HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Monday 15 June 2020

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

Evidence Session No. 7 Heard in Public Questions 61 – 71

Witnesses

Professor Sir John Bell, Regius Professor of Medicine at University of Oxford; **Professor Adrian Hayday**, Peter Gorer Department of Immunobiology at King's College London, and Group Leader, Immunosurveillance Laboratory at Francis Crick Institute; and **Professor Massimo Palmarini**, Chair of Virology and Director at MRC-University of Glasgow Centre for Virus Research, University of Glasgow.

Examination of witnesses

Professor Sir John Bell, Professor Adrian Hayday and Professor Massimo Palmarini.

Q61 **The Chair:** Good afternoon, all, and thank you for joining us today. I welcome our three witnesses, Professor Sir John Bell, Professor Hayday and Professor Palmarini. Thank you immensely in these busy days for you for making time to help us with this inquiry. You are our crucial witnesses today to explore the whole issue of immunity et cetera.

There are apologies from Lord Kakkar, who will join the second session but not the first session. Simon, our clerk, is on the session, but you might not see him; our advisers, Sir Robert Lechler and Professor Ibrahim Abubakar, are both listening in; and Katie Barraclough is watching us all—if there are any messages to be passed on, she will do so on my message app.

The first question is to explore with you the immune response to the novel virus SARS-CoV-2 to find out in what way it differs, if it does differ, from other coronaviruses or influenza viruses, the kind of response that we hitherto know from science, what we do not know about the immune response to this virus, and what knowledge we need to know before it can help us in future with planning for or treating the disease.

Professor Sir John Bell: At a high level, this appears to follow the pattern that you see in most viral infections: that, first, there is a stimulation of some innate immune responses. In that regard, coronavirus has some unique features, and I will come back to them. There is also stimulation of B-cells to produce the humoral or serological response to viruses, which takes somewhere between six and 14 days to get to a respectable level. We now have pretty good evidence that you also get an adaptive T-cell response to this virus, as you do to most viruses. The chances are that they all play an important role in the host's defence to the virus.

There are, however, differences from other viruses, and there are a couple of very important ones which I shall allude to to start with. One is the receptor for this virus, which is the ACE2 receptor. It is at the top end of a complex endocrine system, the Renin-Angiotensin system, which, as one of many functions, is involved in regulating aspects of the immune response. The downregulation of the ACE2 receptor is quite likely to produce a quite dysregulated immune system as a function of where it binds. That is a point that we can come back to in a minute, as it may be involved in the cytokine storm and the problems that you get that produce such severe disease.

The second important difference with coronaviruses is that they are quite cunning, these little guys, and they can separate their replication activities in such a way that they are not accessible to pattern recognition receptors, which are the receptors that activate the cascade that leads to interferon. They have a system for avoiding the interferon response,

which means that the innate immune response is rather disabled from the beginning.

Other aspects of the immune response—the activation of cytokines, for example, which is in part activated by NF-κB—look to be pretty much intact, so there are some aspects of these viruses that make them rather different from, for example, the influenza virus.

Professor Adrian Hayday: I do not have much to add to that, but there is a metaphor that I would draw upon. It is that if you were to look sideways at the Manhattan skyline and likewise at the Chicago skyline, you would say they both have very tall buildings. The two skylines are distinguished by the very specific nature of those individual buildings. The Manhattan skyline has the Chrysler Building, and the Chicago skyline has the Hancock tower.

What we are really looking for in the host-pathogen relationship, as we call it—the way the immune response interacts with this virus—are the very specific issues that might segregate this virus or segregate coronaviruses more generally from, say, influenza. Although there is an enormous amount still to learn, some of those skyline features are becoming apparent. There is, for example, a molecule that relates to the interferon system that Sir John has just spoken about. It goes by the name of IP-10, and it is extraordinarily strongly upregulated and sustained, which is very unusual, and this occurs in Covid-19, in MERS and in SARS-CoV-1.

As Sir John has said, these coronaviruses have very interesting ways of dysregulating the immune system, which may well be why we are dealing with both diagnostic and therapeutic implications.

Professor Massimo Palmarini: I will add something about general concepts from virus-host interactions that might be useful for the discussion.

Viruses cause disease, and how they do so, as Professor Adrian Hayday explained, is in slightly different ways. It is viral replication in the face of host immunity, and these interactions are what determine disease. Every virus has a way to hamper the host immunity in different ways, and coronaviruses have their own ways. How they do it and the timing of when it happens can influence the clinical outcome of viral infection, because in this vital infection, like in many others, there is a whole spectrum of clinical symptoms that go from symptomatic to severe disease. As time passes, more and more studies are coming up on the timing of how the virus blocks some types of response and how it cannot block other types of response. As the discussion goes along, those might come to fore.

Q62 **The Chair:** Thank you. Very briefly, not just yours but other laboratories are working on the response to this virus. What have we learned in the science so far that is encouraging to us as to how we might be able to manage this disease or even, in the long run, try to prevent it?

Professor Massimo Palmarini: What makes many of us optimistic is that the virus behaves as an acute respiratory infection and, as Sir John alluded to, induces an antibody response, a T-cell response. Then, most patients are able to overcome it. There are many aspects that one would think would lead to the possibility of recapitulating the host's immune response, leading to the development of a vaccine. From my perspective, that is what makes me optimistic. But there are many, many obstacles to overcome.

Professor Sir John Bell: I agree. The coronaviruses as a class and Covid-19 in particular have some unique features, but they are more similar to other viral infections than different from them. They produce the same general types of immune response, which gives you hope that a vaccine might work in this setting.

A really interesting observation, which I think is consistent and everybody agrees with it, is that the vast majority of the people who get the disease severely and die are elderly. When young people get this disease, they tend not to suffer very much. I suspect that there are a variety of potential explanations for that, but one might be the state of people's immune system at different ages and the ability of young people to deal with this virus rather easily. As you know, 70% of people who get this disease are completely asymptomatic. At one end of the spectrum, this is not a bad viral disease; at the other end, it is terrible. Understanding those differences is pretty central, and I would be surprised if the immune system was not central to that.

Q63 **Baroness Young of Old Scone:** Perhaps we can move on to the variation between individuals' responses, particularly what factors control why some people get a much more severe response, which comorbidities influence as well, and what we understand is going on in the immune response in the people Sir John mentioned, who have very mild symptoms or are asymptomatic.

Professor Sir John Bell: The answer is that we obviously do not know in great detail. But, as I say, the vast majority of those who get this disease never really know they have had it. It is interesting that, of the people who are sure they have had it—if you wander around London, everybody knows they have had it—only 6% have had it. There is a massive set of hypochondriacs in London who have not had the disease but are sure they have had it. There are two sides of the coin, to be honest. That may be due to the dose of viral exposure that one gets. That may be a key factor. But it may also be due to the state of your existing immunity to coronaviruses generally.

There is interesting speculation, provoked by a paper that came out of San Diego about a month ago, which suggests that many people, particularly in the young or middle-aged groups, may have T-cells that already see coronaviruses—of course, we all get coronaviruses with some frequency as winter infections—and that may well be able to provide some protection against this pathogen when it arrives. I hasten to say that that is unproven, but there is evidence now for cross-reactivity at a

T-cell level at least, which might well help dampen the effects of the virus when we get it.

Baroness Young of Old Scone: What is happening with particular comorbidities?

Professor Sir John Bell: They are all partly explicable, although the data is not clear with this virus. There is a phenomenon called T-cell senescence, which we know occurs in people over 65. They respond badly to flu infections; they tend to get more serious infections, such as pneumococcus and influenza, in later life. Their T-cells are often missing a surface molecule involved in activation called CD28, and they seem to have a defect in their programmed cell death pathways, which tend to accumulate but do not work very well. There is a pretty big literature on this; people have been studying this for the past 15 years. It is quite an interesting phenomenon. It definitely falls off.

There are other aspects of senescence in the innate immune response that we know about. There are certain cell types that are in the mucosa that protect us against viruses that entirely disappear after 65. That might well account for the ageing coefficient, but it is also true that the metabolic syndrome—in essence, diabetes, obesity and hypertension—is known to affect T-cell senescence and make it more aggressive in later life. The story around age and metabolic syndrome could all be pieced together as part of that.

On the ethnic diversity thing, which is real—there is no question it is real—I do not know of any data published in that area, but I would not be surprised if there was a similar theme.

Professor Massimo Palmarini: I want to step back and make sure that we are all on the same wavelength. Sir John referred to exposure to seasonal coronaviruses. With SARS-CoV-2—the cause of Covid-19—the closest sibling is SARS, a virus that sort of disappeared in 2004. It is a similar disease; again, it originated in China and spread somewhat, but there were no more than 8,000 cases. That is the closest relative. Just to give you a number, it is 80% identical to SARS-CoV-2. If we go back to a sort of cousin of SARS-CoV-2, the causative agent of MERS—Middle East respiratory syndrome—it is about 50% identical. It is still circulating but in low numbers, so when it comes to public health, exposure to this virus does not really matter.

Sir John alluded to the seasonal coronaviruses—there are about four of them—that in general induce a mild respiratory disease. By the age of about four, 70% of children have antibodies against seasonal coronaviruses, and about half the people who have been studied have CD4 T-cells. They studied the cells of these individuals—before Covid-19—and found that they have cross-reactivity against some of the proteins of SARS-CoV-2. It is not yet known whether this provides a different clinical outcome for the disease between people who have these reactivity cells and those who do not. That is certainly something that one would have to investigate in future.

It is also important to remember that the disease is only a few months old, and a lot of the immune response, particularly for a virologist such as me, is complex. There are many different angles to consider. It takes years, in reality, to untangle all these different facts. We are just at the beginning, and it will take years to have a complete understanding of the immune response to this virus.

Baroness Young of Old Scone: Professor Hayday, do you have anything that could cast a light on the increased numbers of people from ethnic minorities who are developing the disease and in quite a serious way?

Professor Adrian Hayday: Yes, I can. Certainly, in studies of patients in London hospitals, the clear indication is that black African, Asian and minority ethnic groups show higher rates of admission to hospital. That suggests that they have been more likely to become infected in conditions where the virus doses may be particularly high, but once they are in hospital they do just as well as anybody else. So it is perfectly explicable. The hypothesis is that they are disproportionately suffering from socioeconomic factors that make them more likely to receive high-frequency high doses of infection. That is not to say that hypothesis is correct, but it is perfectly valid until proven otherwise.

In relation to comorbidities, Sir John raised this interesting aspect of the metabolic syndrome. He is right in the sense that there is a very interesting interaction between metabolism and the immune system, but, in addition, the elephant in the room with this disease has been the pathology of the vasculature. The syndromes are hypertension and diabetes, which affect the vasculature. You inevitably put pressure and injury into the vascular system as you sustain those chronic conditions.

The immune system has a very intricate and intimate interaction with the vasculature. Understandably, immune cells have to pass in and out of the bloodstream. When there is injury, the vessels have to be patched up with what is called clotting or coagulation. It is highly likely that what Covid-19 disease is hitting is a pressure point in the interaction of the immune system, some of the products that it makes that are ordinarily very useful to you and the blood vessel response. Individuals who we see in hospital with probably unhealthy vasculature tend to do a bit worse.

Professor Sir John Bell: Just to support what Adrian has just said, if you look at the careful autopsy pathology that has been done, this disease is predominantly a disease of the microvasculature and the vasculature. The best study I have seen has come from Switzerland. It is associated with widespread thrombosis. The vessels themselves are very sick, and there must be an explanation for that above and beyond just the clotting. That is a theme that is running through this disease.

Professor Adrian Hayday: And it is not well studied. We need more study of the interaction between the immune system, coagulation and blood vessel biology.

Q64 **Lord Winston:** I will start my questions by asking Sir John. I am one of those Londoners who has had severe Covid-19 for at least three months,

with all sorts of symptoms ranging through every part of my body—I do not think it has affected my brain, but I am not even certain about that.

Some of my questions have already been asked, but I wonder whether we can do a bit more on age. Can we go to the other end of the spectrum and talk about children and why their immune system seems to behave in a different way from that of adults and older people in this respect?

Professor Sir John Bell: There are a couple of interesting things about the very young. First, there was a rumour going around early that kids did not get Covid-19. The ONS survey clearly shows that they get it at the same rate as everyone else. They swab positive at the same frequency. There is a little tweak in that the survey suggests that you do not transmit this very much in families, and I have not been able to explain that yet. It is an interesting observation, because flu data suggests you spread it very actively in families. That is not the case here, and I cannot explain that.

There is no doubt that children under the age of 16 or 18 usually show absolutely no symptoms of this disease—they are completely asymptomatic—with the exception of a very rare set who get lymphadenopathy in the rather odd syndrome that was well described in London. It seems to respond to corticosteroids and plasma infusions. To be clear, I do not know what is going on there either, except that I do not think it is Kawasaki syndrome, which is what people originally said it was.

Remember that a lot of kids get seasonal coronaviruses. As Professor Palmarini has said, it is pretty common in that population, so many will have quite a strong immunity to coronaviruses generally, I suspect. They may well deal with this relatively easily, which is why they do not get any symptoms. That does not explain, however, why more newborns do not get it. That is a really interesting question, because they will not have lived long enough to get exposure to routine coronaviruses, and although they might get some passive immunity from their mums, I suspect that is not enough. That is a very long-winded way of saying I have no idea.

Lord Winston: Thank you. There are so many puzzles, are there not? Coming to Professor Hayday for a second, one of the puzzles is about black Africans, because the news we are getting from Africa would suggest that there is a population in many parts of Africa that is overcrowded and underfed and has all sorts of challenges to its immune system. Yet, although there may be underreporting, it seems that a lot of African countries have not really seen much evidence of severity of this virus. Is that true or is it just a rumour? Does it relate to what is happening in European countries?

Professor Adrian Hayday: It is very, very difficult to make judgments there at this point. The data are thin and open to many interpretations. I would be cautious. However, if I can deftly link that question to the question you have just asked Sir John, there is a fundamental issue when the immune system reacts to something. It either sees it as completely novel and reacts to it as something foreign and potentially bad, and

something that it needs to make a response to, or it reacts to it as something that looks like what it once saw before.

The simple fact is that all adults past a certain age—let us call that age around 30 to 35—essentially have no thymus left, so our T-cell response is driven essentially by the memory of what we have already seen and whether we can adapt to see things that look a bit like it. Children might have immunodeficiencies quantitively, but qualitatively they are very good at seeing things that are completely new. They have fantastic thymuses. Whether this is because this is a zoonotic agent that we have not seen before or whether the cross-reactivity is a bit of red herring, the issue is that children can see this as something fresh, whereas we are struggling to do that, and that is another perspective. If you begin to adopt that viewpoint, geographically where you see this and what your context of prior infection has been could give you a very varied response to it.

Lord Winston: Thank you. Professor Palmarini, do you have anything to add in the area of age, the incidence and so on of the virus that could be helpful?

Professor Massimo Palmarini: The bottom line is that we really do not know. Professor Hayday and Sir John have some thoughts and a reasonable hypothesis, but there are no mechanistic studies yet that can explain it specifically for SARS-CoV-2. So time will tell.

Lord Winston: Thank you very much indeed.

Professor Sir John Bell: I will just pitch in on the African thing, because with the Oxford vaccine we have decided to go to Africa to do a study there. Our read is that it will hit peak about the end of July. It is growing pretty quickly now. They had a very successful lockdown in South Africa, as you know. They acted very quickly, but because of the dire straits that people were in—they could not get food and people were literally starving—they had to lift it. Now that they have lifted it, it is starting to take off. I think there are bad things still to come in Africa. I would like to think there are not, but I worry about it.

Q65 **Baroness Walmsley:** Some individuals have experienced an overreaction of the immune system in response to Covid-19. I believe it is called a cytokine storm. What is a cytokine storm and why does it occur?

Professor Adrian Hayday: A cytokine storm is when the immune system is pushed very hard by chronic, unrelenting exposure to something. We normally have systems in place that pre-empt this and supress the immune system. Vast amounts of energy in the immune system are used to tune things down and suppress things to prevent cytokine storms occurring.

Obviously when cytokine storms occur it can be very dangerous. They can cause damage to blood vessels and lead to multiorgan failure. The cytokines that are involved are normally things such as IL-1 and TNF.

These are technical terms, but they are important. From our experience studying these patients, we find this in only a minority of patients.

It is true that there is a cytokine called IL-6 that can be expressed at high levels and has been the subject of a treatment approach. In fact, at the NIH in the United States it has been added to an antiviral trial. I have to say that in our experience this would account for no more than about a quarter of the people whom we see in hospital. By contrast, there is something that I certainly would not call a storm but a dysregulation of some key cytokines; I mentioned one of them—IP-10. That seems to be true in all patients who get sick.

So I think the general idea is good, but again, getting back to my metaphor at the beginning of the session, we need to look at the very specific *agent provocateur* here rather than being too generic.

Baroness Walmsley: Thank you, but you mentioned that not so many people get this problem, so what are the risk factors for those who do get it? How are they treated, and what is the basis of the treatment?

Professor Adrian Hayday: The risk factor is high, and they are treated. They can be treated effectively with immunosuppressants such as steroids and glucocorticoids, and they can be treated with molecules that very specifically target those cytokines. That was also effectively deployed against SARS back in 2003. But I would caution against the notion that we have got this licked and this is all about cytokine storms. Clearly it will be great that the few people can benefit from that approach, but more generally that is not how I see Covid-19 disease.

Baroness Walmsley: Is it linked to people who have a lot of allergies?

Professor Adrian Hayday: I will defer to Sir John on that. It is not what we have seen.

Professor Sir John Bell: That has certainly not been recognised as a feature. Adrian makes a very important point. I make a point of not wandering around intensive care units these days at my age, but those who do tell me that there are really three different clinical syndromes. To get back to the point we made earlier, one is associated with lots of thrombosis and coagulation, with high levels of markers of coagulation and lots of coagulation in the lung and elsewhere and a real vascular defect.

A second is the cytokine issue, which is probably driven by sick macrophages in the lung. The alveolar macrophages in this disease are pretty sick. It is interesting that now that people have got around to looking at the monocytes that infiltrate the lung and become those alveolar macrophages, they too are sick and they express the ACE-2 receptor. There is an interesting story there.

The third looks rather more like conventional adult respiratory distress syndrome without the cytokines. People have generalised that this is one clinical syndrome, but it is almost certainly not, I think.

Professor Massimo Palmarini: It is also how the virus replicates, the level at which it replicates, the timing of effective innate immune

responses or the timing of when the virus managed to counteract the innate immune responses. That is all a continuum. In many ways, if you look at how the disease develops, or how we think the disease develops, in the first phrase the virus replicates in the epithelial cells. When it is there, it is able to counteract the cytokine response of these cells, so it keeps it down and not a lot of interferon is released.

You have heard the term "cytokine" and IL-6, IL-1 and TNF. Normally when the virus has replicated enough it starts to induce cytopathic effects whereby it kills the cells, in effect. Then you have immune cells coming in, including microphages and alveolar microphages, and they are the ones that start to secrete more and more of these cytokines.

How this balance plays out will have an effect on the clinical outcome, and on treatment. It is thought that antivirals—drugs that can affect viral replication per se—have a better chance of working if given early, as opposed to when it is getting late in the development of the disease when you have these other immune reactions. They also need to be taken into account to manage the disease.

Baroness Walmsley: So have the antivirals been found to be effective? Do they have to be very specific antivirals to have any effect?

Professor Massimo Palmarini: The virus was discovered only a few months ago. Now the first tranche of experiments are to try to identify antivirals that are already in the clinics and are being used in other settings to see whether they are effective. At the moment, one of the leading components of drugs is remdesivir, which is a nucleoside analogue. Basically, the virus genome incorporates blocks to make chains to replicate, and remdesivir is incorporated into the chains, but then the polymerase of the virus gets stuck so it cannot make new virus. That is in theory, because it proved somewhat effective in other diseases. So that has had some effect, but all the clinical trials and the results of clinical trials are coming along now. Other antivirals being used are protease inhibitors, because the virus needs proteases to replicate efficiently, so they are being trialled at the moment.

These are all what are called repurposed drugs, so they are drugs that already exist and now everybody is trying to see whether they work. There are experiments in vitro, those that have a better chance, and experiments in clinics. It is always a big step for a drug to go from in vitro to in vivo. For a specific drug—for example, we have superdrugs for hepatitis C or for HIV—it is likely to take time to develop specific molecules that interact specifically with this virus. I might be wrong—maybe there will be a phenomenal repurposed drug that will work really well right away—but normally that would be my impression.

The Chair: Right. We have a session later on related in particular to frequency.

Q66 **Baroness Sheehan:** I want to talk about what constitutes effective immunity. Notwithstanding the fact that the virus has not been around very long, can the panel say what they think effective immunity against SARS-CoV-2 would look like and how long-lived any immunity generated

against it would last?

Professor Massimo Palmarini: In essence, it is clear that, almost universally, patients infected with SARS-CoV-2 will develop antibodies. You may have heard the term "neutralising antibodies", which are the ones that we tend to highlight. Antibodies are basically generated towards different components of the virus and towards different proteins and bits of proteins.

One that is really important is the spike protein. If you have a protein against this particular area of the spike, which is called the receptor-binding domain, it does not allow the virus to get into the cell, so these neutralising antibodies are in essence a road block for the virus and the virus cannot get in.

This is one key element of the unit that we said before seemed to be present in most infected individuals with time, but then they seemed to vary in the amount. It seems to be that those who had more severe disease had higher levels of these antibodies and those who had milder disease had lower levels.

How long do they last? We do not know yet, because at the moment it has been only a few months, but the data on SARS-CoV-1 or the seasonal coronavirus suggests that they tend to wane after a while—in some cases, after a year or two—at lower levels. But even when they wane, there is still residual immunity, so the individual can respond better than if he did not encounter the virus at all.

Professor Sir John Bell: This is now the big question for the disease: how good is the immunity you generate to an infection and what is the pace at which that degrades to make you susceptible to a subsequent infection? Obviously, it is also crucial for vaccine development, because you would really like a vaccine that lasts for at least a year, and ideally more.

Professor Palmarini rightly described the state of play with other similar forms of coronavirus. For SARS, the serological reactivity starts to fade after a couple of years; cellular immunity lasts a bit longer. With MERS, the cellular immunity lasts quite a long time. Seasonal coronaviruses are seasonal because people can get reinfected every year, so there is quite a range of protection.

We do not know whether the type of antibody that you see on an ELISA test or an antibody test is really the crucial thing or whether it is the number of neutralising antibodies that you are able to produce. It is more likely to be the latter than the former, I have to say. One of the questions is whether we can set up a study in healthcare workers who have been exposed, have been swabbed positive and have antibodies, and then see whether, when the next wave of virus comes, any of them get reinfected. That will be the gold standard of an experiment to decide whether you get proper protection from your immune response to the first infection.

Baroness Sheehan: Do you know whether that study is being planned?

Professor Sir John Bell: Yes, it is being planned. We are working with PHE at the moment to set that up. Susan Hopkins at PHE has a study called the SIREN study, which will be across healthcare workers. They are hoping to collect 100,000 healthcare workers and then track them. If the seropositivity in healthcare workers is between 10% and 15%, if the next wave is the same size you would expect to get 10% to 15% of people who have been exposed the first time exposed the second time. That gives you the numbers to be able to tell you that, but sadly we will not able to tell people until we get to that point.

Q67 **Baroness Sheehan:** Absolutely. We look forward to that. Looking at the severity of illness, what factors appear to control why some people develop more antibodies than others? Also, is the type or amount of antibodies developed likely to correlate with the amount of immunity generated?

Professor Adrian Hayday: There are several issues wrapped up in that question. At least in our own studies, we have been looking at people who have been ill and in hospital, and we have worked with individuals who have been very little affected but who clearly were infected. Everybody makes antibodies, but it seems clear that the more virus you get exposed to, the more you make. As John has said, exactly how that will translate into long-term protection, we do not know. We are in the awkward situation, which was brought out right at the beginning of the session, that we are not studying the vast majority of people for whom the disease really causes no problem and who probably make perfectly good immune responses, because it is not possible to study them under a rational circumstance, at least at this point in time.

So the most successful human immunity to SARS-CoV-2 at the moment, shown by about 70% of people, is not something that we study or fully understand, just for logistical reasons. We are studying the immune responses of people who have been sick. As John has said, the halfway house is to go about a large study of individuals, many of whom we know have been exposed, and probably to high doses of virus, in their healthcare setting. It will take a while for those data to come through.

I want to come back to our friends the T-cells, which we discussed a little at the beginning of the session. There are reasons for thinking that T-cells may be particularly important here. When this virus infects via the respiratory tract—by the way, that is not the only way that it can get in—it is possible that there are antibodies that block it off early, high up around your throat and upper airway. These antibodies are of a particular type called IgA, and they are not routinely measured. That is because they are not routinely represented in the blood.

That is another issue, but they may be very important. It may be that the virus gets past that block down into the lower airways. It is very difficult to quantitate the virus down there, but that is where the gas exchange takes place, that is where you get into the pathology of acute respiratory distress syndrome, and that may be where you may need the T-cells to kick out the infected lung cells—the pneumocytes, as Massimo called them—as quickly as possible. It is possible that for people with defective

T-cell responses, which would be enriched in older people, that is where they really have the problem.

So it is not just who is providing the protection; it is at what anatomical stage you most need that protection to prevent you going into serious disease.

Q68 **Baroness Rock:** I think Professor Hayday has already touched on my question. Could you elaborate at bit on the extent to which we understand the relative roles of the antibodies and T-cells in the immunity side of things? Is either—I think you have already mentioned T-cells—likely to be more important in conferring long-term immunity? I would particularly like to ask about the relative importance of B-cell and T-cell immunity in the implications for any vaccine development. Professor Hayday, would you like to carry on, then perhaps we can come to the others?

Professor Adrian Hayday: I am happy to start and then I should certainly cede to John over the vaccine strategy.

The immune system is a highly integrated multicomponent system, and of course it has had millions of years to evolve the way it deploys its many parts in a sort of co-dependent way, so it is not a competition between B-cells and T-cells up against each other to see which can be the most important. That notwithstanding, because each virus interacts with the host in a slightly different way—the host in this case being us—the different compartments definitely tend to assert greater importance.

None of us knows just yet whether there is a relative hierarchy, but I am struck by the fact that the pathology that this virus starts is down in the lower airways, where you probably need T-cells to remove the infected cells. Given the age susceptibility occurring in individuals who no longer have a thymus to speak of, I just worry that the T-cells are key and might be suffering a lot in the way they do in sepsis. T-cells get highly dysregulated in sepsis, and although this is not sepsis there may be a commonality there.

In the second session today at 4 pm, I think there will be discussions about strategies to boost the T-cell response, so I will not go into that now. Rather, I will let John talk about how these sorts of thoughts affect vaccine strategy.

Professor Sir John Bell: First, you need to understand that you are talking to two T-cell immunologists here, so we have a certain view of the world.

The Chair: I thought all immunologists had enough of that.

Professor Sir John Bell: No, serologists are not on the same page as us, I promise you.

Antibodies are relatively easy to measure, so you often find people dashing around saying, "Let's measure the antibodies". But I think Adrian is right that this immune system was designed really with three components: an innate component, which is crucial; and the two adaptive

components, antibodies and cellular responses. I suspect that a defect in any one of those would put you in real trouble with this disease, so that needs very serious thought.

With regard to the vaccine, it might be possible to deal with the virus before it gets down into the deeper organs with neutralising antibodies alone; there is experience in other viral infections where that might be the case. But Adrian is absolutely right that once you get deep-seated infection in the lung, the evidence is that you probably need a cellular response. A lot of these patients get a lymphopenia fairly early in the disease; the lymphocytes are probably not just dying but tracking their way into the deep-seated infection in the lung and trying to do their business.

As you track those lymphocytes and what they look like, it is interesting that the sicker people get, the more tired those lymphocytes get; there are exhaustion phenotypes on T-cells, which become more prevalent as people get sicker in the ITU, so they are probably pretty important in the puzzle.

The vaccine strategies—I can speak about adenovirus strategies in particular—have always been attractive, because they generate not just serological immunity but quite serious cellular immunity to the viral proteins. That may prove to be one way in which, hopefully, they can generate rather more long-term immune response. I am of the view that a purely serological response will not be enough; you will need more than that.

Baroness Rock: Professor Palmarini, do you have anything to add?

Professor Massimo Palmarini: I just want to make sure that everybody also appreciates that the B-cell and T-cell responses are all linked. The compartments are not completely separate, although we have B-cell immunologists and T-cell immunologists.

At the moment, it looks as though the level of antibodies corelates pretty well to the CD4+ T-cell reactive against SARS-CoV-2 and to the CD8 cytotoxic cells. This tells us, pretty much as Adrian alluded to before, that the best bet is that they all contribute to clearing infection. In vaccine design, the more you have something that can simulate all the different arms of the immune response, the better the chances. But we do not know yet what the correlates of immunity to this infection are, and it is critical to determine that in the next months.

Viscount Ridley: May I follow up with a quick supplementary question to Baroness Rock's question before I come to my main question? Sir John said something at the beginning that intrigued me; it was about the replication of the virus not being accessible to the interferon response. I think I am right in remembering that interferons and T-cells are part of the same system, but I might have got that wrong. I picked up from a paper recently that bats have something like 20 times as many interferon genes as primates do. Is it possible that this virus was trained in a much more interferon-rich enemy and that it therefore finds our interferon response a bit of a puny enemy?

Professor Sir John Bell: There is something pretty strange about bats' immune systems. They harbour lots of pathogens, not just this one. They also, I think, lack some aspects of a normal immune response; there is a STING pathway which they simply do not have. Again, they seem to have adapted their immune system to be able to live synergistically with a lot of viral pathogens without them killing them. So there is a story there.

There is also an interesting story about what happens when a pathogen finally jumps from one species to another. Of course, there are a number of examples, particularly in animals, where we know that has happened; you confront a system that has not adapted itself at all to dealing with that pathogen, and what you see is probably a bit like what we see with this particular coronavirus—a rather severe disease that is pretty unpleasant, but over generations it gets better. Myxomatosis virus is a good example; initially, it had a massive effect, but the genome of rabbits shows that they have adapted rather well to dealing with it as an endemic pathogen in their population.

There are a lot of very important scientific issues here that we have not got to.

Q69 **Viscount Ridley:** My main question is about cross-immunity from the seasonal coronaviruses, the colds. You have already touched on this quite a lot. I would like to get a bit more information on why they are seasonal, because this one is also proving to be seasonal, by the look of it, and flu is seasonal. Why are common colds quite so seasonal, and is there any evidence that when those four common-cold coronaviruses jumped into our species they were severe epidemics to start with?

Professor Adrian Hayday: Massimo should answer that question.

The Chair: I was going to suggest Professor Palmarini. He might also allude to the earlier question.

Professor Massimo Palmarini: I was going to comment on the bats.

Viscount Ridley: Please do as well.

Professor Massimo Palmarini: The bats are a bit like parties; they attract different perspectives. Some of us, like John, think they are special. My view is that every animal species is special in its interferon response and immunity. There is more interaction with viral hosts, which then create a situation that is more or less prone to zoonotic transmission. There are so many bats; there are more species of bats than any other species. This is one aspect of the richness of the species: that there are then more viruses. That is an interesting scientific discussion. With coronaviruses, the seasonality is often linked to the ability of the host to mount a protective immune response. Then the virus has to drift and change somewhat to be able to reinfect. One scenario is that, in reality, SAR-CoV-2 will with time become a seasonal virus. That is the immune response.

The other point is that during the summer there are fewer chances for the virus to be transmitted, because it is less stable in the environment.

There are combinations of factors, and with a cooler temperature you have a better chance.

Other factors to consider include the interference of different respiratory infections. There is more and more evidence building that if you think about us as human beings and you think about respiratory viruses, different respiratory viruses can compete for us and some viruses do better than others to coinfect. Others seem to block each other. That goes to the other point you may have heard in the news about using different types of vaccines to block SAR-CoV-2, vaccines that are nothing to do with SAR-CoV-2 specifically.

Professor Adrian Hayday: I will side with John on this and say that there may be something special about bats. It is only a word of caution. I worry a little that this virus is not quite as seasonal as people would like it to be. It has gone very global, and it has done extremely well in a lot of hot countries where I think flu would have struggled. Bats have an incredibly high metabolic rate because of their flight, and there is a thought out there that some of these viruses, and this one in particular, may have adapted to living at really quite high temperatures. That is one reason why this massive spike in an inflammatory mediator like IP-10 might be a common part of pathobiology among these coronaviruses. I say this only because of the caution that we need with regard to seasonality.

Q70 **Viscount Ridley:** May I come back to the cross-immunity point? I think that Professor Palmarini said that 70% of children under the age of four show evidence of having been exposed to seasonal coronaviruses. Did I hear that right?

Professor Massimo Palmarini: Yes. By the age of four, 70% have antibodies against seasonal coronaviruses.

Viscount Ridley: Does that not suggest that if there is some cross-immunity, herd immunity will be much easier to reach?

Professor Massimo Palmarini: There are differences. First, the seasonal coronavirus is actually four distinct viruses, with some closer than others. Obviously, cross-immunity is not a total protection. There could be levels of these antibodies, and individuals who have been exposed to these viruses will have different levels of immunity to seasonal coronavirus. At the other end of the spectrum, as we said before the antibodies against seasonal coronavirus in the over 60s tend to wane. The levels tend to go down.

In reality, the truth is that we really do not know. We need to investigate it. I do not know whether John or Adrian know more than me.

Professor Sir John Bell: This is a really interesting question. As you know, the original Anderson and May paper that defined R0 did so in an immunologically naive population. There is no way we are an immunologically naive population, in my view, so it raises questions about what herd immunity actually is in this population. It is a very salient point, and one that will send the modellers into a tailspin.

Q71 **Baroness Manningham-Buller:** We heard earlier from Professor Palmarini that there is quite a lot of work to see whether we can repurpose existing drugs to help with therapeutics for this disease and that some of them may indeed help. He mentioned remdesivir.

My question is really about the immunomodulators. We are coming on to a session on treatments later in this inquiry, but before we leave the subject of with our witnesses today, do any of them wish to comment on that as an aspect of treatment?

Professor Sir John Bell: I am of the view that there is probably some low-hanging fruit for repurposing drugs for this disease that could prove to be pretty useful. That needs to be said with the caveat mentioned by Adrian that not everybody gets a cytokine storm, so they will not help everybody. In fact, one of the issues is selecting your subpopulation to treat them with the most appropriate drug. Antithrombotics may be very effective in some populations and anti-inflammatories in others. There is a rather good list of interesting anti-inflammatories that could be used in people who have a major inflammatory component. There is tantalising data, none in randomised studies, that suggest that drugs such as Anakinra, which is an inhibitor for the IL-1 beta receptor, and even the anti-TNFs might be quite helpful in this disease if you have a significant inflammatory component.

However, before we plough in and start using those in the clinic, we need evidence, which we will get only from randomised studies. That has not happened yet, so it is a really important bit of the agenda.

Baroness Manningham-Buller: Would I be right in understanding that that is now quite difficult to do, given the low rate of infection in the community?

Professor Sir John Bell: I am sorry to say that it is now almost impossible, until we get a second wave.

Professor Adrian Hayday: One thing that has been produced by this extraordinarily rapid and intense research effort is the prospect that we will very quickly be able to stratify patients into their clinical trajectories. As John said, that will help us a lot, because it will get the right drugs to the right people.

Having said all that, yes, these anti-inflammatories can certainly help, and they have helped in certain circumstances, but the fundamental driver of this, the criminal, is the virus. The antivirals have done reasonably well. There are all sorts of qualifications attached to the way the data were interpreted and exactly what they told us, but if you can snuff out this virus in a sick individual, that individual will do better. It is interesting that there was great concern early on that a lot of cancer patients who received treatment to boost their immune system might be vulnerable to these cytokine storms. In fact, so far as we can tell, it is quite the opposite here at Guy's Hospital, where the cancer patients on those sorts of therapies seem to be doing very well. That is consistent with the idea, which I think you will hear about in the next session, of

using cytokines and things such as them to boost immune competence to make it work better.

Professor Massimo Palmarini: From a virology point of view, we get antivirals with all sorts of issues.

Baroness Manningham-Buller: Finally, some of you have said when, not if, we get a second wave. Would any of you like to comment on that?

Professor Sir John Bell: We have certainly seen second waves in other parts of the world. Hong Kong is getting ready for its third wave. There has been a second wave, although a modest one, in many parts of China, and Iran has just been through a pretty horrendous second wave.

It is possible that we might not have a second wave, but given that the lockdown has now largely been released, we are now back in action and we have a rapidly declining but pretty reasonable level of infections in the community. I would be very surprised if we avoided a second wave. The real question is whether we will have a number of single outbursts around the country and then a second wave, or whether we are just going to get a second wave and when that will be. I do not think the modelling is good enough to tell when it is going to be, to be honest.

The Chair: We are bang on time to stop this session, so thank you very much, Professor Sir John Bell, Professor Hayday and Professor Palmarini, for coming. We were lucky that we had 10 minutes extra for this session, because I knew there would be more questions. Thank you all.