HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Tuesday 9 June 2020

11 am

Watch the meeting

Members present: Lord Patel (The Chair); Baroness Blackwood of North Oxford; Lord Borwick; Lord Browne of Ladyton; Baroness Hilton of Eggardon; Lord Hollick; Lord Mair; Baroness Manningham-Buller; Viscount Ridley; Baroness Rock; Baroness Sheehan; Baroness Walmsley; Lord Winston; Baroness Young of Old Scone.

Evidence Session No. 6 Heard in Public Questions 51 – 60

Witnesses

Professor Sheila Bird, Former Programme Leader at MRC Biostatistics Unit, University of Cambridge; and Honorary Professor, College of Medicine and Veterinary Medicine, University of Edinburgh; Professor Sir John Burn, Professor of Clinical Genetics, Newcastle University; Professor Jon Deeks, Professor of Biostatistics, University of Birmingham; Professor Andrew Hayward, Director, UCL Institute of Epidemiology and Health Care, UCL.

Examination of witnesses

Professor Sheila Bird, Professor Sir John Burn, Professor Jon Deeks and Professor Andrew Hayward.

The Chair: We now welcome the witnesses for the second panel: Professor Bird, Professor Burn, Professor Deeks and Professor Hayward. I thank you all for joining us today and we look forward to the session. Baroness Manningham-Buller will start the questions.

Q51 **Baroness Manningham-Buller:** It would be helpful to the Committee if you could give us clarity on the different tests being used to detect and manage the pandemic, including the PCR and antibody tests, and say which work well and which there are some doubts about?

Professor Sir John Burn: Thank you for the question. May I begin by saying that I am professor of clinical genetics at Newcastle University? I am a specialist primarily in inherited cancers, but for the past 12 years I have been on the board of a university-sponsored company, QuantuMDx, where I am also a shareholder. Its aim was to develop point-of-care PCR diagnostics for infectious disease. The engineers and scientists in that company are dedicated to this space, and I will be speaking with knowledge from them. I am also chair of Newcastle Hospitals and can draw on the knowledge of our high consequence infectious disease unit, which was the first to receive a Covid-19 patient.

The first and obvious test, which we see used all over the world, is taking someone's temperature. It is not a very good test, in either sensitivity or specificity, but it picks out some people from a crowd. The second hope, which is yet to be fulfilled, was to be able to identify the proteins that the virus is made from as a rapid test using techniques such as lateral flow, which we use for pregnancy tests. They have yet to come to fruition, but many people are working in that area.

The next one is antibody tests. Initially, they were hoped to be a preliminary test of infection, but, again, early investment did not prove to be successful and the tests were not carried on. We now have two tests in circulation, one from Abbott and one from Roche, which test antibodies against the nucleocapsid protein inside the virus. They are proving reasonably reliable, although we may come back to the specific details later. We know, for example, that 6% of our staff in the hospital are positive for those antibodies, whereas about 16% of our colleagues in another hospital are positive. There is quite a lot of variation between centres, but that seems to be a reliable way of telling us when someone has had the virus.

The test that everyone is focused on is RT-PCR. Polymerase chain reaction amplifies the molecular material. RT refers to reverse transcriptase. We all contain DNA in our cells. It is transcribed to RNA to become a message to turn into proteins and enzymes. Viruses are made either of bits of DNA or of bits of RNA. In this case, annoyingly, the coronavirus is made from RNA, which is rather harder to handle. To analyse it, we have first to convert it back to DNA using an enzyme called

reverse transcriptase. We can then amplify fragments of the virus and identify those either in real time or by using fluorescent tagging. The early tests for PCR were developed immediately after the virus emerged. They were not terribly good because we did not know exactly how it was built, so we were basically using the SARS test developed earlier.

The first generation of assays, which are now widely in use, targeted a piece of the Covid-19 virus that is unique to it. The problem there is that the virus mutates regularly a couple of bases a month. It is about 30,000 letters long, so there is always a chance that it will mutate and the test will stop working. The latest generation of tests, which includes that developed in Newcastle, have multiple features of the Covid-19 virus, so even if one of them mutates we will still spot it and uniquely identify it. These assays are highly specific, but they are still not entirely sensitive for a variety of reasons, partly to do with the sample collection and how it is transported and, as we will discuss, partly to do with a person's exposure, their development of the disease and their development of immunity.

It is a rather complex field, but essentially the PCR test is the gold standard. The antibody test is hugely valuable as a diagnostic tool to tell us who has had the disease. As yet, we are not sure whether it tells you that you are immune. Certainly, the two tests that we are using against the nucleocapsid are not antibodies that indicate immunity; they simply tell you that you have had the virus.

Baroness Manningham-Buller: Thank you, Sir John. Would any of your colleagues like to add anything? In particular, I am interested in the reliability of these tests.

Professor Sheila Bird: Perhaps I may briefly add something about the uses of the tests that have just been described. As we heard, the PCR or swab test—essentially, the "have I got it?" test—is used for diagnosis and most importantly, first off, in patients hospitalised with Covid disease when we had a lack of capacity for testing.

Importantly, the swab test is also being used by the Office for National Statistics Infection Survey, which gives us week-on-week an estimate of the number of persons in the community who currently have infection. As the individuals who take part in that survey are swab-tested weekly, we can follow up those who were negative at the previous swab test and are now positive. In that way, we get an estimate of those who are newly infected, and so we get incidence. That is a very important use of those tests in epidemiological terms.

Neither of the antibody tests currently available—the "have I had it?" tests—has high enough sensitivity and specificity for us to use them for personal diagnosis, but they are extremely useful for surveillance of the proportion of the population that has had the infection. These tests typically begin to signal from about 20 days after infection, but for how long they signal we are not quite sure as yet, and so there is further work to be done to understand the persistence of antibodies. As mentioned, persistence of antibody is not the same as immunity, and so at the moment we do not have tests that would give us an immunity passport.

Professor Andrew Hayward: The other thing to point out about the use of any test is that its accuracy is quite dependent on the prevalence of the infection within those whom you test. For example, even though PCR may have close to 100% specificity, if you were using it in a population where the prevalence was, for example, one in a thousand, which is similar to what has been found in the ONS study just referred to, and even if specificity was 99.9%, you would still expect about half of your positive tests to be false positives. So you do need to consider the frequency of the disease as well. That is less of a problem when you are investigating people with symptoms. We know from the start that they are more likely to have disease than people without symptoms.

As has been referred to earlier, the other important things when it comes to the accuracy of these tests are the sampling modality—what types of swabs you are using—and the timing. We know, for example, that peak viral load will probably be within the first day or two of symptoms. If you are taking tests later, infection and the sensitivity of those tests will go down.

Similarly, we are seeing with the antibody tests that we need to wait beyond 21 days, even a month or so, for some people to reach detectable levels of antibody. Also, there is some preliminary evidence about mild infection as opposed to severe infection, which is what most of the tests have been evaluated on. People with mild infection may have a lower antibody response than people with severe infection. We still need more research in that area.

Q52 **Viscount Ridley:** I will quickly declare again my interest in QuantuMDx, which Professor Burn mentioned and in which I am an early shareholder.

My main question has to some extent been answered, particularly by Professor Hayward just now, as it related to the sensitivity and specificity of the PCR test, so this should not take long. False positives were mentioned. May I press on the question of false negatives? How reliable is the test? Is it possible for someone to test negative and not be negative? If so, are we in danger of missing a few cases? Also, related to that, are the PCR tests capable of identifying the asymptomatic cases?

Professor Jon Deeks: There are two sets of sensitivity numbers, which are badly distinguished in the literature. A lot of the numbers we are seeing, which are very high, are based on taking samples that we know contain the virus and seeing whether they can be detected, so they start with a piece of matter that has been proven to contain the virus.

If you run the test on those samples, you get very high sensitivity, so very few false negatives. What matters to us as public health people is what happens when you try to take a sample from the person. The swabbing process is utterly critical in getting the virus. That part of the process seems to be the weakest link in our being able to detect people who are diseased, and that is where we are seeing false negatives.

There are not that many studies around giving us figures on that. It is quite a difficult thing to do. What we see are studies where people are

tested multiple times; we look at the number of people who are positive in a later sample when they were negative originally. The figures that we are seeing show that between 10% and 30% of infections can be missed; results can turn positive on a later sample. That is a substantial proportion. It is a bit of a concern that a lot of the discussion is about the analytical sensitivity rather than what we would call the clinical sensitivity.

The way in which the sample is collected, who collects the sample and where it is from, matters. Samples from the upper respiratory tract are known not to be as good as those from the lower tract. You get lower-tract samples only from patients who are hospitalised. We really do not know how self-sampling works—how likely people are to pick up viral matter when they are asked to swab themselves compared to when it is done by a professional health practitioner.

Viscount Ridley: Thank you. That is very interesting. Can I also ask about the handling of the swabs after they are taken? I understand that they have to be frozen and that sort of thing. Is there any technological improvement coming in how swabs are taken and how they are handled that will cut down the false negative rate?

Professor Sir John Burn: There are a couple of major developments. The first is in how long it takes to get the swab to the laboratory, which has been a major challenge for us. As you are all aware, there were not as many tests available at the beginning of this process as one would have liked. That is because our virology labs were not set up to do this sort of mass testing. In particular, most of the NHS labs were reliant on the Roche robots, the Cobas 6800's, which are a rather big, awkward structure using very specialised plastics. Roche was not able to mass-manufacture them, so we are still dependent on only 35,000 tests a week from Roche because that is as many as it can give us of its specialised plastics.

I have brought some along. I am not sure if you can see this. This is the cassette that carries the reagents. Without this, the machines do not work, so we can do only 35,000 per week, despite having the capacity to do perhaps 10 times more than that if the materials were available. This led to the creation of the Lighthouse Labs to try to overcome that barrier. Like the Nightingale hospitals, they were a temporary measure. They were hugely successful but intrinsically had the challenge of getting the swab to the laboratory; in the case of Newcastle, it was a 250-mile journey.

The labs have brought together open platforms that can use any assay, and these devices are still all around the country. In the next little while, we need to see the NHS laboratories being allowed or encouraged to take this testing back in-house as they gear up and get their assays working on the open platforms. This will have the major advantage of putting the results into the hands of the clinical professionals straightaway, so that the results are hardwired into the NHS. That will hugely speed up the process of getting the swab tested and getting the result back, which will have an important epidemiological impact.

The second issue is that, at the moment, because this is an RNA virus, everyone is dependent on extracting the RNA before analysing it. Our colleagues in Newcastle and others have been working on developing a direct-from-swab assay. The technical evidence for that is now good. It is not quite as sensitive as a deep swab that has been extracted, but, given that it will take away one whole step in the process, it massively speeds up the process to about 70 minutes. That work is now looking extremely promising. Clinical trials are underway at St George's and in Newcastle to prove the evidence on clinical samples.

These are two areas where we are going to see fairly significant movement in the speed of processing and an improvement in diagnostics as a result.

Q53 **Baroness Rock:** I would like to come back to antibody testing. Witnesses have already mentioned the Roche and Abbott antibody tests. I have a couple of questions on that. How accurate are they, and why would accuracy and reliability differ between the test manufacturers? How are antibody tests calibrated?

Also, Professor Bird mentioned surveillance. I would like to understand how the different antibody tests are being evaluated and, importantly, by whom.

Professor Sheila Bird: There have been two joint evaluations of up to seven tests in the United Kingdom—that is, comparative evaluations done independently. In the first set of about seven tests, none was particularly promising. Those evaluations were done on relatively small numbers of positive and negative samples.

The more recent evaluation has been conducted under the auspices of Public Health England. Jon will perhaps talk a little more about that later. It evaluated the Roche test and the Abbott test, but the evaluation was in different places at different times, and on different numbers of samples. That is hardly like with like, and there were many other problems with that evaluation. It is very important that we develop a platform in the United Kingdom where we can reliably offer evaluation for antibody-tests, to a decent scientific standard, for various companies.

The Medicines and Healthcare products Regulatory Authority, partly in response to interventions from the Royal Statistical Society Covid-19 task force, of which both Jon and I are members, has set out its stall as saying that an evaluation should be based on at least 200 confirmed positive samples and at least 200 known negatives; for example, blood samples taken before the coronavirus was in circulation.

There are of course other criteria such as interferents, which need to be checked. It is a complicated business to do it well. We have not yet had an example of its being done well, but we are perfectly capable of doing it well.

Professor Andrew Hayward: Another important thing in evaluating tests is to use quite challenging tests. Obviously, giving negatives from prior to circulation of the pandemic is important, but we know of other

work, particularly that going on at the Crick. There is a high degree of cross-reactivity with seasonal coronaviruses, so deliberately making sure that you have bloods from people with seasonal coronaviruses, which can be very similar to SARS-CoV-2, can help to increase their specificity. Certainly, the work at the Crick has been doing that. Actually, they been looking at the spike proteins for providing more specific assays than the nucleocapsid proteins.

So there is a wide range of ways of doing this. The initial results from the Roche and the Abbott tests look good, but they are on relatively small numbers and the tests are not that challenging.

Professor Jon Deeks: My team has been reviewing all the studies of all the tests that are available for antibody testing, so we have been reading huge numbers of papers on these.

The idea that there are only two tests available is not correct. In fact, there are nearly 200 antibody tests available. An organisation in Geneva called FIND is trying to keep track of all the different tests around the world. When I looked at the end of May, there were 196 produced by commercial manufacturers. China has given emergency-use approval to seven of those, and the US to eight. Some 185 of these tests have CE markings, so they can be marketed in Europe.

The difference in those numbers is staggering. It reflects the fact that our CE marking, our regulatory process, does not look at how well tests perform; it looks only to see whether the marketing claim matches what is said about the test. At the moment, in Europe, we do not have a regulation process for tests that helps us to identify which will be good and which will be bad.

So we are in a slightly difficult situation. It feels like we are trying to make up a new process with Public Health England to try to evaluate these tests. In doing so, we are mixing up what I was saying earlier about analytical and clinical accuracy. When we are testing banks of sera that have other coronaviruses, it is important to understand that it does not interfere with that. But it does not tell you how well the test will work at not giving false positives when you use it among the general public; it is a necessary but insufficient step.

Similarly, when we are trying to detect the sensitivity of the test and looking at whether it gives false negatives, we see studies being done that are based on sample banks. We do not know how many people they have come from. It is possible that the studies have used five or six samples from the same patients, who happen to have very high antibody levels, which makes the results look good.

This is a bit of disaster in some ways. We are not getting good information from the Public Health England studies, or many other studies, on how well these tests will work when we use them in cohorts in clinical pathways. We found 50 studies published up to the end of April, and there are about another 50 studies up to the end of May that evaluated many different tests. The first lot of results will be published this week, and we hope to follow up with the other evidence from that.

We definitely need to up our game on how we do the science of evaluating these tests.

Professor Sir John Burn: I would reinforce what Professor Deeks has said. The same applies to PCR tests. About 400 tests of varying quality have flooded the market. In defence of Public Health England, it is very difficult for it to keep up with evaluating all these different tests. In fact, the two referred to are the two that had been felt to be reasonably reliable and are therefore being used. I entirely agree with Professor Deeks that there is an inundation of testing; this is obviously now a major commercial area.

The Chair: Thank you. So right now we do not have a reliable test for antibodies in the UK that could be used on a population basis. Is that the case?

Professor Jon Deeks: We do not know whether we have that, because the studies have not been done in a good enough way. It is possible that some of these tests are good enough. The important question is: what does good enough mean? We can tolerate some degree of error. It depends on what the consequences of a false negative or false positive will be. That is what we need to think about when we decide. I am not sure that the process has been thought through completely.

The MHRA figure that has been put out is 98% sensitive and 98% specific, which is exceptionally high. Our HIV antibody tests have only just got to be at that performance level. We are in danger with that figure of throwing away tests that are actually useful, but not perfect.

Professor Andrew Hayward: On the tests used in sero-evaluation, I understand that the Sero-Epidemiology Unit and PHE are utilising tests that are known to have a lower sensitivity, because they were purchased prior to proper evaluation. So we are using them for that purpose rather than for general clinical use.

Q54 **Baroness Sheehan:** Starting with Professor Hayward, may I ask about the timing? To what extent is testing important in different phases of pandemic management, such as containment, suppression and eradication?

Professor Andrew Hayward: I think testing was critically important during the containment phase. One of the criticisms often made of the UK is that we did not test sufficiently rapidly enough in the containment phase, and to some extent that is fair.

I would also point out that it is much easier to do that in the early phases of containment, when you know that the people you are chasing are people who have come from abroad and their contacts. As soon as you start to get widespread community transmission, the task of testing and tracing people becomes much, much more challenging

We are facing a similar situation as we come out of the containment phase. From the point of view of disease control, the times that rapid testing and tracing are most important are during the containment phase and as you come out of lockdown, when you are similarly trying to ramp

down on transmission. During lockdown, the uses are targeted more at healthcare facilities and clinical diagnosis, but also, for example, on preventing outbreaks within institutions such as nursing homes, and other institutional settings such as the homeless sector. How you use the test varies at different times of the pandemic.

Professor Sir John Burn: I have already mentioned that the challenge of the Lighthouse Labs is in our turnaround time of a couple of days. Are you talking about the length of time it takes, or the timing of the tests?

Baroness Sheehan: I am talking about the timing of the tests in the phases of pandemic management. The turnaround time is also very important but not the question I am asking.

Professor Sir John Burn: Okay, I will not add to that question. On the timing, some very interesting information emerged just last week from the cruise liner that went to the Antarctic but was trapped in Uruguay after an infection got on board. It was a very well managed ship, but 128 people still got infected out of 217 on board. What is interesting is that only 24 of them actually became symptomatic.

The point is that a large proportion of people who are infected do not become symptomatic, which we know. This means that we have to look at testing people in those early stages, when they may never become symptomatic but are nevertheless highly infectious and could transmit the disease. So if we are to have an impact on the spread of the disease, testing needs to be made possible, at scale, in the very early stages. At the moment, we do not have the scale or accessibility of testing to meet that challenge.

Professor Sheila Bird: Test, trace and isolate is based mainly on symptomatic testing. If you have one of three key symptoms, you immediately book a test and you and your household are isolated until the result of the test. If you test positive, you continue in your isolation and your contacts are then traced and asked to quarantine. But we do not have any checks on that, and we wait for the quarantined people to become symptomatic.

I would like to see associated with the programme that, at a randomly selected time during my quarantine, I am offered a swab test, so that we can learn about asymptomatic positivity. We will not learn if we do not do that sort of well-designed, random asymptomatic testing. This would have the other benefit of checking that I am at home, where I ought to be, and so it would be a check on compliance as well.

Q55 **Baroness Sheehan:** I will move on to the level of sensitivity and specificity of tests. What level is needed to control the spread of the virus at a population level? Does the percentage have to be in the high 90s or is good enough good enough?

Professor Andrew Hayward: There is a trade-off between the speed of the test results and the sensitivity and specificity. For example, there is a possibility that we could accept lower-sensitivity tests to support the test

and trace programme if those led to our being able to isolate contacts more quickly then we can now.

I would not recommend these tests as standalone, but if they were done in conjunction with more specific and sensitive tests we could get a much quicker result. The key thing in the test and trace programme is speed. All the models show that we really need to isolate contacts within 48 hours of symptom onset of the index case.

That is extraordinarily challenging. In fact, NERVTAG recommended that isolation should initially be based on symptoms rather than waiting for that test because of the importance of speed. I think it was decided not to do this because of the huge amount of disruption it could cause, which is understandable. But speed is really important; the trade-off between sensitivity, specificity and speed needs to be considered.

The Chair: I see the other three nodding slightly, so I presume that they agree. We now move on to Baroness Walmsley.

Q56 **Baroness Walmsley:** My question is about the role of diagnostic testing as the UK eases lockdown restrictions. Professor Bird might like to begin. How important will diagnostic testing be to control the spread of the virus as we ease lockdown? How many people do you think need to be tested, and how frequently, to reduce the spread? And can you say whether there are any groups of people who will be particularly important to test during this phase?

Professor Sheila Bird: We start with those who have one of the three key symptoms; it is clearly important that we test them. However, from the information that we have from the Office for National Statistics Infection Survey, it looks as though individuals with one of the three key symptoms represent only about a third of new infections. This is not doing the whole job, by a long way.

One important aspect is to compare the number that we diagnose as Covid-positive with the daily number of new infections that we think we have in the community on the basis of the ONS Infection Survey. The gap between those two matters; we need to narrow it considerably.

The other approach being taken to testing is to focus on high-risk areas, be they residential homes, hospitals—testing both staff and patients—and, potentially, high-risk occupational areas. If the intelligence that we glean from the test and trace programme indicates that there are certain occupational groups, or locations, associated with transmission of infection, then you would put a testing effort there.

It is important that we do not just test but acquire data, as we have not been doing adequately, about those who are tested: their household size, where they work and, even if they cannot identify all their contacts, whether they are in an identifiable location that might give us a clue to the locations that are at risk.

There is a huge amount to be learned from the analysis of the information that should be associated with test and trace.

Baroness Walmsley: Would you add the primary contacts of people with symptoms? If so, how frequently would those people need to be tested? Would it be more than once?

Professor Sheila Bird: Potentially, if we have the capacity to do it, I have suggested that they should be offered at least one randomly timed swab test; the timing would be chosen from the distribution of when we think they will become infectious so that we get refined information on that infectiousness period. We could offer more than one test, but I suspect that we might then be running up against capacity issues.

Professor Sir John Burn: As you will appreciate, we have already started running into problems in some of our front-line teams where people are being isolated for long periods. Testing will allow us to get people back into work.

In addition, I entirely agree with Professor Bird about the need to get as much data as possible. We also need to use testing to give us the confidence to allow people who are being isolated to come back into play. That will probably mean very regular testing. When we move on to managing the second wave, this whole question of how we expand testing and make it more immediate will be a pivotal issue.

Baroness Walmsley: I see. Can you say how the UK's approach to testing in this phase compares to that of other countries as they have eased the lockdown? Might Professor Deeks be able to answer that one?

Professor Jon Deeks: One concern that has been expressed about contact tracing is the risk of false negatives with the swabs; other countries do multiple swabs on somebody who initially tests negative. I think New Zealand tests them three times. We have started talking about the risk that you will miss the disease. We have a leaky testing problem in contact tracing at the moment; we are allowing the risk of missing disease.

Baroness Walmsley: Right. Can I ask all of you what testing strategies, if there is a second wave of the virus, you would recommend the Government pursue to reduce its impact?

Professor Andrew Hayward: I want to make a point about the number of people who have symptoms that are compatible with Covid. I specialise in community studies of respiratory tract infections. From those studies we can see that, during a normal summer, about 100,000 people per day would have new symptoms of cough, fever or loss of sense of smell. That would rise to about half a million per day during the winter. There is an enormous potential scale to this testing issue which I do not think has been truly appreciated.

That is also relevant to your second question, if we have a second wave during the winter, when we know that we will have way higher levels of respiratory infection. Whether or not we have higher levels of Covid, we will definitely have way higher levels of people presenting with symptoms that could be Covid. So we need to be able to ramp up testing capacity way higher than it currently is if we are to pursue the strategy of test and trace as one of the main means of control. We may—indeed, probably

will—need, in a severe second wave, to revert to a strategy of lockdown, because test and trace will not be sufficient.

Professor Sir John Burn: I reiterate my declaration of interest in QuantuMDx as a point-of-care technology. A number of technologies are now emerging. We have heard about them in the news: SMABA, DnaNudge et cetera, as well as the QPOC from QuantuMDx, which will take the test to the patient, or to the people.

I have in my hand here the disposal cassette that is now in manufacture. I have been given permission by the Secretary of State for International Development, Anne-Marie Trevelyan, to say that the department has given us an award of £16 million to put that technology into manufacture in the coming weeks. So by the autumn we will have a 15-minute disposable test, which can be taken to care homes, dental surgeries and so on. Clearly this is only one technology, but this sort of technology will have to be driven at speed to try to meet the demand and give us an instant answer, if you like, when people are presenting with symptoms.

Professor Sheila Bird: The question that I was going to ask was whether there was any possibility of a saliva test, but what we have just heard about might be as fast and efficient a route.

Professor Jon Deeks: Certainly, the ability to have point-of-care testing rather than lengthy delays and car park queues and so on would make it a lot more accessible. As well as being accurate, you need to be accessible to people so that they can get the test when they need it.

Q57 **Lord Winston:** We have dealt already with the need for speed, so can you give us some idea of how quickly the results will need to be got if we are really to supress the virus? What time interval should we aim for that would be desirable?

Professor Andrew Hayward: The same day.

Professor Sheila Bird: Yes.

Professor Sir John Burn: We are back to the point that, while the Lighthouse Labs are wonderful, they are too far from most parts of the country to give us that same-day turnaround. So we need to get our hospitals back into the game.

Lord Winston: Given the issue of time, and as there seems to be a major problem with the swabs, I wonder whether you feel there is sufficient training for people taking these swabs. Is there sufficient homogeneity among the people doing it?

Professor Sir John Burn: The implication of your question is that if we have a lot of people rapidly being trained to do it, they will not be as good as the best. But saliva is a good source of the virus. If we can get the test done quickly, we can get reasonable sensitivity. It might be worth compromising on sensitivity to get more frequent testing based on saliva. The other point is compliance. If we ask people to undergo in effect a regular swab of their brain stem, they are liable to say that they do not want to do it. So I would emphasise the work on saliva.

Lord Winston: Given that you are presently using two different main strategies to test the virus, do you have any real evidence of the number of false positives that you are getting?

Professor Sir John Burn: I do not think that false positives are a major problem with the PCR test now; it is mainly a problem of false negatives. We now have a highly specific target for all the tests, certainly those that are part of the triple target. So I am not worried about specificity but its sensitivity on all these levels, including the important one you allude to on quality of collection, will always drive that down.

Q58 **Lord Winston:** My last question is about test and trace. Will test and trace ultimately be better or not as good as manual tracing?

Professor Andrew Hayward: I think you are talking about the digital app.

Lord Winston: Yes.

Professor Andrew Hayward: The digital app is critically dependent on uptake, so it requires a high proportion of people to install the app, report their symptoms to it and act on the advice from it.

Lord Winston: Could you give a percentage figure on that?

Professor Andrew Hayward: When I saw the initial models that showed a big reduction in transmission, they were modelling that on levels of uptake higher than those of Facebook—60% or 70%. The modellers have now sort of retreated and said that even if we have 30% or 40% of the population installing it, it could make a difference. With all these things, it is not about whether it or cannot make a difference but about how much of a difference it would make. As it requires both the case and the contact to have it, it is not a linear effect, so uptake is really important.

One of the main advantages of the app that was proposed was the idea of speed—you would not have to wait for people to phone you up to be warned that you have been in contact with somebody. If you superimpose within that system the wait for a diagnostic test result before anything is triggered, it loses a lot of its advantage.

Privacy issues have meant that it has been quite difficult to think about having the app linked to data on tests, which will also limit its effectiveness. It will be an adjunct to what we are doing, but it is by no means a panacea. There is also the issue of how you might get confusion with two parallel systems working. You might have your app telling you one thing and people phoning up to tell you something else. That is potentially confusing.

Lord Winston: Thank you very much. These responses have been very helpful.

Q59 **Baroness Young of Old Scone:** I want to focus on antibody tests and what part they should play in the testing strategy moving forward, bearing in mind that your earlier evidence shows that their reliability is still not quite where it should be.

Professor Sheila Bird: When we are using antibody tests to estimate what proportion of the population has had the infection, albeit during a limited time period, we do not need the sensitivity and the specificity to be as high as we would need for a point-of-care test, if we wanted to be able to offer an immunity passport.

What we do need is the knowledge of the sensitivity and the specificity to be equally precise so as sound an evaluation for useful surveillance as for point-of-care testing. The performance does not need to be at the same level, but the precision of estimation does because we have to take account of those sensitivities and specificities in the population's prevalence, hence we need them to be precisely estimated.

It is also, as we discussed earlier, not entirely clear that the tests will perform equally well for people who had a mild manifestation of Covid as for patients who were hospitalised with Covid disease. We need to know whether we can estimate what proportion of the population had mild infection, as well as what proportion had serious infection. We know a lot about serious infections from other approaches, by back-calculations from hospitalisations and from deaths.

In the case of mild infections, we were told back in March if we were unwell, "Stay at home and don't bother anybody, please, unless your symptoms don't improve within seven days". It is the count of those people that we want to know about. Antibody testing might help us with that if we knew that these tests performed well on people with mild disease as well as those with severe disease. That is still an open question.

Baroness Young of Old Scone: Do you think we will get close, within a reasonable timescale, to having something that would result in an immunity passport?

Professor Sheila Bird: I am not the best person to answer that. We do not know at the moment whether the fact that you have antibodies confers immunity in this particular disease, even if the antibodies persist. Professor Hayward will perhaps give you a more robust answer to that.

Professor Andrew Hayward: My view is that we will not know that until after the next wave. The antibody tests have been developed only after the first wave. We need to measure antibodies in a large number of people and determine the extent to which that protects them from getting disease over the next wave of the pandemic.

So I think these tests have a very limited practical role in the management of people until that time. They do have an important role in our understanding of how common the infection has been in the population, particularly in sorting out our understanding of issues such as the discrepancy in mortality between BAME populations and white populations. Antibody tests will be required to ascertain whether they have indeed had higher levels of infection, or whether the discrepancy is largely because of different levels of comorbidity. I suspect that it is both, but we really need those studies to be done.

Baroness Young of Old Scone: Is sufficient antibody testing happening

to get that information?

Professor Andrew Hayward: We are doing some within a large community-scale study called Virus Watch, and there is the ONS study. I think we need more funding to do more. That will be one of our best ways of understanding what has already happened, as well as helping to predict what will happen.

Professor Sheila Bird: We have spoken about the importance of repeat antibody testing, and of associated information about symptomatology, when the person previously had, or thought they had, Covid. Healthcare workers, of course, would be a very good source of knowledgeable self-completion of questionnaires; healthcare workers have a tremendous interest professionally, as well as personally, in understanding what is happening with antibody levels.

It is a little like going back to the Doctors' study in the 1950s: if you want really good information, ask your healthcare workers. It is not just the biological sample you want; it is the biological sample plus the brief self-completion questionnaire. They will be terrific at answering it. We will then get the information we need and, I hope, some answers.

Baroness Young of Old Scone: Is anybody doing it?

Professor Andrew Hayward: We are doing it at UCLH. There is also a large national study, but I do not think it is really collecting the symptoms as well as the swabs.

Professor Sir John Burn: We are certainly collecting large numbers of antibody tests in Newcastle, but I agree that we are perhaps not documenting symptomatology yet to the degree that we should.

Professor Jon Deeks: In Birmingham, the hospital is doing similar studies. From a public health perspective, looking at serology in those instances helps to evaluate the PPE success according to how many staff have been infected in different roles. So they have a very clear public health impact on advising us how we can best protect staff in a healthcare role. It is important to think clearly about when we decide that immunity is being shown. There is a lot of discussion, and there was an opinion piece in the *New England Journal of Medicine* at the weekend, suggesting that we should move forward, with some uncertainty, whether or not immunity has been shown.

We need to give some thought to what criteria would take us to the point where we can say that immunity is shown. That would enable us to do things like testing at airports to see whether people coming in need to quarantine, testing for this as part of the test and trace programme, and so on. There could be a lot of benefit from these tests if we can get to the step where we identify that they are a good measure of immunity.

The current Roche and Abbott tests require a blood sample from a vein, so they are actually more restricted than a swab test. That will not be successful; we need to be able to have these tests done at a patient's side using lateral flow assays. There is a lot of industry making very good

progress in evaluating and designing the lateral flow assays, which will hopefully be very useful for us in the future.

Q60 **Viscount Ridley:** The World Health Organization has recently said that it thinks that asymptomatic people are not capable of passing on the virus to any significant extent. How does that fit with the patterns that we have seen of asymptomatic health workers spreading it and, as Sir John Burn mentioned, of the Antarctic ship where there were a lot of asymptomatic people and he thought that they were passing it on?

Professor Sheila Bird: It does not fit.

Viscount Ridley: So WHO has got that wrong.

Professor Sheila Bird: I tried to listen earlier today to the conference yesterday to find out the basis for that assessment. It is very different from the inputs there have been to the statistical modelling.

As you say, key examples in hospitals, and in the Antarctic expedition ship, are very much at odds with that. We have not done enough asymptomatic testing to be able to nail this. We must change that. Then, perhaps, we will more authoritatively, rather than by using bespoke outbreak examples, be able to challenge or agree with that position. We need to be testing asymptomatically.

Viscount Ridley: The WHO did come back with a clarification that it was not talking about pre-symptomatic infection.

Professor Sir John Burn: Yes.

Viscount Ridley: Would that make a difference?

Professor Sir John Burn: I suspect that people who go on to develop symptoms are, in the main, highly infectious in the day or two before they develop those symptoms. But there may well be a group of people who are never going to develop symptoms, who in fact can contain the virus. They have it if you swab their nose, but it is not transmissible.

The Chair: What evidence is that is based on? It does not make common sense.

Professor Andrew Hayward: It is very hard to get the evidence. It is really hard to design the studies to look at the infectivity of asymptomatic infection.

The Chair: If there is no scientific evidence for WHO to say that, WHO should not have said it.

Professor Andrew Hayward: I would agree.

Professor Sir John Burn: It is potentially dangerous.

The Chair: Yes. I think we have run out of time. I am told that I must stop at exactly 12 o'clock. I do not know why, but I must. I thank all four of you immensely for a session that could have run for another hour to get all the detailed information. I can see from my colleagues that they were all eager to ask more questions. This is an important issue; we are being told that testing is what we will all rely on. You have also thrown

some good light on some of the aspects that we must not rely on. Thank you all very much indeed. We appreciate it.