Transcript: Webinar - COVID-19 challenges and solutions 8. Infection, reinfection and outcomes | 4 November 2020

Watch the webinar

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

Panel members:

- Dr Cornelia Adlhoch, Expert for COVID-19 and influenza at European Centre for Disease Prevention and Control
- Dr Deirdre Brady, Consultant Microbiologist, Mater Misericordiae University Hospital and Cappagh National Orthopaedic Hospital
- Sergio Alejandro Gómez Ochoa, Research Coordinator, Cardiovascular Foundation of Colombia, Floridablanca, Colombia.
- Dr Mohammad Raza, Consultant Virologist, Sheffield Teaching Hospital NHS Foundation Trust

Chair: Dr Surabhi Taori, Consultant Microbiologist, NHS Lothian, Scotland

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Surabhi Taori 0:18

So I would like to introduce our panellists today so we have Cornelia Adlhoch.

Cornelia Adlhoch 0:43

Good evening, I'm from the European Centre for disease prevention and controlling and I am a virologist and epidemiologist working on seasonal influenza and now also expert in COVID

Surabhi Taori 0:55

Thank you for joining us Cornelia. Then we have Deirdre Brady.

Deirdre Brady 1:00

Hi, yes. I am Deirdre Brady consultant microbiologist clinical lead for infection prevention and control for the Mater Misericordiae University Hospital Dublin. Thank you for inviting me.

Surabhi Taori 1:12

Very glad to have you. Then we have Sergio Gómez.

Sergio Gómez 1:19

Hello to everybody. Thank you for being here today. I am Sergio Alejandro Gómez Ochoa I am a physician and bioinfomatics statistician candidate with the role of Research Coordinator at Cardiovascular Foundation of Colombia, Floridablanca, Colombia.

Surabhi Taori 1:39

Thank you very much for joining us today and then we have Dr Mohammad Raza.

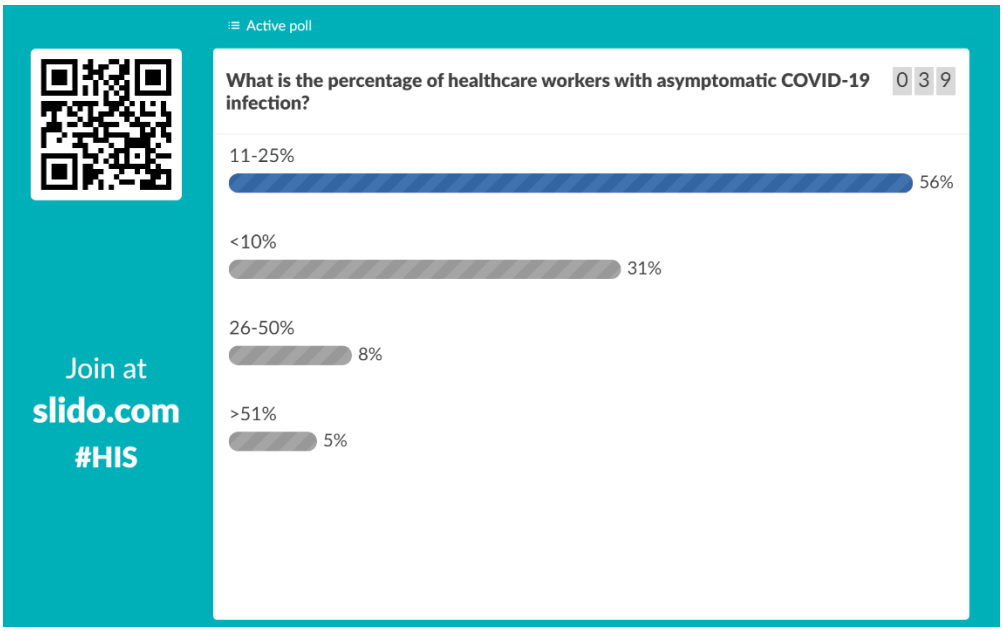
Mohammad Raza 1:41

Nice. My name is Dr Raza, and I'm a consultant virologist based in Sheffield Teaching Hospital in the UK. Thank you for having me.

Surabhi Taori 1:52

Thank you for being with us. So, thank you to the audience for joining us today. And before this webinar we asked you to submit questions to put to the panel, we have selected eight of the most popular questions for the panel today which we'll be discussing in the first 40 minutes of the webinar. During the last 15 minutes of the webinar we will answer the live questions which you can submit via Slido. Throughout the event you will also be able to use Slido to express your opinion, by voting, on

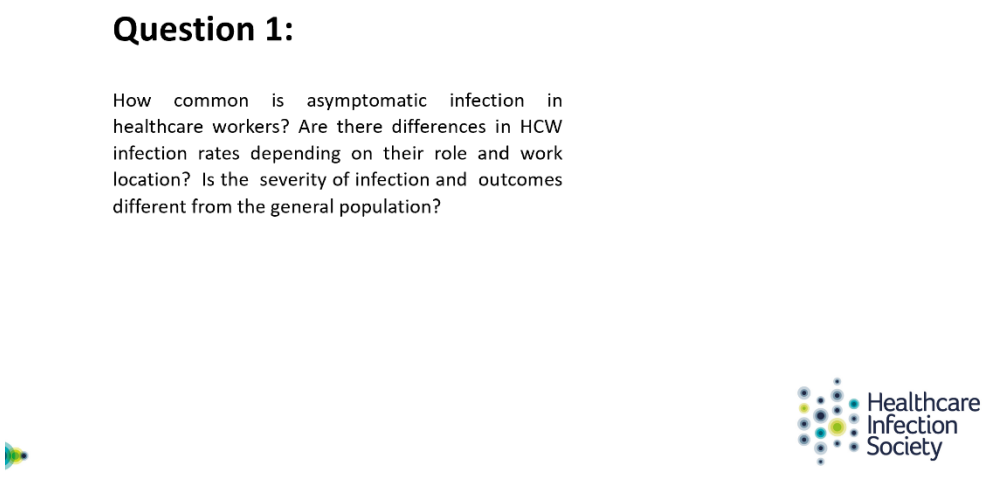
live polls. To participate in polls and questions, please open the Slido app, and enter the code #HIS. I think we can start with the first poll.



Just to get a minute wait for the audience to contribute.

So, the majority of the audience feel that it is 11 to 25% so now let's go on and hear more.

So, the first question.



Sergio, would you like to answer that?

Sergio Gómez 4:23

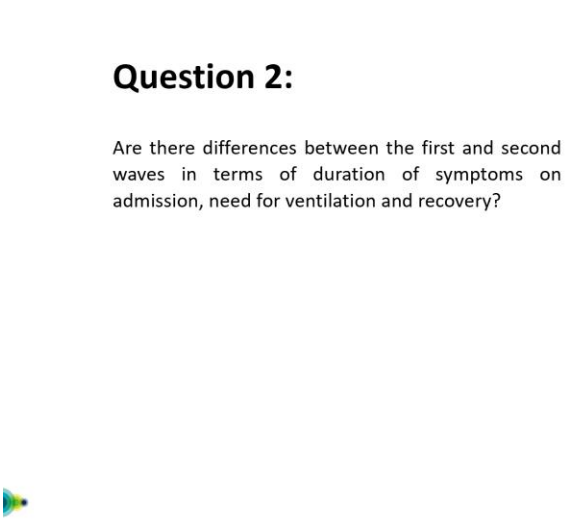
Of course. Well, this is a crucial question for deciding optimal preventive measures in the clinical context. In our systematic review and meta analyses of COVID-19 healthcare workers, we observed that among healthcare workers that were screened systematically (this means that they were screened despite their symptoms at the moment) around 40% of the positive ones by RT PCR were in

fact, asymptomatic at the start of screening. After the publication of our manuscript we have seen a consistent trend of around these value in the articles that were published after ours so we think that we got near the actual real value that we are observing worldwide, in our healthcare workers. On the other hand, according to a recent meta analysis, the proportion of asymptomatic individuals in the general population is around 20%. This difference really acquires a relevance due to the potential risk of asymptomatic nosocomial transmission. Therefore, I believe there is an urgent need to promote the process of continuous systematic screening of all healthcare workers. If the resources of our centre institution, allow this. On the other hand, in a restrained resources setting the systematic screening could apply for the high risk areas, and could be accompanied with a low suspicion of imparting of infection in low risk settings, is to promote early identification and early isolation of the infected healthcare workers to prevent cross infection. Finally this reinforces the need of promoting an adequate PPE supply and use, not only to prevent the infection to be transmitted from the patients to the healthcare workers but also to prevent this transmission from healthcare workers to fellow colleagues, and to patients.

Regarding the second part of the question about the infection rates depending on the role and work location. This is a really important question also. The results of our study suggested that the higher body of the infected healthcare workers were not in the perceived high risk settings, but specifically general clinics and wards, I will explain this in a moment but another finding was that most of the infected healthcare workers were in fact nursing staff - 48% of the total, followed by physicians with around 25%. And finally, other healthcare workers such as respiratory therapists and radiologists. These high number of nurses that were positive for SARS-CoV-2 in our study could be explained by the longer time these staff nurse initially spent with direct patient care, involving tasks performed mostly at the bedside, such as drug administration. They also will present the first line of response, in case of any patient complications. However, with respect to this result, also by the higher number of nurses working in almost every setting, compared to other professionals. However, we certainly need to know more about this specific role, and how we can mitigate the spread of the disease in our nurses. On the other hand, as I mentioned, most of the infected healthcare workers were not working at the emergency rooms or ICUs but are the general clinical clinics and wards with around 42% of the total cases reported. This difference may be attributable to workplace exposures of these healthcare workers, a difference in PPE use such as that PEE use in healthcare workers in clinics and wards would be not as strict, or they could not be as protected as those in higher risk settings. And also by the presence asymptomatic patients being treated for other diseases. Finally, regarding the outcome. We did not find any difference in the symptoms and outcomes of the healthcare workers by their role or setting. Therefore, we believe that social demographic and clinical factors may be more relevant for predicting outcomes in this population, rather than the role or setting they are assigned in their hospital.

Surabhi Taori 8:51

Thank you very much. Would anybody else like to add to what Sergio just said? If not, let's go to the next question.



Mohammad, would you like to answer?

Mohammad Raza 9:29

Thank you very much for that. So, what I would say is that a lot of this, the concept of the first wave and the second wave in regards to pandemic is coming from the influenza where we know much more about the virus and how it behaves. Now, in terms of how the 1918 influenza pandemic behaved there were three waves. And in the second wave that have a lot of deaths and a lot of young adults seemed to be affected predominantly because that's how the pneumonitis etc. set in that particular population so that was a disproportionate aspect of the infection which is usually only seen in the elderly population and the vulnerable one. But there were some differences in those days which were predominantly happened at the time and the First World War was finishing and people were coming back. The soldiers the armies, there was a lot of mixing happening, but overall, there's a belief that those were sort of things with lack of public health interventions, which led to all these high deaths and high rates of infection.

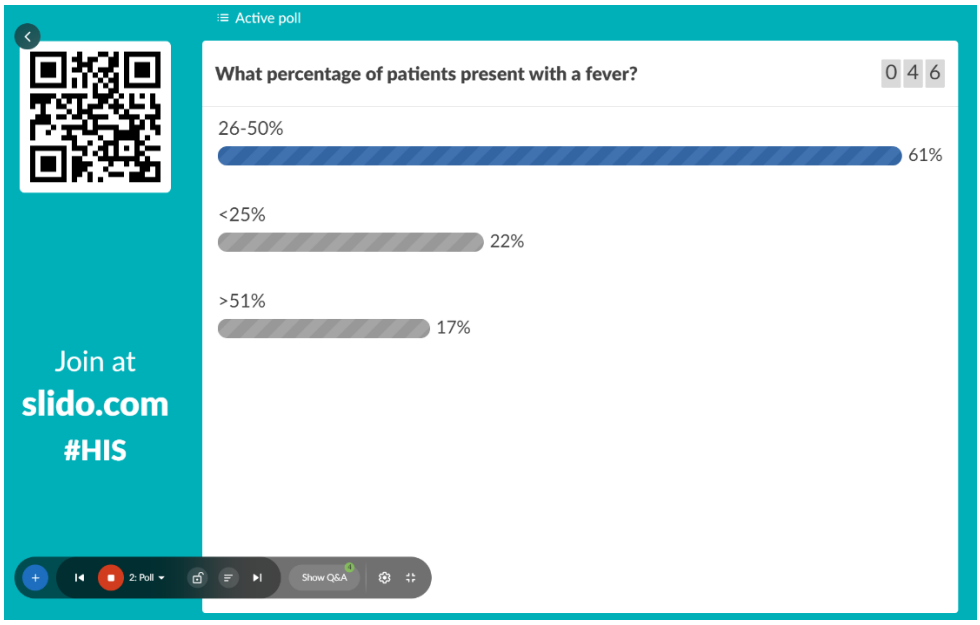
Now from a first and second wave point perspective, it's an early time. We can't really just say for sure how the second wave is going to evolve and what we are going to see. But certainly in terms of if you think of it as any respiratory infection, you do expect very very similar symptoms - but whether it will have any effect on the ventilation or recovery. I personally think it's early days, but I would expect that to be no different. However, the feeling on the ground, which you may have seen in your local hospital is that you are seeing more admissions but there are not that many people proportionately who are being affected. We are seeing a number of infections. But the proportion of those on ventilation recovery are not that high. And you are seeing saturation of hospitals more than what you saw in the first phase, but there are so many other variables which may account for that. You had almost empty Casualties when we started off because of the fears, which the infection induced. But now, in other life, other important functions of hospitals are happening, and the hospitals are full the nosocomial transmissions are happening.

This has been the main difference that nosocomial transmissions, and the outbreaks, which we are seeing more and more, and that has been the biggest challenge in the recent days. And one of the other things which we noticed, or is different at this particular time is the number of asymptomatic screenings which are happening, so the denominator may well have been different from the first

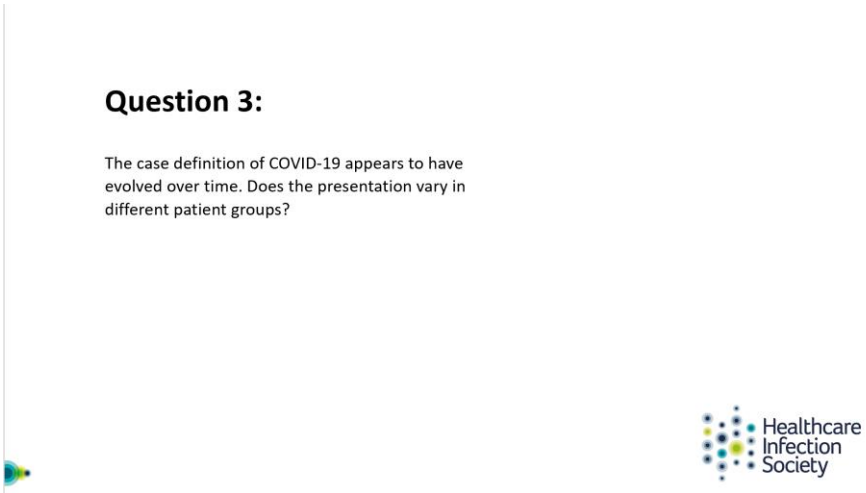
wave, and now you know there are more people than you knew in the first go. So, I suspect the need for ventilation recovery. The overall disease history, the natural way the infection is supposed to progress, may not change because your population hasn't changed. But it may be that, because you know there are more people, and the proportion of those will be lower, but I don't see any reason to believe that the second wave will behave differently per se, as far as the virus is concerned, from the sequencing point of view, although people have recovered viruses, which are different from the first strain with which an individual was infected. So, what I mean is reinfection - I'm sure there's a question on the infection. But from that perspective, even if you were reinfected, which then becomes a different question, people who get infected for the first time, you can see exactly how the dynamics are supposed to be very, very, very similar and I personally don't think that will be any different, but I don't have any data to support that because I would love to have some data. There are modeling available, but at the end of the day, modelling is the best guess.

Surabhi Taori 13:50

Thank you Mohammad. Lots of unknown variables there and I'm sure as time goes by, we get some more concrete data to help support our understanding. Adel, do we have another poll?



Oh, that's interesting. The majority think it's between 26 and 50%. And then the rest are divided between more than 51, and less than 25. Okay, so the next question, which would be for Deirdre.



Deirdre Brady 15:11

Thanks, Surabhi. Yes, so it's interesting to see the results of the poll there.

I think in the first instance it's important to say that in fact case definition has not changed hugely since the start of this. And that when we're dealing with an infectious outbreak, case definition is an epidemiological tool to assist in identifying and close down transmission and prevent onward spread. And so, at the start of any outbreak, case definition very much depends on the cluster that has been identified and may be quite narrow, and in the case of COVID you know severe acute respiratory illness and essentially a community acquired viral type pneumonia that wasn't being diagnosed correctly identified as a new coronavirus virus.

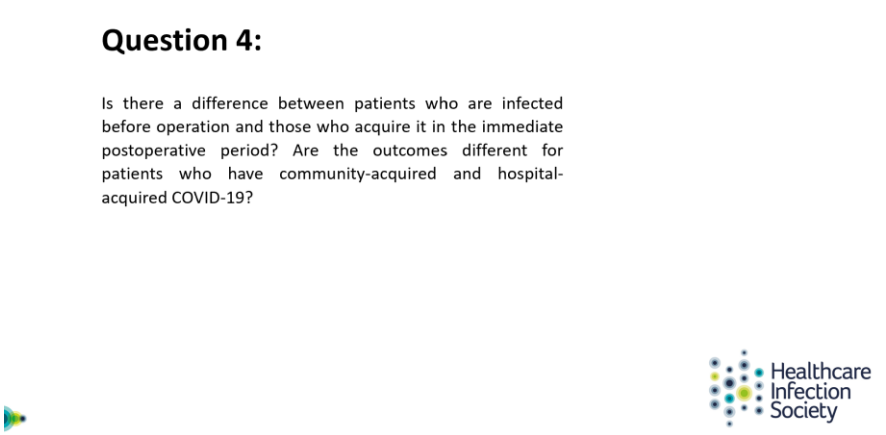
So, as time has gone on because it's a long time now since December 2019 in Wuhan, it is clear that there are more people being tested and therefore positive cases have maybe slightly different symptoms. According to the WHO still the most common symptoms are fever, cough and tiredness globally, but of course, an altered sense of smell and taste - anosmia and ageusia - have been added to the definition and across most, and epidemiological agencies, such as ECDC, WHO and in local agencies in individual countries. And as we know now as well, I suppose, given that there are more people being tested, anything from asymptomatic to life threatening infection is reported in all age groups, and but obviously asymptomatic cases are identified only on screening usually our contact screening or outbreak investigation because they're not primarily presenting with symptoms. So in people presenting with symptoms. And as I said again the most common symptoms are fever dry cough and tiredness and alterations and sense of smell are seen, myalgia, headache sore throat nasal congestion and all those other things I've seen to a lesser extent, and GI upset has come up, skin rash has come up, and depending on the studies that you see it does seem like in the paediatric population I know it can be a little bit different. And certainly, and across the literature it's clear than patients who are elderly for example often present atypically, and we need to remember that patients may not be able to report symptoms accurately. So in patients with the likes of cognitive impairment and dementia the history may not be elicited and there may simply be a delirium that presents, and is undiagnosed and similarly the absence of fever in patients with things like chronic diseases, immunosuppression, age and certain medications has been noted in past reviews of all types of infection and seems to be becoming an issue in COVID as well.

And probably this has contributed to some of the outbreaks in the hospitals and residential care facilities where there's afebrile elderly infected patients. And in relation to an actual confirmed case of COVID, we need to remember that across all agencies again, the confirmed cases – actually the

laboratory confirmed cases that are PCR positive for SARs-CoV-2 nucleic acids, and that hasn't changed yet, so whether we deal with suspected probable and confirmed cases as per WHO. Possible probable or confirmed cases as ECDC. It looks like in the UK seems to be mainly suspected or confirmed cases, and in Ireland we follow along with essentially the ECDC situation. That your confirmed cases are actually are those which are PCR positive. Despite some because of the multiple types of presentations I think it's very difficult to narrow down to a single case definition for anyone with COVID.

Surabhi Taori 19:33

Thank you, Deirdre. Shall we go on to the next question.



Sergio?

Sergio Gómez 20:07

Okay, this is a really debated question. This area is similar to others in COVID-19, we want to solve this puzzle but we still lack some important pieces. Unfortunately, most of the centres around the world don't have the resources to test every single patient going into surgery. So, our capacity of identifying SARS-CoV-2 positive or asymptomatic individuals in this context is very limited. Because, for example, a study performed at UCLA revealed that the prevalence of asymptomatic COVID-19 infection among patients undergoing surgery was around 0.13%. However, the study was performed in a period of time between April and May 2020, in which the prevalence in the general population of the country was much lower compared to the months that came after. Very few ones have assessed the propriety prevalence of SARS-CoV-2 by using a protocol in which everybody is tested. So, we will still need to know from the base the real picture of this in most scenarios. Now, entering into the outcomes aspect, the literature in this area is currently very intriguing. However, when trying to consolidate this result. I have found some valuable points that are similar and I'm going to speak about them specifically.

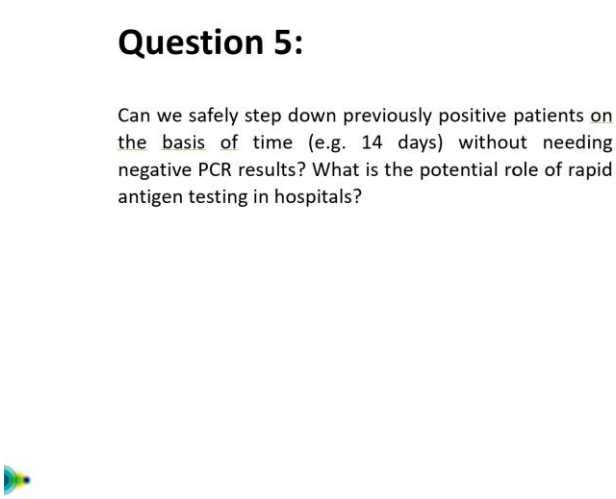
Regarding the question yes there is a differential risk for patients if they are diagnosed preoperatively versus those that are diagnosed postoperatively, and this question was assessed by an international cohort study which assessed around 1,100 patients who were COVID-19 positive, who had surgery between January and March in around 24 countries, they observed that compared to the ones that

had a pre-operative COVID-19 diagnosis, those that have that had post operative diagnosis, had a significantly lower risk of seven day mortality around the 75%. In this context we can also highlight that pulmonary complications were significantly important in that upper unit 82% of the total patients who died, and been significantly saved with high higher 30 day mortality rates. Therefore I think routine preparatory screen for SARS-CoV-2 is specifically used in rapid tests, who, hopefully have a low false positive rates might aid in the mitigation of the impact of this infection, however hospital acquired infections, still remain a challenge does a we need also strategies that minimize these in hospital SARS-CoV-2 transmission such as proper PPE availability and use adequate sterilization, adequate hygiene measures.

Okay, finally regarding the second question, nosocomial COVID-19 is fairly infrequent with the majority of in hospital COVID-19 cases coming in and originating from the community. Around 85% of the total, according to some service. However, there is a scarcity of large epidemiological studies assessing this. Regarding these outcomes, there is a pretty interesting study performed in the UK, which compared nosocomial COVID-19 patients with community acquired ones. The nosocomial COVID-19 patients were ordered and frailer, and were admitted, because of other pre-existing reason. Although these pre-existing reason lead to larger hospital stay, the patients with nosocomial COVID-19 showed a lower mortality rate compared to the younger and healthier community acquired COVID-19 counterparts with a reduction of 25% of the risk, even after covariate adjustments. We may ask ourselves why this happened - the nosocomial COVID-19 patient had almost all the odds against but they still came out winners, one hypothesis may suggest that, as these patients were daily assessed - daily evaluated. It is likely that their disease was recognized earlier. As soon as COVID-19 symptoms appeared, leading to prompt diagnosis and laboratory and clinical assessment, while the community acquired COVID-19 patients may have tolerated their symptoms at home for a period of time before requiring hospital admission, potentially worsening their prognosis by delaying optimal treatment of the infection, contrary to the case of nosocomial COVID-19 ones could have received therapy as soon as possible. A low rate of these nosocomial infection could be in fact the result of rigorous and robust infection control practices. However, we need to acquire larger epidemiological data in order to make sure that this result of similar outcomes or even better outcomes and common ones is definitive, so these may provide some kind of reassurance to our patients as some healthcare systems start reopening progressively.

Surabhi Taori 25:24

Thank you, Sergio that was very detailed answer. Shall we go to the next one.



Mohammad would you like to answer this question?

Mohammad Raza 26:05

So, this has been quite a common question, especially at the start of the pandemic. And I would like you to take this as any respiratory viral infection, and we know the natural history of most of them, most of the viruses behave in similar ways. And what we have found with our continuous monitoring of the very vulnerable patients, especially the stem cell transplants which get tested quite frequently. They tend to shed the virus for a long time and in our experience the transmission has been lacking. And what we have always believed is any respiratory viral infection the shedding and the transmission. That is dependent and is very closely linked with the patient symptoms so as soon as the patient symptoms disappear, which can be variable. But if you take it say five to seven days as the upper limit, and the belief that the transmission goes down to a very very low level. And this is supported by some of the virological studies. Now the data is not as robust as we would like it to be, but whatever smaller studies are there the proxy for transmission, or infectivity is viral culture, and the culture, the upper limit is about 10 days although some people have quoted 19 days, but the vast majority of the patients were not positive beyond seven days or beyond the symptom cessation. So what I would say is that patients are very or highly unlikely to transmit once the symptoms have settled down. So, what we usually say is that we should try not to re-test patients unless you have to for other reasons. But the reality is that patients will get tested for very valid reasons for all the policies, which are in place for example, somebody's gone home and is coming back for surgery back to the hospital, they will inevitably get their pre surgery screens, and then you will come up with a situation where, you know, the patient was positive, and is continuing to shed the virus. Now, in those cases what we have done in the UK, is that we have defined a cut-off of 14 days. If somebody is in the hospital. Then we give a big safety buffer so even though as virologists we believe that they're not infectious beyond their symptomatic phase, we have said that you take 14 days as the safe period. For community based ones initially we had we had seven days from symptom onset symptoms cessation was taken as standard. But now that has been extended to 10 days just to give a safety margin. So what I would say is after 14 days. Just take patients as non-infective, and do not - try your best not to retest those patients because chances are, there will be persistent positivity and my impression dealing with all these cases

of persistent setting is that we are seeing it more frequently than we've seen in the other viruses but that's because probably or maybe we've taken the microscope and we are just closely following every single case of COVID positivity and this is what is being reflected So, my question is where is your control group? Do you really know your seasonal coronaviruses do not behave in similar ways what about RSV, does that get shed? We don't even test for those viruses. So there has to be some sense which has to be instilled within the overall management because otherwise we'll go mad - if not already.

Surabhi Taori 30:04

Thank you. Would anyone else like to add from their experience?

Deirdre Brady 30:10

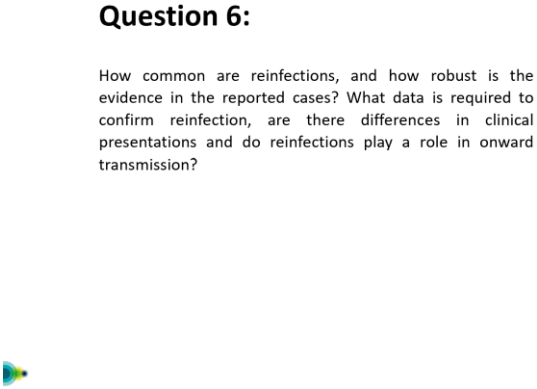
Certainly in the Mater we've had an awful lot of COVID patients who have been with us for a very long period of time, I'm aware of one lady with haematological disease who was tested I think about 18 times during the course of a few months of admission and certainty tests were going positive and negative, persistently positive, you know, you really couldn't guess. I suppose in trying to push the no repeat testing - much like Mohammad there, and I keep trying to remind people that you know there are thousands more people in communities and hospitals without COVID, and anyone who's in the community and recovering at home. And going back to work is not getting retested. So why are we retesting our patients in hospital. You know, we do obviously have patients who are going through surgery who got retested in Ireland and we're testing people before transfer to residential care, and there's a couple of other reasons you know for public health reasons that they are tested but certainly we certainly see repeat positivity in a large number of patients.

Surabhi Taori 31:27

Thank you Deirdre. So that brings us very nicely to the next poll which is have you seen suspected reinfection in your daily practice, yes, no or I'm unsure.

Surabhi Taori 32:20

So around 23% of people think they have seen reinfections in their daily practice. And so brings us to the next question.



Cornelia?

Cornelia Adlhoch 32:48

Yes, thank you and thank you for the opportunity to really speak to that exciting topic. And yes, reinfection is a topic that has been also studied for seasonal coronaviruses and reinfection has been demonstrated to happen, even within over three, three to six months. So,this is not really happening unexpectedly and also for the, for the new SARS-CoV-2 virus.

Currently we have quite a solid report - about 24 cases globally from the US from South America from Europe, from the middle east from India and from Asia so kind of our fair distribution around the globe. However, many many more, and I think the poll says also that there are more suspected cases of reinfection out there, which are investigated, but it's also very difficult to really confirm such cases as it has been based on the limited testing in the early phase of the pandemic where you know diagnostic testing has not been made and sequencing was not available so and to really confirm the case you need more than just clinical data and clinical information but you need to have evidence based on sequence data which means you need to sequence information from the first episode of the virus or from the first isolate of the first episode, as well as sequence information of the second episode, and then you need to compare the sequences. And based on the, on the number of differences in the genome, either by the time or also clustering phylogenetic areas in the in the overall tree, you can estimate or assess the likelihood of such a case being a reinfection case or, more, more, such as a long term shedder, or long term PCR positive case.

So, it's not really a trivial thing to confirm a case, and several groups globally look into that to find definitions to have this solid estimates and solid case definitions, but I think that we're learning every day and we also need more and more data on how to confirm a case. Then, and coming to the part of the clinical presentation so what we have seen, or what has been reported in this 24 cases is kind of a mixed bag. We have seen asymptomatic in the first episode, and then being symptomatic or even

severely ill in the second episode or mild, and then turning into severe or being an asymptomatic in the second. We also have seen that there was one fatal case in this following reinfection so I think we cannot say at the moment we see just milder cases in the second episode we have all of the different possibilities that that are available in terms of the clinical illness and severity out there. And for the 24 cases, there was no report that there was onward transmission happening. However, the limited information on 24 cases would not rule out still there is a possibility and patients might have a very, very high viral load. And so, they should also be treated, in that case, as they would be a first episode case so it kind of new infection and to have all of the personal protective equipment available, and to avoid any further onward transmission. However, we are still in the in the learning phase of such cases and episodes.

Surabhi Taori 36:56

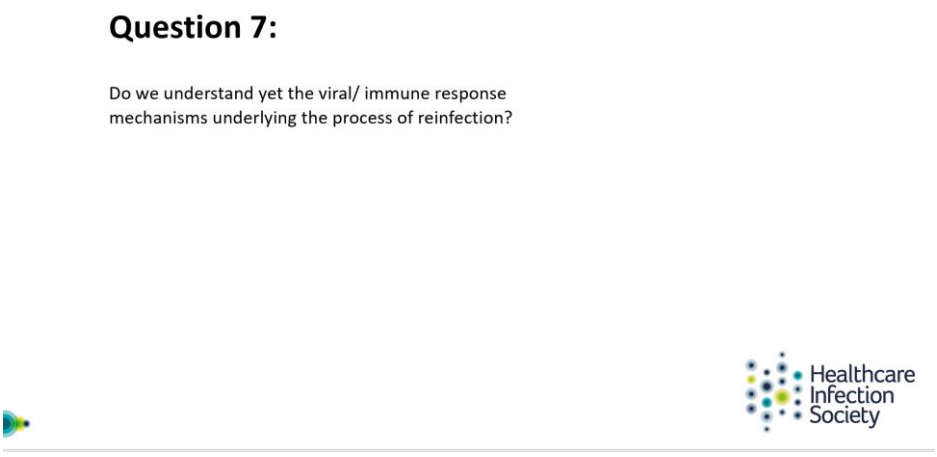
Thank you Cornelia. It is indeed a very interesting phenomenon, to see reinfections. And if only 24 cases are really been reported that's a very very tiny proportion of the overall burden of COVID. Does anyone else on the panel have any experience they'd like to share but reinfections or relapses or any experience at all in investigating?

Mohammad Raza 37:25

It's a question which keeps coming up not necessarily in the COVID context. But for the other viruses. And one of the difficulties we've got is that long term shedders. If you get any respiratory illness, which is of non-respiratory viral origin, then there is a risk that you will attribute that illness to the re-activation, reinfection - whatever you want to call it. Either it's another strain or something else and the diagnostics which are available in real time, they are simply not up to the mark. There's no way you can confirm the reinfection and - 24 cases - we need more data to say, reinfection is something which is common then what it appears so I think there's a big hole there.

Surabhi Taori 38:23

Indeed, so this brings us nicely to the next question. Cornelia?



Cornelia Adlhoch 38:43

Yes. I mean we should not only talk about the immune response, because I think we also need to take all of the circumstances of such potential reinfection rates in terms of understanding the comorbidity-the situations where such reinfections happen in terms of viral load. So far what we have been seeing is that both healthy people as well as, as people with comorbidities have been kind of identified with reinfections. We have seen young ones we have seen old ones, it's male it's female, so it's it's nothing where we can say like there is a trend that it might be only the ones having some comorbidities. It cannot be only related to such factors and the data shows on these reinfection cases. Of course there's also limited information on the immune response available but for some, they are data about the IGG antibody level that has shown to be at a very low level between or after the first episode, or between the two episodes. And, but then after the second episode just shoot up again like kind of have a booster effect.

There is not much available on the cellular immune response and also on the different patients. There is still a lack of data available about the role of the, of the different antigen and antibody levels in the patients after the first episode of the disease where we have seen that mild infections might not really cause a high level of IGGs following this infection. And what's the role, or what's the likelihood of such patients to, to get a reinfection. And what's then also the cellular effect and impact on those patients, and to prevent the second mainly severe infection or kind of an only have a have a mild infection as the second episode. So I think we, we need much more data than what we have available but I think it's also very difficult to screen all of the different patients and to get IGG tests performed over time and to have it have patients really monitored closely to make this kind of assessment, but I know that there are cohorts out there which are really closely followed up so I hope that we have soon much more data that helps us to understand, when such re infections could occur. And also give more information about the frequency of the occurrence of such reinfections. Without having done all of the, the sequence data with having whole genome sequence data available for both episodes, so that we can at least have some prediction tools to assess people or to assess if there might be a severe infection or disease coming with the second infection. Yeah, more for us to learn.

Surabhi Taori 42:03

Definitely more data is required, but thank you for that answer. Anybody else would like to contribute? If not we are ready for the next question.

Question 8:

Some patients describe a long course of several months of debilitating fatigue post COVID-19 infection whereas others have recovered rapidly - do we understand much about the process underlying this and why there maybe such different recovery courses? Do some co-morbidities predict a worse outcome than others?

Deirdre?

Deirdre Brady 42:48

Thanks Surabhi. I suppose, fatigue is a common symptom associated with viral infection in general, and persistence of fatigue is well describe after some other viral infections acute phase has passed for example, a lot of people will be familiar with EBV and its long term effects thereafter. As we've already discussed, COVID-19 is an infection with a wide range of presentations from asymptomatic to life threatening infection. Clearly some patients will be fatigued and the short to medium term after having losses and acute flu like illness that has seen them take to their bed for a week and not use their muscles and not have restorative sleep and that kind of thing. And, as well as that any patient who has had severe illness requiring hospitalization and especially admission to critical care may have myopathy, and may require physiotherapy to regain relatively normal muscle function and all the associated physiological improvement that comes with that. And there's I suppose three parts to fatigue with COVID with number one being that acute phase secondly I suppose fatigue might be a symptom of a complication of COVID, and three main complications such as cardiomyopathy and persistent lung disease, have all been described as complications of COVID-19. And they're certainly more prevalent in patients with underlying conditions who require care, but they also occur in patients who have actually remained in the community for the acute phase of their infection. And, in looking into this, I see early autopsy studies from Germany, identified SARS-CoV-2 in patients who had died from COVID and demonstrated infection in the heart but didn't associate this with an influx from inflammatory cells so to suggests myocarditis. And since then, as well we've heard the virus in the interacts with the angiotensin-converting enzyme-2 receptor, and that this kind of disruption might lead to cardiomyopathy, cardiac dysfunction and heart failure.

So, the feeling of fatigue post COVID may be generated by hypoxia arrhythmia etc and warrants investigation. Assuming normal physical examination and vital signs, then it's unlikely that the fatigue is due to serious complications such as this. So then, thirdly we get down to prolonged fatigue, after a viral illness, that it seems patients are experiencing. There are countless reports in the media - we know ourselves in hospital where our healthcare workers have been infected. We look forward to them, passing their isolation period and coming back to work and yet some of them are off for weeks or months with persistent symptoms. And that's happening in the community as well. And so is there a kind of a chronic fatigue type post viral syndrome happening? If there is there are examples in the literature of a small number of patients experiencing similar symptoms of fatigue syndrome after SARS, and the study on Toronto healthcare workers was a very small number. But, and they did have neurological symptoms and signs consistent with a chronic fatigue syndrome type of post viral syndrome, and the possibility of that happening when SARS-CoV-2 has already been postulated, and a comparison has been made with the brain involvement via the olfactory pathway of SARS, and the fact that anosmia is a common presenting symptom SARS-CoV-2. Maybe there's something underlying that that we've not, we're not quite sure yet what it is. And, and, as I said, many healthcare institutions are certainly acknowledging anecdotally, the absence of infected staff members from work for extended periods. And I'm interested to see the WHO press conference last week they had patients come on to tell their stories of their lives being affected for months after what they hope was the acute virus. And I see a pre-proof/pre-print, and study from a hospital that I worked with myself here in Dublin in St James's Hospital under a group with a consultant immunologist, who have actually done a study, small number, but I think important things on some of their COVID patients they would have had a lot of large numbers of COVID patients during first wave of pandemic, and they offered every person who was COVID positive follow up outpatient appointment. They looked into the persistence

of fatigue in this patient population. And they offered us to 233 patients - 138 patients took it up, and they actually found that more than 50% of those patients were describing fatigue symptoms at 10 weeks post their acute COVID illness. And interestingly what they found is that it wasn't associated with COVID severity - so they looked at the requirements for hospitalization for supplemental oxygen or critical care - and there wasn't a significant association with these. Likewise, there wasn't a significant association with routine laboratory markers such as white cell counts. And what they also looked at, and the presence of pro inflammatory markers such as IL6 and found no correlation with that either so they're working I suppose I'm trying to find the cause for this post viral fatigue which is seen in a substantial proportion of patients and but as yet nothing has really turned up. They did find that female gender, the history of anxiety and depression were overrepresented in the population, that described ongoing fatigue - which I suppose has been similar to other type of fatigue type syndromes across medicine before. And so this is awaiting publication, and what I think is really highlights that there are certainly a substantial number of patients who are describing fatigue going on after this. Now obviously you could argue the participants who picked up the outpatient appointments were more likely to be more persistent symptoms but people who didn't have gone about their daily lives recovered and were well, and the proportion of patients with fatigue might be lower than what was reported. But I do think it is a significant aspect of this disease. We just need to we need longitudinal studies to really see how it's affecting people in large numbers.

Surabhi Taori 49:40

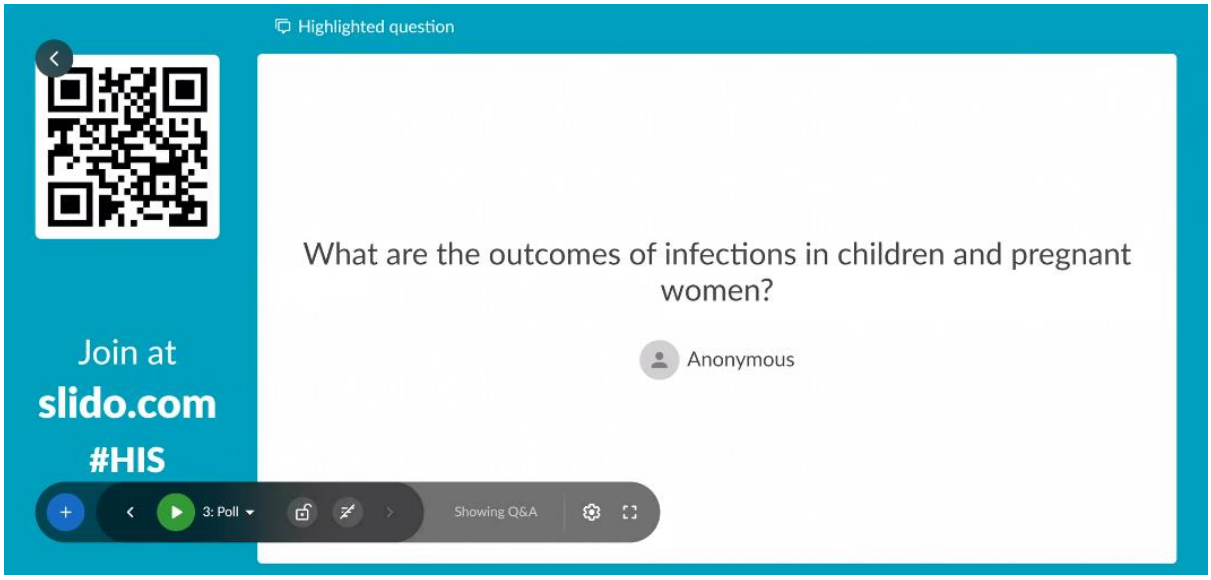
And to do that, again, another area of need, which needs a lot more work to understand that. Would anyone else like to add from their experience? I know one of my colleagues had anosmia, which persisted beyond two months of recovery from the acute phase of COVID so miners of disturbance but definitely very uncomfortable.

Deirdre Brady 50:00

I've heard the same.

Surabhi Taori 50:20

And so, if there are no further comments Then shall we go to the audience questions.



Segio, would you like to address this?

Sergio Gómez 50:32

Well, at first, pregnant women represent a very special population, you know, we can have some physiological conditions such as gestational rhinitis that may even mask the typical symptoms of COVID-19. However, when entering into the symptomatic profile of pregnant women with COVID-19, we observe a similar symptoms profile compared to non-pregnant women and men. Moreover, we have also observed that the outcomes of pregnant women with SARS-CoV-2 infection may be even better when compared to those that have been historically report for SARs-CoV and MERS-CoV we have an estimated fatality or case fatality rate of around 0.1% for SARS-CoV-2. While in the case of SARS-CoV, it was around 18%. In the case of MERS-CoV it was an impressive 25% in our pregnant women so we certainly have a better picture today. Nevertheless, we cannot put down the guard as clinical studies have proved that COVID-19 does increase the risk of for example needing admission to the ICU, needing invasive ventilation for our pregnant women. So, I think we must stay conscious that our thought is not as severe as other similar viruses, it still causes harm and leaves a deadly footprint.

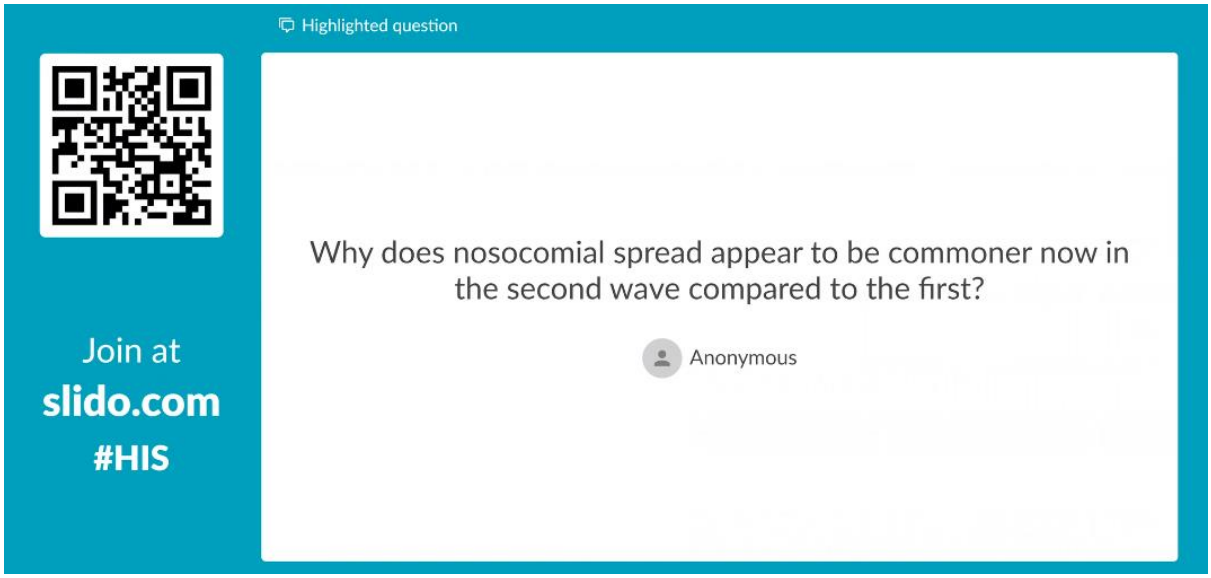
Speaking about specifically the baby's outcomes. We have a very low rates of miscarriage around 2%, while the prevalence of intrauterine growth restriction is around 10% according to a recent meta analysis. The most common complication is a preterm birth, with around 40% of the total, pregnant women. Now, the second part was about the children right there are some interesting differences when comparing their outcomes with those of adult patients at first radiologic findings tend to be specific and milder compared to adults. They usually require a less frequently supplemental oxygen. They less frequently require ICU admission. Around 2 to 3% compared to 6% in adults and over as age increases, and also their mortality rate is also significantly lower with a recent meta analysis, suggesting our observing case fatality rate of around 0.3%. However, it may be even lower. As a according to the data from the CDC from around 200,000 cases reported in patients below 19 years old - with a cut-off point of say September since the last time I reviewed it - only 0.06% of them report a fatal outcome. There are many hypotheses that have been trying to explain these differences, and I'm going to list three or four of the most relevant in my opinion.

At first we must remember the differences in the immune system between adults and children, especially elderly adults. Some nice models of infections, with SARS-CoV showed both a CD4 and CD8

T cell responses, along with antibody responses play a significant role in viral clearance. Children, in fact have a stronger innate immune response. Also a higher proportion of total lymphocytes, higher absolute numbers of T cells - natural killer cells, which might help them fight the virus. Furthermore, and this is also important they have a lesser magnitude for the inflammatory cytokine response, which could also protect them from this phenomenon cytokine storm, which we know, play an important role in the pathogenesis of severe COVID-19. The second factor relies on the lower prevalence of a comorbidities, you know, pretty significant risk factors for adverse outcomes in adults are arterial hypertension, chronic heart, lung, kidney disease. These conditions are almost upset, children so this may be another reason why they're having better outcomes than the adults. The third potential explanation could be for example, the common circulation of coronaviruses, which are really frequent or fairly frequent in this age group. They represent in fact around 8% of all acute respiratory tract infection. So we think that it will be feasible that this pre-existing potential immunity – potential cross-reacting antibody reaction to SARs-Cov-2 may have a protective role. At last, we must remember the mucosal colonization by viruses and bacteria that children usually have - this could also limit colonization of SARS-CoV-2 through a process of bacterial interference and competition.

Surabhi Taori 55:48

Thank you, Sergio. Shall we go to the next question.



Mohammad Raza 56:10

I alluded to this particular point earlier on in my answer. And it's to do is to do with - I think there are different practices. The first thing is that the spread in the communities happening more. When people come to the hospital they seem to be more - in terms of the realization of infection. In the first wave, it was the number of cases, which did not simply come to light and they were really more at home than they came to the hospital Personally I think it's it's to do with the activity - that we are noticing it more - rather the dynamics of it. I don't know of any reason why things have changed between the virus or the way we handle things which explain this. And I believe it's the nature of the infections - the transmissibility, which we were not seeing in the first wave which is more prominent in the second one, I don't know whether somebody else has any view, but this is what I think it is

Surabhi Taori 57:24

You mentioned previously that we almost emptied our hospitals in the first wave, so there were no susceptible patients to acquire it. And anybody else who would like to mention Cornelia?

Cornelia Adlhoch 57:36

I think it is also kind of biased by the number of tests performed. So, as we know that in this in the first wave the number of tests being performed also in the hospital setting has been quite limited also due to available equipment and so on. So I think it's could be also based on a kind of bias view that we test more so we see more nosocomial outbreaks now. Maybe this is what what we are seeing here on the number of hits performed overall which has been increasing dramatically over the last few months.

Mohammad Raza 58:12

Corneila, maybe you are right because maybe this has happened over the last many many decades, we just simply didn't notice it - and now you've got the microscope.

Surabhi Taori 58:22

Would anyone else like to add anything?

Deirdre Brady 58:30

I think yes, the screening of contacts certainly is playing a role here, we've seen more than our fair share of healthcare associated COVID, and a few outbreaks during the first wave. We weren't testing contacts routinely, and for the first short while of the first wave I think I'm sure there are patients who had asymptomatic COVID who maybe didn't really transmit it, and were never picked up, whereas this time round, we are hunting for cases much more

Surabhi Taori 59:04

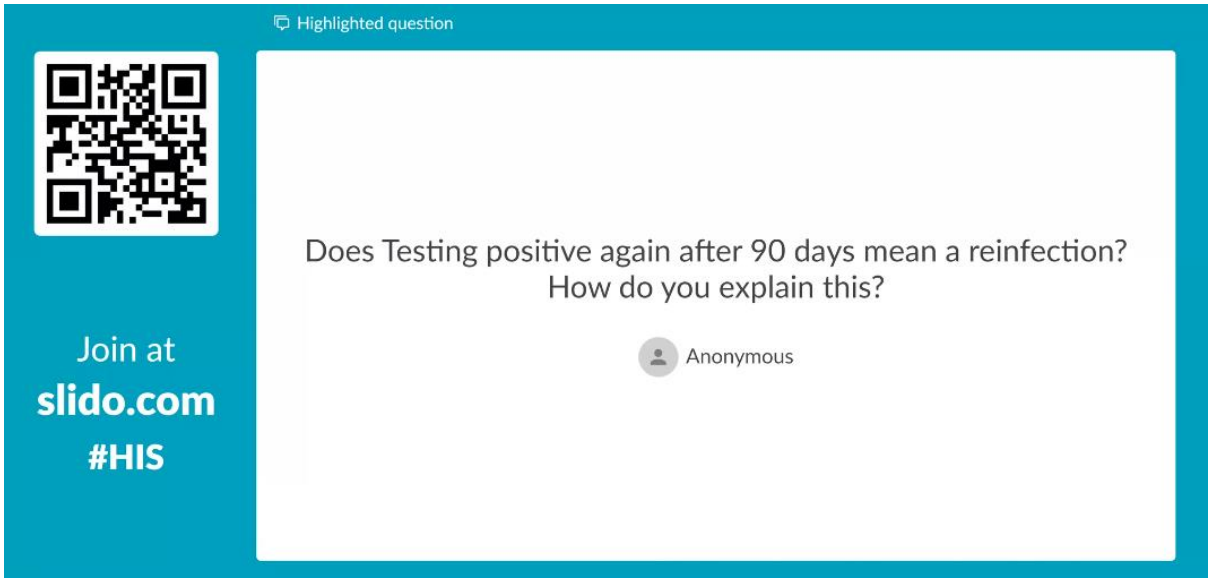
I also wonder whether we're not really comparing like for like. There were quite a few differences just in the availability of PPE etc. Where, although there's so much more available now, we're still seeing more cases.

Mohammad Raza 59:18

I suppose you could rephrase the question. So the question: Is in a way open ended is nosocomial transmission happening more than more than the first wave?

Surabhi Taori 59:35

Okay. Shall we try one more question we've got a few minutes left.



I think we've discussed this at least a little bit but Cornelia, would you like to take this?

Cornelia Adlhoch 1:00:00

Well, I would not put like it's 90 days threshold or any timing threshold into all of the definitions of a reinfection - although there are debates. And, which would leave and also this kind of long term shedders. What our clinicians have now also said that you have people who shed who are PCR positive over long stretches. And so that would then also kind of per definition fall under reinfection. So I think that we need much more data and based on epidemiological findings that you need to also have a negative test in between the different episodes that you need that the sequence that gives more information and confirmation about really that it's two different isolates that cannot also consider that the virus evolve, kind of in your own body, you know, acquiring different mutations over time that this would kind of lead to two different viruses.

So, you need to really be sure in terms to identify instance and confirm these reinfection cases. Setting this 90 day threshold, or whatever - 60 day threshold, we have seen cases which have kind of very short average intervals, like for three weeks only for 12 days only so I think the variations between these different episodes of the reinfection cases is so variable that we cannot rely on one measure to say like this is cut off and everything with this earlier than 90 days or later than 90 days is an infection case or not and so on. I think this timing is very difficult and we should have more, much more data from the epidemiological side from the patient side from all of the circumstances comorbidities immunological data. Plus, and most importantly, the viral data.

Mohammad Raza 1:02:06

In my books, it's the sequencing which really nails it, because how do you know what the virus is? Is it the same virus I know you alluded to the PCR negativity and positivity but we see this all the time that people have got a low level of virus and it comes back again depending on the frequency with which you're testing the patient may present six weeks later, or a day later or six months. Is it the persistent

shedding, or is it reinfection? So, based on the traditional rules I wouldn't really diagnose a case of reinfection. And as a virologist, you can convince me its a different sequence altogether.

Surabhi Taori 1:02:53

Okay, so thank you everyone. It's just about 6 o'clock so I would like to thank the panel, for joining us today and sharing their valuable time with us. For the participants those attending the session certificates of attendance will be sent out after the event, a recording and transcript will also be available after the event, and also previous webinars and other COVID-19 resources are available on the HIS website. So, may I also thank Adel and the team who worked behind the scenes and make all this happen. So, thank you so much everyone keep joining us today.