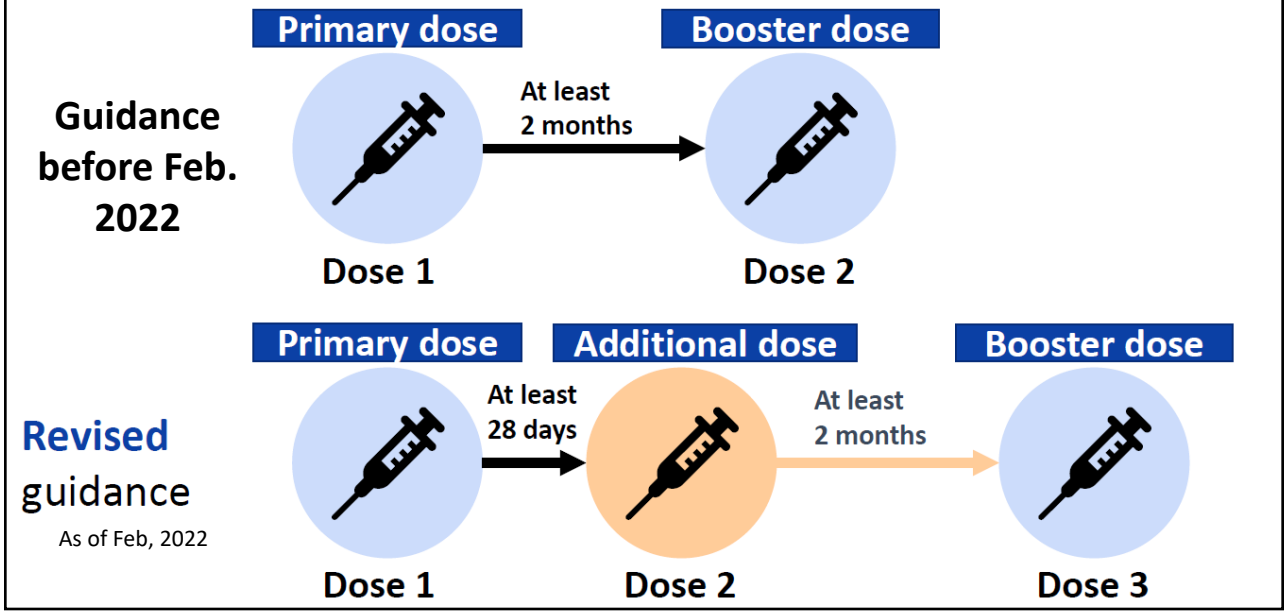
Clarification of Existing Recommendation for mRNA COVID-19 Vaccine Primary Series

Feb, 2022

- People who are moderately or severely immunocompromised should receive:
  - 3-dose primary series
  - 1 booster dose



Schedule for People Who Received a Janssen COVID-19 Vaccine Primary Series



Updates for People Who Are Moderately or Severely Immunocompromised

- Shorter booster interval after an mRNA COVID-19 vaccine primary series
- An additional dose after a Janssen COVID-19 Vaccine primary series
- Revaccination for certain sub-groups **HCT patients**
- Case-by-case clinical decision making

CDC, updated February, 2022

Revised Guidance for a 3-Month Booster Interval After an mRNA COVID-19 Vaccine Primary Series

Guidance before Feb. 2022

People who are moderately or severely immunocompromised should receive a booster dose **at least 5 months** after the last (third) dose of an mRNA COVID-19 vaccine.

Revised guidance

As of Feb, 2022

People who are moderately or severely immunocompromised should receive a booster dose **at least 3 months** after the last (third) dose of an mRNA COVID-19 vaccine.

Rationale for 3-Month Booster Interval After an mRNA COVID-19 Vaccine Primary Series

- Concern about initial immune response and **loss of protection** over time, particularly during period of **high community transmission**.
- Small studies in people with immune compromise demonstrate **immunogenicity** of a 4th dose when administered **~1-3 months** after the 3rd dose.
- Multiple studies in the general population demonstrate **immunogenicity** of a booster as early as **3 months** following a 2-dose primary series.
- Multiple countries have **implemented booster doses as early as 3 months** in the general population following a 2-dose primary series.

Revaccination for Certain Sub-Groups

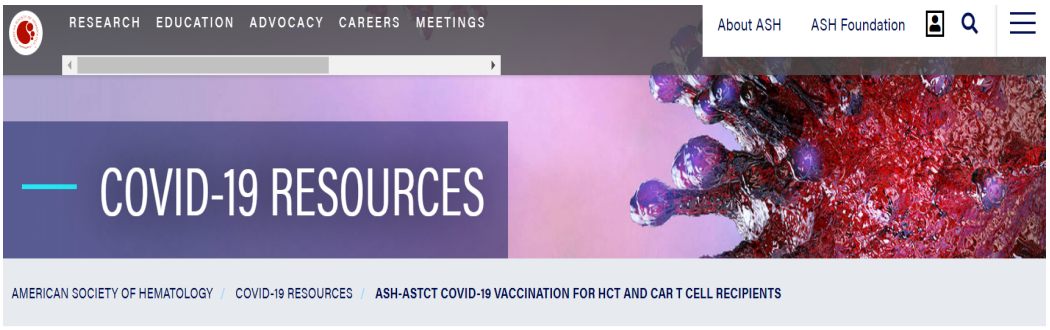
- **Prior guidance:** Limited to recipients of hematopoietic cell transplant (HCT) and chimeric antigen receptor (CAR)-T cell therapy.
- **Revised guidance:** Recipients of HCT, CAR-T-cell **or other B-cell depleting therapies** who received doses of COVID-19 vaccine **prior to or during treatment** should be revaccinated for doses received before or during treatment.
- Based on clinical judgement, revaccination may also be considered once immune competence s regained for people who received COVID-19 vaccines doses during **chemotherapy or radiation treatment.**

Case-by-Case Decision Making Based on Clinical Judgement

- On a case-by-case basis, providers who care for moderately or severely immunocompromised patients may administer mRNA COVID-19 vaccines outside of the FDA and CDC dosing intervals **based on clinical judgement** when the benefits of vaccination are deemed to outweigh the potential and unknown risks.

Several considerations to ponder about the COVID-19 vaccine

- The response to the vaccine peaks 10-14 days after the vaccine
- A COVID-19 monoclonal antibody present in the blood at time of vaccine probably neutralizes the vaccine
- These considerations suggest:
  - Wait for some time after a COVID-19 monoclonal antibody or infection before vaccination
- Try to avoid drugs that suppress immune responses or the cells that produce immune responses after the vaccine



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

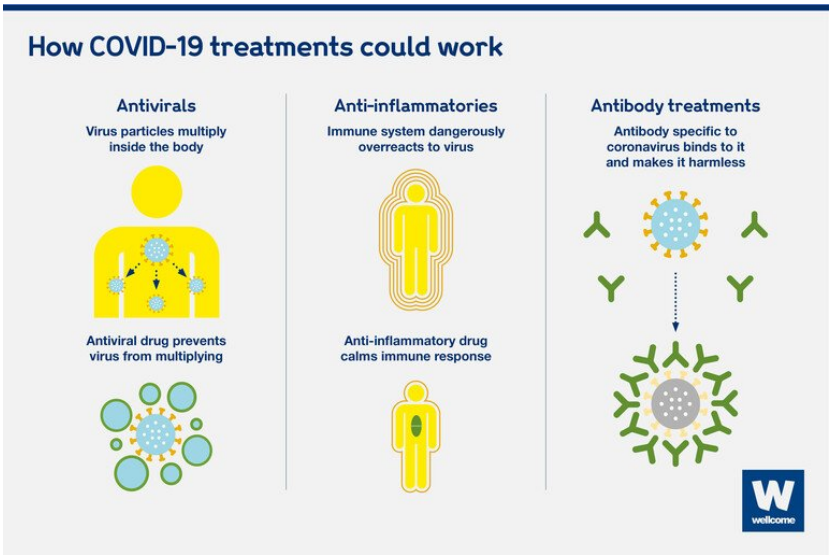
hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients

Is there something to do if your immunity is so suppressed that you are not likely to respond to the vaccine?

Tixagevimab co-packaged with cilgavimab (Evusheld)

- COVID-19 Monoclonal antibody, approved for **pre-exposure prophylaxis**
- Good activity against omnicron variant
- Tested in patients with moderate to severe immunodeficiency
- found to cut the risk of developing symptomatic Covid-19 by 77%, with protection lasting for at least six months after a single dose, given as two injection
- This is for patients who would be expected to have poor or suboptimal vaccine responses
- Short supplies required rationing initially, supply has increased
- https://www.fda.gov/media/154702/download
- Wait for at least 2 weeks after COVID-19 vaccine

What Treatments are available?



Which treatments work?

- Some therapies work for some variants, but are not so good against omicron
- Some have been studied only in moderate to severe infections
  - Low oxygen level is a key indicator of severity; get a pulse oximeter
- <u>Early start of therapy is crucial</u>
  - Some are IV
  - Some new drugs are oral
    - in short supply
    - have potentially serious drug interactions

Which treatments work? cont'd

- Nirmatrelvir plus ritonavir (Paxlovid) (Pfizer) is very promising
  - For those with
    - at least one risk factor for progression to severe disease and
    - not vaccinated and
    - treated within 5 days after onset
  - hospitalization or death dropped from 6.31% to 0.77%, a relative risk reduction of 88% Hammond NEJM 2.6.22
- **Be careful of drug interactions**

I just got infected by COVID, how do I decide what is the best treatment for me?

UF Health Outpatient COVID-19 Treatment Guidance

TIER	Clinical Risk Factors for Severe Illness	Preferred Outpatient Therapy Options *Patient should receive ONLY ONE of the following agents, listed in order of preference AND if available*
1	**Regardless of vaccination status aged ≥12 years:** • Severe Immunocompromised patients (Box 2)	1. Paxlovid oral twice daily x 5 days (review Box 1 for Drug-drug interactions (DDI)) * 2. Sotrovimab IV x 1 dose* 3. Molnupiravir oral twice daily x 5 days (if major DDI to Pax or other agents unavailable) *
	Unvaccinated:	1. Paxlovid oral twice daily x 5 days (review Box 1 for DDI) *
3	**Unvaccinated or vaccinated without booster:** • BMI > 30 kg/m2 • Cardiovascular disease • Chronic kidney disease • Chronic lung disease • Diabetes • Sickle cell disease • *Multiple co-morbidities*	1. Paxlovid oral twice daily x 5 days (review Box 1 for DDI)* 2. Remdesivir 200mg IV x 1 on day 1, 100mg IV daily on day 2, 3 in 23hr FSC 3. Molnupiravir oral twice daily x 5 days (use if major DDI to Pax or no supply of 1st line agents) a. Caution in women of child-bearing age b. Contraindicated in pregnancy
	Pediatrics ages 12-17, regardless of vaccination status: • Obesity • Mild to moderate Immunosuppression • Complex chronic disease and medical complexity with respiratory technology dependence	1. Sotrovimab IV 1 dose (if supply available) 2. Paxlovid oral twice daily x 5 days (review Box 1 for DDI)* - ONLY with risk-benefit counseling. 3. Remdesivir 200mg IV x 1 on day 1, 100mg IV daily on day 2, 3 in hospital
4	**All other FDA EUA clinical risk factors not included in the above sections**	1. Paxlovid oral twice daily x 5 days (review Box 1 for DDI)* 2. Molnupiravir oral twice daily x 5 days (if major DDI to Pax or other agents unavailable)

*Symptom day 0-4, preference oral therapy if available; symptom day 5-10, preference Sotrovimab therapy. Remdesivir to be used inpatient day 0-7 of symptoms

You don't: It's complicated! And it changes week by week. Contact your transplant team.

Sources of authoritative COVID-19 information

- Centers for Disease Control (CDC)
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- American Society for Hematology (ASH)
- American Society for Transplantation and Cellular Therapy (ASTCT)
- Your transplant team

https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_111.pdf

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Questions?

John Wingard MD

Celebrating a Second Chance at Life Survivorship Symposium 2022

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