HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Monday 15 June 2020

4 pm

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 Kakkar; Lord Mair; Baroness Manningham-Buller; Viscount Ridley; Baroness Rock; Baroness Sheehan; Baroness Walmsley; Lord Winston; Baroness Young of Old Scone.

Evidence Session No. 8 Heard in Public Questions 72 – 78

Witnesses

Dr Elizabeth Whittaker, Consultant in Paediatric Infectious Diseases at St Mary's Hospital NHS Trust, and Lecturer in Paediatric Infection and Immunity at Imperial College London; **Professor Mauro Giacca**, Professor of Cardiovascular Sciences at King's College London; **Dr Manu Shankar-Hari**, NIHR Clinician Scientist, Reader and Consultant in Intensive Care Medicine at King's College London; and **Professor Beverley Hunt OBE**, Consultant in Thrombosis and Haemostasis at Guy's and St Thomas' NHS Foundation Trust.

Examination of witnesses

Dr Elizabeth Whittaker, Professor Mauro Giacca, Dr Manu Shankar and Professor Beverley Hunt.

The Chair: I welcome our witnesses to the second session. Thank you very much for helping us today with the important aspects of the pathophysiology of this disease, which we learn different things about every day. I warn you that we may have a vote during this session, because a debate is going on in Parliament. If we get notice of a vote, I will have to stop the session at that stage for a few minutes. It should not take us long to come back on, but at that stage, whatever we are talking about, I will have to stop you and then start again as soon as everybody has had the opportunity to vote, which should not take very long. We will not have to leave to do that.

On that basis, thank you and welcome. I ask Lord Mair to ask the first question.

Q72 **Lord Mair:** Could you start by giving us a brief overview of how the SARS-CoV-2 virus causes Covid-19 in humans? Professor Giacca, would you like to start?

Professor Mauro Giacca: With pleasure. I listened with much interest to the discussion over the last hour. However, I have to say that I completely changed my idea of the disease in the last two or three weeks when I had the chance to see the lungs and other organs of more than 40 patients who died of Covid-19 in Italy. I am Italian; I joined King's College London just last year. I am a medical doctor by training and carry out cardiovascular research, in particular on how to find new treatments to regenerate the heart. In this period, we have reconverted all the activity of my laboratory to search for anti-Covid-19 drugs. We can speak about that later.

In the context of my connection to Italy, I had access to samples, as I said, of more than 40 patients who died of Covid, several after 30 or 40 days in an intensive care unit. As you know, post-mortem information is largely missing in the literature, because there have not been autopsies around the world.

What you find in the lungs—we can speak about the other organs later—of people who have had the disease for over a month before dying is completely different from what one would find after normal pneumonia such as influenza or even SARS-CoV-1, the SARS virus. First there is massive thrombosis of the micro- and macro-vasculature. Some of these patients even have lung infarction, depending on how large the vessels were that were hit. There is also a complete disruption of the lung architecture. In some microscopy fields it is even hard to recognise that the tissue used to be that of a lung. Again, this topic may be worth speaking about later, because patients who survive the infection with a severe disease might have real problems afterwards.

Another first striking feature was that a large amount of the virus persists in the lungs. I believe the idea that there is a first phase, in which there

is viral replication and then a second phase, in which the virus somehow has less importance while this phase is characterised by hyperinflammation and cytokine storm is true clinically but not virologically. We can see that there is massive persistence of the virus in the lungs throughout the disease by identifying the presence of the viral genome via a technology that permits the visualisation of both viral RNA and viral antigens, particularly the spike protein which is so important for the virus. This means that the virus persists and that its proteins are expressed.

A third characteristic that has remained largely undetected is that there are a large number of very big fused cells—very large virus-positive cells with as many as 10 or 15 nuclei—which biologists call syncytia. This is a known feature of the spike protein of this virus; the spike protein fuses the virus with a target cell but also fuses one infected cell to another. Basically, I am convinced that this massive persistence of the virus in the cells explains the unique pathology of Covid-19. This is not a disease caused by a virus that kills cells. This has profound implications for therapy; I believe that an antiviral therapy might work in the early phases but will most likely not be an effective cure for Covid-19 patients with more advanced disease.

Dr Manu Shankar-Hari: If I may highlight the start of the viral infection, it is primarily a respiratory virus that causes respiratory tract infection. It affects the ciliated cells in the respiratory system and the particular type of cell in the lung that produces something called a surfactant. It does so with great efficiency because of the spike protein on the virus—if you think about the spike protein as a nail, on top of it there is a domain called a receptor-binding domain which very efficiently binds to the ACE receptors.

There are a few important differences between this virus and something like SARS-1 and the MERS virus. The efficiency of the ACE receptor interaction is different. To carry on from the previous discussion about the interferon responses, patients who get a robust interferon response early in the infection tend to recover quickly. Those with a delayed, sustained interferon response often tend to do worse. That is linked to the immunosenescence discussion from the previous session.

Q73 **Lord Hollick:** Can you tell us about the natural history of Covid-19? What happens in the body after the onset of the disease and how quickly does it progress? By what mechanism does the infection cause damage to organs including the lung, heart and kidneys?

Dr Elizabeth Whittaker: As a paediatrician, I have been lucky that most of my patients have not followed the natural history you have seen in adults, but arguably that makes them a good place to study it. Professor Hayday made a good point in the last hour about how studying those who have not have severe infections may give us the answers to protection. Looking at children and in particular comparison with the group of children who have had a very distinct presentation with severe inflammation may give some answers on that.

Professor Hunt might comment on this, but the endothelial involvement, which was also commented on in the first hour, is likely to be really crucial to understanding pathogenesis here, because those cells are present in all the organs. We are increasingly recognising that the virus is replicating in all sites of the body. It is not just a respiratory infection; it may enter through the lungs and the mucosa, but actually it is affecting every organ in the body and endothelial involvement may be key to that.

We have seen this particularly in children who have had the severe infection. They are quite a distinct small group, which makes them easier to study; they have nearly all had cardiac involvement, either through myocardial dysfunction or the blood vessels being affected. That has really given us a place to focus some of our investigations and understanding of pathogenesis.

Professor Beverley Hunt: The first part of the Covid infection binds to the ACE-2 receptor on the pneumocytes and then enters the body. Unfortunately, a lot of cells have ACE-2 receptors on them. As has been mentioned, the endothelium is a target, macrophages are a target, lymphocytes are a target, adipocytes are a target, the small intestine and myocytes are a target. When you look at the extent of damage caused by Covid within the body, it seems to relate to where Covid binds through the ACE-2 receptor.

Most people do not have moderate or severe Covid ie they don't have Covid pneumonia, which is really where the problems start. Once COVID causes pneumonia (that affects mainly the periphery of the lungs), there is a profound inflammatory response to it. Some of the biomarkers of inflammatory response—ferritin, fibrinogen—are extraordinarily high in most of the patients who have moderate or severe Covid.

The inflammatory response to Covid will switch on coagulation. The blood gets very sticky, which increases the risk of having thromboses. Two types of thrombosis are going on in the lungs. We know that if you go into hospital and you are unwell you have a high risk of deep vein thrombosis and pulmonary embolism, which is known as hospital-associated venous thromboembolism. Patients with Covid-19 have high rates of this.

The other thing we see is that in patches of lung there are areas of thrombosis in the small vessels where there are high levels of inflammation. We call it immunothrombosis. Furthermore I would expect someone who died of Covid to have thrombosis in most vessels due to the severe hypoxia causing disseminated intravascular coagulation.

The studies you were thinking of are extraordinarily helpful, but I do not think they are telling us what is happening earlier on in the severe phases of Covid. Anyone who is dying of hypoxia and Covid will have generalised thrombosis, because they are so short of oxygen and it really stimulates clotting.

Lord Hollick: Does Covid affect the central nervous system and the brain?

The Chairman: Is it neurotropic?

Dr Elizabeth Whittaker: There have been cases of CNS involvement in adults and children. In fact, some of the children who recovered who have had MRI scans have quite distinct findings that indicate that it is involved. Because of thrombosis, ischaemic events are happening in the CNS as well. It is reasonable to presume that it is also affecting the brain, this may be due to vasculitis and endothelial involvement.

I would like to go back very quickly to something someone mentioned in the first session: neonates not being affected by severe coronavirus even if their mothers are infected. Despite skin-to-skin contact and ongoing exposure, these babies are not getting COVID-19 disease. It is worth considering what is different about the neonatal immune response. IgA, which has been mentioned, is likely to be really important and that initial innate clearing of the mucosa I mentioned before, but the components of breastmilk which the baby is receiving might also be important. That is a crucial area for trying to understand immune correlates of protection, which are a little elusive. Also, neonates do not have such robust T-cell responses, which was also mentioned in the previous session.

Lord Hollick: What lies behind the fact that the fertility rate of Covid-19 appears to be lower than SARS and MERS? Do you have any insights into that?

Dr Manu Shankar-Hari: Natural history might explain some of the things that we are seeing. SARS-CoV-2 has a distinct natural history in that there is an incubation period. People who are incubating the virus tend to get infective three or four days before the symptoms occur, so the chance of transmission at that phase is high.

When you think about the case fatality rate for any epidemic or pandemic, the number of patients infected becomes the denominator. In the case of SARS-CoV-2, that denominator is rather high. As was highlighted earlier in the session, for SARS-CoV, infection was roughly 8,000-odd patients. We are well into the millions in this pandemic. Part of it is explained by that and part of it relates to the immune responses and the differences in immune responses with age that could influence the outcome.

Professor Mauro Giacca: In our experience, we do not see viral infection of the brain or of the kidneys, or it is really exceptional. If there is brain disease it must be indirect. We see lots of the virus in endothelial cells, which might well explain thrombosis. We see infection of the gut. This could well explain diarrhoea, which is a common symptom of a large proportion of patients with the disease.

The other information I can add about the difference between SARS and Covid-19 is related to the spike protein. If you have a cell infected by the SARS virus, it expresses the spike protein on the surface, but this protein cannot fuse to other cells. This happens only when the virus enters the cell. A cell infected by the SARS virus is neutral to the tissue where it is located. Instead, a cell infected by SARS-CoV-2 fuses to the other cells. This might explain why there is thrombosis with Covid-19 but not with SARS.

Q74 **Baroness Hilton of Eggardon:** We have touched on some of this before, but are there risk factors you can identify for the acute respiratory response? Can you predict which people will be most affected? Are there different systems of treatment?

Dr Manu Shankar-Hari: I am an ICU physician, so I can answer that question, which is about acute respiratory distress and risk factors. Based on the published literature, we see that ARDS, or acute respiratory distress syndrome, happens in roughly 10% of patients with SARS-CoV-2 infection. Often it occurs roughly seven to 10 days after the onset of symptoms. One consistent finding is a low lymphocyte count when they become more unwell. Alongside that, they also have exuberant inflammatory response, as described earlier, with an increase in CRP, for example. If you were to measure cytokines, those patients often have high levels.

There are two other findings that may be relevant here. If you have a co-morbid condition such as diabetes, it increases your risk of having ARDS. It is just a hypothesis, but it is probably related to the ACE2 receptor expression differences in patients who have diabetes. Probably the small blood vessels are different in patients with long-standing diabetes.

Baroness Hilton of Eggardon: Can you predict who is likely to be affected?

Dr Manu Shankar-Hari: Prediction is a hard game. We do not have any risk models to consistently predict who is likely to develop acute respiratory distress syndrome. The risk factors are underlying lung disease, diabetes, a low lymphocyte count, fever or early signs of increased oxygen deployment. They might progress to ARDS, but there is no risk profile that predicts ARDS in these patients.

Dr Elizabeth Whittaker: We initially tried to predict through our shielding criteria who we thought was going to be at the greatest risk of COVID – and this was based on those at risk for severe flu. We looked at people who we always recommended have a flu vaccine and recommended that they shielded. We are increasingly recognising that that was wrong, so things that would normally put you at more risk, such as underlying lung disease, asthma and things like that, are probably not as great a risk.

As somebody alluded to, oncology patients do not seem to be at such a great risk. That might be due to their treatment or the underlying process, whereas the triad of the metabolic syndrome seems a greater risk. It is unfortunate that we cannot be more specific about who we need to shield from a vulnerable perspective at this stage. It just means that we have to take a very large population group and say, "Some of you might be at risk", which is very difficult for people to understand.

The Chair: As we have learned more and more about how to manage these patients over time, are the correlations getting better at identifying prognostic factors that may tell them early on not only how to manage the patience but how to improve the outcome?

Dr Elizabeth Whittaker: I think Dr Shankar-Hari is probably the best person for this.

Dr Manu Shankar-Hari: The simple answer is that within any pandemic or epidemic, if you monitor outcomes over time, generally patients get a better outcome in the latter stages of the pandemic compared to the earlier phases, partly because the healthcare system and clinicians set up a process that works best. We hone the knowledge that we already have to avoid harm and probably identify patients who might benefit from certain interventions and understand a bit more about the biology. If you take that sequence of steps, the number of clinicians who can predict who is likely to do badly is not great. It has never been great. I do not think that is a good way.

We have not developed any prognostic scores to date. We now understand that if patients have greater lymphopenia and a greater cytokine response, they have a more severe illness, and if they require mechanical ventilation their outcome is likely to be bad compared to those who do not.

My last point is that as the illness persists—if you get a severe respiratory failure that persists into the second week—the risk of an adverse outcome is higher. I would probably ask Professor Hunt to comment on the thrombosis element of it, because that is relevant to this.

The Chair: Professor Hunt and Professor Giacca too, because of cardiovascular issues.

Professor Beverley Hunt: Sorry, I could not hear you very well. I was going to talk about the fact that the original studies in China suggested that a marker called D-dimer had high prognostic indication if it was measured when patients were admitted to hospital. D-dimer is a marker of clot breakdown, and we have always thought about it in relation to a marker of having blood clots. However, if you go back and look at the data on D-dimer, it is also a marker of inflammation in the lung. The lung itself—the pneumocytes—have an ability to produce activators of clot breakdown called urokinase, and we know from some of the animal work with SARS and MERS that the higher the dose of inoculation of these viruses in a mouse, the higher their levels of D-dimer. So the lung itself is producing this D-dimer, which is a marker of information in the lung. We are waiting for more evidence from European and North American studies to see whether it applies to our populations too.

Professor Mauro Giacca: I can add to Dr Whittaker's comments that thrombosis is really a hallmark of the disease. Histologically, we see it in more than 80% of people who died of Covid-19. It is endogenous to the lung, because in autopsies we can see thrombi at different stages of organisation, which means that there are thrombi that occur at different times. That means that thrombosis is a process occurring within the lung—it is not due to emboli coming from outside. Thrombosis can well be explained by infection of the virus of endothelial cells that become dysfunctional. These cells start expressing markers of the pro-thrombotic state.

However, an observation that could also be related to thrombosis is that we sequenced the RNA present in platelets and found that these tiny pieces of cells express of the viral ACE2 receptors. We found that if one takes platelets and exposes them onto the surface of SARS-CoV-2 infected cells, there is a strong tendency to adhesion and aggregation. So, there might be a component of the pro-thrombotic state that is specifically related to the surface of the infected cells and probably to the presence of this spike protein.

Q75 **Lord Browne of Ladyton:** Why are some categories of people—for example, older people, people from the BAME community and even men, some people think—more susceptible to severe forms of this disease?

Professor Mauro Giacca: Nobody wants to start, because nobody knows the answer, I guess!

Professor Beverley Hunt: There is no answer. We know that these people are at risk. If we look at the underlying issues, we know that as you get older, your immune system changes, and I know that that was covered quite extensively in the previous hour. Also, they have a slightly more pro-thrombotic state—a higher inflammatory state. Obesity is a big issue, as is diabetes. However, it is difficult to know whether poverty and the environment are also part of all this. We are not clear how much is genetic and how much is environmental, and I think we will find those things out over the next few months. I know that big genetic studies are coming through, which will tell us about that. There is an obvious relationship with socioeconomic class, for want of a better term, in that it is a disease that seems to be worse in those who are poor.

Dr Elizabeth Whittaker: I want to echo that it is so multifactorial, and this is absolutely a disease of poverty. That is echoed even in the paediatric cohorts. The GenOMICC and the ISARIC studies are two extraordinary UK and international collaborations that will, I hope, get some answers to this quickly. One of the things that the UK has done well on is the ongoing studies. I wish we knew the answer to your question, but I suspect that we will have a much better idea in a couple of years.

Professor Mauro Giacca: I can only add that there are many mysteries in this disease: there is the phenomenon of "happy hypoxia"—some people sometimes present with a very low level of oxygenation but feel quite well themselves, which rarely happens with other conditions; people sweat as a symptom of the disease; people lose their sense of smell and taste in a vast proportion of cases. These are mysteries related to this specific disease.

Dr Manu Shankar-Hari: If I may, I will just add to the heritability question that has been discussed. The TwinsUK cohort study from Professor Tim Spector's group at King's College London has recently added to the literature on the symptoms of anosmia—impaired smell—in twins; fever explains 50% of the symptomatology that you see between twins.

So there is some hereditable element of the disease, but as somebody who does a bit of immunology I think that the heritable component of the

disease may not be as striking as the social aspects of the disease. The question relating to BAME and ethnicity is probably intricately linked to the socioeconomic differences. A hypothesis to add would probably be the dietary differences: the carbohydrate-heavy diet and presence of comorbidities such as diabetes and hypertension in that population. Those are the other things to consider.

Dr Elizabeth Whittaker: Probably vitamin D and possibly other nutritional elements may be important from an epigenetic perspective as well as from a direct viral perspective.

The Chair: In the phenomenon of low oxygen saturation in people feeling well, are they really well? Does the prognosis differ in them?

Dr Manu Shankar-Hari: Low levels of oxygen mean that your gas exchange is impaired, so you are immediately in a different risk category, as it were, in terms of the severity of your illness, because you now have respiratory dysfunction—impaired respiratory system function. So if you have hypoxia, quite a lot of simple scoring systems that we use in hospital, such as a NEWS score and other things, to identify unwell patients immediately highlight it.

Q76 **Lord Borwick:** Lord Browne's question was about why some people get it worse. The other side of the question is why people get the effects of this virus so much less; children and many people seem to be asymptomatic with the virus. Do we know much more about why these people are treating it in this way?

Dr Elizabeth Whittaker: There was a little bit in the first hour about children, who are the obvious group to study. If we look at the incidence among children, the attack rate in paediatric cohorts is so much lower than it is in adults. Is it because they are just meeting coronaviruses more commonly? There are studies measuring coronavirus antibodies that would suggest that, although in our cohort, which is the PERFORM study at Imperial College, we have not seen coronavirus very much on respiratory PCR panels in children who were admitted to hospital, so I do not know whether that is true in our setting.

The data about antibodies comes from the Far East, which might explain why they have had a different pathogenesis there. The ACE2 receptor seems to be important, particularly perhaps in the paediatric cohort who are just not getting ARDS at all. There is a handful of children who presumably have something different genetically to explain why they are having ARDS, and I think the ACE2 receptor is the most likely thing that is relevant there.

As a paediatric immunologist, I like to think that the innate mucosa and the immune response that is happening at the very first level before the virus even gets into the lungs might be responsible for protection. It is really hard to study, so we are trying to set up a saliva IgA and nasal IgA study to look at that within a household setting. It is crucial to study these groups so that we understand. Funding the kind of studies that will go into schools and households, and the ongoing healthcare worker

study, will be crucial to understand why those exposed are not getting unwell. It is really good question to try to answer.

Professor Mauro Giacca: There is an interesting observation right in this period in the countries that have reopened their activities. Italy is obviously one of them. It seems that there is not only a reduced number of cases, which could be explained by less propagation and less diffusion of the virus in the population due to the lockdown—it is a good consequence of the lockdown—but also in the severity of cases, and so the proportion of people who end up in intensive care units is significantly reduced.

In the past week, there has been a debate at the level of the World Health Organization about the possibility that social distancing and the use of facemasks do not necessarily prevent infection completely but may reduce the viral load, so the amount of virus with which a person gets infected could somehow be influencing the severity of the disease.

This conclusion could be consistent with the observation that healthcare personnel, for example, especially at the beginning when there were was insufficient protection, were very severely affected—according to WHO, approximately 20% of people who died of SARS in 2004 were healthcare personnel—probably because they are exposed to much higher viral loads. To the best of my knowledge, there is no real scientific study addressing the issues of viral load, but all these observations are consistent in trying to explain why some people get a worse infection and some people a more benign infection. It does not explain it all, however, nor the problem of the children, I guess.

Dr Elizabeth Whittaker: The viral load story is interesting, and I have heard it a lot, particularly from my Italian colleagues. It is really tricky. Talking with my colleagues at Imperial, it is very hard to explain that immunologically, but it is certainly possible to test that in an animal model. That clearly needs to be done, and I am sure that—I hope that—someone will do that.

The other point was about healthcare workers. It is important to say that when you look back at the data, healthcare workers did not have different outcomes to the rest of the population. That was felt to be the case at the time and was particularly highlighted in the media. They may have picked up infection at work, but it was usually healthcare worker to healthcare worker transmission. Much transmission also occurred in the community. I am sorry to contradict you there.

Lord Borwick: What is the current understanding of why some children experience a Kawasaki-like disease in response to the virus? Dr Whittaker, this is again your subject.

Dr Elizabeth Whittaker: This is literally my subject and my "Mastermind" moment. This has been such a fascinating phenomenon. I do not think many people in their career have their ability to see something emerge, describe it as it happens, and try to come up with research to address it. Given that it started to come out six weeks ago, it is pretty extraordinary how much we already know. It has unfortunately

been called a Kawasaki-like syndrome, and as somebody said earlier it is not Kawasaki disease; it is quite distinct. These children are not having any ARDS, and they likely had their infection four to six weeks earlier. They very rarely have evidence of viral DNA from a PCR swab, but they mostly have antibodies present. It begs the question whether there is an antibody-mediated inflammatory response that is related to the spike protein that we have all been talking about, or whether it is immune complex mediated.

It is important to note that a really small number of the population are getting it, so it is not a reason for great alarm, but it is worthy of studying to try to understand what is happening from an immune perspective. These children are presenting excessively inflamed. By that I mean that they are very febrile, very red, and worryingly some of them are getting heart problems, which comes back to the endothelial question from earlier.

It also goes back to the other question that came up earlier about which immune modulatory treatments might be of benefit. Actually, all around the world, many different types of immune modulatory therapies have been used and they all seem to work. That is not surprising, because I think it is actually just a massive storm of inflammation, so if you turn off any element of it you turn off the cascade.

This group of children are key to understanding what is going on. The ongoing multinational collaboration to try to do that is a credit to scientists and medics around the world.

Lord Borwick: But a very small percentage of children get it.

Dr Elizabeth Whittaker: The issue is that we do not have a denominator. The total number is very small. There have been about 80 children in intensive care, and probably around 200 overall in the UK. If there are 15 million children in the UK, without doing complex maths, it is a very tiny proportion of children, but we do not know how many children in the UK have had infection to know the true denominator. Even so, it is quite a small number in terms of risk and how much we need to worry about children. I think we can be relatively reassured about that. The other good thing is that with immunomodulatory therapy they are largely getting better and most children affected during the peak are already at home with their families. However, we don't yet know the long term outcomes, so they need to be followed up.

Someone earlier alluded to the need to follow up all the people who have had Covid, because we have no idea about what will happen in the long term. There are already signals that people who have been unwell for weeks and months and who may not have ended up in intensive care with severe disease, have lung damage or endothelial damage which leads to ongoing problems, so, much like the children, they will need following up to see how big an impact it has in the long term. I want to be reassuring [about the children with inflammation] without saying, "Don't ignore them", if that makes sense.

Dr Manu Shankar-Hari: I want to highlight that alongside the Covid-19 adult patients my research group has been studying these kids and their immune system. As highlighted in the previous session, there is the innate response system, which is a kind of rapid response system, and the adaptive immune system. We have studied 30-odd kids and we see that their innate immune system is excessively activated. A cell called a neutrophil has quite of lot of activation markers on it. The activation marker levels of another cell in the innate immune system called a monocyte are not that high. The lymphocyte count is extremely low, and whatever lymphocytes are there appear to be activated. The immunology in this population is very interesting as well, as Dr Whittaker highlighted.

The Chair: If they have an innate system that is activated, why does it not get stronger?

Dr Elizabeth Whittaker: I think Dr Shankar-Hari was just saying that it is the children who are having cytokine storm that he is measuring.

Q77 **Baroness Blackwood of North Oxford:** There was some discussion a couple of questions ago in which some scepticism was expressed about the role of genetics in determining susceptibility and severity. We have heard from Dr Whittaker that we do not really understand the profile of those who are more at risk and that our shielding category is probably not particularly well defined. We heard from Sir John Bell that you could define the syndromes that are being observed in clinic: a cytokine storm or an immune response, a vascular response, and more classic ARDS. Defining how and who will get what is quite challenging at the moment. If you were to identify a use of Covid-19 pathophysiology that would appear to have a more genetic basis than others, where do think it would lie?

Dr Manu Shankar-Hari: It is a difficult question, because genetic susceptibility to the illness is very difficult to prove during a pandemic. Perhaps when the GenOMICC and ISARIC studies come out with their genomic data we might be able to understand a bit more. If somebody was going to put some money on this, ACE receptor polymorphism would be the first target.

On the question of whether a predisposition will relate to severity, again I do not know the answer. I do not think that we do not understand the disease well enough to come up with an answer.

Professor Mauro Giacca: There is a cartoon which I sometimes show my students which has a big monster and a scientist with a microscope looking just at its tail, forgetting all the rest. If there is a genetic predisposition, it does not have to be linked to viral replication, as people have looked at this so far.

We have now screened 3,800 different drugs that block viral replication and the formation of infected cells, so they should block pathogenesis. The top three drugs have nothing to do with replication of the viral genome—they block specific aspects of cell biology that are exploited by the virus for its propagation—and we are now speaking with UKRI on the rapid repositioning of one of those drugs. I expect that if the genes that

are targeted by the drugs in the cell have polymorphisms, this could somehow be linked to the pathogenesis of the disease.

As Dr Shankar-Hari was saying, we really need to wait for big cohort studies to be performed to understand the role of genetics. There is certainly such a role. Here is the UK, there is a lot of discussion about social and economic influences on disease severity in BAME people and so on. In Italy, where the population is much more uniform, there is clear evidence that genetics play a role. In the UK, there is the possibility of assessing a very large genetic dataset, so it is certainly possible to understand what the genetic role is, but this is not something one can do in a hurry in this period. We await larger studies later.

Dr Elizabeth Whittaker: It is likely that there are genetic predispositions. Going back to the children again, for Kawasaki disease, which is different but a kind of cousin of what we are talking about, the Japanese and east Asian populations are definitely more susceptible to the severe end of the spectrum. However, in Japan, South Korea, or China, where they would be genetically quite different to Europeans, they have not seen any cases of what we are describing.

We also know that, in our setting, black African children get worse Kawasaki and a condition called lupus, which is an autoimmune condition. When one of the immune cells presents a pathogen to a T cell, part of the recognition involves something called HLA receptors. When T cells interact with pathogens [like COVID 19], the HLA phenotype is very important in determining the response. The HLA type, which can differ with genetics, may be different in different populations and have a role to play in stimulating inflammation.

However, as you say, until we do a massive study it is hard to pull that out. It is also quite hard to know what you do with that data. Just because you have a predisposition that increases your risk, it is usually from very low to slightly higher (eg from 0.01% to 0.02%), rather than from 10% to 20%, so you cannot necessarily use the information to make policy and other decisions on how you manage patients, but I guess that if we had real personalised medicine, you could use the information to make decisions.

We talked about antivirals a bit earlier. One of the flaws in many of the studies is that we are giving them to patients who are severely unwell and a fair way into their infection and we are not giving them to people when they have just been exposed or are in the very early stage of replication. If we identified some people who are more susceptible, it might make sense to give antivirals that look to be better at an early stage before those people become unwell.

That might be one of the times when an intervention based on genetics could have role. I think we are a year or so away from being able to comment on whether we would do that based on ethnicity or genetic markers, but it is nice to think eloquently about how we see the future of medicine in terms of personalised medicine and being able to use this information to predict outcome and need for treatments/vaccines.

It may not help at this point in the pandemic, but may be relevant later. It may have a role in vaccine responses as well. We just do not know yet.

The paediatric inflammatory condition raises some questions about the safety of vaccines if it is antibody-mediated, which I know people are worried about. From discussions with colleagues at Oxford and Imperial who are running the vaccine studies that they are monitoring the situation very closely to ensure that that is not going to become a problem. It is something that people were aware of as a potential issue from the very outset.

Baroness Blackwood of North Oxford: The points you made about intervening early are very interesting and I would like to follow up on them, but Dr Shankar-Hari made a point earlier about one particular datapoint that is well understood: rates of recovery of those on ventilators versus those who are not. What other conclusions are made about those who get severely ill but recover? Studies of those who recover can lead to some interesting conclusions. What have we learned about the virus from rates of recovery and the nature of the recovery?

Dr Manu Shankar-Hari: The first point I would like to make is the one I made earlier about early interferon responses being important for the rapid resolution of the illness. Those who do not have an early interferon response are those who have a sustained, long interferon response leading to lung inflammation. They have a slightly longer, complicated course.

Let us say that day 0 is when they become acutely unwell and come into hospital. We see consistently that by day 7 or day 10, if you do a PCR almost all these patients are virology negative. If you do the serology around the same time at repeated time points, you see a gradual increase in the antibody response to the virus.

The thing that probably marks out the patients who recover quickly is an ability to clear the virus in an enhanced antibody response. This is driven partly by the fact that we can measure antibodies. Perhaps the much more underpinning biology there is that the particular subsets of lymphocytes known as the helper cells and the CD8 cytotoxic cells clear the virus and the helper cells help to produce a sustained memory and antibody response that clears the virus. If we are to understand what happens to those who recover, the immune trajectory may be one important aspect of it.

The second element is probably what Professor Hunt highlighted earlier: the thrombosis and the microvasculature, and how the response to the initial intervention was not necessarily targeted against the coagulation system but general supportive care. I do not know whether that answers your questions.

Baroness Blackwood of North Oxford: That is helpful. Professor Hunt, do you want to follow up on that?

Professor Beverley Hunt: What are we doing for our patients with severe Covid? We are giving them oxygen and anticoagulation as two positive things that we know will help the situation. The anticoagulation is

to prevent them from getting deep vein thrombosis and pulmonary emboli.

We are not clear that this immunothrombosis—this small microvascular thrombosis in the lungs—responds to anticoagulation. It is a consequence of inflammation. I am always saying that we need to treat upstream: we need to give anti-inflammatories or antivirals. If we did not have so much profound inflammation, we would not get so much small-vessel thrombosis in the lungs.

We know that Covid is affecting the endothelium. It is activating it and making those vessels very likely to clot. We also have the inflammatory pathway working. It is quite a complex situation, and more aggressive treatment with anti-inflammatory drugs is probably where we need to be going.

Q78 **Lord Kakkar:** I should just remind the Committee of my own research interests in thrombosis, which has been mentioned frequently.

I turn to the understanding of the longer-term consequences of Covid-19 infection. I know that we are very early in this pandemic, but do we have a sense of what we might look for from an understanding of previous infections such as SARS and MERS, which happened some time ago and where there are cohorts of patients who have survived?

Secondly, is there a sense that we have the mechanism to properly follow these patients so that we can learn as much as possible over time to predict early in a natural history those who might have an impact on their long-term health?

Dr Manu Shankar-Hari: My research is into sepsis survivors. This is an infection-related complication, so there are some similarities in the immune response to sepsis.

On what we can learn from SARS or MERS, when you follow patients who have recovered from SARS or MERS, there are a few important findings that we know of. The first is their serology. Their antibody type varies over time. Peak antibody response to SARS is roughly at four months. After 12 to 18 months, their antibody T-cells have gone away. If you measure their T-cell memory, that memory pathway is impaired or decreasing by two to three years. So any vaccine that we designed would be informed by some of those observations.

The second point I would like to make is about the lungs. Patients who recover from SARS infection and MERS infection have underlying lung fibrosis. Therefore, their respiratory function seldom returns to normal. That is not unique to SARS or MERS but is a fact for anyone recovering from acute respiratory distress syndrome.

My third point is about thrombosis. Even sepsis survivors and patients who will recover may need enhanced thromboprophylaxis for a protracted period of time. It is too early to decide for how long or what to give, but studies are needed to understand how best to do that.

The fourth point is that when patients recover from severe illnesses such as this, as the severity of illness goes up, cognitive impairment and the inability to return to their usual work becomes an important problem. That is relevant when we think about the public health consequences of coming out of a pandemic.

My last point is that the healthcare requirements of these survivors, especially those who survive a severe illness, are likely to be greater than those of others.

Those are the observations from sepsis literature and from the general SARS literature that I understand.

Dr Elizabeth Whittaker: That is really eloquently put. I want to pick up on ongoing follow-up in the community. You were talking about the obvious, distinct, severely unwell cohort. There are also all the patients who never made it near a hospital who are equally experiencing many of the side effects that you have described.

We need to address how we are going to manage this. The problem at the moment is that most community care where this should be occurring, such as rehab, speech and language therapy, occupational therapy, is not happening at the moment because of the risk of transmission. Those people go from household to household or they are in community centres where transmission is a risk, a bit like in care homes.

We really need to do some planning on how we look after this population over the next two three years while we understand the longevity of these issues. Investment will be key here. We have had the really awful bit which the NHS coped so admirably with. We cannot let them down now by not continuing that process over the next couple of years.

Lord Kakkar: Are there cohorts being developed, as you rightly identify, of severely ill patients who have survived and those who have had less severe illness, or indeed non-hospital-treated illness? Are there systematic programmes to follow them so that we can start to understand the true natural history of this disease and its true burden?

Dr Elizabeth Whittaker: I run a joint respiratory service for the adults at Imperial, and there is definitely a plan for following up cohorts who have been significantly unwell. I am a paediatrician, so I do not know what is happening for the less unwell cohorts in the community. I do not know whether any of my colleagues are able to speak to that, but I would think that is an urgent research need.

Lord Kakkar: Professor Hunt, looking at the endothelial/thrombosis phenotype, what would you expect of this primary small artery thrombosis in the lungs? Would you expect it to manifest itself, post-discharge in survivors, in potentially thromboembolic pulmonary hypertension or other manifestations?

Professor Beverley Hunt: You are describing immunothrombosis, as we are calling it. I think there has been some confusion with classic venous thromboembolism. We expect hospital-associated venous thromboembolism. A lot of patients have deteriorated in intensive care.

They might become hypoxic and they have been having CT pulmonary angiograms. We have noticed that many of the patients have many subsegmental lesions on the pulmonary angiograms, rather than having large pulmonary emboli; and we have come to the conclusion that those tiny lesions represent immunothrombosis. This is capillary thrombosis and damming back of flow, so you will have a little bit of arterial thrombosis as well.

For me, thrombosis in these small vessels is a manifestation of inflammation. Also we find fibrinogen levels and the endothelium in these patients, will be very activated. We have known for years that one of the end points of inflammation is thrombosis, so I do not expect that immunothrombosis will continue to develop if the patient gets better and their chronic inflammatory state settles.

The problem is that we have not followed the patients for long enough. If somebody leaves hospital with a fibrinogen of eight and they still have quite marked inflammatory changes, I do not know when that will resolve. History and an understanding of previous pneumonias would suggest that it would have settled by 12 weeks after discharge. But they are going home with quite a profound post-thrombotic state and there is a tendency in the UK, as in other countries, to send them home on extended (post discharge) thromboprophylaxis. We are giving two to four weeks from the prophylaxis here.

There is an issue with research on thrombosis. We do not have any national trials in the UK. The haematology community have submitted studies for funding review, but because of the very slow, bureaucratic nature of current research assessment, we do not have anything approved. We have an anticoagulation arm on the critical care platform REMAP-CAP. We are trying to add various arms to that, but it has taken such a long time and it feels as if the horse has bolted in that we now have few hospitalised COVID-19 patients in the UK. However REMAP-CAP is taking off in Mexico and Brazil, and I suspect that those countries will come up with the answers on the benefits of the heparins, which is great but terribly frustrating for the research community here who wanted to do the research.

Dr Elizabeth Whittaker: On the long-term outcomes, which I think you are also asking about, we can look at other diseases like tuberculosis, which is not such a big problem in this country, but we know that the long-term chronic lung disease outcomes for patients with tuberculosis in low and middle-income countries is quite significant. Whether immunemodulation needs to occur, even beyond the 12-week period that Professor Hunt is talking about, is something that we should be exploring to prevent this and optimise respiratory outcomes. You are right that we have probably missed that boat in the UK, but those are things that should be considered in countries like Brazil, Colombia and South Africa, where they are really starting to see the outbreak take off.

The healing process for inflammation is scar tissue. With Kawasaki disease, when they get problems in their vessels they get stenosis—they get very stiff. If you get stiff lungs, that has lifelong implications, so it is

key that we understand how that is happening and whether there any interventions we can make to prevent that being a chronic problem.

Lord Kakkar: Do you have any evidence of an alarming subgroup of patients, where very early after discharge from hospital there is evidence that they are taking a poorer course in their subsequent natural history?

Professor Beverley Hunt: Manu is in the best position to answer that one. We have had patients come back with deep vein thrombosis and pulmonary embolism, but Manu can answer that best.

Dr Manu Shankar-Hari: I do not think we have a consistent understanding of what happens to these patients and how many of them come back into hospital early. That question needs to be understood at a national level, and that can be done with the currently available databases. We just need to get on and get it done.

The Chair: Thank you very much. I am sorry but I am getting signals here that my time is up, so I thank Professor Giacca, Professor Hunt, Dr Shankar-Hari and Dr Whittaker for coming to help us today. It has been a most interesting session. We have learned a lot about pathophysiology and I can see that we have a lot to learn yet. Thank you very much indeed for coming.