Transcript: Webinar - COVID-19 challenges and solutions 5. The role of SARS-CoV-2 testing in the IPC management of patients and staff | 15 July 2020

Watch the webinar

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

- Dr Colin Brown, Consultant in Infectious Diseases and Medical Microbiology, Public Health England
- Carolee Fry, IPC Lead, Public Health England
- Dr Tom Lewis, Consultant Microbiologist, North Devon District Hospital
- Dr Catherine Moore, Consultant Clinical Scientist, Wales Specialist Virology Centre, Public Health Wales
- Dr Malur Sudhanva, Consultant Virologist, South London Specialist Virology Centre, Lead Clinical Advisor for COVID mass testing Lighthouse Labs and local advisor for Milton Keynes, Clinical Director of Pathology for the Viapath laboratories at King's College Hospital

Chair: Dr Muhammad Halwani, Associate Professor/Consultant in Infection Control, Al Baha University, Member of the HIS Professional Development Committee

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Muhammad Halwani 0:00

Good evening, everyone. Thank you for taking time out, and being here today. It's my pleasure to welcome everyone to our choice webinar tonight. Muhammad Halwani Consultant in Infection Control, and Associate Professor from Saudi Arabia. I am delighted to chair this webinar tonight. I would like to invite the panel members to introduce themselves.

Colin please.

Colin Brown 0:25

Hi, so I'm Colin Brown Consultant in Infectious Disease and Medical Microbiology. Normal day job is working in the Healthcare-associated Infection and Antimicrobial Resistance Division of Public Health England. Clinically as an infectious disease Consultant at the Royal Free Hospital in London. And I also work with global public health, supporting laboratory development predominantly in Africa.

Muhammad Halwani 0:51

Okay, thank you. Carole?

Carole Fry 0:53

Good afternoon, my name is Carole Fry, I'm the infection prevention and control lead of the PHE COVID-19 response. I normally work on healthcare associated infection and antimicrobial resistance.

Muhammad Halwani 1:06

Thanks, Tom?

Tom Lewis 1:09

Tom Lews I'm a Consultant Microbiologist in North Devon and one of the clinical leads for the Get it Right First Time program for pathology.

Muhammad Halwani 1:19

Thank you, Catherine.

Catherine Moore 1:23

Hi, yeah I'm Catherine Moore I'm a Consultant Clinical Scientist for Public Health Wales in the Department of Virology, and my specialist area is development of molecular testing for respiratory viruses.

Muhammad Halwani 1:38

Thanks, Sudhanva?

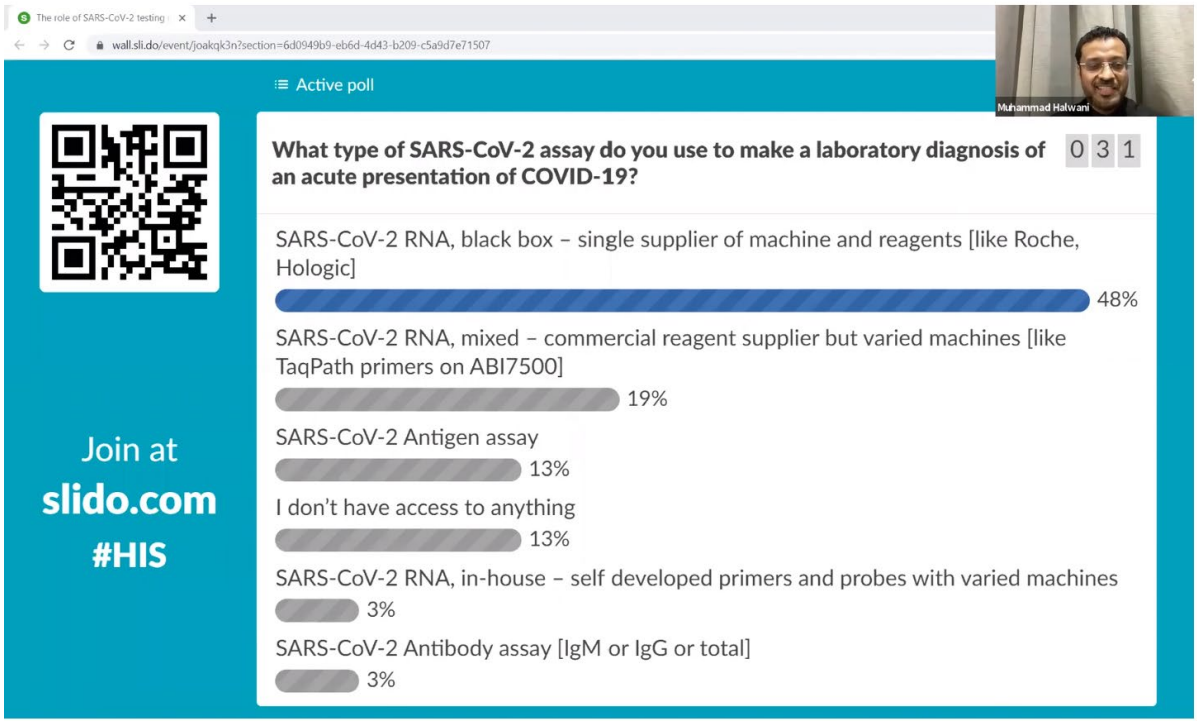
Malur Sudhanva 1:40

Good evening. I'm Dr Malur Sudhanva, Consultant Virologist at King's College Hospital in London, Clinical Director of Viapath laboratories at King's College Hospital also advisor for Lighthouse Labs for mass testing of COVID in the UK, and chair of panel of examiners for the Royal College of Pathologists, in London. Thank you.

Muhammad Halwani 2:00

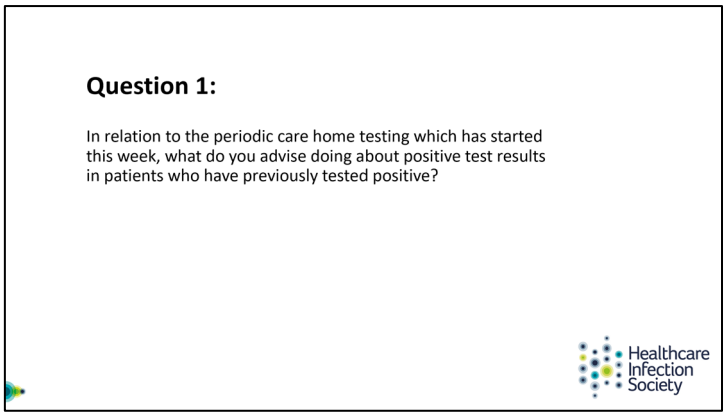
Thank you all for joining the COVID-19 challenges and solution audience-led webinar series. Today's webinar will focus on the role of SARs-CoV-2 testing in the infection prevention and control management of patient and staff. Before this webinar, we asked you to submit questions to the panel, we have selected eight most popular questions for the panel to discuss during the first 40 minutes of the webinar. During the last 15 minutes of the webinar we will answer live questions, which you can submit via Slido throughout the event. You will also be able to use a Slido to express your opinion by voting on live polls. To participate in the polls and questions please open the Slido app, and enter code #HIS or scan the QR code.

We will start now.



Okay so around 43%, saying that a SARS-CoV-2 RNA, black box single supplier of machine and reagents, like Roche for example.

Okay, so let's go to the first question



Colin Brown 4:28

This is a question that's come up, not just in care homes. It's come up in hospital settings, and it's been widely reported in the literature that people test positive serially for a long period of time, and there is quite long tail end of PCR positivity that does not reflect infectious virus. When people are asymptomatic that would have mattered less because it would only be when people develop new symptoms that they would get tested again, but as we have a rolled out testing capacity, particularly in certain settings like care homes, and in some hospital settings, and perhaps a few other workplaces. There is more routine testing, and sometimes weekly, or twice a month, and you can enter a cycle where someone has a clinical illness, gets excluded has their own personal test, feels, they've reached the end of their isolation period, they're well, they're back at work, then they get part of a routine screening program, which is there for the whole safety of the workplace setting in the residential patient population. And then they test positive again and it could be two to three weeks after their initial illness, and there are no clinical symptom. They feel well. But, by default, the guidance as it stands says that they should have to self-isolate again.

And so we've compiled a lot of information together that's being looked at by a couple of different government advisory groups NERVTAG and SAGE, and most recently, the Chief Medical Officers, and they are considering an exclusion period where, if you test positive, on the assumption that you have no new symptoms, you would be exempt from having a retest. This is likely to be four to six weeks. And it will be decided on shortly. And then that will work its way into the national recommendations in the upcoming weeks. And once that is finalized and there is an agreed go live date, we'll be sure to try and publish it through all various routes, and we can definitely do that through the Healthcare Infection Society as well.

And so we're working towards a viable way to act safely but to ensure that people who are well, and are just on the tail end of their PCR positive illness, but no longer with any symptoms and are infectious are able to return to work.

Carole Fry 7:16

Given some of the uncertainties about some of the testing and long positivity, in my mind it really reinforces the need for very good infection prevention and control practices, because you don't know when some virus is viable. And so it doesn't really matter whether its hospitals or care homes - to really just keep reminding people to do their infection prevention and control precautions really well, all of the time. And I think that's important to protect residents, patients and staff.

Colin Brown 7:48

And the uncertainty that was there in the recommendation for PPE, with all staff patient or staff resident encounters. It was to try to limit any potential for cross transmission. And so I think there is a bundle of infrastructure in place to help prevent the transmission, and then finally the exclusion from retest will be done as we roll out more widespread testing and on routine basis. These people will repeatedly get caught up.

Carole Fry 8:22

I think that all of us who have been working on this feel that this is people get very caught up in all the PPE issues. I think it's also worth reminding people, pulling those on like a record with the needle stuck, it's about safe systems of working and you have to keep reinforcing that whilst PPE is important and has a role to play in protecting people, its about looking at working safely and keep reviewing that and keeping it safe.

Colin Brown 8:50

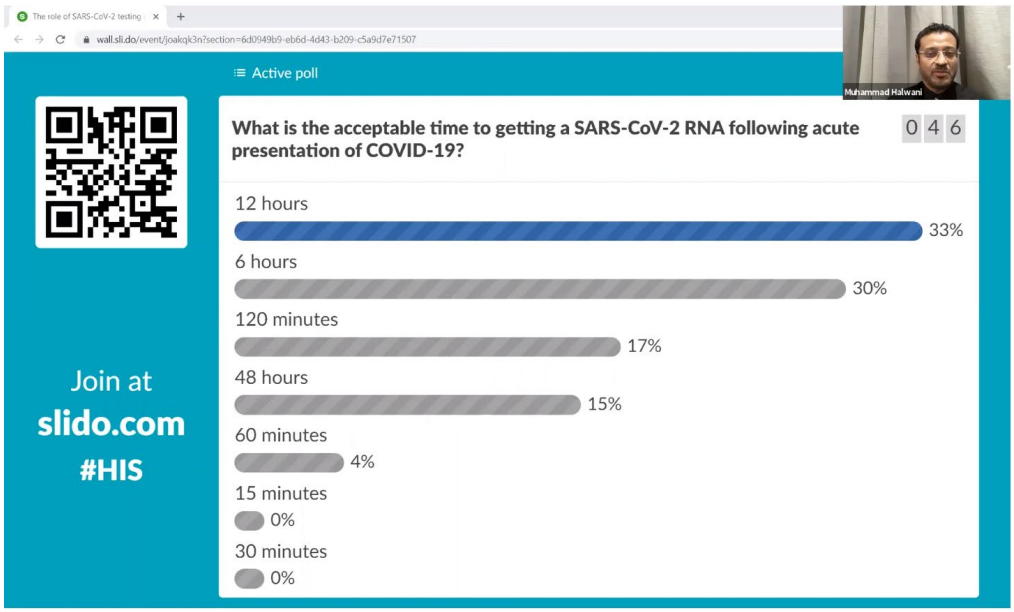
It's also to say that if there is an exclusion policy will be for people that are asymptomatic, so should anyone do any recurrence of symptoms of new symptoms, then they will need to get tested again and if that is positive, even if we don't know whether it is a new illness and we're just picking up the tail end of the PCR positive result or whether it indeed is indicating some continuation of a virus then they'll be excluded.

Muhammad Halwani 9:25

Anybody wants to add anything?

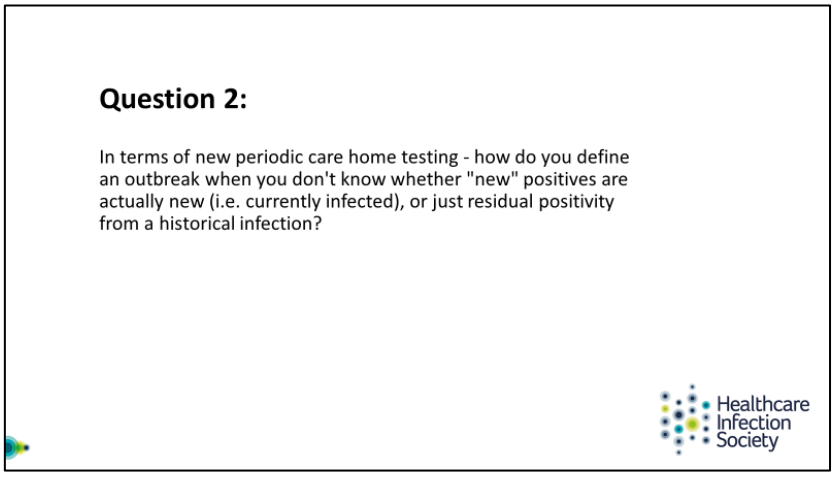
Okay, So, shall we move to the next poll.

So, let's join Slido



Okay, so most think 12 hours.

Okay. So I think we move on to Question 2.



Tom Lewis 11:06

What's interesting thinking about this question, about the about our approach our breaks in hospital. And so I had to actually go and read our hospital policy which I never read before, which said two cases linked in time in place. And I guess the observation from that is that as infection specialists, we don't really rely on policies for defining outbreaks - they are something that we're trained to recognize. And it's very hard to be prescriptive about these things because the, the evidence on which we're basing that case definition is moving all the time.

It requires knowledge of the particular risks in an environment, it requires knowledge of who's around, what the nursing capacity is, or whatever it might be in that particular situation, and we deal with that every day in hospital. I mean you wouldn't really dream of managing a flu outbreak remotely in a hospital setting and so I guess the problem we now having care home settings with significant spotlights on them, is that we don't necessarily have the infrastructure in place.

So dealing with an outbreak remotely is extremely difficult. I think when you have partial information, which is difficult to complete at pace, means that you're always working somewhat in the dark and I think one of our challenges is going to be as a country, I guess, is how do we provide infection control support to areas which possibly have been underserved in the past.

So I guess my simple answer to that is I don't think there is a simple answer to that, I think, I mean you can define it simply by two cases linked in time in place but actually, what does that mean in reality? I should think we've all dealt with cases in our hospitals where it's been quite difficult to really nail down, whether it's an outbreak – that has felt to some extent a semantics decision, which hasn't actually had an operational impact. Certainly, that's not been our finding locally, it's something that we've dealt with on a case by case basis and hasn't actually changed the way we actually manage the cases. I don't know what others think about that but that would be my personal view.

Catherine Moore 13:34

Okay so, there actually quite an interesting caveat around, declaring an outbreak in pandemic settings. It's very hard to declare an outbreak when there is widespread transmission of any pathogen in the population. And so, as you say, a standard definition of an outbreak is two cases connected by place and time. And that means that we would be calling outbreaks for households to households in a pandemic situation. So you have to look at the caveats around that, you have to look at the fact that we are in pandemic, and so things do change, you might shift the boundaries slightly.

It should be when you find a new case, how does that relate to what's going on in the community around you, what does it relate to in the home?

So, in Wales when we have a case of coronavirus in a care home, for example, we test the whole home. We look again at what's going on in the wider population, whether r not there is connectivity between the community coming into the home or whether it's isolated within the home itself.

So, I think it's, it's much more difficult, and like I say, the standard definitions are out there, and we can apply those in a normal seasonal situation, but we're not in a normal situation we're in a pandemic.

So, it might be worth looking through your pandemic plans and looking at all those caveats to see where those lines are, and you can see that the lines are often blurred, and that actually defining an outbreak is not easy in this scenario.

Colin Brown 15:06

Given all of the learning that's gone on in care homes, and the scale of the problems that have been faced by care homes there's now an abundance of caution. And so one unexpected case in either staff or residents is going to be treated as an incident and trigger an investigation, and then an outbreak account if there's two cases. The standard definition, being applied is two incubation periods - to close it for 28 days.

Now, in terms of the original question 'Will you pick up people that are historically positive?'. I mean absolutely you may well do, and I think it's very difficult. We can talk about whether we can begin to interpret CT values, , looking at kind of a mixture symptom onset CT value, potentially even antibody status, all of that is difficult, and certainly there's no national guidance on that at the moment but in

terms of deciding if a case is old historic. I think on the abundance of caution principle and it'll have to be treated as a current case.

Muhammad Halwani 16:22

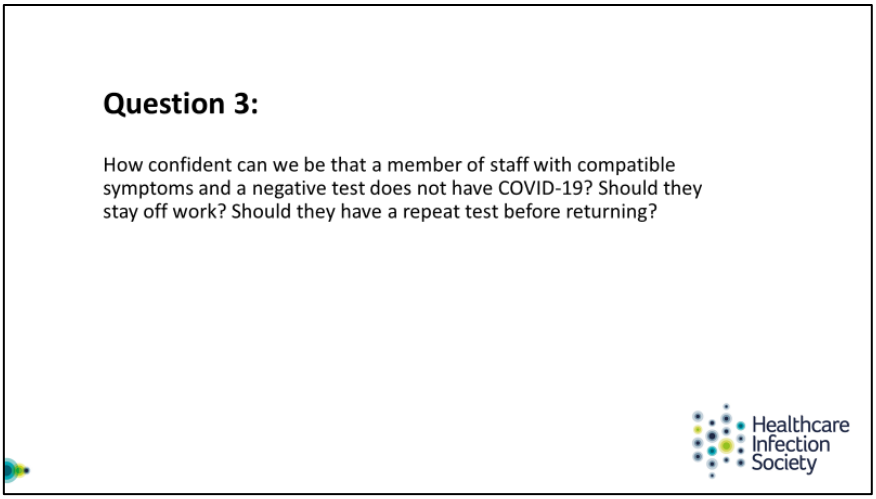
All right, thank you very much. Anyone want to add anything? All right. Thanks. Okay. Carole, please.

Carole Fry 16:30

A slightly tangential point, but I think what we've learned with the care home outbreaks is that as a workforce they're quite mobile - often moving between different care homes, which adds another complexity. And the other thing we've learned fairly recently is that they may have other jobs outside of care homes, so they're mixing with other people - so it's making the whole thing much more complicated to bring under control. I think it's quite difficult for some care homes to restrict staff to one floor or to one care and I think that has probably amplified the problems with care homes.

Muhammad Halwani 17:07

Yeah. All right. Okay, thank you.



Colin Brown 17:39

Yeah, so I mean I think it's challenging.

If you look at the text of the exposed health care worker and social care worker policy that we have at the moment says

> "Staff who test negative for SARS-CoV-2 can return to work when they are medically fit to do so, following discussion with their line manager and appropriate local risk assessment. Interpret negative results with caution together with clinical assessment."

And I mean that might seem a bit wordy but I think it does suggest that there is uncertainty around what a negative test result means, in the absence of another diagnosis and where you've got symptoms that are compatible.

This clearly will fluctuate a bit depending on where we are both in season, and in outbreak. , I think it's highly likely that when you've got, very limited local incidence and prevalence. Your negative predictive value goes up quite considerably, and consequently your positive predictive value goes down for what the test result means. It will get even more difficult come that winter season where there's other winter viruses arrived, and people may or may not be getting full respiratory panels of what there's a full restriction panel mean? Different hospitals have different interpretations of what that is.

So, I think that's a long winded way of saying that mostly negative test results, probably mean what they say, but if someone has really compatible symptoms of COVID, particularly if they're going to work in an environment where they're working with vulnerable individuals and there's risk of spreading. That test should be viewed alongside ongoing symptom presence. Do we completely believe in the swap was taken correctly? Any test is only as good as the swab, this whole chain that every bit about. I think there's a there's a recognition that a negative test - if someone's got purely compatible symptoms - might seem to be consistent with COVID particularly because, , high risk exposure then, , that negative test result has to be used within the context of everything that's going on with that person.

Muhammad Halwani 19:56

What's the proportion of false negative?

Colin Brown 20:00

That's a very difficult question to know because, if you have a negative PCR? There are studies haven't been done where they've done serial viral culture on everyone with a PCR result and then, in a sense, I think that is a very difficult one to know the answer to. And numbers have been bandied around. I'd be interested to know what Catherine will say, so I think it's difficult. I think it probably will depend again on what type of population. We know for those that are intubated, just like with other respiratory viruses, you can become negative in your upper respiratory tract, but a positive lower respiratory tract sample, so the sampling protocols suggest therefore doing both. And it is challenging but I would say that if you've got a very consistent diagnosis or consistent syndromic presentation, then you should just rethink whether the one negative test is correct. For the purposes of excluding people from work.

Muhammad Halwani 21:07

Okay. Catherine, if you want to add something.

Catherine Moore 21:09

Yes, the issue here is that defining your clinical sensitivity of any molecular tests, so we're talking about molecular tests in general. So we in the lab always, when designing these kinds of tests, we look at what is the lower level of detection that that test can actually detect and for most of these tests it's infinitely tiny amounts (I call them homeopathic levels) of virus, most of these tests will detect very small fragments of RNA, essentially in a patient sample. And actually, what Colin's alluded to is that actually the beginning of a pandemic has a lot of negative press which has come out around the PCR is due to poor sampling. And people were not taking samples properly, it wasn't something people were doing on a high throughput basis - we were testing far more than we ever have done before, and people weren't sure whether they should be taking throat swabs or nose swabs, whether they should be combining those samples.

And actually what I like to think going forwards, is because so many people have acquired those skills, that the analytical sensitivity and clinical sensitivities of these tests will have improved over time. And that's probably why we're seeing a lot of these low level positives and more and more becoming more of an issue for us because we're just getting better at sampling, clinical sensitivity is improving

Muhammad Halwani 22:33

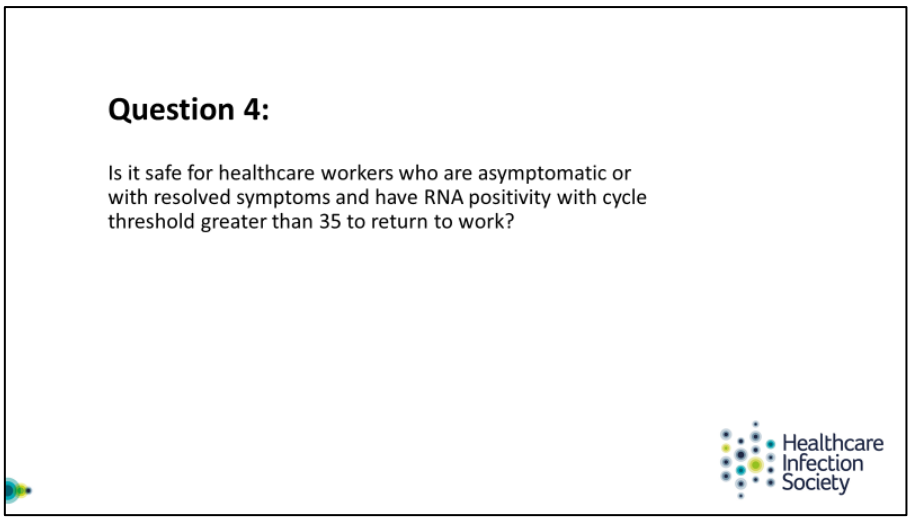
Carole, you want to say something in brief?

Carole Fry 22:35

Just to pick up something Colin said, not so much about test results. Colin you've mentioned flu and planning for the winter. I think what this relatively quiet period, over the summer, I think as an infection community think about what that's going to look like in the winter because obviously we assume that there will be circulating flu, and we assume that people might get their flu vaccine this year. Unlike most years, when it has been a struggle to get health care workers. Really to use this time now over the summer as to how we're going to get services in a shape. People are going to present in ED somewhere with respiratory symptoms, and I think we need to use this time to prepare for that and that's really important.

Muhammad Halwani 23:18

Okay, thank you. So, I think we move on.



Catherine Moore 23:45

If you look at the CT values, the CT values relate to the threshold crossing points at which the test becomes positive. And we're fairly confident that a lot of data now out there suggests that when you get to 35, in most of the molecular tests which are available - and bearing in mind that not all molecular tests, give you a threshold crossing point. Some of these will actually give you just a level detection, some endpoint detection some give a fluorescent signal. So none of these are actually easy to interpret, so we're basically just looking at the RT PCR, to give us a reliable level of low level of detection. So data is now coming forwards to show that essentially during the infection phase and day two post your symptom onset you have your highest viral load, and then over five days, that viral load will decrease really quickly about day seven. And then as everybody intimated some people have this very long tail, where they share virus or RNA for long periods of time. And data that's come out from places like Germany have shown that probably after day eight of your infection you are not excreting a lot of infectious virus. So when you challenge those samples with cell culture the positivity rate in cell culture is very low. We'd like to think that we get to that day eight point and that generally coordinates with a CT value in most of the PCR relates to around CT 35. And so anything after that is generally not likely to be infectious. If you have a typical symptomatic infection with classical onset dates that you can define and that 8-14 days after that you are recovered and are asymptomatic then the likelihood is you are not shedding infectious virus and that what we are detecting is residual RNA which we can detect for weeks and months. And that is proved for most respiratory viruses. Flu for example can have low level positives for weeks after resolution of symptoms. Whether or not you are safe to return to work, will depend on you as an individual. If you are in any way immunocompromised we would be less comfortable with you coming back to work because you may still be shedding infectious virus at a low level.

But if you are a healthy person, with a normal immune response, then yes you would like to think that at that low level you're not shedding infectious virus, but whether or not the policies will allow a positive result for you to come back, it is less clear.

However, I think, guidance will change over time I think as we get more used to how this virus dynamics are in the person and how your immune response - we'll put that into the mix here at the moment - whether your immunity is neutralizing at that point and if you correlate those together with an antibody plus a low level RNA, it may be that you're not infectious anymore and that you can return

to work. And, again, it's all down to you as an individual and I think that's what we have to take. It's the patient we are managing, not the infectivity.

Obviously other people will have opinions as well.

Muhammad Halwani 27:20

Oh, thank you. Anyone wants to add anything?

Malur Sudhanva 27:22

I agree.

Colin Brown 27:28

I think the question about "Will the guidance ever allow someone with a positive test for the CT value?". Possibly, as Catherine said - as we learn more, the guidance evolves, certainly there's increasing evidence for looking at CT cut-off values in relation culture and the slight problem with that is that with everyone using different platforms, different batches it'll be tricky to completely say that you'll be able to get one finding that is a cut-off across all.

But I think, as more and more gets published about where the culture threshold is according to CT value - accepting that obviously culture in and of itself may not be completely sensitive - there will be adaptations to guidance based on that, perhaps even for repeat testing. And, maybe not completely on the initial testing but looking at what happens if someone - if they test positive beyond whatever our exclusion (4-6 six weeks or whatever is going to be) then that might be the time to look at CT values, and we just need to generate more information on that.

Tom Lewis 28:52

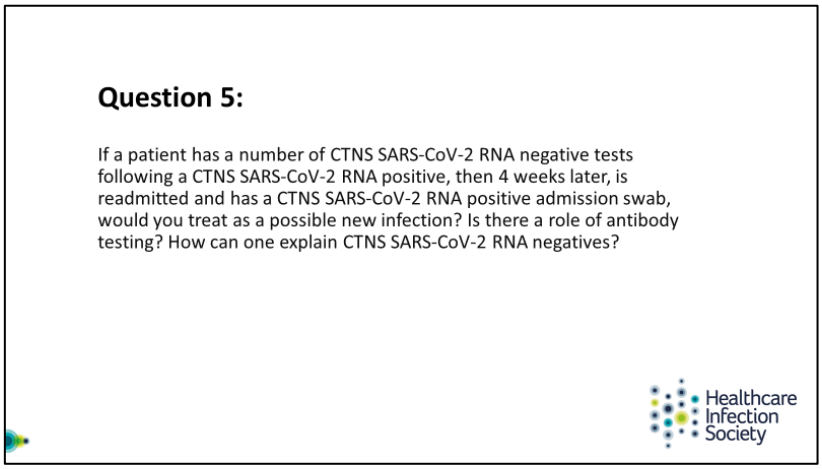
One thing that worries me most at the moment is actually under occupational health policies and our approach to illness generally in staff. So I think the last the last few questions for how we manage and syndromic disease in staff. Most of us are used to working with minor colds. I have not seen, I mean, there has been some behaviour change - but I think how we actually get people to fundamentally change the way they themselves behave, and how they tolerate the behaviour of their colleagues who may not come to work with minor illness is going to be very difficult for us.

Colin Brown 29:25

I think particularly as we go into winter that's going to have to be the message is reinforced. We all in the NHS operate with a large degree of presenteeism and have for decades and changing that narrative is difficult because people don't want to let their colleagues down they don't want to feel, they're creating a burden by causing an extra work for us, particularly when, the system is under such pressure as it was before. But I think it's reinforcing those messages.

Muhammad Halwani 29:55

Yeah, I agree. I would like to apologize there is some sound interference so I'm sorry. If that is already affecting the way you are actually hearing our voices.



Malur Sudhanva 31:16

Thank you. So, going back to the question I feel is the most of the answers have already been elicited by Catherine and Tom and Colin and Carole, I'll just break it down - so you had a positive and a negative and a positive.

Now, to call the positive one which comes up later on as significant, is probably not right now because the virus is very stable. It's not like A infection followed by a series B infection. Here we're looking at a stable virus where mutations happen 1-2 month. So that's so in spite of spreading to the human race.

So, we have to be careful to call this as a new infection. This is just a respiratory infection as Catherine said earlier. The studies that came out from various other parts of the world, to say that this is a second infection, our flawed is a contamination, or maybe I don't want to go into details of it we just may have to look at it as residual. Then the role for antibody is not very clear but we could say that the antibody can be used for example if it's a PIMS-TS in paediatric situation or you don't have a positive result at all in the past.

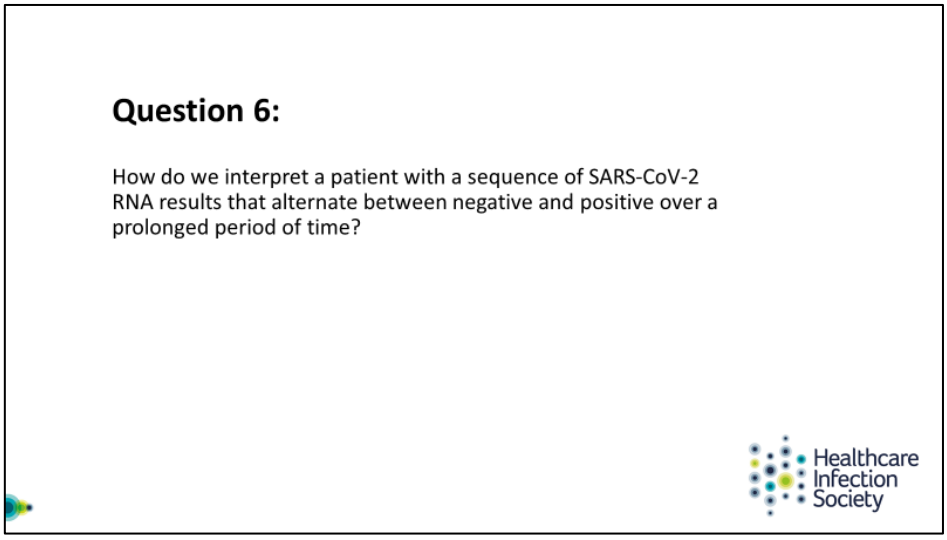
Regarding the negative results. Catherine touched on the analytical sensitivity. You have the analytical sensitivity which goes down to just a few copies per ml. Then you have the clinical sensitivity. Now, that's because that's because the virus moves to the upper respiratory tract and goes to the bronchi and that is positive, but not the throat swab. But when the patient has recovered from ITU and coming back in the throat swab is negative but then recovered and then is coughing up, then this is real or anaemic. So, your clinical sensitivity is again affected.

But we as virologists should look at it very carefully and come to the third category of classification, this is a clinical significance of this, we should be bold enough to say, “Hey, this is not clinically significant”. Classic example is a patient this morning, who's giving organs he is brain dead, and we tested a respiratory sample and it was clearly, clearly, positive on one N gene, but the corresponding S gene was negative in all of assays. We use an alternate assay. And I say that was clearly negative, and we retested our original assay. And that was clearly negative. So what we have is an N gene, which appears at the limit of detection of the assay.

So, we should be bold enough to say, this is not clinically significant. So, we have analytical sensitivity. That's where the antigen assays failed spectacularly. So, someone's said some percent of the people in this audience were actually use antigen assays. That's not right. Because you need to have a sequential RNA assay to confirm the negatives. So, then you have the clinical sensitivity that varies according to the way the virus proceeds. And finally, to summarize, we have the clinical significance. Again, immunosuppressed and immunocompetent is our argument.

Muhammad Halwani 34:50

Thank you very much. Anyone wants to add anything I mean it is actually a tricky subject. Anyone want to add anything about it? So, I think we move on.



Catherine Moore 35:14

Okay, so this almost reverts back to the same issues that we were talking about earlier about sort of people at the end of infections. What you really need to look at is the contracts and who the patient is that's giving you these results. So if it's somebody who is acutely unwell has had a positive result is still within the first eight days of their infection, it could be that virologically the virus just isn't being excreted from where you're taking the sample from. So if you're taking nasal swabs, or throat swabs, you may be seeing fluctuations just naturally as that person begins to clear the infection.

So you may see alternation between positive and negative within the phase itself, the best time to detect any infectious disease is within the first 48 hours of symptom onset. Then if you're looking at somebody who's perhaps more severely unwell, so has gone to intensive care, and you're seeing fluctuations, and it again look at what sample you're taking.

So if you're taking an upper respiratory tract sample for somebody has confirmed SARS-CoV-2 RNA positive at the beginning of their symptoms. It could be that you need to go deeper and take a deeper sample, where you will still see viral replication occurring, and you will get a positive result at that point. So again, it's the context of the patient that you're looking at.

And again, we come back to this. Once you've cleared the infection once you're, you're getting better, you will see, natural fluctuations at that low end of detection so Davers implied that you can see certainly there's some of the gene targets they are sort of at that lower level of detection so they come and go. If you repeated a test 10 times at that lower level of detection you might only pick that up, 50% of the time, so you're going to see that fluctuation particularly as people clear and get better. But if you're talking about somebody who is more severely unwell, go deeper, try a deeper sample and see if that sample is still positive, because that's more likely due to the course of infection.

Muhammad Halwani 37:36

Thank you.

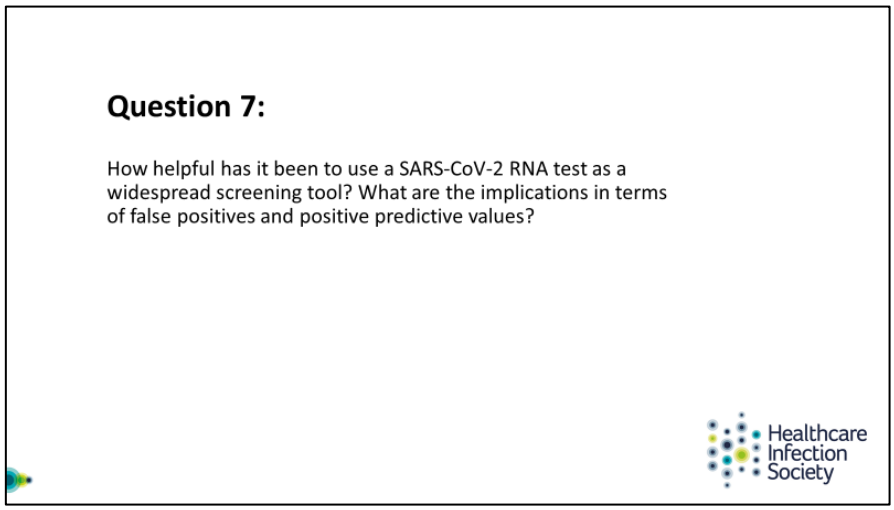
Colin Brown 37:40

It relates somewhat to this point but also the previous point about the very long term.

These are positive people so we're hoping to develop a case report form which we will try and get in place by next week, whereby if people can send us information on all the cases that they mentioned. We are seeing on the British Infection Association chat forum and other places that these increasing long term PCR are positives, and they may or may not function in between negative and positive, but they're not written up as case reports in one individual's experience. It's very difficult to sort of, base evidence-based guidelines on it. So we're going to try and pull together case report form over the next couple of days. And then we'll ask people if they had these individuals to send this in and we could begin to sort of pull out some thematic elements from other that'll help with interpretation.

Muhammad Halwani 38:54

Thank you. Question 7.



Malur Sudhanva 39:11

Let me divide the question into two parts. 1) mass testing for the entire community, and 2) in the hospital.

The reason for mass testing is giving assurance to the public, the politicians the policymakers and epidemiologists whether the virus is in the community or not. So, we didn't have the capacity a while ago, we have the capacity now. So, also that can be tailored to look at the entire city's population, if there's an outbreak. So that's what happened in UK in Leicester recently. And there are also means we can release parts of UK and parts of cities, which are locked down, to exit. For a lockdown exit to work we need to have mass testing, followed by the action on that, which is tracing the patients who are positive, and isolating them. But also the mass testing is required, so that the Office of National Statistics can get accurate predictions based on anonymous surveys that they can do.

So, that again will pick up the pockets of infection. So, there is supposed to be a second wave that's going to happen. We are not likely to see the second wave, as a sudden peak for the entire nation, we're likely to get pockets of infection. That means you need to be ready to be able to test the entire pocket in London or Leicester or whatever city where you have an outbreak and that's what we need to have.

Yes, there are disadvantages to this you need to have a system the logistics the public health has to be at the basis of divinity and there has to be a political will to make it happen.

Now, scaling it down to the hospital setting. The reason for testing is the patients want reassurance that they're entering a hospital, and they're with other patients where the infection isn't there, and also the testing of the staff will assure the patients, the staff themselves do not have the virus. But against testing is in a hospital setting, this is very very disruptive, unless you have an urgent pathway or routine pathway, and people have mentioned that they want to have all the results by 6% majority of the people in the survey.

So, there are painful delays in various elective surgeries, or emergency surgeries emergency in any kind of manipulation in the hospital. So, but at this time. And there's the there is a reassurance that needs to happen and that's where the role for that is.

Going to the second question - false positives. Yes, it is a worrying thing - we have to treat all positives, when low prevalence. Right now prevalence for the microlab where I work is 0.49% of samples that come in our facilities of 35,000 samples tested on last Friday. Only 0.49 were posted that means every post you have to be careful about. You have to retest them. That's what you would want to do, just like as if it's a new HIV positive, you would want to get a second sample and retest. And also, the lab has a multi-gene assay rather than a singular gene assay which is separate from the first one. That way you can look at a different part of the genome so in case there's a contamination we can pick it up. So by doing that, we can cut down on the false positives and the possibility value at this point in time we are very careful about it because the prevalence is low, the positive predictive value is likely to fall, and that's where it's linked to the false positives.

Muhammad Halwani 42:45

Okay. Okay guys in brief because we have to have the open questions,

Catherine Moore 42:53

Okay, so my only issue is that we're using a diagnostic tool, as a screening tool, and the two are not the same. And whenever we do screening we have algorithms which we follow so we use less specific more sensitive tests. We want to pick up everybody who's potentially positive, but then we have a system of testing which goes on after that, to confirm that that is a true positive, none of that is in place at the moment for mass screening, so we're ending up in a scenario where we're testing people positive, but we have nothing to follow that on with. And then if you do follow it on so you instigate these algorithms, you delay the results. So suddenly we are back to 48 hours, 72 hours, whilst we try and confirm the original positive. So it's the tools that we're using, and we're stressing them out, it's we're stressing the system. We're using a diagnostic tool in a screening capacity, and ideally what we need is to get people to do the screening on board to advise us on how we change and how we manage this better, so that we can get those results out quickly to manage cases in in in those small numbers of cases that we are picking up, and then making sure that those results are correct, because the implications are massive when you're delaying surgery, delaying chemotherapy, on the basis of the single positive result.

Malur Sudhanva 44:15

You're talking about the hospital, right?

Catherine Moore 44:17

No, I'm talking about the general population as well. We're not using the tool in the right way.

Malur Sudhanva 44:23

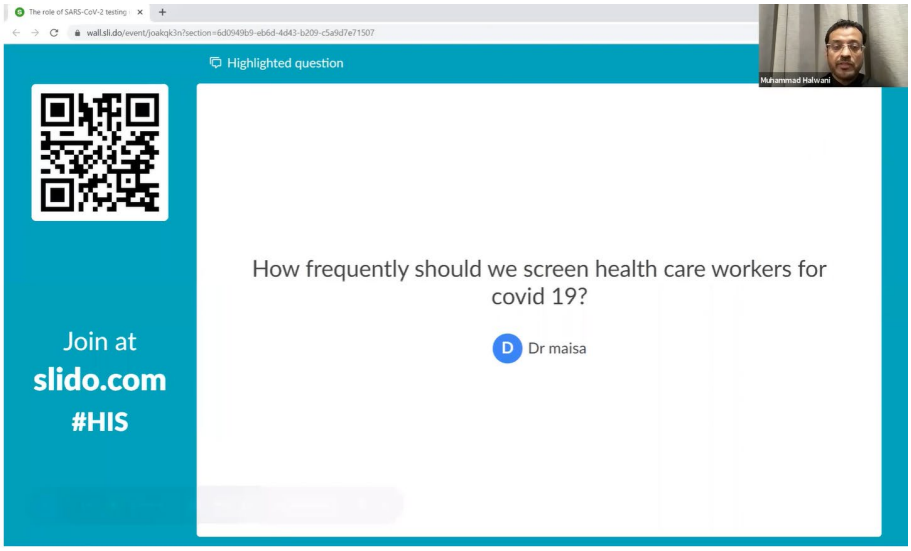
For the general population, the current thing is we have highly sensitive test. We are worried about the sensitivity of the test because it is so sensitive. The tracers are supposed to get in there very, very quickly, or at least the regional testing sites the current statistics 80-90% of results are getting back to the system back to the patients within 24 hours. That's happening. The tracers need to know about the cases, need to know about these things, those IT systems are in place and they are the ones that are getting very very quickly, and then you have the secondary where these results have come from using hospital based system or another Lighthouse lab.

Now comes to the problem, what do you do we all the false positives are coming as you mentioned?

So that's where the clear-cut guidelines are coming out from the government and from the PHE, to say what to do. There are clear cut scripts on what exactly to do with these patients who are positive.

Muhammad Halwani 45:22

Thank you very much. I think now we finished the questions that were sent before the webinar will have the chance for the people who want to ask questions. So, let's see.



Tom Lewis 46:00

Well, I'll get my opinion on this I think following on from Catherine's point of view. I mean I'm not a fan of screening in any situation really I think the capability we need to build is around rapid detection of cases which is having a fairly let's say not using the case definition for screening stuff. So, on the back of any symptoms at all, making sure people can get results back quickly, and then making sure that we've got a contact tracing capability which can deliver a meaningful service within - trace every contact trace within 48-72 hours. That's to me how we manage infectious diseases, I don't really get the case for asymptomatic screening. I've seen it used in some places where there have been outbreaks and so-called Green hospitals, because people take their eye off the ball from the basics.

Muhammad Halwani 46:49

Okay, so you didn't recommend that even people who want to just get screened, in order to make sure that if they are actually infected or not?

Tom Lewis 46:59

I don't think that that has been shown to work. And I would caution against it. I think you can throw up unexpected outcomes whenever you screen any population and I think we, I personally think we should stay with the tried and tested approaches to infectious disease which is rapid case detection and contract tracing.

Muhammad Halwani 47:28

Okay, thank you. So let's see the next question from the participants.

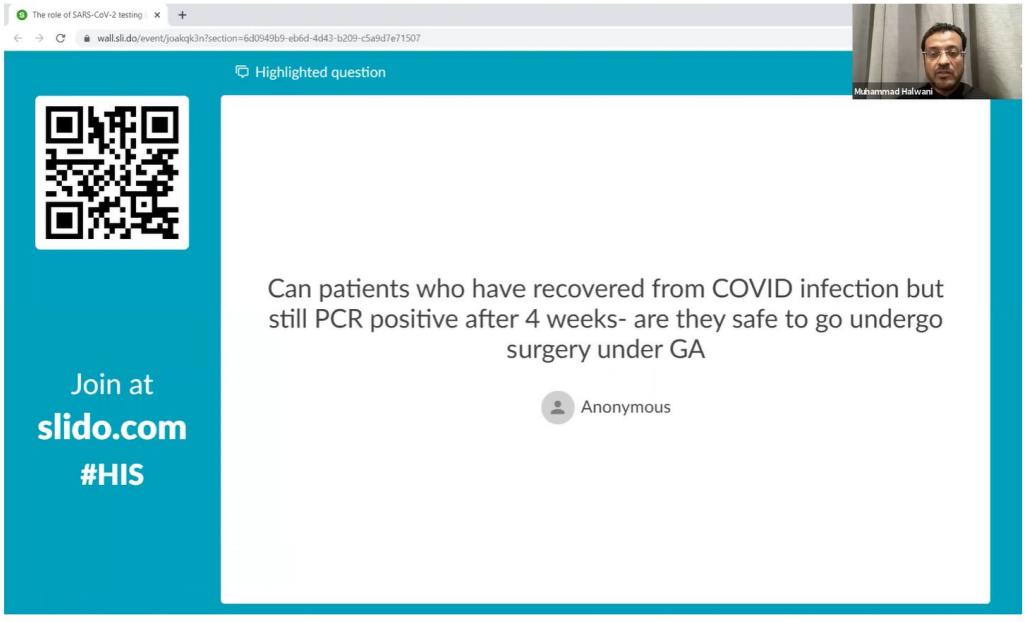
Colin Brown 47:30

I'm just saying I think there have been very clearly usage where the widespread testing of asymptomatic admissions has helped, particularly furthering our understanding what was happening within care homes and certain other outbreak settings where it's shown high rates of asymptomatic carriage. In particular in outbreak settings where it's helped understand both epidemiology and inform public health practice. I think once you extrapolate that outside of this specific outbreak settings it's very difficult to interpret, particularly for all the points we talked - incidents at the moment where your positive predictive value goes, is considerably down.

Tom Lewis 48:13

My response that would be I agree. I suspect the asymptomatic testing there is really a poor man's contact tracing. And if contact tracing can be done at pace - so how we would manage an outbreak in any other situation. I suspect we'd have ended up with a different position so essentially what you've done there is contact tracing.

Muhammad Halwani 48:49



Colin Brown 49:10

The answer will probably depend on a variety of things, of everything we talked about in terms of; are they still symptomatic? Have they had a bad physical illness or not? Ideally what is the CT value now

compared to what it was when they were initially symptomatic? The exclusion criteria that are being developed predominantly will be for the healthcare settings, but will also apply in this in this type of scenario. But I think all of these are going to have to be an individual decision based on looking at all of the factors regarding everything Catherine was saying. Is the patient immunocompromised? What is our pre-test hypothesis around what we think the result would be, initially? Or even if it was positive, what do you think the rationale would be, is it just being on the tail end of PCR positivity, or is there something about that individual patient that, that means that they're likely to potentially have transmissible infectious virus at that time? So, it's difficult to give a one size fits all.

Muhammad Halwani 50:19

Sudhanva, you want to add something?

Malur Sudhanva 50:22

I would be very clear about it. Treat the patient, not the result. As Colin says, if it's an N gene only positive at the limit of detection, the clinical significance doesn't exist. The patient is safe for surgery - operate on the patient. If the patient doesn't require surgery, or surgery can be postponed then - Yes, fine. But we have a new era of highly sensitive tests where we have to come to judgements based on the clinical significance.

So, have had two such cases where transport would have been denied or transport around happened, don't happen if we had believed the test result. So was there one particular patient had anosmia three months ago, and the N gene was still present. So, treat the patient, do not hesitate to treat the patient.

Muhammad Halwani 51:19

Okay. Thank you very much. Let's see the next question then.

Colin Brown 51:26

Before we do I've just been thinking about this contact tracing element that we talked about before, when I think that's not completely true because, by nature we don't test asymptomatic people in contact tracing either. So, I do think that there are scenarios where the testing of widespread populations gives us significant evidence for what is happening in that combination over and above contact tracing. So I do think it has utility over and above contact tracing in select circumstances. It's just that it shouldn't be applied routinely to everyone.

Tom Lewis 52:02

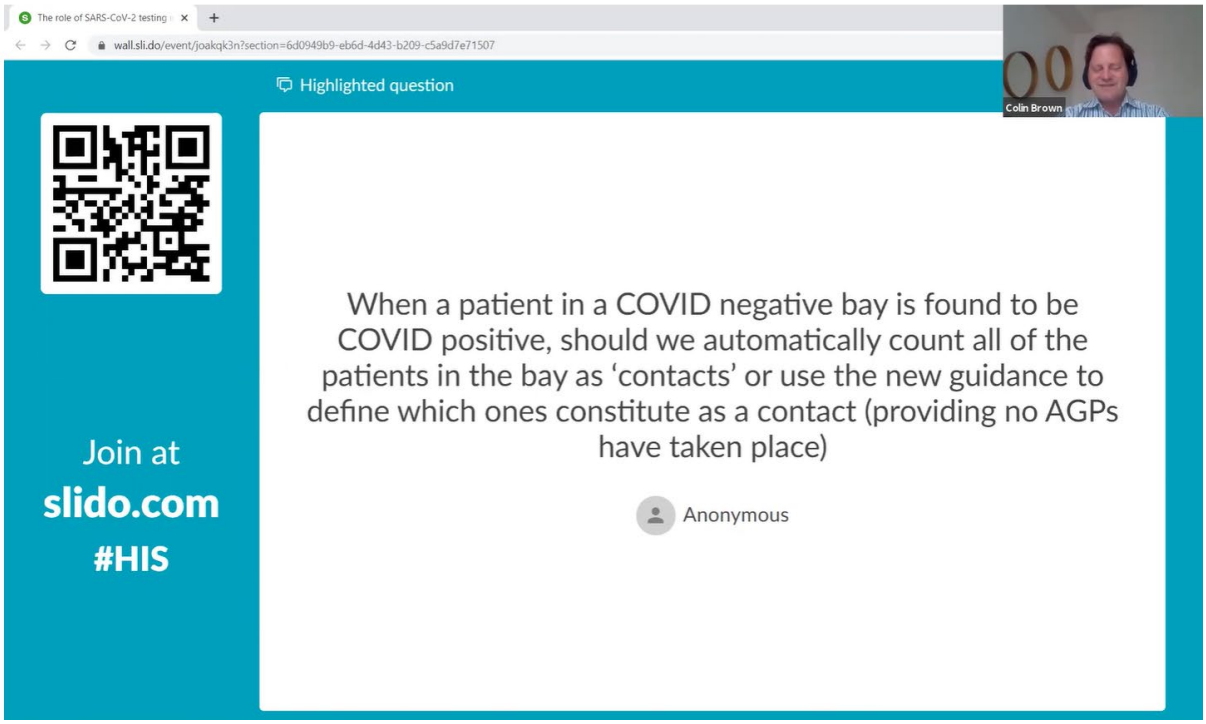
I mean I would agree with you. I guess our approach to contact tracing has been to test asymptomatic contacts.

Colin Brown 52:11

Well then in that case they would be very comparable.

Muhammad Halwani 52:17

Okay, so we see the next question.



Colin Brown 52:53

I would say, yes.

We have been back and forth with various Trusts regarding with who is the contact. I mean again there is no easy catch all to this, it depends how big the bays is, the shape of the ward. Did they even share toilet facility? Are people on the commodes? It's difficult to say that in the context of no AGPs, it's a respiratory virus so I would say, anyone in the bay is a contact.

Tom Lewis 53:36

And I do wonder whether dichotomizing people into contacts or not contact is unhelpful at times actually and whether they're intermediate risks - where we can manage them in another way. So, so follow up swapping or something, just so you don't just disrupt the flow of the hospital, which I think we've seen a few outbreaks around the country where they have been exacerbated by flow problems I wonder whether there are ways of managing people that we don't dichotomize quite as much.

Colin Brown 54:04

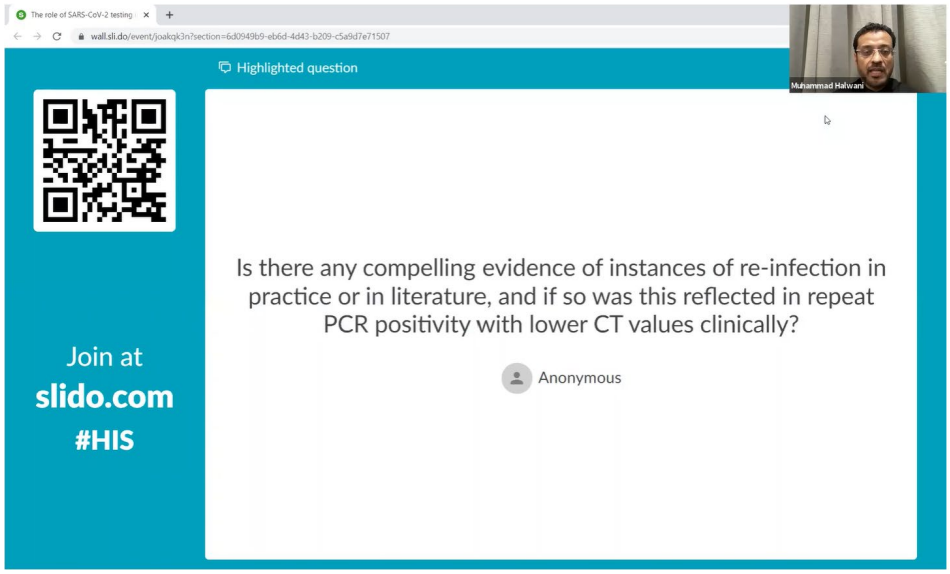
And I think we are certainly looking into that, in terms of serial testing for exposed people. And presumably after time, your risk will diminish as well so someone who is asymptomatic and negative at day nine is very different than some of the day one. I mean I think is different ways to look at it. Carole.

Carole Fry 54:25

I mean I think you touched on a good reason not to count them as a contact. I think we are going to have to look at things differently over the course of the autumn. We can't just do same old, same old.

We might have to have some type of gradation of contacts. Looking at different risk factors. You said the instructions to the flows are pretty seismic we need to get hospitals going.

Muhammad Halwani 55:04



Malur Sudhanva 55:56

We answered it already. The virus is very stable. So we know most of the cases of viral re-infection they are flawed studies, so we can know next year when the virus changes dramatically, whether there will be infection with a slightly different strain. Right now there's one stable virus going through. And it's your assays, giving you negatives/ positives depending on where the virus is so I would ignore it, for the moment.

Colin Brown 55:55

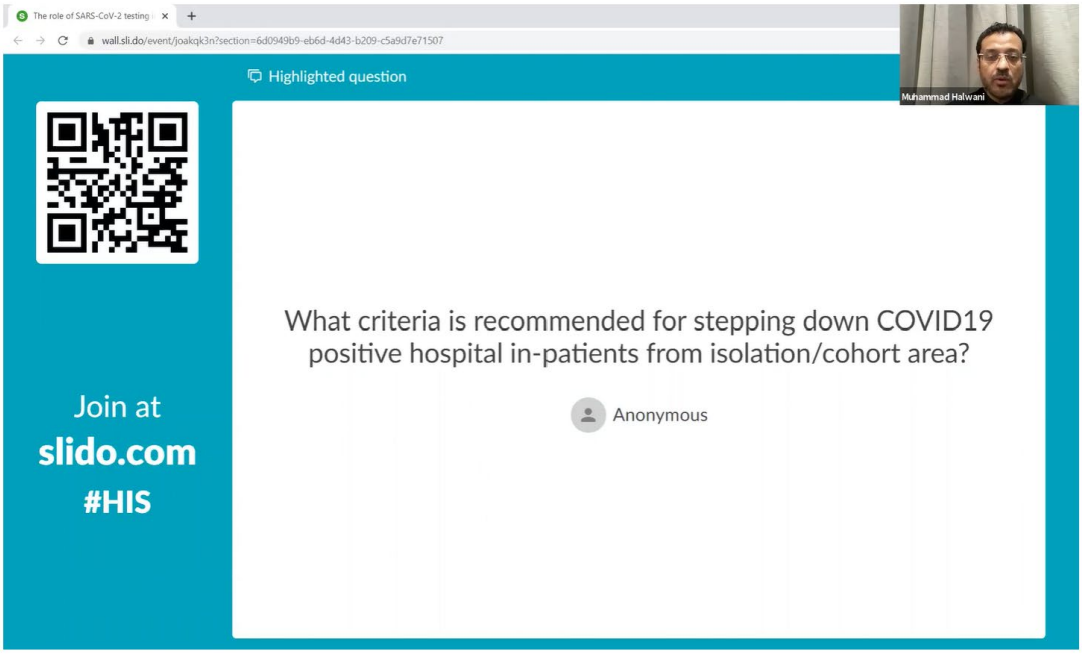
So, I'll come in and promote the SIREN study here, which is looking at initially 10,000 but it's inputting 100,000 healthcare workers to look at exactly this. I mean it's got massive widespread implications of

about what does an antibody test result mean, and how long does it mean, does it mean the same thing for each individual person? Does it depend on the titre? There are all manner of questions, so we are looking at exactly this question with SIREN to see whether people who are antibody positive can get repeat infection.

I think a point of caution. We've worked with a local hospital who were very good and we discovered, someone who'd had a positive antibody result and then a positive PCR result, and some months after only on one target and two very high CT value. And we went back to all the original specimens retested the original serum, retested it was indeed positive. We tested the PCR and did a full respiratory panel, and the SARS-CoV-2 did not retest positive. That was very positive for rhinovirus and enterovirus. So that could have been promoted widely as a reinfection. So I think we have to be very careful. And I would be very wary of reinfection - not to say that it cannot happen and that's really what we're trying to look out for, but I would love to see proper evidence on it.

Muhammad Halwani 57:20

All right, thank you. I think we take one more question, please. From the participants questions.



Tom Lewis 57:52

I think it goes back to what Colin was saying earlier, it's hard to be completely prescriptive I think you have to be on a case by case basis we use a combination of time, PCR positivity, symptoms, serology. I think be interested in what the others think about serology. I think sera positivity does correlate mostly studies with loss of infectivity, but in fairly small, possibly slightly artificial situations.

It's, that's the approach we've taken, but we haven't had that many cases to really test that out so I think others would probably be better qualified.

Colin Brown 58:33

I mean the guidance says 14 days as the minimum, absence of fever or any other significant symptoms apart from coughing and anosmia, and if there's any concern about people's immunocompromised status or if you've got, the testing capacity available at a time, then you can repeat test them at will until negative to stand on.

And if they remain positive you can decide at an appropriate point after 14 days, assuming no other ongoing kind of symptoms of concern to move them down. I think the antibody point is really interesting because I think that is reflected well in studies. But it's a very narrow group of people that that's been shown in. And I think if that really does gain traction, through increased case reports and increased large, case studies and I think there will be an argument at some point very soon to see about - not for the purposes of 'can you get reinfection' - but for the purposes of can you de-isolate someone in infectivity, does that fit into the mix somewhere where it does, So I think we will be definitely looking at that. Caroline, I don't know if you've got anything….

Catherine Moore 59:44

The use of PCR and serology. I mean, we've consistently shown that people who are PCR positive will sera convert. The length of time, you may have to wait a while before they actually do sera convert. But like I say that we just don't know how long that reading is going to last , so if you've got somebody who you are just constantly testing and they're still PCR positive you might want to revert to serology test, just to see that they have sera converted because we know it does happen. And, you just can't give it any more than yes - this person is sera converted.

We don't know what that means immunologically-wise, and whether it's long term. We think, particularly if you're targeting, your assay targets spike protein. It probably does correlate a bit better to neutralization antibodies. If, however, you've got a nuclear capsid target antibody test, then the correlation is probably not as strong, but we just know that over time people do sera convert. So it is a possibility, we could look at that going forward. Okay, thank you.

Muhammad Halwani 1:00:54

Any addition before we close?

Okay, then. Thank you everyone for participating and attending. So our next webinar will be on that 29th July, the same time, 5- 6pm.

Certificates of attendance will be sent out after the event, recording will on the website as well. And because we're unable to answer every question, we receive, or we'll be tweeting some of the ones we have using @HIS_infection. We would love the audience to get involved, and share their thoughts. Last but not least, I would like to thank Adel and Richard, who were working behind the scenes to make this webinar, easy and enjoyable. Thank you and goodbye.