This FAQ was developed to answer additional questions raised by participants in the webinar LLS Research Now: *NEW Research on COVID & Blood Cancer*, held on October 20, 2022.

LLS cannot give individual medical advice and does not provide medical services. Questions that included personal medical details are addressed below in general terms. Patients and caregivers should address specific questions with their cancer care team.

Evusheld: eligibility, timing, effectiveness, and safety

Eligibility and timing

Who should receive Evusheld?

Please refer to the LLS chart, FDA-Authorized Monoclonal Antibody Therapies for information about FDA authorized use of Evusheld, including who should receive it, how often it can be given and what level of protection patients may expect from it.

How often should I receive Evusheld? Should it be given more than once?

Evusheld is authorized for repeated dosing every six months for patients who need ongoing protection. Evusheld is given as two consecutive injections into the muscle, one for tixagevimab and one for cilgavimab. Evusheld should be given at least two weeks after any COVID-19 vaccine (including the bivalent booster). However, vaccination does not need to be deferred for any period after Evusheld administration.

Is two weeks enough time between the bivalent vaccine and Evusheld? Can I receive Evusheld and covid booster at the same time?

You should not receive them at the same time. You should wait to receive Evusheld until at least two weeks after your COVID-19 vaccination. This is because Evusheld may reduce your body's immune response to the vaccination.

When will Evusheld be available for blood cancer patients who aren't currently in treatment?

You do not need to be in active cancer treatment to be eligible to receive Evusheld. Evusheld is FDA authorized for patients who may not mount an adequate response to vaccines because they are immunocompromised due to a medical condition or immune-suppressing treatment.

Based on research from the LLS Registry and others, there are certain therapies that will suppress a response to vaccination even up to one year after completing the therapy (for example, rituximab or obinutuzumab), and therefore these patients may benefit from receiving Evusheld.

Your healthcare team will determine if you qualify as immunocompromised, even if you are not currently going through treatment. For more information see the FDA FAQ and refer to the question on page 3: *medical conditions that may lead to an inadequate immune response to vaccination*.

I did not respond to any of the three vaccines I received and received Evusheld in March. Should I receive another dose of Evusheld or a booster?

While you may not have a measurable *antibody* response to vaccines, there are other ways the immune systems respond to vaccines that may offer some protection (for example, by producing certain T-cells). LLS encourages blood cancer patients to receive all COVID-19 vaccines, including the new bivalent booster, as recommended, unless their oncology team counsels them otherwise.

Evusheld is authorized for repeated dosing every six months for patients who need ongoing protection. By 90 days after treatment, the antibody level from Evusheld in your blood is expected to be about one half the amount compared to when it was initially injected. **LLS is aware of certain medical centers giving Evusheld every three months to some patients.** Consult your physician to determine if and when you should get another dose of Evusheld.

Is Evusheld an option in pregnant women with current immunosuppression from medications and history of recurrent nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)?
Evusheld should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. There is insufficient data at this time to evaluate the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. No dosage adjustment is recommended in pregnant or lactating individuals.

Should CML patients who are under treatment and have a response to the vaccines get Evusheld?
Some physicians believe that if their patient produces a good level of antibody after vaccination, Evusheld is not needed. Speak to your physician about whether to get Evusheld if you are known to produce antibodies levels after vaccination. (See section below, *Understanding antibody and T cells levels*, for additional information about what is a "good" level).

Eventually will we have to pay for Evusheld?
At this time, Evusheld is available at little or no cost to patients. However, there may be an associated administrative fee.

<u>Effectiveness</u>

Does Evusheld provide protection from COVID-19 variants?
Based on laboratory studies, Evusheld has the ability to prevent infection with certain variants. However, Evusheld effectiveness is reduced against current Omicron variants (BA.4 and BA.5) compared with the original strain of the COVID-19 virus or even earlier Omicron variants like BA.1. We expect that this will mean that Evusheld will have reduced ability to prevent infections against the newer variants. LLS is analyzing the results of a survey examining breakthrough infections after Evusheld at this time; results will be reported soon. In short, LLS strongly encourages those who receive Evusheld to continue taking additional precautions, including masking and social distancing, for an extra layer of protection.

How well does Evusheld work for someone who has not responded to vaccines?
While Evusheld offers protection against many circulating variants, there are some new variants of SARS-CoV-2 that are not neutralized by Evusheld. This means that Evusheld may not provide protection against developing COVID-19 if individuals receiving Evusheld are exposed to those variants. This is why LLS strongly encourages those who receive Evusheld to continue taking additional precautions, including masking and social distancing, for an extra layer of protection.

If signs or symptoms of COVID-19 occur, patients with blood cancer should test for COVID-19 and immediately seek medical attention.

Is the Evusheld I received before treatment still protecting me?
As long as the antibodies from Evusheld are circulating in your blood, they may have protective action. However, the amount of antibody decreases over time, and redosing with Evusheld is suggested every six months for those who qualify to receive Evusheld. It is also important to note that, based on laboratory studies, Evusheld is not as effective against currently circulating strains as it was against earlier Omicron variants and the original COVID-19 virus. This may indicate that Evusheld will be less effective at preventing breakthrough infections in patients.

How long does Evusheld last? Is it completely gone from your system after a certain amount of time?
By about three months (90 days) after receiving Evusheld, the antibody level in your blood is expected to be one half the amount compared to when it was initially injected. The recommended time to get a second dose of Evusheld is six months after the first injection. There are some medical centers that are giving Evusheld every three months, so speak to your physician to see if this is appropriate for you.

How well does Evusheld work in patients with Waldenströms and multiple myeloma?
Evusheld is expected to work just as well in these patients as any other immunocompromised patient. It is important to remember that breakthrough COVID cases are possible for anyone receiving Evusheld, just as they are after vaccines. Since Evusheld is reserved for people with weakened immune systems, LLS strongly encourages Evusheld recipients to continue taking additional precautions, including masking and social distancing, for an extra layer of protection.

Can you have too many antibodies from receiving Evusheld?
No. Evusheld is safe to be given as directed.

<u>Side effects</u>
Are there any cardiac side effects? Should patients with cardiovascular disease or arrythmias get Evusheld? Can someone have a cardiac reaction three to six months after receiving Evusheld?
Serious cardiac adverse events (such as heart attack and heart failure) were infrequent in the clinical trial evaluating Evusheld. However, more trial participants had these serious events after receiving Evusheld compared to placebo. These participants all had risk factors for cardiac disease or a history of cardiovascular disease before participating in the clinical trial. It is not clear if Evusheld caused these cardiac adverse events. Speak to your physician before receiving Evusheld if you have known cardiac complications.

Is nausea a common side effect after receiving Evusheld?
The most common side effects after Evusheld are headache in 6% of patients, fatigue in 4% of patients and cough in 3% of patients. These percentages were only slightly higher than the rates in patients who received a placebo injection in the clinical studies. However, nausea and vomiting have been reported after receiving Evusheld.

I've received the full dose of Evusheld twice. What do we know about any risks to re-administering every six months?
There do not appear to be any additional risks with Evusheld redosing.

Does Evusheld impact the body's immune system to activate against covid if you get sick?
No. Evusheld does not activate the immune system. Evusheld contains antibodies that block COVID-19 infections. These antibodies work by blocking the ability of COVID-19 to latch onto cells in the body and

cause a COVID-19 infection. Evusheld is only for prevention of infection. Evusheld is not FDA authorized to treat COVID-19.

I'm allergic to rodents and cannot take Evusheld. What are some other options?
The first line of defense is to get all of your COVID-19 vaccines as recommended, regardless of whether you can receive Evusheld. If you cannot receive mRNA vaccines (Pfizer, Moderna), consider the Johnson & Johnson or recently authorized Novavax vaccine against COVID-19. LLS strongly encourages patients who are immunocompromised to layer on additional precautions to lower their risk of getting COVID-19, including masking, social distancing and avoiding indoor and poorly ventilated spaces. Read more about COVID-19 Preventive Actions from CDC.

Understanding antibody and T cells levels

Are there any tests that provide reasonable estimates of immunity? How do you measure vaccine response? Can we and should we get our t-cell and b-cell response to vaccine tested?
There are laboratory tests to determine the level of anti-spike antibodies in response to a COVID-19 infection or vaccination. Tests are commercially available from companies like Lab Corp or Quest. They must be prescribed by a physician. The tests require a blood draw. Each anti-spike antibody test is different, so results cannot be compared directly between different tests.

There are also tests to determine if T-cells are made in response to vaccination or COVID-19 infections. FDA has provided emergency authorization for the T-Detect™ test from Adaptative BioSciences to evaluate if an infection has occurred. This test also requires a blood draw.

Tests cannot determine if antibodies or T-cells are functional, although in general high antibody levels correlate with the ability to neutralize a COVID-19 infection. A positive T-Detect test suggests the subject has been infected with COVID-19. Further studies are underway to evaluate if vaccinated patient who are positive after a T-Detect test are protected from COVID-19 infections or reduced severity if infected.

What is considered a good vaccine response?
An exact antibody level that is considered "good" in response to vaccination has not been determined. In addition, the exact value depends on the type of antibody test being done, as different tests have different ranges. However, as a general rule, for the LabCorp test, values above 100 U/mL are considered the minimal value needed to provide anti-spike antibodies to neutralize a viral infection, while values over 1000 U/mL are likely protective. In the non-immunocompromised individual, anti-spike antibody levels typically are 2500 U/mL or higher. These are the values that are achieved about two to three weeks after two or more mRNA vaccine doses. The anti-spike antibody levels decay over several months.

Can having COVID-19 stimulate antibodies?
Yes. A COVID-19 infection will cause the immune system to make anti-spike antibodies and T-cells. However, in patients with blood cancer, either the cancer itself or certain treatments can impair the immune response. Patients with blood cancer remain more vulnerable to COVID-19 infections, prolonged infections, and possibly a worse prognosis. Blood cancer patients who get COVID-19 should consult a physician immediately as there are treatments, such as monoclonal antibodies or antivirals, that can help them avoid severe outcomes.

Is there a correlation between antibodies and T cells? If you had no antibody response or low response, how does that affect the job that T cells are supposed to do?
In general, yes. A recent study by LLS indicates that about 50% of patients have a positive T-cells response to vaccination regardless of whether they made antibodies in response to the same vaccination. However, a positive T-cell response is more likely in those who make antibodies to vaccination. It is important to note that a positive T-cell response does not necessarily mean that the T-cells are functional, although other researchers have conducted such tests that indicate that the T-cells are functional. The exact type of T-cells made in response to vaccination is important, as only certain T-cells can kill infected cells. This research is on-going.

Is there data on studies of T-cells or anything else that will allow us to predict protection level?
A recent study conducted by LLS indicates that about 50% of blood cancer patients have detectable T-cells in response to vaccination regardless of whether they have detectable antibodies after the same vaccination. However, a positive T-cell response is more frequent in people with detectable anti-spike antibodies to vaccination.

It is important to note that a positive T-cell response does not necessarily mean that the T-cells are functional. The exact type of T-cells made in response to vaccination is important, as only certain T-cells can kill infected cells. This work is on-going.

One of the advantages of a T-cell response is that the T-cells are directed to a part of the virus that has not gone through dramatic changes. This means that the T-cells produced in response to the vaccine should be able to kill cells infected with new variants and not suffer the same loss of activity as anti-spike antibodies to the new variants.

Vaccine response and vaccine safety

How do the new variants affect our protection from vaccines (and Evusheld)?
The new variants of COVID mean that antibodies from prior infections or from prior vaccinations may be less effective. In any case, antibodies from prior vaccinations diminish over time. Just as with annual flu shots, updated COVID boosters may be needed periodically to boost and sharpen immunity against circulating strains as they change. Antivirals and antibodies against COVID may also lose some activity. PLEASE check the FAQs and COVID resources on LLS.org often for up-to-date information on the changing spectrum. It is important to keep up-to-date and maintain precautions, particularly as winter approaches.

Should people like me get the vaccine when there is no clear lasting benefit?
COVID-19 vaccines offer at least some protection to the majority of blood cancer patients. The LLS National Patient Registry has shown, though, that immune response to vaccination varied based on a patient's type of cancer and treatment received. LLS encourages people with blood cancer to get all vaccine doses as recommended by CDC, unless their oncology team advises otherwise.

Will patients on venetoclax make antibodies to the vaccines?
It is not entirely clear that venetoclax alone blocks the antibody response to vaccination, since venetoclax is often given in combination with other therapies (such as ibrutinib or rituximab) and patients that receive venetoclax have diseases that might suppress the antibody response.

Can you tell us in general which blood cancer patients make antibodies to vaccines and which don't?
In general, patients with myeloid diseases (CML, Myeloproliferative Diseases-polycythemia vera, essential thrombocytopenia, myelofibrosis) are able to mount an antibody response after immunization. Nonetheless, we recommend that all patients with blood cancer, and their caregivers, get vaccinated and act unvaccinated, including receiving the new booster.

Patients with lymphoid diseases (CLL, NHL) particularly those on Rituxan, Obinutuzumab, BTK inhibitors (e.g. ibrutinib, acalabrutinib, or zanubrutinib), or patients who have had a recent stem cell transplant or CAR-T, are particularly at risk of not making sufficient antibodies after vaccination and should be particularly cautious. This includes patients who are within a year of their last dose of rituximab or obinutuzumab, even if they are not currently receiving treatment.

Caregivers and other close family contacts should be up to date on vaccines and maintain precautions in order to not infect their loved ones.

You can read more about how different forms of blood cancer and their treatment affect vaccine response in studies from LLS that report results after both two and three vaccine doses. There are charts toward the bottom of those pages showing the percentage of patients by cancer type who make antibodies. You can also read the full scientific papers in the journal Cancer Cell here and here.

How long do I need to wait after chemotherapy to get vaccinated?
Many patients do not make a good antibody response after chemotherapy, particularly those patients receiving therapies that attack the lymphocytes which are the primary cells responsible for making antibodies. Research by LLS and others has shown that some patients may take 6 to 12 months post-therapy to recover a full response. No specific recommendations can be made, but patients unlikely to make antibodies are often eligible for other anti-viral therapies. This should be discussed with your health care provider.

How safe is the vaccine? Are there studies on side effects of the covid vaccine and blood cancer patients?
LLS collected real-world data from blood cancer patients and survivors through the LLS National Patient Registry. The vaccine side effect profile is very similar in blood cancer patients and survivors compared to the general public. Read more about the results here.

Is there any information about COVID vaccines causing other heart problems?
Myocarditis and pericarditis, inflammation of the heart muscle or covering, are rare side effects of COVID-19 mRNA vaccines. Young males are most likely to be affected, however the effects are usually limited and can be successfully treated with medications and rest. It is important to know that COVID infection itself is more likely to cause heart issues than the vaccines, particularly in older patients with pre-existing conditions.

Should I stop taking Ibrutinib to receive a COVID vaccine? Is there information about daratumumab and COVID vaccines? Should patients that have received obinutuzumab get the most recent COVID vaccination? How long does it take for B cells to come back after treatment ends with Rituximab?
These are extremely important questions. Since the situation for every person is different, we recommend discussing the timing of your COVID-19 vaccination with your healthcare team. Generally, it is best to vaccinate before treatment as the immune response to the vaccine may be impaired in patients receiving cancer treatments that affect the immune system.

However, if you are already undergoing treatment that does not mean you should forego vaccination, including getting the new bivalent booster. Even if your immune system does not respond fully to vaccination, some protection is better than none, especially for a disease as serious as COVID-19, which tends to strike cancer patients harder. For this reason, it is advisable for patients with blood cancer to encourage family, friends and others they come in close contact with to get vaccinated too.

What is recommended for people who are unable to receive either one of the mRNA vaccines?
The first line of defense is to get all of your COVID-19 vaccines as recommended. If you cannot receive mRNA vaccines (Pfizer, Moderna), consider the Johnson & Johnson or newly authorized Novavax vaccine against COVID-19.

Bivalent booster, when, which and why?

Should I receive the newest booster if I have not responded to previous vaccines or if I already had a great antibody response? Should I wait longer to get the booster If I had COVID recently? What is the schedule for the bivalent booster?
The bivalent booster is recommended for everyone 5 years of age and older regardless of their immune status. All patients and caregivers should receive the new bivalent booster. Currently this booster is only recommended as a single shot. You can also receive the flu shot at the same time.

General recommendations from the CDC are that the booster should be given at least 2 months after your last booster, regardless of the number and type of prior boosters. Because having COVID should provide protection for a short time, it is reasonable to wait 3 months after a COVID diagnosis before receiving the bivalent booster.

Even if you did not make antibodies to the prior booster, it is worthwhile for you and your close contact to get the new bivalent vaccine. The same is true even if you had a good response to prior vaccines and/or had COVID and recovered. This vaccine provides more protection for the dominant Omicron virus variants currently in the U.S.

If I am in active treatment, should I receive the newest booster? Should I get vaccinated on a different schedule I recently had a stem cell transplant?
Patients in active treatment or who have completed treatment in the last year should discuss the timing of the booster with their healthcare provider.

When should we receive vaccinations after receiving chemotherapy or other therapies that affect the immune system?
Specific recommendations about how soon after chemotherapy you should receive vaccines should be discussed with your healthcare provider. Many patients do not make a good antibody response after chemotherapy, particularly those patients receiving therapies that attack the lymphocytes, which are the primary cells responsible for making antibodies.

How long after receiving Evusheld should I receive the bivalent booster?
Patients who have received Evusheld can get the bivalent vaccine any time after Evusheld. If your provider is planning to give you Evusheld to prevent COVID, the vaccine should be given at least 2 weeks before, if possible.

I received the newest booster and have a large nodule in my arm. Is that normal? My arm became very swollen, red and itchy after vaccination; does this indicate a positive response to vaccine or not necessarily? Should I take something to help with the discomfort?
While reactions to the booster have been similar to previous vaccines (arm pain, swelling, fever), any symptoms that are persistent should be attended to by your healthcare provider. While these responses are a reaction to the vaccine, they do not guarantee that you are making an effective immune response, so all blood cancer patients and caregivers should remain cautious about potential exposure to Covid. CDC offers helpful tips to relieve side effects from vaccination.

Even if you've had Evusheld and been fully vaccinated against COVID-19, CDC and LLS recommend that blood cancer patients and survivors should continue wearing a mask and taking other precautions to avoid infection. This is especially important since some blood cancer patients may not get optimal protection from the vaccines and may be more susceptible to infection and severe outcomes of COVID-19 after vaccination compared to the general public. You can find more information on LLS.org.

Research by LLS and others has shown that some patients may take 6 to 9 months post-therapy to recover a full response. No specific recommendations can be made, but patients unlikely to make antibodies are often eligible for Evusheld, a monoclonal antibody that can help protect them from COVID-19, and for antiviral and monoclonal antibody treatment if they become infected. This should be discussed with your healthcare provider.

Can you please comment on the use of Novavax as COVID booster shot versus an mRNA bivalent vaccine for blood cancer patients?
Novavax is the most recent COVID-19 vaccine authorized or approved by the U.S. Food and Drug Administration. It is unique in that is uses a more traditional vaccine technology. There are no head-to-head comparisons between different vaccine brands. In clinical trials, Novavax COVID-19 vaccine was 90% effective against mild, moderate, and severe disease. Its booster, however, has not been updated to target the latest circulating variants, while the mRNA vaccines have (Moderna and Pfizer-BioNTech).

COVID treatment

Paxlovid apparently has an impact on the kidneys. For those of us with impaired kidneys, how should one navigate treatment if there is a positive COVID test?
Drug doses are often altered in patients with impaired kidneys. Because the anti-viral Paxlovid is being used under an emergency use authorization and not a full FDA approval, there is information we do not have yet, including the proper dosing for people with significant kidney disease. Patients who have kidney dysfunction need to consult with their healthcare provider before taking Paxlovid.

What can you tell us about Paxlovid? Who should get it and who needs to avoid it?
Paxlovid is an antiviral medication used in patients who are at high risk of progression to severe infection from COVID. In clinical trials it was highly effective in preventing hospitalization and death. The sooner it is started after symptom onset and a positive COVID test, the better, but it must be started within 5 days of symptom onset. Paxlovid is taken orally as three pills twice daily for 5 days.

Paxlovid can impair the efficacy and safety of certain cancer medications, so it should be used with the guidance of your oncologist.

Is there any chance doctors can prescribe prophylactic Paxlovid for immunocompromised patients?
Paxlovid is not authorized for use as pre-exposure or post-exposure prophylaxis (a study found it was not effective in preventing infection in this way). It is for use only in people with confirmed COVID-19 to keep mild-to-moderate infection from getting worse.

Can one go on Paxlovid for each COVID infection? Is there too much Paxlovid one can take?
We have not heard of any restriction on taking Paxlovid for a second, completely independent case of COVID after having taken the treatment earlier. However, this does not apply to rebound cases. Rebound is recurrence of COVID symptoms and a new positive viral test 2 to 8 days after initial recovery. Rebound appears to be more frequent for people who take Paxlovid, though it also happens in people who don't take the drug. So far, there have been no reports of serious disease in patients who have rebounded after Paxlovid.

Are there any studies on Ivermectin?
Ivermectin is an anti-parasitic medication. It was tested in the laboratory and found to inhibit the COVID virus. However, the concentration of ivermectin necessary to be effective in humans is higher than it is possible to reach at approved human doses. Analysis of 14 independent studies of 1,678 patients, as well as two recent randomized controlled clinical trials ("gold standard" trials) published in the Journal of the American Medical Association (JAMA) and the New England Journal of Medicine, show that ivermectin treatment does not reduce the risk of medical admission, severe respiratory illness or death from COVID-19.

Understanding personal risk level; when to resume normal activities

What do you consider immunocompromised and how do you know when you're no longer immunocompromised?
While there is no specific definition of "immunocompromise," most blood cancer patients fall into a group of moderate to high risk of immunocompromise. This includes people in active treatment, but also those who have blood cancers that impact the B-cells and the body's ability to make antibodies --- even if they have not been treated or are a distance from the most recent treatment. Discuss your risk level with your care provider

In addition to cancer diagnosis and its treatment, age, other medications and other health conditions can also cause the immune system to function less vigorously when exposed to infection. Blood cancer patients, whether they are currently being treated or not, may be immunocompromised and have worse outcomes and even death from COVID-19 infection.

Therefore, patients should receive the most current bivalent vaccines as soon as possible. This is true if they have had previous vaccines (wait 2 months after the last booster) or if they have had COVID-19 (wait 3 months after documented COVID infection). Previous vaccines are LESS PROTECTIVE against the new variants, so in order to be protected, patients need to continue to be vaccinated according to CDC recommendations.

Is it safe for me to attend crowded events if I wear a mask and have received the newest booster? Is it safe to go to an office if no one is wearing a mask? What can I do to protect myself besides wearing a mask and vaccinations?

The most important thing you can do to protect yourself is to get your COVID-19 vaccines as recommended by CDC and your oncology team. This includes getting the updated bivalent booster as soon as you are eligible (two months after your last vaccine dose or three months after a confirmed COVID infection) COVID-19 vaccines are safe and offer protection to the majority of blood cancer patients, even if the protection is not optimal for everyone.

Fully vaccinated patients and survivors, including those who have had Evusheld, should continue wearing a mask and taking other precautions to avoid infection. This includes avoiding crowded indoor spaces, hand washing and interaction with people who are ill. This is especially important since some blood cancer patients may not get optimal protection from the vaccines and may be more susceptible to infection and severe outcomes of COVID-19 after vaccination compared to the general public. CDC provides guidance how to protect yourself and others.

LLS National Patient Registry: joining and what's next

Who can join the LLS National Patient Registry?

Our LLS National Patient Registry is continuing to recruit and accept new participants. The Registry is open to any and all types of blood cancer diagnoses, including some that may be considered as a precursor to blood cancer such as MGUS. Participants living with other chronic conditions, such as diabetes or heart disease, or are pregnant are welcome to participate.

What is the current focus of the Registry?

We are continuing to monitor COVID long-term outcomes. Currently we have stopped actively testing for blood levels of COVID-19 antibodies. Our focus at this time is examining breakthrough infections in patients who have and have not received Evusheld during the Omicron and post-Omicron surge. As the SARS-CoV-2 virus continues to create new variants, such as BA1.1, should there be future questions regarding vaccine or monoclonal antibody effectiveness, we may invite participants to again have their antibody levels tested as well as participate in surveys to assess breakthrough infection rates We continue to review the blood cancer landscape planning for what other studies would be prudent and worthwhile.