Lymphoma action
Inform | Support | Connect

COVID-19 vaccines webinar #2 your questions answered

Webinar Q&A with panel

Lymphoma Action webinar: COVID-19 vaccines – your questions answered
This webinar was held on 11 August 2021
The following is a transcription of the webinar.

Host:	Professor John Radford (John)
Panellists:	Dr Graham Collins (Graham)
	Dr Shirley D'Sa (Shirley)
	Dr Wendy Osborne (Wendy)

Transcription

John: Good afternoon, everybody. I'm John Radford. I'm president of Lymphoma Action and I'd just like to welcome you all very much to this Lymphoma Action webinar, which is focused on COVID19 vaccines. And we look forward to having an excellent hour of discussion.

Various questions have already been sent in, and these are going to be dealt with in a number of separate areas of importance, and are going to be dealt with by three excellent panellists, who will introduce themselves very shortly.

What I should stress at this point is that we don't know all the answers, and we will provide you with the best information that we have, our experience and our clinical intuition where appropriate. But the three people on the panel are experts in the lymphoma field, and I'm sure you will get a great deal of value from them. So Shirley, do you want to start off by introducing who you are, where you work, and your area of expertise. And then we'll move on to Graham and Wendy.

Shirley: Thank you, John, and thank you to Lymphoma Action for putting this webinar on and welcome to everybody. I'm Shirley D'Sa and I'm a haematology consultant at University College Hospital in London and I specialise primarily in the management of Waldenström's macroglobulinaemia and IGM-related conditions.

John: Thanks Shirley. Graham.

Graham: I'm Graham Collins. I'm a haematologist and the lymphoma lead in Oxford and my particular interests are high-grade lymphoma and Hodgkin lymphoma, but I treat all 'flavours' of lymphoma.

John: Thanks Graham. Wendy.

Wendy: Hello, I'm Wendy Osborne, and I'm a consultant haematologist in Newcastle upon Tyne. And I also look after patients with all subtypes of lymphoma, and have a clinical interest in both clinical trials and medical education.

John: So that's your panel: thank you everyone. What we thought is that we'd group the questions into topics and then one of the panellists would lead off on that. But obviously everybody else will chip in as required. And I should just say that I'm based in Manchester at the University of Manchester and the Christie Foundation Trust.

Vaccines for people with lymphoma

Vaccines for people with lymphoma: that's an important area, and clearly vaccines have made a huge difference to everyone in the United Kingdom. But there are some particular challenges for people with lymphoma. And in the clinics, we see people who are concerned about the effectiveness, the relationship of vaccines to when treatment starts, whether the vaccine is actually being helpful or not and so on.

So Wendy, an important first question is, what are the current recommendations for people with lymphoma having a COVID-19 vaccine and what are the commonest vaccines that are being employed right now?

Wendy: I think the most important message that we are stressing to our patients is that they have the vaccine as soon as possible. And hopefully our patients were offered vaccine early on in the roll-out program, because they are deemed to be a higher risk group.

So, we are keen for our patients to be vaccinated. I know that there's a lot of discussion about response to vaccination that we will come on and talk about. But we feel that some response to vaccination is better than no response. And certainly, having seen the data that we have now for patients, it does seem to reduce admission to hospital if patients have been vaccinated.

So there are three vaccines available: the Pfizer vaccine, the Astra Zeneca vaccine and also the Moderna vaccine. And, essentially, at the start we were advising whichever vaccine you're offered please just take it, please just have it as soon as possible.

There have been now some data that we are less likely to offer the AZ (Astra Zeneca) vaccine to younger patients: they are more tending to be offered one of the other vaccines, because of some rare possible side effects. But, generally, the main message is to have the vaccine as soon as possible, and if you haven't had it then please do go ahead and have it.

John: Wendy, thank you, that's very clear. I suppose one of the things that people worry about, and certainly there's been a lot of buzz about this in the press, is safety. Do you have any

comments to make about the safety of the vaccine, both in the general population and especially for people with lymphoma? Does that make the risk of adverse events greater? What are your thoughts about that?

Wendy: I think that's a really good question, because we know that every treatment we offer to our patients always has a possible side effect, and we have to weigh up the risks and the benefits. In fact I've be discussing that very question with my 16-year-old son at the weekend who has just been offered the vaccination. Obviously, he has different risks, because he doesn't have an underlying lymphoma, and we know that younger people are at lower risk of problems with COVID-19. But there are other benefits, both to him (we don't know the consequences of long COVID for example) and we also have to think about the impact on the rest of the population.

So there are always risks to anything. And I think that what we must remember is that we have to also be mindful of the benefits. During the pandemic, when there was so much prevalence of COVID, and so much unfortunate hospitalisation and illness associated with it, that the very small reports of risk of vaccination seem to be much outweighed by the benefits of vaccination for our patients.

And so now, certainly for patients I see each week in clinic, although they are asking me about the rare seen side effects, I still strongly strongly encourage them to have the vaccination. And, having had that discussion, my son also had his first dose of vaccination at the weekend.

John: Thanks, Wendy. And before we open it up to the rest of the panel, one final question for you on this area. What are the benefits of the vaccination? Do you have any data that you can tell us in terms of what is the impact on the incidence of infection, the incidence of severe illness, the incidence of mortality? Are you able to tell us more about that?

Wendy: Yes. I think we know two things: first of all we know how it has impacted on the population as a whole, and we know that patients who are vaccinated, even though they can still go on and get COVID-19 their risk of being admitted to hospital is much reduced. And we're certainly seeing that. We had, sadly, our fourth wave here in Newcastle, but our admission rates have been lower for vaccinated patients.

So for a population, as a whole, I think we have clear evidence of how effective it is at reducing the illness and reducing transmission between people and, although some people can still have developed COVID-19, it has reduced that as well.

I think what we are trying to understand more is in our population: the patients with lymphoma. I know that there are clinical trials ongoing, and that Graham will come on and talk about that in more detail, but certainly there appears to be effectiveness both in all patients as a whole, and that we should continue to still really encourage vaccination of the general population and particularly our patients who are deemed higher risk.

John: Wendy, thank you very much. It is very clear from what you've said that getting the vaccine is important. The side effect profile relative to the danger of COVID is very obvious 'in favour' of being vaccinated. And vaccinated people: the key thing is they're not getting as sick,

and the risk of being really very ill and dying from the disease is much reduced from having vaccine.

Shirley or Graham: do you have any additional comments to make on this area, before we move on to the next topic area?

Graham: John, I would make one comment about safety. Because one question we sometimes get asked is from a patient who has low platelets, because sometimes patients have low platelets due to the lymphoma or due to the treatment. And some people have heard of the side effect that Wendy alluded to: very rare, of blood clots associated with low platelets and I get asked "I've got low platelets, does that make me more likely to get that side effect?" The very clear answer is: 'No, it doesn't make you more likely'. It's not the fact that low platelets increase the risk of blood clots, it's just that this very rare side effect is blood clots with low platelets as the side effect. So low platelets does not increase your risk of that side effect.

John: That's a really important point, Graham, thank you for raising that.

Vaccines and treatment

So, vaccines and treatment: Graham you're going to lead on this I think. Do you have any comments about the best time within a particular treatment schedule to have the vaccine? And are there any instances where it's recommended *not* to have the vaccine? Any comments on that?

Graham: Yeah, that's a good question John, thank you. And potentially, quite a complicated answer, I guess. But I think most of us feel, and the recommendation that we give our patients, is that if you need treatment for your lymphoma, ideally you should get both vaccines first.

Now, there does need to be a gap between both vaccines. I'm sure most people listening to this will be aware that the usual gap is 12 weeks. But you can get that shortened, if there are specific reasons for that. And we worked with our GPs, particularly, to enable our patients to have that second vaccine earlier, perhaps at 3 or 4 weekly intervals if chemotherapy is due to start, and the rationale there is that then the patient can respond to the vaccine without having their immune system impaired by the treatment.

The other thing we're beginning to appreciate now, is the effect of specific treatments and, indeed, specific lymphoma subtypes on at least the antibody response to the vaccine. And I'm sure we'll hear more about this, but just looking at the antibody response may or may not be a very good guide to how well the vaccine's worked. It's a difficult one, but it's the easiest measure we have to look at the anti-COVID vaccine antibody response.

There was a study recently, which is ongoing in the UK, rather oddly called the PROSECO Study (unfortunately, no sparkling wine is part of that trial) but what that looked at was patients with lymphoma of different subtypes at different parts of their treatment and looking at how well they had mounted an antibody response to the vaccines.

And what it showed was that, if people had been treated *within* six months of the vaccine, in other words, let's say you'd had R-CHOP and been vaccinated three months after that and then

you had your second vaccine, you were less likely to mount an antibody response, or at least a significant antibody response, compared with if you were given the vaccine six months or longer *after* treatment.

And it also suggested that the antibody responses were lower generally in patients with low-grade lymphoma, compared with high-grade lymphoma. Now, there was a spectrum: some patients with low-grade lymphoma responded well, but on the whole, low-grade lymphoma patients had a worse – or a lower antibody titre (amount of antibodies within a person's blood) if you like – after treatment, compared with those with high-grade.

Now again, the caveat on that is, what does it mean? Low versus high? What's the right cut-off to use? We don't know. So antibody responses are just a sort of idea of how well the vaccine is working.

So, vaccine first, if possible. If you have your vaccines six months after treatment, particularly for high-grade or Hodgkin, that's probably a good time. But, you know, as we've all heard, there are a lot of cases around, and I wouldn't suggest waiting five months in order to get your vaccine after your treatment, I would get it really as soon as it's offered to you.

The one caveat to that is for patients who are coming up to a transplant – a stem cell transplant – if you're literally just a few weeks away, quite a lot of transplant physicians are saying, 'look, just wait until you've had your transplant before having the vaccine because it's just going to wipe out any immunity that you may have gained'.

So there are certain very specific instances where the clinician may recommend waiting, but on the whole: have it when it's offered, have it before – if possible – any treatment.

John: Is it worth mentioning Graham, in terms of the PROSECO Study, the fact that patients with Hodgkin lymphoma seem to be better off in terms of antibody response? And have you addressed the point about people who really need treatment urgently? So, some people, as you know, they might have a big lump in the chest and that's pressing on the wind pipes and so on, and we need to get on with therapy, and their waiting is not a good option I would have thought?

Graham: Absolutely, yeah. Everything in medicine – in life really – is risk versus benefit. And if you can wait, and it's safe to wait to get both doses of vaccine, that's great. But, sure, there are some instances when chemotherapy urgently is lifesaving, and so it's not appropriate to wait then.

I think what we would say is: our patients – and credit to our patients here – they've done an incredible job of initially shielding when they were asked to shield, and then even when that sort of shielding recommendation has been relaxed they've still been very sensible on the whole in the precautions they've taken. So yes, we've seen infections in our patients, but you know, perhaps less so than in the general population because of these additional steps that they've taken. So absolutely, there are instances when we should get on and treat.

John: So, another great question here and I must say, I haven't quite come across this before.

The question was around could the vaccine make the lymphoma worse, could it make the side effects of treatment for lymphoma worse, or are there any other complicating factors, as it were, in giving vaccines in somebody with lymphoma?

Graham: Excellent question. So there's been some interesting data: its only case reports really so do take this with a pinch of salt, but where actually giving somebody with active lymphoma a vaccine has actually led to a reduction in the amount of lymphoma present. There was a report in one of the journals that many of us haematologists read, of somebody with Hodgkins which seem to go into remission after the vaccine. So I'm not suggesting the vaccine should be used as a treatment for lymphoma, but it could work that way.

And, in fact, I saw a patient today who has had both doses of vaccine, and shortly afterwards, he noticed a reduction in the lump of his low-grade.

So in occasional cases, it may actually make the lymphoma get better and I'm not aware of any reports of the vaccine appearing to speed up lymphoma progression. Of course it can be very hard to dissect a link in that sort of thing.

So, I'd be very reassuring on that score. I have certainly had patients who have had chemotherapy and *during* chemotherapy have had a vaccine, and they have had a reaction to the vaccine and local reactions are quite common. And it might cause a fever, and of course if you get a fever on chemo you have to ring up – please do ring up your triaged (clinical contact) numbers – and they've had to come into hospital for antibiotics. But that was probably just a standard vaccine reaction. But obviously, if somebody's on chemo you have to respond in a more assertive way – maybe that's the way to put it – than in somebody who isn't on chemo. But, again, there's no reports that I'm aware of, of the vaccine actually making the side effects of treatment worse or indeed impairing the effectiveness of that treatment.

John: Absolutely. I mean, something that I think is being reported, and that we've seen in our MDT (multi-disciplinary team) meeting, is people who've had a vaccine get PET scan positive nodes under the arm on the side of the vaccine, or even in the neck, which then disappears over the number of months. And so, because the body is responding to the vaccine, which is a good thing, it's causing the lymph node to become 'hot'. So, sometimes, that might be an area which could lead to some confusion, potentially, in those patients. Have you seen that in your practice Graham?

Graham: Oh definitely, and in fact the PET radiologists are very 'on this' now and they ask the patient, have they had the vaccine, which arm was it? So, when they write the report, they do now say. But, yeah, absolutely: we've had our confused moments in our MDT of not being certain how to interpret those little nodes under the armpit.

John: Thank you. Wendy and Shirley: do you have any comments about the timing or the safety, the effect on the treatment and so on?

Shirley: I was going to say, in terms of the potential flare up with lymphoma symptoms certainly in the setting of Waldenström's – which is a very immunologically-driven and active disease – certain patients have experienced a slight flare of their immune problems such as

cryoglobulinemia which is not very common but I've seen cases of more active cryoglobulin activity after COVID infection.

And so, I think there is potential for that, but it's very anecdotal: we have to just take it as it comes, assess everyone individually. But, otherwise, I agree wholeheartedly with what Wendy and Graham have said. I think any protection is better than none: COVID can be a very nasty disease, the vaccine undoubtedly reduces the risk, not for every single person, but on the whole.

And prevention is definitely better than no cure. I think that's one has to remember that, and I think the risks from the vaccines, they've been 'rushed through' in inverted commas. But the development hasn't been short-changed: there's been a lot of scrutiny in the trials, it's just been done – as it were – neck and neck with the trials, which is unusual. Normally, it's done in a sequence.

So, I think as things go, the vaccines are so, so important, and people should really only *not* have them if they have had some form of anaphylactic reaction or something. And in that case – I means that's extremely rare – but that would need to be dealt with by a specialist individual. Other than that, I think really, they should have them, notwithstanding the timing issues in regards to treatment which your clinician should be able to discuss that with you.

John: I think the point that you've made there Shirley about the importance of the vaccine, the speed at which they were developed, and tested, approved, and implemented in the real world, has been absolutely staggering.

And a great comment about the value of clinical science and clinical trials in bringing treatments from the lab through to the clinic. In the case of this vaccine, in double quick time, it really does show that it is possible when there is such a huge threat.

I think we will have learnt a huge amount about how to do things in parallel, rather than sequence, which I think is a critical point. And also, I think, it's raised with the general public – I mean our lymphoma patients were already aware of this – but with the general public the importance of clinical trials and clinical research in improving treatments and improving approaches and introducing new therapies into the clinic. So it's been, I think, an eye opener for so many people and that's absolutely fantastic.

Wendy - do you have any comments about any of this that's been discussed?

Wendy: I think that fabulous question about 'is this going to impair my lymphoma treatment?' is something I hadn't thought about. But I agree with Graham: it makes sense that if you're stimulating the immune system, maybe you'll get some patients responding to their lymphoma.

I had a patient who was about to go into a clinical trial with relapsed refractory follicular lymphoma and nothing was touching it he was needing a bi-specific antibody on trial. He had his vaccines, we scanned him four weeks later as per trial, nothing in between, and he'd gone into a complete remission.

Now I know, as Graham said, it's anecdotal and we all need to write up these case reports so that we've got a little bit more evidence. But I definitely wouldn't have it if I feel it would interrupt my lymphoma treatment. I'm not worried about the false positives that we see on the PET scans because, as Graham said, PET radiologists as part of the questioning often ask which arm have you had the vaccine in. So you know, I agree with that.

John: Thanks Wendy. So I think we should move on to the next section and that is vaccine response and efficacy.

Vaccine response and efficacy

John: Shirley – there's a great question here. So, we want a bit of an immunology lesson I think. How does the vaccine work? And how does the immune system mount a response? How does all this happen? You give something into the arm, and a few weeks later after a second dose, we've got our ability to fight the disease. How does the body do that?

Shirley: Well vaccines have been around for many, many years in some form. So the principle, I believe, is still the same: that you administer some sort of 'target': a trigger that resembles the infective agent in some way, and it gives the immune system the impression that some invader has come in, and the immune system then has to do something about it.

We talk a lot about the immune system: we manipulate the immune system a great deal as well in our treatments, and then we try and rescue the consequences.

It is really so much more complicated than any of us really know, can even measure, or appreciate. It's highly simplified the way we think about the immune system by definition, because you may suppress one bit of the immune system, but another bit comes up to compensate. And this kind of resettlement of the whole system is constant and there's no test, no lab-based 'thing' that can reproduce that.

So I think that's one thing to mention at the very outset: it's very complex system. But if we were to break it down: when a substance is administered, if you have an infection for example, at a sub-microscopic level really, the immune system cells come out; there are different bits of the army (or whatever you call it): different 'groups'. There's the 'first responders' who will literally come and try to attack these incoming invaders physically, by rupturing the cells and so forth.

With viruses, it's a little more subtle than that because viruses themselves are not cells: they come into *our* cells and they use our cells as machines to reproduce themselves. So, there's not that virus target as such. What they do though, is cause our cells to produce some slightly odd expressions, which can then be the source of alarm to the rest of the immune system.

So, we get a response in the two broad groups of our immune system which are called B cells and T cells. There are other ones as well, which interconnect in a very complicated way.

The main job of the B cell is to generate antibodies. They don't do that themselves, but they give rise in many cases to what are called plasma cells, and the plasma cells are cells that simply, their job is to generate antibodies.

So that's, again, a simplification, but by virtue of the signals received that some foreign invader has arrived, these cells are produced in large numbers, they produce antibodies and they tend to sort of spike up in response to an infection. And then they come back down again, probably, to undetectable levels, but they are sitting in there: it's like they go back to the barracks and they wait. If there's a further infection, they come out again and they have a bigger response.

So by vaccinating people, that is what you're trying to do: you're producing a little group of, if you like, soldiers who are ready for the next onslaught, and they can then come out in force.

There's also the T cells. Now we can measure antibodies, we've talked a lot about this already, it's a relatively simple test in the lab, although I'm sure we've talked about the fact that there are many caveats when interpreting the results. But T cell function is very much more difficult to interpret and measure and test.

I think some people speculate that the response by T cells is almost perhaps even equal in the COVID setting. So just because we can't measure them, it doesn't mean it's not there.
So T cells help B cells and other aspects of the immune system to continue this response. And so, what you have in the end, it's a very sophisticated reaction to these things which happen, incidentally, automatically.

The problem arises in patients such as our blood cancer patients who may have immune systems that are already suppressed or we've given them treatment that suppresses things, that these responses are blunted. And this just means that they would like to produce antibodies but they may not be able to do so.

So, that is the problem and that that is where we start talking about what is the degree of response, does it really neutralize the infection, is it going to last a long time, do we need further doses of the vaccine?

So, that is my understanding of the way that we respond to vaccines.

John: So, just so I get that right: there are antibodies produced by B cells. And then there are T cells that in their own right attack the virus. So for there to be an effective response, you need both bits. And what we can easily measure is the antibody response, but that isn't necessarily the whole story. And assessing the whole story is rather difficult. So, even if a patient has a low or absent antibody response, that does not necessarily mean that there is no immune response available, because the T cells might be a critical part of the mix.

Shirley: Yes.

John: Wendy and Graham, do you have any additional thoughts on that? Because this worries a lot of people, I think.: 'have I got antibodies or not', but actually there's more to it than that.

Wendy: I think that's a really important point that you and Shirley have both raised, and we got to be cautious that the trial data that we have that suggests that some patients who have lymphoma don't produce antibodies (so the ones Graham pointed out: patients who have had chemo within six months, or patients with low-grade lymphoma), but we mustn't automatically think, well, they're not making antibodies, therefore there's no benefit in the vaccine.

Because as Shirley clearly described, there are other functions of the immune system, and we're not measuring T cell response. It's a bit like how we worry about fertility with all of our patients and we can measure lots of hormone levels, but the only way we really know if our chemo has impacted fertility for our patients is to measure how many babies are born. So with COVID we need to make sure that we're really clearly looking at how many patients develop COVID who have had lymphoma and vaccinated, how many patients are admitted to hospital because of a COVID infection. These surrogates are important: measuring antibodies, but we know for viruses it's not just about the antibodies. And so what I don't want is a patient to say 'oh well, I see that I'm not going to get antibodies, why bother with the immunisation?' I don't think that's accurate.

And we've also got to be mindful about antibody testing, that we're testing the right thing. I don't routinely check antibodies on any of my patients, I do as part of the clinical trial; we're recruiting to the PROSECO study that Graham mentioned. But we know that there are some antibody tests that we're only testing for if you have had the infection: so the anti-N antibodies, or there's the anti-spike antibodies that are looking to see if you've had the vaccination or the infection.

So, there's still so much that we don't understand, it's really important to collect that data. But, it's really important that we collect the data of illness due to COVID and actually how that has had the impact. So I'm a bit cautious about how we interpret these data.

John: I think this is a really important area isn't it? And there's a lot of questions about this, so I'll just read out a couple of them. Are antibody tests routinely available, and if not, why not? What are the recommendations about having routine tests? What number of antibodies is required to give protection? And somebody says here 'I produced no antibodies, what does this mean for me; can I be re-vaccinated?

So can we begin to sort of try and understand some of this, because it sounds to me from what colleagues have said, that it's not all about antibody response, although that clearly is part of it. And Wendy said that she's not routinely testing people for antibodies. And the key thing is being able to look at the real-world data in terms of how many admissions occur following vaccination, how many people get seriously ill, and so on.

So, Graham, do you want to add anything?

Graham: I'll take the question in the middle John, about the antibody level, because I think that's a real additional complexity, and the other complexity is there's more than one antibody test. So, there are different companies that make the antibody tests: one is called Roche and the other's called Abbott and they both produce different results.

So, we really are learning with this and if you vaccinate somebody who hasn't got a background of any lymphoma, blood cancer or immunosuppression, often they'll generate antibodies in the thousands of units per mil (that's the units they generally measure). Whereas, perhaps in our patients, we might get an antibody level of, let's say, of 800 units per mil. Now, does that mean the 800 units per mil person is less well protected than the 2,000 units per mil person? We have no idea. And what about 50 units per mil? That's a very low level compared to most other people but, does that mean they've got no protection due to those antibodies? We just don't

know. So it really is difficult. And I think that answers why the antibody testing isn't routinely available, because we don't know the outcome.

I always feel a bit guilty actually with this because in Oxford we do have it available, and I can just test it. And it's partly because we've got some academic microbiologists who are very interested in this sort of thing and want to accrue more data and so they've just made it available to anybody who wants it, but we have to go through a process of consenting patients and documenting that consent. So, we can make sure we've explained to patients, that we'll get a result but we don't really know how to interpret that result. And perhaps more importantly, the result shouldn't really impact your behaviour. So, if you've got an antibody level of 2,000, does that mean you can take off the mask and go to a nightclub or whatever? Actually, the results shouldn't impact on that decision. What should impact on that decision is the lymphoma you have, your other risk factors, and a discussion with your treating medical team. So we have got to be very cautious around interpreting those antibody results.

John: I think that's a key point actually Graham. So it's great that, in your area, antibody tests are being performed, but actually it doesn't inform the management for that individual. All it is doing is providing a clinical trial, essentially, isn't it? It's providing really valuable data that you can then correlate with future clinical events. So, it's important data, but it doesn't inform anything at the present time, it might do in the future, but not currently. So, I think we can probably reassure delegates on the webinar that antibodies are clearly important, but we don't know how important, and we don't know the relevance of the various tests and there are different tests. So, actually it's a sort of moot point in many ways, isn't it?

Shirley: Aside from vaccine-induced antibodies, many of our patients actually have low antibodies of their own, because either they have a disease which causes means their immune system can’t produce antibodies or they've had rituximab or other treatment. But it's interesting to me that if you take a lot of people with the same level of low antibodies, some may have infections and have real problems with them, others have absolutely no problem whatsoever. But on paper, they look much the same.

So, I think that is a kind of an illustration of the fact that irrespective of vaccines, the denominator problem is often very different in different people. And that is a starting point: adding the vaccines is yet another layer. So it's not straightforward, it's not black and white: it's not a binary thing that's for sure.

John: Yeah, so not black and white, and the fact that you've got a test result doesn't mean that we know what the meaning of that test result is. And I think this is a really, really important point.

This moves on quite nicely to booster vaccines.

Booster vaccines

John: So with any vaccine, the effectiveness of it tends to wane over time: not in all cases but often that's the case. So what's the current ‘beat on the street’ as it were with respect to boosters? I think that this has been discussed by the Joint Committee on Vaccination and Immunisation (JCVI). Shirley – do you have any information about this?

Shirley: I haven't read the latest missive, but it's on the cards, before long. I think in the Autumn is when I've heard that people who are clinically extremely vulnerable will be offered a third vaccine, because it is felt that this should augment the response that they may have had to others. I don't think this is related in any way to any responses etc because it's more a part of the rollout rather than any clinical trial.

But there are trials. There's something called the OCTAVE DUO trial: it's either underway or is planned. But that's looking in a more formal way at boosters for immunocompromised people, so I think it's on the way for those who clinically extremely vulnerable, and, I think ultimately, on the way for all of us in time. It's a question of numbers and rolling it out I think.

John: Do you have any information about swapping the vaccine? There are some trials aren't there – double-blind – where people are being given Astra Zeneca vaccine or a Pfizer vaccine first. And then in some cases, they're getting the same vaccine second or an alternative vaccine second. And there's some thought that exposing the immune system to different versions of the same invading virus is a good thing? Any comments?

Shirley: I think there is a lot of rationale for that, and there are some emerging data, as always on this topic there's data on both sides. But I think that it does make sense to consider that. There are a few other things to consider, such as whether you react in some form due to these various different methods of delivery of the vaccine.

And then, of course, there's also the pool of patients and people who are different themselves. So I think there are many variables and the Venn diagram would be rather large in the end, but I think it makes sense. I didn't know if any of my fellow panellists have any further information on this topic?

John: Graham, Wendy?

Wendy: in terms of booster vaccines, our local primary care units have been planning to start these from September onwards. Obviously, it will vary. But certainly that's what they've informed us.

I think that often with these rollouts: it's a massive thing for the whole population. There are changes week-on-week to make sure that we are doing the best for each group at each time, but certainly September is when I'm starting to warn my patients that they may be called but obviously it may be later.

John: Is that the same in Oxford Graham?

Graham: As far as I've heard, yes. It's all a bit tentative at the moment. One thing I would add is there is a bit of booster data in patients who've had a solid organ transplant. So, in other words, not lymphoma patients, but patients who've had a kidney transplant or a liver transplant, who generally don't respond very well with antibody levels to two doses of vaccine. And there is a bit of data, a small number of patients, but suggesting that a third vaccine, i.e. a booster dose, in a reasonable number of patients did lead to a significantly increased level of antibodies.

So, I think it's a very important thing to look at with our patients. And OCTAVO-DUO is recruiting and actually lymphoma patients is one of the key cohorts of patients that they are recruiting. So we will have some data specifically around the effect of the booster vaccine with OCTAVE-DUO, and also that trial is doing the interesting thing of comparing different products of vaccines.

So there is a randomisation there as to what booster you get: whether you get the Pfizer or Moderna boosters. So, we will get some idea as to whether having the same or a different booster jab is better or makes no difference. So it's a sort of 'watch this space', I think.

John: So that segways nicely into clinical trial data.

Clinical trials

John: Graham - we've got your name against that. Do you want to highlight any particular trials where the results are published and where we can gain some knowledge from those results? And perhaps go on to trials that are in progress. And then, I've got a couple of other questions that I'd like to pose to you later on. So, trials that have published and trials that are ongoing. Do you want to take us through those?

Graham: I have mentioned already the PROSECO trial and there are similar studies now that have published, looking specifically at blood cancer patients and lymphoma patients, showing very similar things. That recent treatment does seem to blunt the antibody response at least to vaccine.

A lot of those trials – such as the PROSECO trial – is also looking at T cell responses, but because they're more difficult to do, they take longer, and we haven't had the results of those yet. So we're waiting to hear about that.

Again, in patients who've had solid organ transplant, some of them who have low antibody responses have very strong T cell responses. So it just underlines the fact that we shouldn't assume that with no antibody response, the vaccine hasn't worked. So I think we wait with eager anticipation to see what those T cell responses are.

Another trial I'd quite like to highlight, which isn't necessarily in our patients but I literally saw it this morning online, is a very important trial looking at preventing infection in patients who have come into contact with COVID.

So, what that was looking at is if a patient had COVID, they looked at the household contacts. If there was a household contact they would ask them to take part in the study whereby they would administer *that contact* a monoclonal antibody – so a preventative treatment given under the skin of recombinant antibody (in other words, it's made in a lab and designed against the COVID virus). And they were looking to see if that dose – given within 96 hours of that patient being diagnosed with COVID – prevented the household contact from getting COVID. And it wasn't just the disease they were looking at: they were also looking at whether they had a PCR positive test (so they could be well but still be infected). And essentially, what they showed is that in this group of patients, there was a dramatic reduction – about 81% I think it

was – in COVID disease in those household contacts. And it was a proper randomized, placebo-controlled trial, so not all patients had the antibody, so they could compare very well.

So, that was a very interesting result because it made me think, maybe in vulnerable patients/ immunosuppressed patients, this could be a very nice strategy. Now, this is very early data, obviously it's not being assessed by regulators, so we can't get access to that, but it did make me think in a group of patients where we are worried about vaccine efficacy being low, this could potentially be a very interesting way of preventing them getting COVID when they've been exposed to a known case.

Those are the trials I wanted to highlight. OCTAVE-DUO I have also mentioned. John, I know you also are involved in an early phase study so it's probably best for you to talk us through that.

John: It addresses a question that 'I've had both my vaccines, are there any trials that I can take part in now?' So I think the answer to that is there will be, shortly, such trials available. And it's trying to address the issue of patients with lymphoma, and in the case of the particular trial I'm talking about – and this is in partnership with a company called Gritstone in California in the US. They developed a vaccine to stimulate T cell production. So, for people who haven't produced much in the way of antibodies, and bearing in mind that an immune response requires both antibody and T cell activation, then if we've got a vaccine that can stimulate T cell activation, then that might be a very good thing. So in the coming months, there are going to be trials opening that are going to be addressing these sorts of interesting questions.

And certainly in the clinics that I take part in, patients when I've discussed it with them, are really very keen to hear more about it and want to be contacted when we've got more information.

So I think the whole issue of antibody response is something that is really being considered very carefully. And various colleagues are coming forward with ideas to try to overcome it.

I think this is very re-assuring to people that it's not down to the vaccines that are being developed – good as they are – but developing new approaches that can help to overcome COVID-19 in circumstances where an antibody response can't be generated.

So, Wendy and Shirley I don't know if you have any information about similar trials or you're taking part in them yourselves?

Wendy: We have the PROSECO Study open, and all I can say is how fantastically enthused our patients are at taking part in these studies. I think that everybody wants to really understand the benefit, and not just for them, but for other people with lymphoma. Speaking to many patients each week about the PROSECO Study I can't even remember anybody saying 'no'. It is a simple blood test, but there is inconvenience in having to come back for that blood test, so I would just like to thank all of our patients for that enthusiastic response to try and improve our understanding of how we can best manage both vaccination and this disease.

John: Thanks, Wendy, for making that really important point because that's how we understand things, isn't it? The only way that we can understand what a virus, or a treatment or any intervention can do, is by studying it in a clinical trial and observing what happens. And so I just

echo that: thanks to everybody who takes part in clinical trials, because it's only by doing so that we can learn more about the diseases in question. And for something as concerning as COVID-19 has been and continues to be, we've got to do that quickly and at scale, so that we can learn as fast as we can about the ways in which this causes disease, how it affects people and what we can do about it. So, a great point there Wendy, thank you very much.

John: Shirley, any comments from new approaches to treatment of COVID-19 in clinical trials, anything going on at UCLH?

Shirley: We've been involved in some of the trials already mentioned and also a trial looking at haematology cancer patients. I think in fact results are being published this week, so it's along similar lines of looking at B cell and T cell responses.

I think my own view is that we get nuggets of information with each new trial, but putting it all together I think, will take some time to really make sense of it, because at the end of the day the proof is in the pudding and that's the number of infections, and the severity of infections and so forth.

My own view is that I'd love to know more, but I don't think we're in a position to know more than we do now. And that is why I think the LLS* approach which says 'get vaccinated but act unvaccinated' is the one I really stand-by. Go for all the protection but assume you don't have any, for now. I mean, it sounds a bit depressing because we're trying to come out of lockdown and everything else, but I think over the next few months, the data will keep coming together and on an exponential level we'll probably get more answers than we are right at the moment; we're still at that end.

**LLS is the Leukaemia and Lymphoma Society in the US.*

John: Thank you, Shirley. While we're still talking about clinical trials, we haven't mentioned RECOVERY (trial) and of course that's been a huge success in terms defining – internationally – the first standard of care ever identified, so quickly, and that's the use of dexamethasone for the treatment of people with established COVID-19. And that we know is extremely effective in a proportion of people about limiting the conversion from ward-care to intensive-care and also reducing the incidence of death. So that, again, is a great example of a quickly set up, fairly straightforward clinical trial, in a randomized way, adding sequentially different new treatments to a standard of care. And I think that's demonstrated to the world actually, that the NHS, and all the structures that we have in place are really well-suited to doing these sorts of cutting-edge pieces of research, which can provide answers very, very quickly if we do it correctly.

So thank you to everybody who's taking part in those trials if they have: it's such valuable work and I know that it's really appreciated it everywhere.

Behaviour and how to 'live with' COVID-19

Now we can move on to the final section about behaviour following vaccination and the whole thing about shielding, which is a word that tends not to be used anymore, but I think we know that people with lymphoma are more vulnerable. How do we behave?

I think Shirley's already alluded to this in one of phrases: ‘get vaccinated but behave as if you haven't been’. I think we could have a bit of a discussion about this. So what's your advice Graham to patients right now? They’ve got lymphoma; let's have a few scenarios: somebody who's young, who’s had Hodgkin lymphoma, was treated to complete response, they had radiotherapy to the chest, but they finished all that two years ago, and they're 25 years old. What’s your advice to that individual? That was completely made up by the way.

Graham: You’re illustrating a point John, which is that it really is a patient-by-patient basis that we have to have this discussion: there is no ‘one size fits all’.

I think one thing we have learned just by way of preamble is there's been this very big project called the UK Cancer Coronavirus Monitoring Project, which has looked at the outcome of patients with all cancers, not just blood cancers, not just lymphoma, who have been infected with COVID (so a PCR positive with COVID). And there's been a lot of focus on the blood cancer patients including lymphoma patients. And what we've learned from that is that, actually, patients with lymphoma, yes, they are at higher risk of a worse outcome with COVID than somebody without cancer, that is true. But they're not as high risk as some of the other blood cancers such as acute leukaemia or myeloma. And that gives some degree of reassurance: I appreciate it’s not *that* reassuring - there is still a higher risk, but some degree of reassurance.

The other thing that I found very reassuring from this project, albeit I should say this data isn't published yet (we're still in the process of analysing it), but there didn't seem to be a very bad effect of recent chemotherapy or indeed rituximab treatment. We sort of assumed that at the start of COVID if people had had recent chemo, they would have much worse outcomes with COVID because of the immune suppression. But, so far at least, we just haven't really seen that. So obviously, we do need to be cautious about COVID but there are some reasons to be cautiously optimistic.

What was *very* important, though, are the ‘traditional’ if I can put it like that, risk factors that we already know about COVID, such as age, such as dare I say sex (men do worse than women) and other comorbidities such as kidney problems, heart problems, high blood pressure, lung problems.

So for a young patient as you've outlined John, who's a while away from treatment with Hodgkin, actually they are pretty low risk. And, yes, I would be still saying take sensible precautions. But if they said to me ‘look Doc, should I be shielding?’ I'd say, ‘no, I don't think I would be recommending that’, but I would be saying stick to the government guidelines as laid out for the general population, for that specific patient.

John: So, let me bowl another one at you. So somebody in their mid-seventies who's got follicular lymphoma, they've just finished some immuno-chemotherapy, they're about to approach or considering rituximab maintenance, they've also got diabetes and hypertension, and they've been a smoker of 30 a day for some considerable time. What's your advice there?

Graham: Clearly they’re higher risk of a worse outcome if they do get COVID because of their age, because of their other medical problems, partly as well possibly because of their previous treatment, although with the caveats that I've already mentioned. And also this sort of patient we would be worried may not have responded quite as well to their vaccine.

And just one quick word about maintenance rituximab: as I appreciate lots of people are on that or will have been on that, that probably does still impair your vaccine antibody response. Going back to our previous discussions, it doesn't mean you shouldn't have it, but it just means that these things should be weighed up in a discussion with the clinician of the importance of the maintenance versus the effectiveness of the vaccine.

So that patient is clearly higher risk. I still wouldn't necessarily be saying 'you must shield' although some patients do interpret risk, or handle risk, differently so some patients would say, 'I want the least chance of getting COVID as possible because I'm worried that I would die'. Fair enough. And so some patients are still shielding and that's fine: I think if that's how they approach that, then I would support that. But I wouldn't necessarily say everybody has to do that, but I would say take sensible precautions. So what do we know are high risk pursuits: we know that being indoors for long periods of time in badly ventilated buildings, in crowds, I would probably say many forms of public transport particularly in busy times, these are relatively high-risk places for contracting COVID. So I would be advising to reduce risk in that sense. So yes, I think it's still OK to go out, but perhaps stay outside if you go to a bar or restaurant if there's outside seating seems sensible, or sticking to times where it's likely to be less crowded or less busy. So it's about taking sensible precautions plus as I say, different patients will interpret risk differently and adjust their behaviour accordingly and that's OK.

John: Thanks Graham, that's very helpful. Shirley: what's your practice, what's your advice at UCLH?

Shirley: Again, it does depend on the patient and their subtype of lymphoma, whether they're on treatment, whether they're on watch and wait, whether their treatment was a long time ago. Broadly, very much along the lines of what Graham has outlined, it's a somewhat individualised, sensible approach that you can live with really. Because it's a long time that this has been ongoing, and people *do* want to reconnect with their families, and so forth. My own personal view is it's easier in the summer, because we can be more outdoor-based. And I do think for this air business of being outdoors with fresh air flushing the virus away is actually probably very important.

I think as it gets cooler, and as we see how things pan out over the autumn, we'll all just have to rethink, using the most current situation of what's going on, about numbers, about other flus because I think there is a feeling that the non-COVID flus are going to go upwards because they were previously not so prevalent and people didn't really mix, so it's going to be a big problem there. And that'll confuse things further.

So I think as the autumn and the winter sets in, unless there's some miracle that happens, I think more caution probably should come back in. I think really by the end of the year and into spring is honestly more likely a time when we actually have even some semblance of a handle on the way things are really going beyond very, very broad base data.

John: Thanks Shirley.

So on that very sensible precautionary note, I think we should pull this webinar to a close. It's been an absolutely excellent hour. It's gone very quickly.

I hope everybody who has logged in has enjoyed it. I certainly have, and it's been made so easy by the excellent panellists who have given of their time and expertise so well.

So I'd like to thank all of you for attending. It's been great to be part of this webinar also to Graham, Shirley and Wendy for their great contributions and also to Lymphoma Action for hosting this. I should just point out that Lymphoma Action do great work supporting people with lymphoma, and they remain open for business day in day out. So if you have concerns, worries or require information, do get in touch. And, of course, they'll also be very happy to receive your financial contribution, if you feel able to do that.

So, thanks everybody. It's been a great afternoon, and have a great rest of day and rest of summer, and see you all again soon. Thank you very much.

For more information about lymphoma and COVID-19 please see:
www.lymphoma-action.org.uk/COVID19

For more information about lymphoma, COVID-19 and research studies please see:
https://lymphoma-action.org.uk/about-lymphoma-covid-19-and-lymphoma-covid-19-vaccine-information/how-effective-covid-19 (DO WE HAVE A VANITY URL?)

This is a transcription of the webinar. Please note that this comes from an automatic transcription from the webinar software. Although every effort has been made to ensure the content is an accurate representation of what was said, Lymphoma Action accepts no liability for any inaccuracies.

All views or opinions expressed in this video are that of the webinar panel and do not represent that of Lymphoma Action. This information does not constitute medical advice. For more information view our disclaimer at lymphoma-action.org.uk/Disclaimer

3 Cromwell Court, New Street, Aylesbury, Bucks HP20 2PB
General enquiries 01296 619400