Transcript: Webinar - COVID-19 challenges and solutions 9. Updates on treatment, vaccines and prophylaxis | 16 December 2020

Watch the webinar

During this webinar our audience submitted their COVID-19 IPC questions to our expert panel.

Panel members:

- Dr Daniele Bryden, Consultant in Intensive Care Medicine, Sheffield Teaching Hospitals Trust
- Professor Graham Cooke, Professor of Infectious Diseases, Imperial College London
- Professor David Lalloo, Director, Liverpool School of Tropical Medicine
- Professor Peter Openshaw, Professor of Experimental Medicine and Senior College Consul, Imperial College London

Chair: Dr Mike Ankcorn, Infectious Diseases and Virology Registrar, Sheffield Teaching Hospitals

Disclaimer

The HIS webinars may contain expert opinions and preliminary reports of work that have not been certified by peer review. They should not be relied on to direct clinical practice or health-related behaviour and should not be reported as established information without the consent of the panel members.

Uncertified transcript

The following transcript of this HIS webinar, or any portion thereof, is being delivered UNEDITED and UNCERTIFIED by the Healthcare Infection Society and Panel Members and was created using artificial intelligence software. The reader agrees not to disclose or copy this uncertified and unedited transcript in any form (written or electronic) to anyone. This is an unofficial transcript, which should NOT be relied upon for purposes of verbatim. This transcript has not been checked, proofread, or corrected. It is a draft transcript, NOT a certified transcript. As such, it may contain computer-generated mistranslations, resulting in inaccurate or nonsensical word combinations.

Mike Anckorn 0:04

Okay, welcome everyone. And I think we're just waiting a few more minutes for everyone to join and then we'll start. Okay, so we're about to start. Thank you all for joining us. This our ninth webinar, on Wednesday, the 16th of December, in the COVID-19 challenges and solutions series. It is an audience led webinar which will focus on updates on treatment, vaccines and prophylaxis. We've got a fantastic panel today, I'm going to allow them to introduce themselves, and tell us their current position and role. So we'll start with Professor Graham Cooke.

Graham Cooke 0:30

Thanks Mike yeah I'm Graham Cooke I'm a research professor based at Imperial. My clinical interest used to be in hepatitis and now is mostly in COVID.

Daniele Bryden 0:44

My name is Daniele Bryden, I'm a consultant in intensive care medicine in Sheffield, and I'm also the Vice Dean of the faculty of intensive care medicine.

Mike Anckorn 0:55

Thanks Danny, and we've got Professor David Lalloo.

David Lalloo 0:59

Hi, I'm David Lalloo I'm Director of the Liverpool School of Tropical Medicine. I'm an infectious disease physician and had a particular interest in prophylaxis against COVID, in the last few months.

Mike Anckorn 1:08

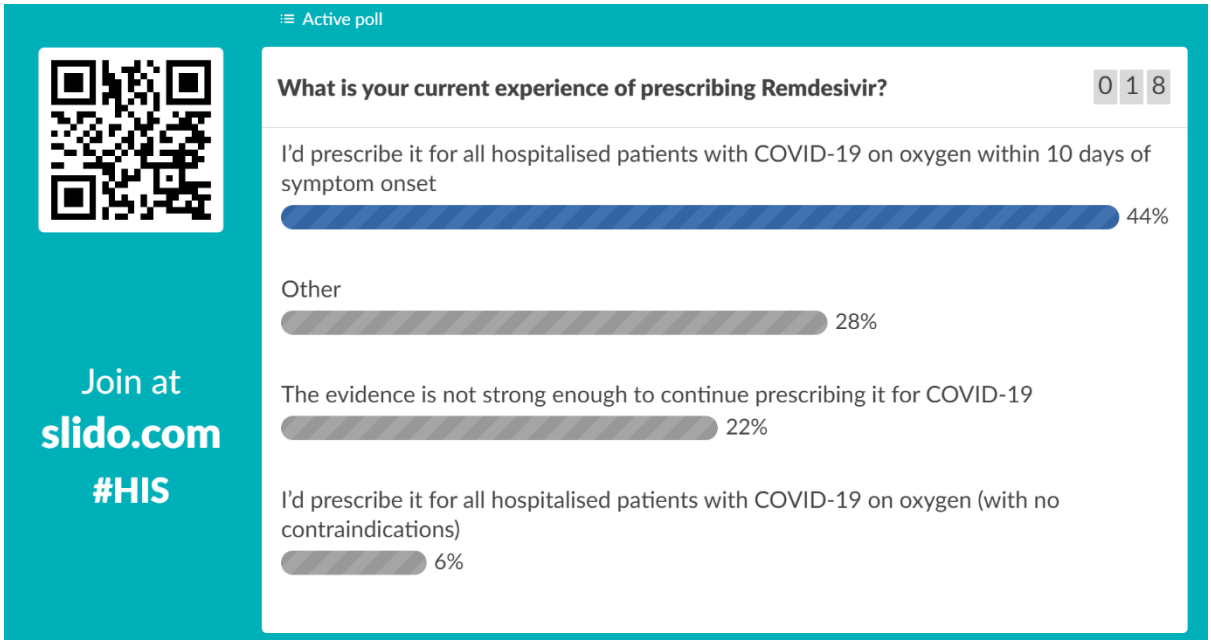
Thanks David, and finally Professor Peter Openshaw

Peter Openshaw 1:14

Hi everyone I'm professor of experimental medicine at Imperial College, and I'm a member of NERvTag which is a committee that feeds scientific advice up to SAGE into the government. So I'm really a respiratory immunologist.

Mike Anckorn 1:34

Thank you so before this webinar we asked you to submit questions to put to the panel. We selected, about eight or nine questions and the most popular questions for the panel to discuss in the first 40 minutes of the webinar. And then during the last 15 to 20 minutes, we'll answer live questions which you can submit via Slido. Slido is the app which you can download and throughout the event you can use the Slido app to express your opinion, by voting on live polls. To participate in the polls and questions please use that app and enter #HIS. So if we can start with the first poll and then move on to the questions. The first poll is about your current experience of prescribing Remdesivir.



Okay, great. So thanks everyone for voting. So interesting majority of people chose "I'd prescribe it for all hospitalized patients with COVID-19 requiring oxygen within 10 days of symptom onset".

So, if we move on to. Let's just to focus everyone's minds on the first question. So, first question is, do any treatments including Remdesivir, have any efficacy during early infection. But those at high risk of developing severe illness.

Question 1:

Do any treatments (including Remdesivir) have any efficacy during early infection for those at high risk of developing severe illness?

Healthcare Infection Society

And that's a question to put to Graham start with.

Graham Cooke 3:38

Thanks Mike. I guess it's helpful to start with a sort of broad view of treatments and how it sits in different, different stages of illness. I think one of the key things to understand about the treatment of COVID is that there's a progression of illness where early on, it's dominated by virus in the upper respiratory tract and the local response. And then the subgroup of patients who progress, then increasingly there's a host response that comes in and inflammation that then drives the disease, particularly in the lung but not just in the lung. And that progresses over time. And so when we're thinking about treatment then probably different treatments are targeting different parts of that path, and some will be focused on the virus and some will be focused on the host response and I think, you know, for those of us who've done infectious diseases, then this will be a familiar concept, particularly in TB for example. TB is a really good example of where we where we treat the pathogen but in some specific circumstances we also have what we would call host directed therapy. So I think when we're talking about Remdesivir then we're talking about virally directed therapy. And it's likely that that's going to be more useful early on in the disease course and so Remdesivir is a nucleotide analogue it's, it actually started life is supposed to be a Hep C drug but it wasn't any good at that. And it was repurposed initially as an Ebola drug but it wasn't much good at that. But it was quite safe and so based on *in vitro* evidence, it was evaluated early on, for use in COVID. And then we've got four or five trials now and it's fairly clear that the effect on mortality certainly late on in that progression of illness is minimal at best. And I think in terms of the studies that were done initially in China, and laterally through the WHO platforms and so forth, its effect on mortality is low at best. But obviously, it does seem to have some clinical benefits and probably the best quality study is the ACTT trial that was placebo controlled in a relatively small number of patients and there were various caveats to it, but it did seem to show a clear benefit on time to recovery from 15 days down to 10 days. And in the secondary analysis there was some trend to mortality that maybe reached significance but it did suggest it was having some clinical benefit. And I think within that it's quite clear that there were subpopulations that seemed to have a different level of benefit from Remdesivir.

You can debate how valid is to split up different subgroups but it's fairly well recognized now I think in COVID it's useful to do that. And we've seen that approach taken to dexamethasone data for example, but it's clear that where do see a benefit. With Remdesivir you do see it in that that group will require oxygen, but the effect is not really there later on or early on. And so when we talked about earlier than, I guess, if we can get a bit distracted by where we are. And I think in hospital medicine we're really often quite late. And so it's important to remember that when we mean early really we mean community treatment and we've got very little evidence on that. And of course, Remdesivir is intravenously delivered so doing that in the community is hard. And we really don't have very good….well we don't have any good oral antivirals that we think are going to work at the moment there are still some things being evaluated. And until we have those, then you know the idea of really early treatment I think is difficult. And really we have to look to other things so you know even some of the interventions being evaluated are slightly optimistic, the idea that antibacterials are going to work against the virus I think is rapidly being shown to be optimistic. This erythromycin data that came out yesterday and principal may tell us otherwise but it would be a great surprise if it did. And so we're kind of left then with other therapies like monoclonal therapy convalescent plasma for example which could be delivered early in infection but again you know logistically hugely challenging so. So it is a challenge I think Remdesivir does have some benefit and I think that the poll reflected majority of people use it I think there is confusion because obviously the WHO has recommended against using it, but based on weak evidence. And that's a separate conversation you might come to in discussion so if it was my parent being admitted on oxygen they'd be getting Remdesivir, I think.

Mike Anckorn 7:56

Thanks Graham. Anybody else got anything to add to that question? Great. Okay, so we move on to question number two, then.

Question 2:

Studies have shown those with severe COVID-19 may have a blunted or poor interferon response, is there any evidence (or ongoing studies investigating) that interferon may prevent severe disease if administered early?

Graham Cooke 08:22

Yeah, so the question is whether the evidence that there may be a blunted interferon response in patients with severe COVID in evidence that interferon may prevent severe disease. So, I mean, clearly, we know that type one interferons typically play a key role in many viral infections and from, from previous coronaviruses that have been studied it seems to be clearly type one his parents have an important role. And before COVID came along that was interested in interferon therapy, sometimes in combination with Kaletra for example the HIV treatment for other coronavirus treatment like MERS and there are trials underway for those conditions. So, it was obviously something that people were thinking about very early on in potential treatments for a novel coronavirus. And I suppose one of the features of this epidemic has just been the pace, and scale and achievements of genomic science which has given us a very early insight into aspects of pathogenesis that I don't think we even got to at all in some previous pandemics even with Peter's fine work with flu. Consortia like ISARIC have done amazing work and genomic in particular, so we do have some evidence now that the interferon pathway is important in severe disease so some of that comes from the big genome wide association study that's been published, which seems to suggest an association between variation in interferon alpha receptor 2 which is part of the interferon pathway. And there's been other work done looking for rare variants in the interferon signalling pathway that might predispose to severe infection, and they do seem to be overrepresented in those with severe disease so we have some good evidence to think that the pathway may be important.

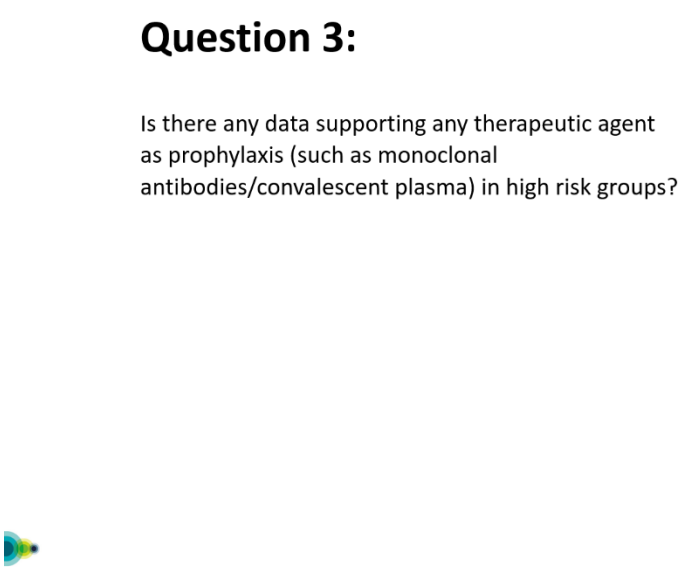
And along with some interesting evidence that perhaps the generation of auto antibodies against interferon may also be associated with severe disease so various pathways suggest this could be pretty relevant. And then we have at least a couple of trials suggesting that therapy. Well, so we have, the WHO trial again a large platform trial which looked at interferon one beta, which I think was an injectable treatment in in relatively advanced disease again going back to the idea that you know hospitalized patients are probably quite late on in the pathway, we might debate, what we think interferon will do but we probably think it's more likely to be in the antiviral camp than the host directed camp. So, perhaps not that surprised that wasn't a big effect seen there. But then there's obviously, the possibility of inhaled interferon which has been quite exciting and a small spin out company from Southampton I think that has shown some interest in phase two data with inhaled interferon one beta which does seem to have a significant clinical benefit in a small number of patients and I think that a single centre study and all the usual caveats - but that does seem to be useful and that may reflect the fact that you can deliver a relatively high local doses which are important into the lung without the systemic toxicity that you get from interferon.

So, I mean, I think that's been taken forward to phase three but again in a relatively small number, I think. Originally, some people will remember that when recovery started it was going to evaluate this as an intervention. And actually it looked like one of the more interesting interventions. Still does, but what were the priority criteria for selecting drugs into recovery was the ability to scale up within the life of the pandemic. This was going to be a challenge for this particular drug so we don't have the big numbers that have been done for other agents, but certainly I think it's something that looks interesting. And we should be getting some more data coming through, continuing I think there are various studies going on throughout the world but again I would imagine that the earlier you can get into the, to the, to the illness, the more likely you are to see a bigger effect. My guess would be, others may disagree.

Mike Anckorn 12:19

Right, thanks Graham. Anything to add to that? Great, thank you.

So, question number three. Question number three is looking at therapeutic agents so is there any data supporting any therapeutic agent as prophylaxis? I think this question is for David please.



David Lalloo 12:40

Thanks, and certainly since the beginning of the pandemic I think there's been an interest to, to look at whether we could find prophylactic agents of the population or particularly high risk groups against COVID, and that we will all remember the excitement at least in the first few months about all health care workers taking hydroxychloroquine to prevent us getting this this disease. I think over time we refined our thinking about prophylaxis and of course, in the context of vaccines we'll talk about later on. Prophylaxis I think becomes a really interesting question about certain groups, but certainly if you think about prophylaxis either in the, in terms of protecting certain high-risk workers, such as the healthcare ideas, or in the use of a public health intervention to prevent disease developing in those that have actually been exposed to an outbreak. And I think where we've got to now, given that it looks like we've got pretty good vaccines coming through, is to particularly think about prophylaxis in those groups that may not respond well to vaccines, for whatever reason, because we know senescence or because they are immunocompromised and so won't get a normal vaccine response.

We don't actually know yet about vaccine responses in many of those groups. So, I think there are still a lot of things to be thinking about. But I think that's where we'll see prophylaxis being focused over the next year or so. Other reasons why the vaccine escape and poor duration of vaccine responses - that does mean that the prophylaxisis not yet dead.

I could have answered the question in a single word which is no, and effectively I don't think we have any evidence of any good evidence of any agent being effective prophylaxis. There are ongoing hydroxychloroquine studies have mixed results on small hydroxychloroquine studies but none of them I think will convince anyone that there's going to be an exciting prophylactic agent. We've got

something like 200 trials in prophylaxis going on around the world. Now, 11 of those in the UK. And that varies from mixers and monoclonals- the AstraZeneca mixture, for example, to ivermectin due to all sorts of different agents which are affecting both the antiviral pathways and immune pathways, but I think very simply, at the moment we really don't have anything that I think is a convincing prophylaxis and the search for that will continue.

Mike Anckorn 15:13

Thanks David. It's clear that a lot of the data that's been generated has been generated from really high quality trials, recovery study and others around the UK. Graham I think one of the questions I had was from a registrar point of view, they're on the call - how can they get involved in some of these controlled trials ready to help drive research forward?

Graham Cooke 15:35

Yeah, so, I mean I think recovery is a good example and I think many people listening probably have been involved or are involved in some way. And I think certainly early on in March and April, then I think there were a lot of people. And particularly, you know, junior doctors on the front-line seeing patients and really wanting something to offer. We're finding it very helpful, and interested in being involved in the study. I think through conversations with, with the team in Oxford and in NIHR there's been a scheme set up for associate PIs in recovery, which I think is a really good initiative and it's a good way to bring people into to early stage clinical research because it's often hard to get going and really understand whether this is something that you really like or not. And so I think if people are interested. Certainly enquire locally as to whether that's a possible thing to get involved with but most people who are running these studies are very grateful for anyone's who has be interested in supporting. I would just encourage people to reach out and and talk to investigators, you know, in other studies too and certainly in, if you've got an enthused local investigator make the most of it, I think, Daniele may have comments too based on ITU.

Daniele Bryden 16:46

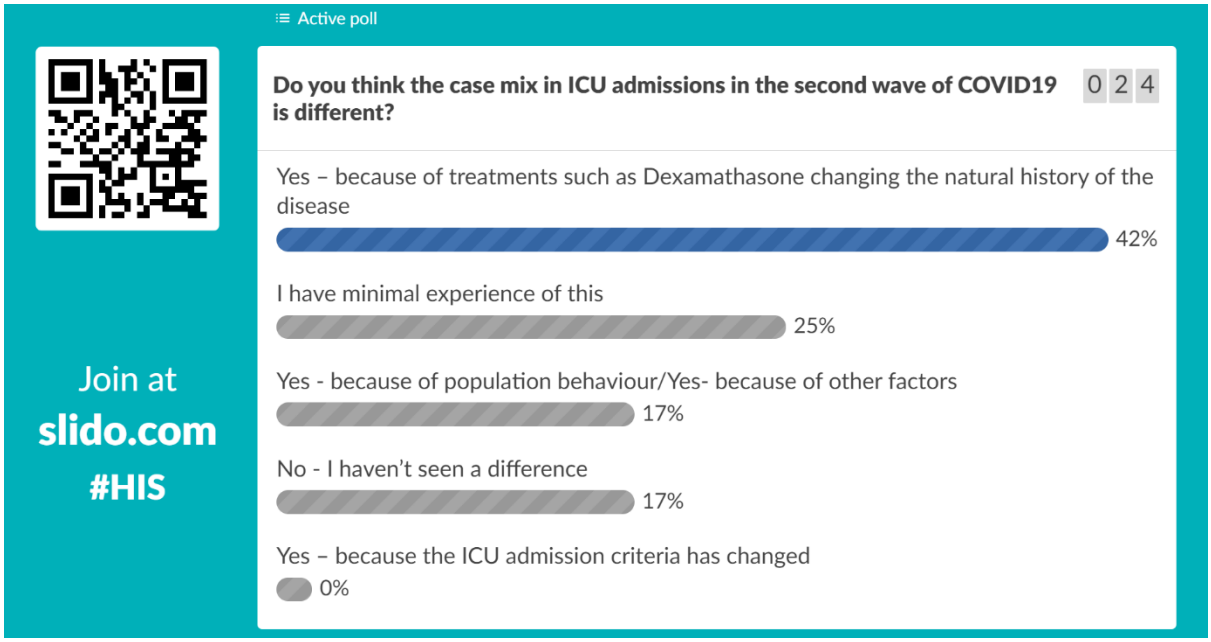
I would support that entirely particularly around the NIHR scheme which I think has only recently been pushed hard. Certainly all the Colleges have been asked to get behind it. It's just focusing on the fact that anybody who may have an interest in research and wants to get involved should be being directed towards the scheme. So again, it doesn't necessarily in, you know, sort of, mandate you to be working in a particular job or role. This is applicable probably to intensive care people emergency medicine people, whatever. And certainly within, within the ICU community there's been a lot of activity going on in research, but I think unlike infectious disease/microbiology we haven't had as a strong a kind of national research base. And I think one of the things that has come out of COVID is pushing the, the importance of all units recruiting patients in research and getting involved in research there's definitely support.

David Lalloo 17:51

I think there are important points that need to made about research here, and we can criticize the UK response in all sorts of ways. But the one thing I think we should celebrate is how well we've done in research, and ironically, you can go to the US and Australia, and the headline on the newspapers, saying how the UK is doing well, research and I think I hope that in fact we will see a significant shift in how we get young, young doctors and nurses and pharmacists involved in research in the future. I really hope this catalyzes an ongoing change in our attitudes, but I do think this has been an enormous success, both in the community and in hospitals and we should really celebrate that.

Mike Anckorn 18:44

Yeah, thank you David. So in the interests of time, we'll move on to the next poll. If you get your Slido app out and start voting



Okay, slowing down now in terms of voting but it looks like most people believe that the case mix in IT admissions in the second wave is different because of the treatments that have been available, such as Dexamethasone, which have changed the Natural History of the disease. So, over to Danny. So you've got two questions I think so.

Question 4:

Is the case mix/demographics of admissions to ICU different in the second wave and have you seen different complications/Case Fatality Rate?

Daniele Bryden 20:20

OK, so this is interesting because this is kind of - yes but no, but yes - type answer. So we have the intensive care National Audit and Research Centre which is obviously collecting data from all intensive care units, not including Scotland but everywhere else within the UK, and it's producing reports every single week so we've got real time data we've got good historical comparisons.

And in terms of the patients that we're seeing in the second wave they're not that different from the first wave in some, some demographics so particularly around the ages are very similar so the mean age is around 60, and the social deprivation is perhaps slightly more pronounced in the second wave than in the first wave. And some of the ways that we're treating patients is obviously different but they're not any sicker in the way to present to intensive care APACHE score, but their lungs are worse in terms of their P/F ratio. We measure the parameters we use to assess the degree of severity they are is what we call the P/F ratio that's a partial pressure of oxygen against the amount of inspired oxygen. And so it's a kind of a mixed picture what we think we are seeing in the second wave is that the patients that are presenting to intensive care with the benefit of dexamethasone are a different group, but probably the Dexamethasone is selecting out patients who were going to go down that route of prolonged inflammation and lung disease that we saw in the first wave. And the patients that we had in the first wave that had good recovery and good outcomes from ICU. Some of them are, if you like never coming to what's now, probably because of the Dexamethasone. And so, it is different, and I think the Dexamethasone is having an impact, but not directly in the way that we are looking at the numbers on intensive care.

And if you look at intensive care survival. And there's a there's a lovely graph within the ICNARC data set that very clearly demonstrates that mortality is coming down on intensive care before the 16th of June when Dexamethasone was introduced, and since then it's flattened out and started to go up again. So it's a very complicated picture and Dexamethasone isn't the complete answer. And you'll have to remind me of the other half of the question.

Mike Anckorn 22:49

So is the case mix and the demographics of admissions different? And have you seen different complications and case mortality rates?

Daniele Bryden 23:00

Well everybody knows about the difference in the sort of the way that the first and the second waves hit. The first wave was London and Southeast and spread up the country where a second wave is very much bigger pockets and pockets in the Northwest and Northeast, Yorkshire, Midlands. So those, those sorts of demographics are different as well which obviously has different indices in relation to the population health. The complications we're seeing again I think are different and partly due to the fact that we've got smarter in how we're treating patients, because in the first wave, because the numbers were so huge because it was coming so rapidly. People resorted to type. It was a new disease. We knew that there was lung disease, and a significant level pathology from what we've been told in China. So, we assumed that the treatment was to treat it like a blanket generic ARDS-type picture.

And I think we've very clearly understood now as you guys probably knew all along and well nod very wisely when I say this, that it's not just a respiratory disease. It is a multi-system disease with a lot of inflammation everywhere else, which we didn't twig. We were slow I think within the intensive care community to get that. So, we weren't quite on the ball about looking for thrombotic complications we weren't quite on the ball and looking for neurological problems, and the degree of of kidney injury we had particularly very early on the first wave we had 20% degree of acute kidney injury in the first wave. We've got much better and much smarter now in terms of how we treat patients. So I think the complications were partly of our own making. And now the complications we're seeing were the ones we know to look out for. So we're perhaps being a bit smarter in terms of how we address them in a prophylactic way. I'll stop there because I guess the other guys will want to say something as well.

Peter Openshaw 25:00

But maybe, maybe I can just add. I think it's interesting that nobody's said that the virus is evolving and changing. I raise that just say that actually I don't think there is any evidence that the virus is evolving into a more benign entity as yet, but that may happen over time and is something which I think we ought to keep an eye on.

Question for Danny and maybe for others. I mean the use of antibiotics is very very prevalent now. Is there any way that you can avoid the use of antibiotics and do you think that would be beneficial, or is it just inevitable that you're going to give antibiotics to everyone?

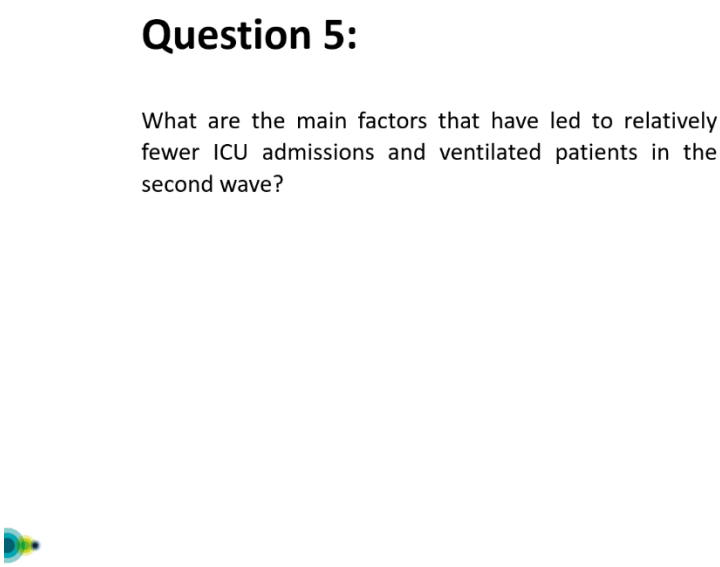
Daniele Bryden 25:39

Um, yeah, I think antimicrobial stewardship is a real worry, there is a, an NIHR funded trial 'Adapt sepsis' which is looking at Procalcitonin and duration and antibiotic use, and my own unit's not involved in that but I think that's a useful trial but we are going to be able to embark on to help guide us. I think, again, one of the first wave concerns was particularly around missed fungal infections and, and we've probably put enormous pressure on the laboratories that are now measuring beta 2 glucan

galactomannan by the number of requests that we're probably putting in as a community for this kind of testing. So yes, I think antimicrobial stewardship has gone out of the window, and because we have limited ability to do some of our normal intensive care treatments in terms of we're not doing as much bronchoscopy as we would normally do. And these patients are very sick and we're, we're not physically able to do it as well as the kind of concerns around infection and aerosol generation. I think we have resorted to using perhaps more antimicrobials in a way that we would not be doing, were we able to indulge in some of our normal intensive care practices

Mike Anckorn 27:01

Thanks Danny. And so moving on to question five just because of time. Question five is again about intensive care



This is clearly partially answered by your first response. Danny, have you anything else to add to that?

Daniele Bryden 27:23

Yeah, I would say, a note of caution which I think again the first wave was all about ventilators and everybody knew to focus on 'Have we got enough ventilators for people who need to be ventilated?' and then that switched, partly based on the fact that they just ran out of ventilators in Italy and realized that actually you could manage patients on CPAP or a number of patients on CPAP perfectly well - that we switched as a community to using non-invasive ventilation treatments and many hospitals have adopted delivering those treatments on the wards CPAP on the wards - proning patients on the wards, and saying we don't need those intensive care beds now we don't need that pressure on intensive care.

But I think what we're starting to see because there's now this upswing in mortality - is we're starting to be concerned about the number of patients who are being managed on non-invasive ventilatory

modes for prolonged periods of time, particularly when they're on steroids and the morbidity that has been being created by that. In terms of pneumonia destining pneumothoracies and also the perception amongst the public that ventilation is bad for you and harmful and they equate being ventilated with dying and managing to stay off a ventilator is giving them a better chance of survival.

So, we've, we've swung the pendulum too far away from invasive ventilation, and we need to pull it back again. And I think that's only just starting to come through and past sort of month, six weeks where people are thinking, Oh, you know, we need to start thinking a little bit more carefully about how long we keep people on non-invasive ventilation for.

Mike Anckorn 29:06

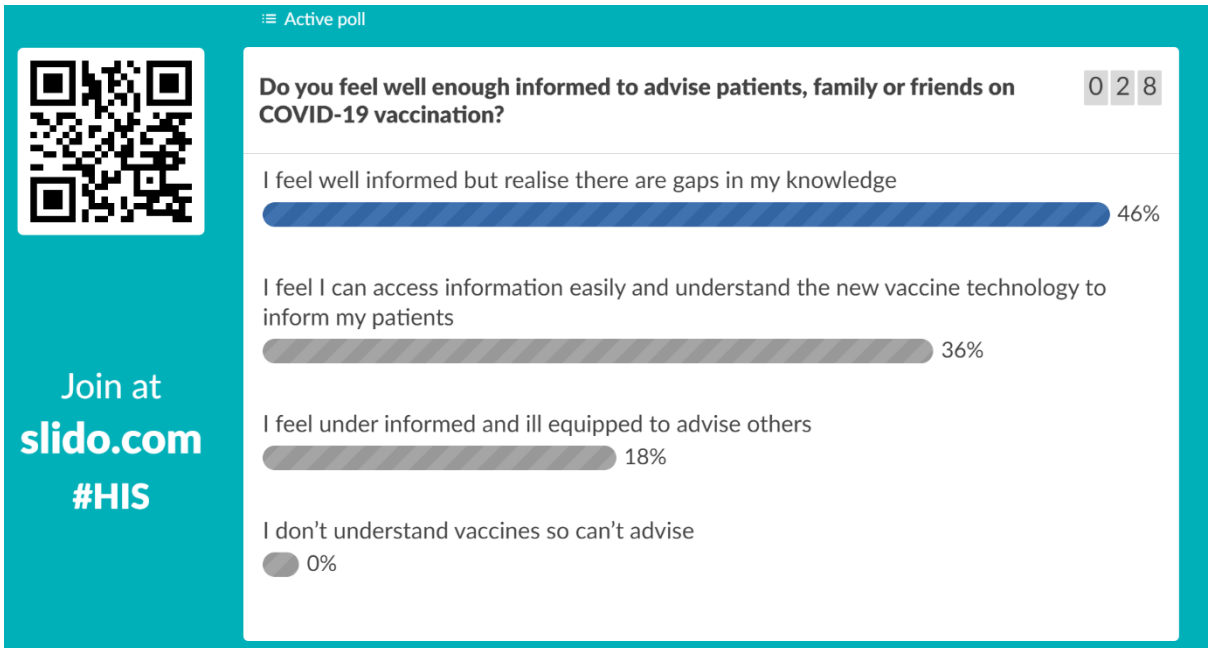
Danny that's very interesting thank you. Okay, David did you have anything to add to that, either?

David Lalloo 29:20

No, I don't think so I think that Danny's experience chimes very much without us dealing with the second wave in the Northwest. How are we are re-thinking these paradigms.

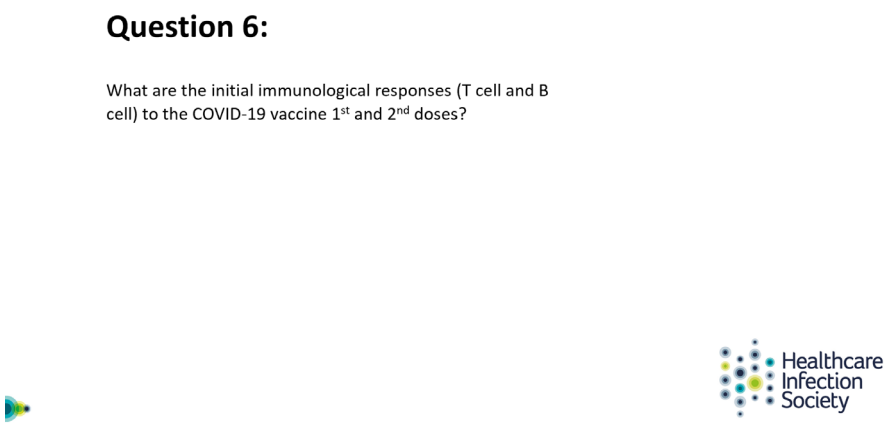
Mike Anckorn 29:31

Thanks very much. So, again, due to time I think we'll move on to the third poll. So the third poll if you get your Slido out and start voting is about being informed, how well informed you feel on the ability to advise patients family or friends on COVID-19 vaccination.



Great, I think voting is slowed down so I think the overwhelming majority feel that they still have gaps in their knowledge about vaccination which is completely understandable given the evolution of knowledge in COVID vaccines in just the last few months. So I think there's gonna be quite a few questions on COVID vaccines, so move on to questions six, please.

So question six is, what are the initial immunological responses both T cell and B cell responses to the COVID-19 vaccination in relation to the first and second doses? So that's over to you, Peter.



Peter Openshaw 31:15

Yeah, well, so I think these vaccines are quite extraordinary. It's amazing to be able to move from first recognizing the virus to having vaccines that actually work within less than a year. But there is there's quite a huge diversity of different vaccines, in, in the pipeline. Now literally hundreds of different vaccine approaches have been tried. And of those, there's close on 20 which are in fairly advanced clinical testing in one way or another, and even some which are now licensed so absolutely remarkable from the immunological point of view.

A couple of decades ago we were, we were expecting a vaccine to take maybe 12 to 18 years to develop. And now we are getting vaccines which have come through in very very quick time. In terms of how they work, there's all the different approaches. There is the conventional approach which is to grow the bug in *in vitro* and then inactivate it in some way. And then inject it and then that is still being done, and in particular, some of the Chinese vaccines, take that approach. Then there's the recombinant approach using adenovirus vectors which are either from chimpanzee or from human, so the Oxford ChAdOx1 vaccine the chimpanzee adenovirus vaccine developed an Oxford ChAdOx1, which incorporates a gene which expresses the coronavirus spike protein, so it doesn't incorporate that actually into the, into the virus. It just expresses it in abundance in cells during the abortive round of replication. So these are disabled viruses they're not live in the sense that they cannot disseminate so they're not live agents. Whereas, you've got things like this Sputnik V adenovirus approach where they've taken two different human adenoviruses and they've expressed SARS coronavirus spike protein in those as a vector. And that's a two-dose regime, with two different human adenoviruses. And that's been given at a very high dose whereas the Oxford, and adenovirus vaccine has been given us a more modest dose, but with that there's a more modest immune response that's generated.

Let's say some of the most impressive immune responses are from recombinant antigen which has been recovered from baculovirus system and then incorporated into nanoparticles. And that that

vaccine from Novavax is is very immunogenic in terms of the amount of antibody that it generates, and the antibody seems to be impressively neutralizing.

And then we've got the RNA vaccines, most notably of course the BioNTech vaccine which is just superb to see that now that novel technology is producing such good antibody responses.

But I think all of these approaches have to realize, are injecting into into muscle and expecting a systemic immune response to somehow spill over and protect the respiratory tract. So, you know, in terms of trying to protect the respiratory tract of course what you want to do as an immunologist would be to prime in the respiratory tract, particularly during the first round of priming so that the immune system focuses its immunological activity into the respiratory mucosa, which is actually where you want it, whereas all of these vaccine approaches are directed towards generating a systemic antibody response, and the systemic T cell response and hoping that there will be spill over from that systemic compartment into the respiratory mucosa, which is where you want to their response to be.

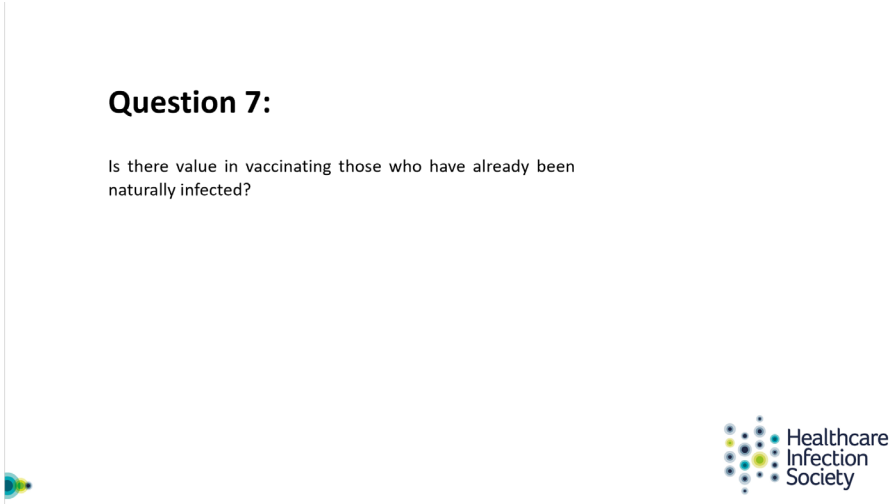
So I think, you know, in terms of the fundamental immunology, all of this is perfectly, you know, conventional obviously we'll prime for a very strong antibody response mediated by B cells, and the T cell response which helps to sustain the antibody response, and is necessary for long term B cell memory. So, you know, I think it's extraordinarily promising, and very interesting.

You know, we all wonder about you know how long the antibody will persist. Will it persist for longer if it's acquired as a result of natural infection versus vaccine induction? You know, we've got quite a lot of evidence that the natural infection induces a peak of antibody which then declines to a plateau, but that plateau is actually reasonably stable and looks like it's going to confer levels of protective resistance to reinfection for maybe three months, perhaps six months, maybe even longer. We just don't know as yet. We know with common cold coronaviruses that reinfection can happen repeatedly every year. And sometimes people who've had a documented infection with a particular common cold coronavirus when they're reinfected more than 80 days later, seem to actually have higher viral loads than they did if they hadn't had that previous infection. The reasons for that are not perfectly understood, but you know we're all wondering about the possibility of some sort of immune mediated enhancement. But that I think is is a question in our minds rather than anything which is, which is really proven that based on evidence with COVID-19, so just a question in the minds of immunologists and vaccinologists.

The second dose will obviously boost the immune response which has been primed by the first dose and establish the immune response has a much higher level. So, you know, that's the reason for these two dose regimes but in practical terms, particularly for global rollout, having a single dose program would be so much better. So I think that's more or less covered that first question. Is that right?

Mike Anckorn 37:49

Yeah, that's great. And so the next question is really talking about the kind of practical aspects of vaccination. So one of the questions that came up time and time again, from the HIS members was, “Is there any value in vaccinating those who have been naturally infected, you think this will add extra immunity and increase longevity and an immune response?”



Peter Openshaw 38:15

Yes, I mean, I think it's, if it was me, I think I would be very happy to be to be boosted with a vaccine if I'd been naturally infected before, because that first infection would be primed via the mucosa, because the immune system would have, would have would be able to recognize to remember to recall that this is a mucosal infection that has a mucosal orientation. And when it's boosted then by a peripheral vaccination, it will boost that natural immunity, which will, by by all the rules of the immune system will also boost the immune response back in the mucosa.

I mean, if you look at the advice on the BioNTech vaccine, which is obviously the most, we have most information out there, the advice there is that if somebody has is already got COVID, then you shouldn't give them the vaccine concurrently. And indeed, you should wait for for four weeks after their recovery in order to to vaccinate them. But the people who have been in those trials who have had naturally acquired immunity through infection, and they haven't responded adversely to being vaccinated. So it doesn't sensitize you to, to a worse response to the vaccine. And indeed, it would be impractical on a on a mass scale to start screening people for antibody or for COVID symptoms, it wouldn't be a practical way to run a vaccine campaign. So it's fine to vaccinate people who've been infected in the past. And then that might actually give you a different quality of resistance in the longer term, so might be a good thing.

Mike Anckorn 40:07

Peter we've seen that problematic screening borne out in practice with Dengvaxia vaccine with pre-vaccination testing. So that would be problematic if we had to do that.

So thank you for that. And so that's great. Is it all good? Have you got anything else to add about vaccinating those have been naturally infected? Great, so question eight, then is for you Peter as well.

Question 8:

What evidence is there that vaccinated individuals (or those with previous infection) can acquire the virus in the nasopharynx, and then transmit it?

Peter Openshaw 40:48

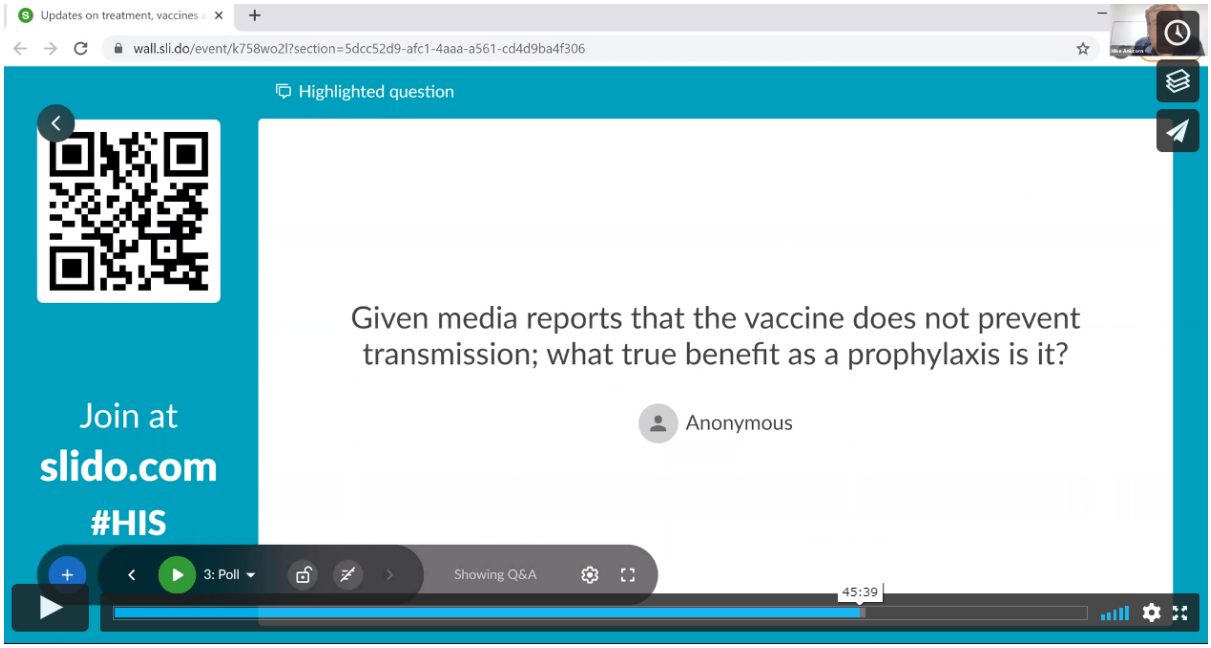
I think this is another crucial question. And I think it also brings with it another question, you know, what do you do with if you're issued with a vaccine certificate or vaccine passport? You know, what practical use is that. So at the moment, I think it's important to emphasize that most of the phase three trials have been to ascertain in 10s of 1,000s of people, whether the frequency of symptomatic disease is reduced by being randomized to the vaccine. And the results are pretty stunning. In that respect, you know, both of the RNA vaccines, it looks like disease is pretty solidly prevented and seems to be pretty solidly prevented even after the first dose after about day 12 to 14. So that's amazing.

I mean, in terms of what else it does, we are still really waiting. So the Oxford study the ChadOx1 study, Andy Pollard and his crew did did something which was pretty hard work, but very, very important prescient to do was to they did actually get their people in, in the UK limb of their study, to do lots of self-testing. And that's allowed them to say that there is a very significant reduction in the frequency of asymptomatic viral replication in the nose.

Now, I think that it's perfectly possible that there's an even greater effect in terms of the ability of those with asymptomatic infection to actually transmit the virus, you know, it could well be that the virus which is being detected by PCR is is relatively non-infectious, in which case it will have an even better effect on community circulation and transmission. But that's a bit uncertain at the moment. So, for the present, we're saying that we need more evidence, and that the vaccines have been tested in in in their ability to prevent disease. But that is unproven, whether people who have been vaccinated might still be able to replicate the virus, and potentially transmit it to others. And that's a problem which has resulted from the fact that this is a peripherally delivered vaccine into the muscle. And it's not really directed towards creating a very strong local mucosal immune response. So that is, that is a problem. And it's a problem, which is very much in people's minds in terms of what you do with the, with the card that you're given them to say you've been vaccinated. What does that mean, in practical terms?

Mike Anckorn 43:38

Thanks for that insight Peter. And I think we've got loads of live questions that have been voted on and uploaded and moderated whilst we've been live. So we're gonna move on to the live questions now.



So given the media reports, the vaccine does not prevent transmission. What true benefit as a prophylactic, is it?

And this is really what you've already alluded to. Isn't it really

Peter Openshaw 44:15

I think there is some reduction in viral replication, probably by about two thirds. In general, and that's, and that's pretty good. I mean, what we don't know is about transmission. So if you know, measuring viral replication isn't the same as measuring transmission, and it's quite hard to measure transmission in these in these studies.

Mike Anckorn 44:42

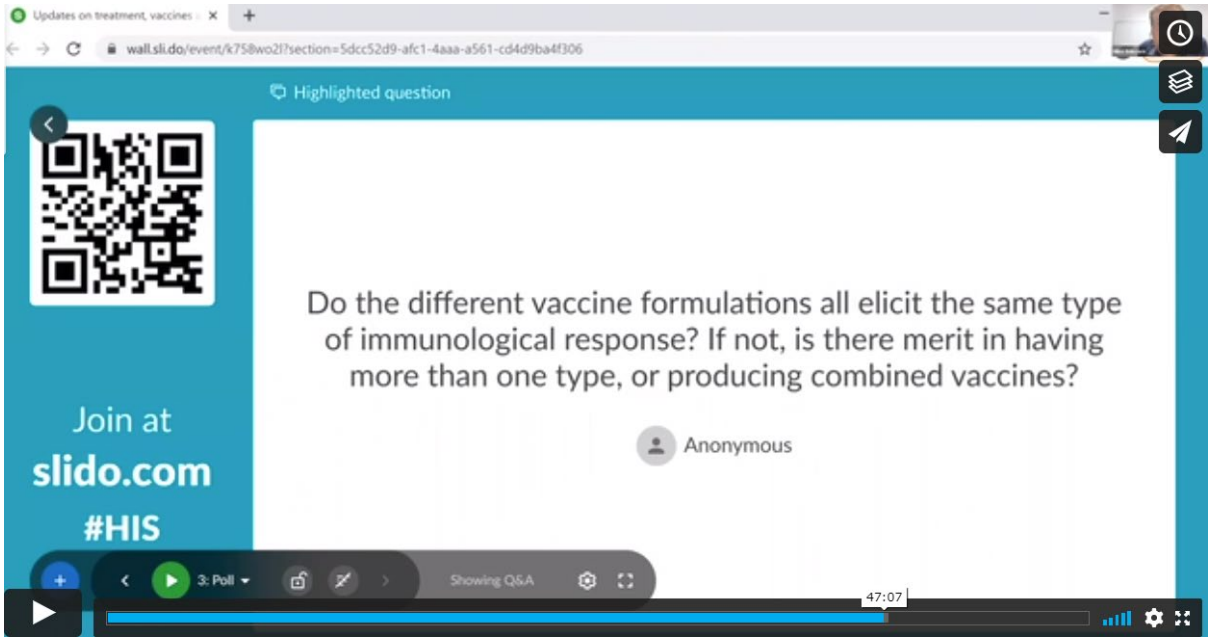
Yeah. Okay, we'll move on.

Peter Openshaw 44:45

Maybe I should add obviously if it's going to prevent disease in the most vulnerable, then actually, maybe we just don't worry too much about the virus circulating because it won't impact too much in terms of the people who are over 50 and who are most likely to get disease. We will still see long COVID and you know, the unfortunate few who are under 50, who get that disease as well. But, but at least at least at least you're protecting the older people.

Mike Anckorn 45:28

The next question is also about vaccine formulations.



Peter Openshaw 45:45

So the immune response which correlates best with, with, with neutralizing activity, which is quite hard to measure is the antibody against the receptor binding domain, the anti-RPD antibody, which is quite easy to automate and make high throughput. And all the vaccines have been tested for their ability to induce anti-RPD antibody. And all the ones that are in advanced development basically, do induce that that sort of immunity. And what was the second part of that question?

Graham Cooke 46:25

It's probably worth making the point about combinations of different types of vaccine..

Peter Openshaw 46:27

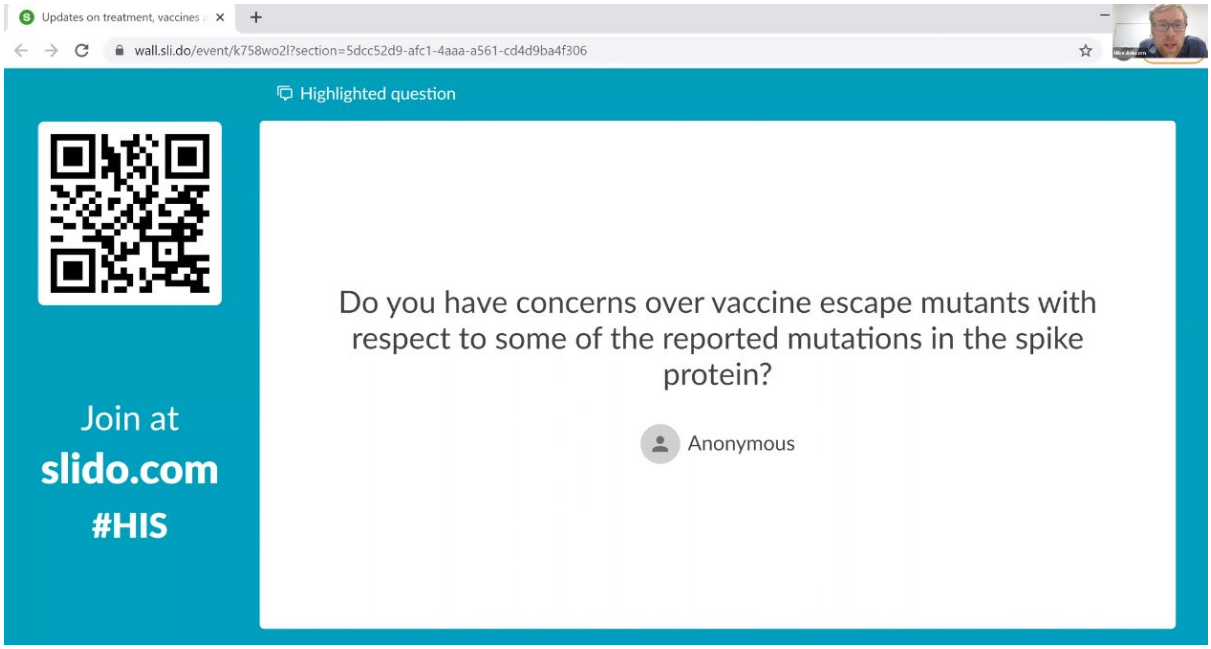
Yeah, yeah. So certainly, there's a lot of a lot of benefit in perhaps having, you know, a prime and a boost of, of two different types of vaccine you can see the from the immunological point of view that would be highly logical. And indeed, there is a trial going ahead in Oxford to test just that approach. However, that's not the way the vaccines are going to be initially licensed. Because the trials have been done with one vaccine given - usually two doses as a prime boost. From the immunological point of view, giving two different vaccines which contain the same essential shared elements of the spike Coronavirus is a very logical thing to do.

Graham Cooke 47:14

The thing that caught my eye last week was the announcement that he said, we're going to pair up the Oxford vaccine with Sputnik vaccine. And I think it reminds us that we talked about three vaccines, but actually we have a couple of others that are sort of less in our eyesight that may be effective, and including Sputnik and the idea that perhaps the different anti vector immunity might be different between the vaccines, it might be beneficial to combine different adenovirus constructs and so forth. So, you know, we have the combinations of viral constructs and RNA vaccines. There's going to be interesting for future when we're looking to boost people potentially as well.

Mike Anckorn 48:00

Great, thank you. We'll move on to the next question, please. So again, this is a obviously, a lot of our questions are focused on vaccinology



.

Peter Openshaw 48:15

So that there is a concern. I mean, the I think we've got a wonderful set up in this country for monitoring the different mutations which are occurring and of course, a virus like like Coronavirus is going to mutate at a reasonably high rate. You know RNA viruses do have a very high mutation rates although Coronaviruses have got a way of correcting those mutations. But they do evolve. And the main evolutionary pressure in the in the earliest stages when there isn't much community immune response is going to be driven by the more transmissible sub strains.

And that seems to be what's happened with the strain that is emerged out in Kent and now in northeast London is is is it is more transmissible. And looking at the sequence, there are mutations in the spike protein which could affect perhaps some of the detection methods and also some of the antibody, but not much of the antibody that seems to be directed against the receptor binding domain.

So, at the moment, I think what we're saying is this is one to watch. It's nothing to get too worried about at the moment, but just be alert to the possibility that some of the detection methods could actually not pick this one up if they're based on antibodies to regions of the spike protein that are mutating. And also PCR, which is based on amplifying spike protein - can be negative with this new variant.

Mike Anckorn 50:05

That's interesting. Majority of diagnostic assays don't target that aspect do they?

Is that another many commercial artists that do target that that would be a concern?

Peter Openshaw 50:14

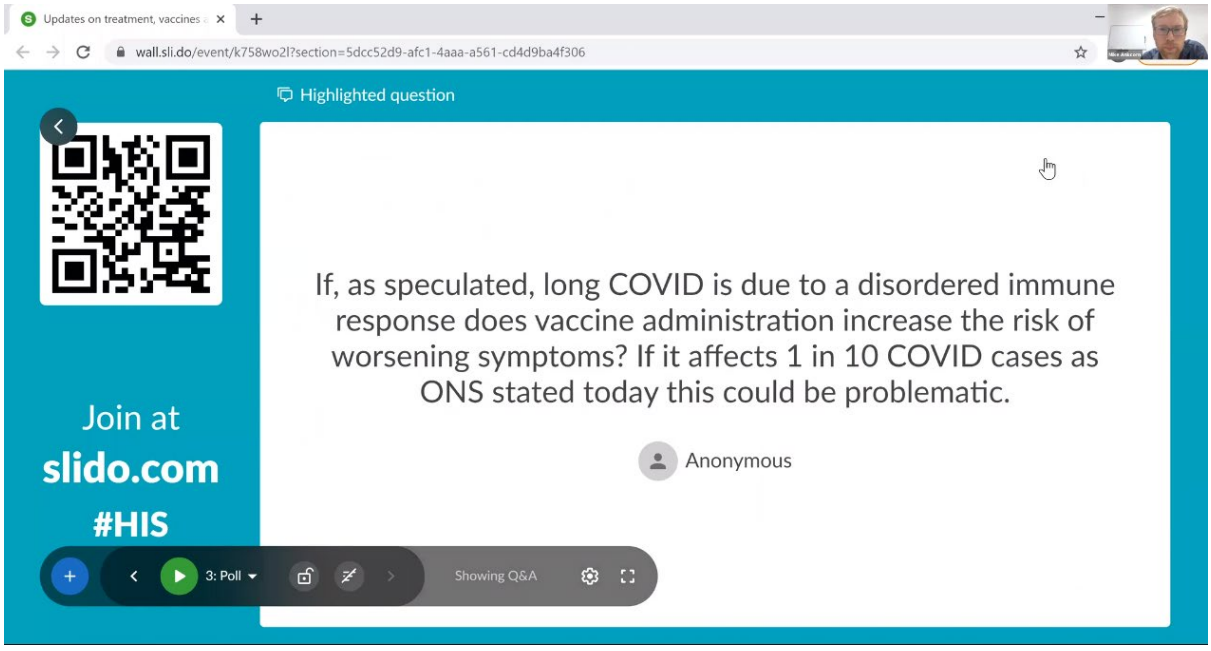
Graham is much more experts on these on these assays, actually.

Graham Cooke 50:20

Yeah, you're right. It's mostly NME targets I think. So some of them are using more than one target. But I'm not sure that any of them are really focusing on spikes. I hope that's a theoretical concern. But clearly there's other targets could mutate and then it would be helpful to have more than one in an assay I think.

Mike Anckorn 50:39

Yeah, that's great. Thank you. Anything else to add about that last question? Adel, any more questions?



Graham Cooke 51:23

I'm going to say one thing I've learned in COVID, is how to answer a different question. I'm going to sort of come back to something I wanted to sort of mention earlier, I think, which is related, I'll get to why it's related to this. But I think that Daniele was talking about learning about the disease early on. And I think one of the things that was really helpful for me was colleagues who set up a post-mortem program very early on in the epidemic, and you can read what you like and hear what you like. But it's until you start to see understand the relationship, what you're seeing in the patient, you really understand the disease. And they gave it to very early insight into things like thrombosis.

But one of the other things that stood out to me in that was the fact that even quite later on this, you can find virus. And so you know, you can look for some genomic RNA in patients who've been in hospital for a month, and it's they're replicating outside the lung. And that is very much flavoured my view on treatment slightly in that, okay, Remdesivir might not improve mortality in this group, it's probably doing something. And I do wonder this is slightly provocative comment. But I do wonder whether if we will be using more antiviral therapy, we might be seeing quicker recovery to patients.

You know, there are a lot of people out in the community, particularly young adults, who were very, very sick, who basically experienced the natural history of infection. And it's not surprising they take a long time to recover when they've had no antiviral, and no post directive therapy whatsoever. And I don't think we factor that into our thinking very often, because we haven't seen very good long term, you know, 90 day, 180 day follow up on on treatment versus non treatment. So I put that in the mix. It doesn't answer the question about vaccine, particularly, and I guess, others better placed - but I thought I'd just them. Thanks.

Mike Anckorn 53:05

Thanks for that Graham.

David Lalloo 53:08

I might just then ask Graham, does he believe Remdesivir is that right antiviral to use in a widespread fashion? Accepting the, the difficulties of delivering Remdesivir, but do you think it's sufficiently potent, that you would actually advocate that it as a, if you had an oral form of Remdesivir?

Graham Cooke 53:26

For now. I mean, I'm hoping that you'll find me something better. I'm very partial to SOF and Daclatasvir and, you know, I think hopefully, there will be better antivirals coming through. And if we're looking longer term, then there's a huge gap. And there's lots of things that have happened amazingly quickly. But what we haven't had is a whole load of off the shelf oral antivirals that work. And if we could have something sitting in the locker for next time, that would be active against a range of viral - or we think might be active against - a range of viral infections, would be incredibly valuable to have to realize and evaluate them in early phases to see I mean, I think I, I've got my own personal preferences about other potential things. But I mean, I certainly wouldn't make a case for Remdesivir being that good. But if you've got something better, let me know. Because I'd be keen to find it.

Peter Openshaw 54:15

Secondly, because I just add, I mean, coming from the hepatitis field, maybe the view of antivirals is rather more rosy than it is generally amongst people in the respiratory viral field. I mean with these acute infections I think we've been I think it's, it's perfectly reasonable to say that, you know, we've been a bit disappointed about the efficacy of Tamiflu in real life situations.

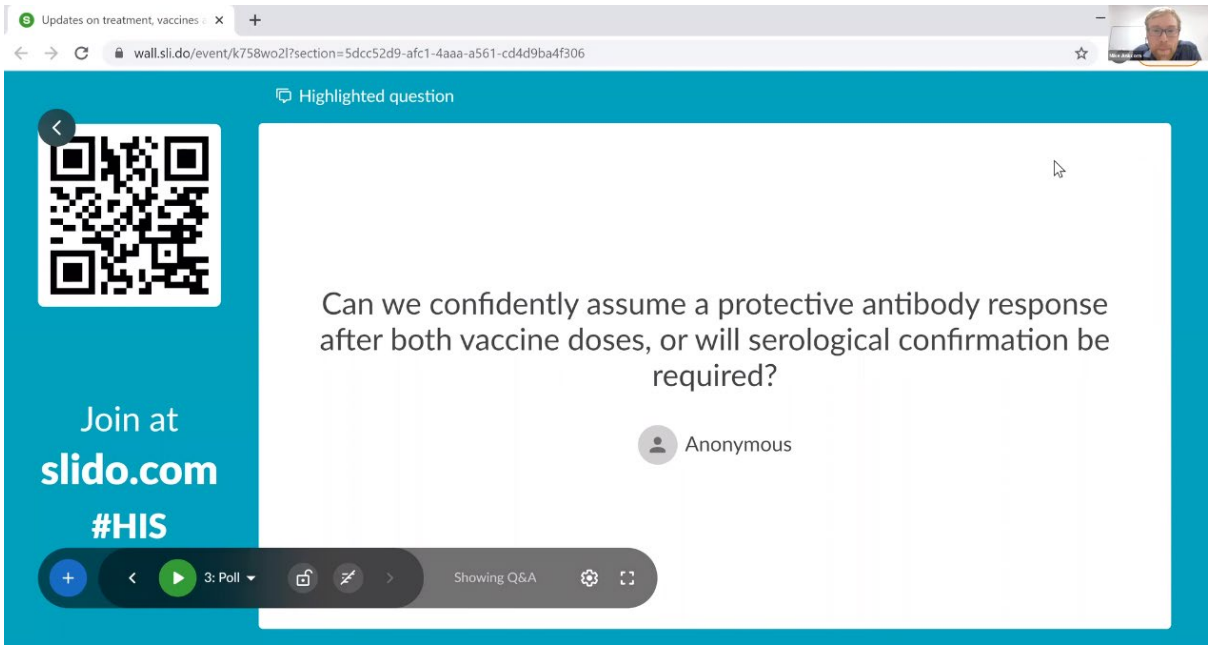
Although under experimental conditions, it works quite nicely. But maybe, you know, combination antivirals, maybe other antivirals are going to work better. But there's also been quite disappointments in the RSV field, about anti virals which should work really nicely in experimental situations, even in the human experimental challenge with RSV, but actually in clinical practice have been disappointing.

Graham Cooke 55:05

Well one of the things you've always told me, Peter is it's a very bad career move to go into something curable. And I think very well. And I think if you if you were being optimistic about antivirals, I think the next generation of flu antivirals probably look better. I don't know if you'd agree with that. And, you know, what's been out there hasn't been great. But clearly, it's where there's a market and an investment that can be made, then its potential to make progress. We could imagine in the world that emerges from this, that actually getting investment in rare viruses for antivirus might be feasible when it wouldn't have been a year ago. So it could be. I mean, I guess you're right. I do have faith in antivirals, but probably too much.

Mike Anckorn 55:55

Guys, I think we'll try and squeeze in one last question, and then wrap up.



Okay, so the last question is about protective antibody responses.

From a lab perspective, I'd be very reticent to recommend that serological confirmation of vaccinated individuals. But Peter would you like to comment on this?

Peter Openshaw 56:32

So for me, that's a yes - and a no. If you look at, if you look at the studies, the vaccine recipients are pretty tightly grouped along the top end of the graph. There's not much variation at all. And whereas after natural infection, there's quite a widespread. I can't see any practical way in which you could you could benefit from measuring antibody responses.

Mike Anckorn 57:03

Great. Thank you for that.

Before we finish, then if anybody else got anything else you would like to add?

No, that's great. Well, I thank you all very much for sharing your time and expertise today. And I'm sure the HIS participants will have really enjoyed seeing all the questions answered. There's still a lot to learn, obviously. And I think people will hopefully have some ideas about how they can get involved in trials if they're not already done so. So, thank you very much to everyone.