HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Tuesday 23 June 2020

10 am

Watch the meeting

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

Evidence Session No. 9 Heard in Public Questions 79 – 89

Witnesses

Professor Arne Akbar, Professor of Immunology, Division of Infection and Immunity, UCL, and President, British Society for Immunology; **Professor Peter Openshaw**, Professor of Experimental Medicine, Imperial College London, and Honorary Physician, Department of Respiratory Medicine, St Mary's Hospital; **Professor Ultan Power**, Professor of Molecular Virology, Queen's University Belfast.

Examination of witnesses

Professor Arne Akbar, Professor Peter Openshaw and Professor Ultan Power.

Q79 **The Chair:** Good morning, everybody, and particularly our witnesses. Thank you for coming to help us this morning; we are going to have two very interesting sessions. I have apologies from Baroness Manningham-Buller, who is on a strategy board away day, but she has sent me some messages.

You have heard that I will co-ordinate a one minute's silence at 11 am. We will kick off straightaway with the questions, because time is always precious.

Q80 **Baroness Blackwood of North Oxford:** We have heard in previous sessions that while most people who are infected with Covid-19 develop antibodies, there is some uncertainty about whether prior infection and the presence of antibodies indicates immunity to reinfection.

I start by asking the panel to indicate something of our current understanding of the level of immunity conferred by Covid infection, and how confident we are that prior infection confers some level of immunity.

Professor Peter Openshaw: That is a key question, and we have been waiting for answers to it, particularly from Wuhan. It has been an issue with previous coronavirus infections, where we have seen immunity waning over time. With this particular coronavirus, we are in new territory. This is a novel virus; it has not been in the human population before. We are starting to see some profiling of the rate of decline of antibody, showing that there is quite a strong plateau level so far, but this has only been in the human population for a few months and we are waiting to see. At the moment, I am a bit more optimistic that there will be more durable antibody levels than there were a few months ago, but this is an emerging field.

Professor Arne Akbar: I want to stress that while antibodies are very important for immunity, that is not the only answer to how we mount an immune response. There is another side of the immune response involving the T-lymphocytes—the T-cells—which has been very little studied so far. Papers are just emerging now looking at the T-cell response; I know of at least three groups that have data on this.

In the next few months we may focus a lot more on T-cells and how they change with the infection than on antibodies. Ultimately, we need to look at both together. We cannot get a picture of the immune response and know whether people are being protected or not by looking only at the antibodies.

Baroness Blackwood of North Oxford: Thank you. Professor Power, would you also like to comment on that? Also, how does our understanding of immunity compare between this virus and other coronaviruses?

Professor Ultan Power: That is the point that I was going to address. For MERS and SARS-CoV-1, evidence suggests that the antibody responses wane fairly rapidly after infection, but they last for at least a year or two. One study, for example, suggests that the antibodies may last for longer than 12 years. How that fits specifically with SARS-CoV-2, the current pandemic, remains to be seen. As Professor Openshaw said, we are obviously in the early stages of the pandemic and this information will be got in the future, not now.

With those kinds of viruses, it looks quite promising. For the other coronaviruses, the common-cold varieties, evidence again suggests that antibodies wane quite quickly—within six months after infection—and reinfection can happen reasonably quickly for some of the viruses. However, the percentage of people who become reinfected is quite low.

There is still a lot to be learned about the duration of immunity. It is not all doom and gloom. There is a possibility of reinfection, but the severity of that also remains to be seen. Evidence from other coronaviruses suggests that it may be reduced, compared to the primary infection that one gets.

Baroness Blackwood of North Oxford: Do we think that the current antibody testing strategy and the research in the field are providing the information that we need to understand the immune response that is being described by all of you, or are there other kinds of testing, or research strategies, that we need to be deploying at this point?

Professor Peter Openshaw: To me, something that is missing is the ability to monitor what is going on in the moist surfaces of the lung and nose, in the mucosal tract. At the moment, we are very reliant on measuring things in the blood. That is sometimes a good measure of what is going on in the site of interest, but it is not actually the site of interest.

A focus on the mucosa, and new ways of measuring mucosal immunity, has great potential for the future. Things are definitely moving in that direction. That field has been very active for a few years now, but it does not represent the sort of traditional understanding of immunology, which was more centred on the peripheral blood in humans.

Professor Ultan Power: What Professor Openshaw says is absolutely correct. Another big aspect of it is indicating the quantity of virus-neutralising antibodies that are present in the peripheral blood. Most of it is ELISA-based assays that do not necessarily show functionality. More information about the functionality of the antibodies, even in the peripheral system, will also be important. That will inform subsequent strategies for the protective efficacy of vaccines, which you will hear about later.

Professor Arne Akbar: My expertise is really on the other side of the immune response—the T-cells. I bow to the knowledge of my two colleagues on the panel.

Baroness Blackwood of North Oxford: Fair enough.

The Chair: Professor Akbar, are there any B-cell immunologists?

Professor Arne Akbar: There are many B-cell immunologists. I think you have probably met a few. Janet Lord, for example, does some B-cell work. There are various committees that we are trying to build to look at the impact of immunology on Covid-19. There are a lot of B-cell immunologists on that panel.

The Chair: What role does B-cell immunity have in Covid-19?

Professor Arne Akbar: These cells are the source of the antibodies that we have been discussing, but they go beyond just being factories for producing antibodies. As the cell, they can do other things, too: they can contribute to inflammation; they can make a lot of mediators that interact with other cell types that co-ordinate immune responses. However, those aspects are less well studied. People think of B-cells as the source of the antibodies that are being produced.

Q81 **Lord Borwick:** I want to ask about the duration of immunity, which we do not know a vast amount about. As I understand it, the most important factor is the mutation of the virus. This appears to be a fairly slow-mutating virus, which presumably implies long-term immunity. What duration of immunity is considered worth while for the development of a vaccine, and what further data is needed to fully understand the duration of immunity that it covers?

Professor Peter Openshaw: There are many layers to the answer to that question. On durability, viruses often have a way of modulating the host's immune response. They have evolved this to tune down the immune response that is generated by the virus. One would suspect that that would usually be particularly strong in a virus that has had a long time to co-evolve with human hosts.

What surprises us is that this novel coronavirus, which has only recently jumped from bats to humans, already seems to have a lot of immunological tricks up its sleeve and be able to interfere with the immune response and to disseminate in a way that you would not expect from a virus that has only just moved into the human population.

We wonder why that is; we would not have thought that a virus would behave in such a complex way when it has only just been introduced into a new species. Maybe there are tricks that it has learned, while evolving in another species, that have some cross-species effect. I hope that is not too philosophical an answer.

As regards the evolution of the virus, coronaviruses have among the largest genomes of all the RNA viruses. In order to preserve their genome, they have developed methods of genome editing to try to eliminate the mutations that might otherwise destroy their ability to infect. That is unusual among RNA viruses, but it means that the genome has a fairly regular progression in the way it accumulates mutations with time. It acts almost as a biological clock, allowing you to track back how long that particular strain of virus has been evolving separately.

It is not particularly evident that coronaviruses are evolving to escape from the immune system. Influenza is very fast-moving and fleet of foot; it mutates all the time under immunological pressure. That has a relatively small genome; it is very mutable—it tolerates mutation quite well. That is the way that it escapes; it constantly changes its form. It is a shape-shifter virus.

Coronavirus is more slowly evolving. It is not evident that it is being driven by the host's immune response, which makes us suspect that it is among that class of viruses that has ways of controlling the host's immune response and modulating the defence that would otherwise interfere with the infection of its progeny.

Lord Borwick: That would imply that a new vaccine could work for a longer duration.

Professor Peter Openshaw: Our hope for a vaccine is that we could induce even better immune responses than can be induced by the virus itself. If the virus is indeed neutralising multiple checkpoints in the immune system to its own advantage, a vaccine might be able to induce a good immune response while not interfering with the host's immune response in the way that a live virus would. This is all a bit speculative because, again, this virus is relatively new to us.

Lord Borwick: Indeed.

Professor Ultan Power: As Professor Openshaw indicated, it looks as though the virus is not evolving rapidly in humans. We have seen that with other viruses like RSV where we do not see a huge amount of change over time other than maybe in certain antigens that are present. However, they do seem to have the capacity to modulate the immune response. This may be a factor that will render vaccine development more difficult than it would be for influenza, for example.

My other slight concern is that we have seen an outbreak of this virus in minks in the Netherlands. So the virus has the potential to jump species, from humans to species like mink, for example, and then back into humans. We do not yet understand whether that jump between species will have any impact on the genetics of the virus itself. When it comes back into humans after a passage in another species, will it change somewhat?

It is very early days, we do not know much about it yet, but we need to keep a reasonably close eye on this.

Professor Arne Akbar: I have a comment that is slightly tangential but very related. The selection pressure on viruses is normally from the host immune response. We cannot think of the host as being just humans. There are different kinds of humans, and this virus, as we know, affects older humans more severely.

The immune response in older people is very different from that in younger individuals. If the virus is going to infect a young person compared to an older person, the outcome could be very different. It is very important to understand the changes that occur in the immune

response of older people, and then super-impose the effects of the virus on to that.

We cannot think of young people as being the model for an immune response and just look at the effects of the virus on those individuals. It is older people who have the most severe impacts from the virus on their health.

Q82 **Lord Browne of Ladyton:** Recognising that we have already entered this area of discussion, my question is about the implications of our understanding of natural immunity for the development of vaccines.

Is there evidence that vaccines will be able to confer a greater level or duration of immunity than natural immunity confers? I suspect we have already covered part of that, but it is a very specific question.

Professor Arne Akbar: Work that is emerging right now suggests another form of natural immunity: that is, immunity before you are even infected with the SARS-CoV-2 virus can exist in some people. Some individuals who have never seen the virus have T-cells—T-lymphocytes—on the other side of the immune response that can actually recognise the virus, and there can be a big expansion of these cells.

It is currently thought that these cells might be cross-reactive to a previous coronavirus. So some people might have immunity that has cross-reacted with a different organism. This might explain why some individuals do not have very severe symptoms; they might have some pre-existing immunity.

That does not answer your question about whether natural immunity might be better than vaccine-induced immunity, but some people do have immunity already to some aspects of the virus.

Professor Peter Openshaw: When we think about what we call natural immunity, there is obviously the cross-reactive immunity that has been brought about by infection with viruses that have similarities.

To come back to my moist mucosal surfaces, there are also resident T-cells in the mucosa. Within the mucosa, there are cells sitting there that have perhaps been primed to some other agent but which have some capability to respond very quickly to an unknown threat. They form part of what we call the innate immune response within the mucosa, which has a non-specific but highly beneficial effect and may explain why some people who are highly exposed to the coronavirus do not become infected.

This may account for a very large proportion of the variability in infection. We have been doing deliberate infections in volunteers with both pandemic flu, H1N1, and with RSV, a virus to which Professor Power referred.

Although many people lack antibody, either by selection or by nature, that has very little power to explain who becomes infected with those two viruses in our volunteer studies. A lot of the variability seems to be down to this innate mucosal defence, which is in part mediated by locally

recruited T-cells that are resident and which follow previous infection, but also represent part of a much more complex innate defence, which underlies the immune system and has very primitive origins going right back in the evolution of mammalian species and beyond.

Professor Ultan Power: With regard to the pre-existing T-cell immunity, I am somewhat confused about that. A recent paper that Professor Openshaw was involved in suggested that there was no pre-existing T-cell immunity. Whether a different technique was used for the other papers, I am not quite sure yet.

Also important are the challenge studies that have been undertaken with other common-cold coronaviruses. These give an indication of how effective one infection is in preventing a second infection and therefore of the immunity induced. A couple of notable studies are worth citing. In one, six volunteers were infected resulting in detectable symptoms and detectable virus in all the individuals. When those individuals were re-infected 12 months later, zero of the six had symptomatic infection subsequently. This suggests that protective immunity is possible with the endemic human coronaviruses.

A second, similar study was done with nine volunteers one year apart. In the second exposure, again, zero of the nine developed symptomatic disease. This suggests that natural infection, at least with these endemic human coronaviruses, is capable of inducing protective immunity that lasts up to a year.

Lord Browne of Ladyton: Do we understand yet whether inducing a B-cell or a T-cell response is more important in providing protective immunity? As a supplementary to that supplementary, is a vaccine targeting only T-cell immunity likely to be a worthwhile development?

Professor Arne Akbar: I do not think we know right now whether T-cell immunity or B-cell immunity is more important. What we do know is that, to get appropriate B-cell immunity by making antibody, you need the interaction of the T-cells to give optimal antibody production.

The immune system is an interacting system, and you cannot look at one cell type in isolation from all the others—they actually collaborate to create the best immune response. So my feeling is that to get the appropriate immunity you need co-ordinated immunity. What we do not understand yet is the extent of co-ordination we are having right now, because we are focusing mainly on the B-cell side, not the T-cell side, at the moment.

Professor Peter Openshaw: We have been studying T-cell immunity to RSV, the bronchiolitis virus, for a long time. In that case, a vaccine was trialled in the 1960s that caused increased disease severity, which appeared to be related to a strong T-cell priming in the absence of priming for neutralising antibody, or priming for antibody that waned and was then replaced by predominantly T-cell immunity.

We know that in the later phase of Covid-19—in the second week, when there is a lot of inflammation in the lungs—that may be related to an immunologically overexuberant response. I would be fearful that a

vaccine that just induced T-cell immunity might indeed augment that type of pathology. It is hypothetical at the moment, but from what we know of other fields, like the RSV field, it is a distinct possibility. I would very much want to see the neutralising antibody response, which seems to be a better indicator of protection, particularly if it is measured in the mucosal fluid.

Professor Arne Akbar: We are thinking of immunity as beneficial right now, but we know that there are certain cases where your immune system can work against yourself. With autoimmune disease, for example, it is your immune system attacking your own healthy tissue which causes problems.

My research group has shown recently that, towards the end of their life, T-lymphocytes—the very other cell type that we are trying to boost to enhance the immune response, may actually work against your own tissue; they start using a different set of receptors. We do not understand where the pathology is coming from in the lung in patients with very severe disease. It is not ruled out that this later stage of the disease may be because these cells have gone to a certain new mode of activity that is actually attacking healthy tissue. We need to have the histological data on that to add light to this.

Professor Ultan Power: Obviously, a virus-neutralising antibody would be a main target for it, but there is potential difficulty on both sides with the T-cell and the B-cell; if you get the B-cell antibody responses to a non-neutralising epitope, you also have the possibility of getting what we call enhanced disease. That needs to be studied very carefully. I guess you will talk about it a lot in the second session in relation to vaccine safety, but evidently all these elements are evolving at the moment and need to be looked at extremely carefully as we go forward.

Q83 **The Chair:** Thank you. This discussion leads on to my question quite nicely, although some of it has been covered.

Can you outline the different approaches to developing a vaccine, including for Covid-19, and what would a good vaccine for Covid-19 look like? Are there advantages or disadvantages to the different strategies that could be used? That might be a long question, but you can give me a short answer.

Professor Ultan Power: It is a very long question, with multi-components for sure. Many different strategies are available at the moment. They range from live attenuated approaches; the current technology being used is codon deoptimisation, where you change the codon in the live attenuated virus, so it does not operate quite on all cylinders within the body. The hope there is that you still maintain the capacity of the virus to induce good immune responses, but it is not capable of setting up a pathogenic response. That is a live attenuated approach.

As I am sure you will hear later on, an awful lot of the other focus is on the subunit viruses targeting the S protein, or the receptor-binding

domain of the S protein. That can be delivered either as a purified subunit protein itself or by virus vectors. Again, you will hear a lot more about that later on.

On the other part of the question, about what represents a good vaccine, that remains to be seen. Often we have a predilection of what we would like to see in antibodies, and often nature tells us what really should be there. Yes, virus-neutralising antibodies are likely to be very good; the preclinical data suggests that good neutralising antibodies, particularly to the receptor-binding domain on SARS-CoV-2, are likely to be very promising, but that remains to be seen. The clinical studies will tell us everything we need to know in due course.

Professor Peter Openshaw: Another way of thinking about this may be what level of protection we are looking for. If we are looking for protection against nasal infection and therefore against spreading the virus in the community, a vaccine that will induce strong nasal immune responses, including secretory IgA, for example, will protect the actual nose. The systemic injected vaccines might induce good levels of antibody in the blood, which might be more protective against the second level, which is the lung. So protecting against lung infection might be viewed separately from protection against nasal infection.

The third level is protection against the very severe consequences that are seen in late stages of Covid, where the virus appears to cause disseminated effects, multi-organ failure, thrombosis inside the vessels, renal failure, and so on. There is better hope that antibodies circulating in the bloodstream might protect against that, but we still do not know whether there might be antibodies that could be circulating that might augment that and somehow cause this immunological overreaction which Professor Akbar referred to. So thinking about it in terms of nose, lung and systemic—three different levels—is quite important.

Professor Arne Akbar: I hate to keep bringing up the flies in the ointment. To have a good vaccine is very important, but vaccines do not work very well in older people. This has been shown with many other vaccines in the past—

The Chair: Thank you for telling me that.

Professor Arne Akbar: —so we might need to have something else as well as a vaccine to get optimal protection for older people. You have heard the recent excitement about dexamethasone, the steroid that can block inflammation. For older people, you might have something like an anti-inflammatory drug, maybe like dexamethasone, together with vaccine responses to give you the maximum benefit. The vaccine alone will help the younger people, which will be good, because if the younger people are not infected they will not spread it to the older people. But it will not directly help the older group very much, and they are the people with the most severe disease right now.

Q84 **Baroness Hilton of Eggardon:** I think you have already addressed part of my question, which is about the variability of the immune response in older people and the fact that they respond less well to vaccines. What

implications do you think that has for population-wide vaccine distribution, and who would you target first for vaccines? Would it be appropriate to target the oldest, who are most vulnerable, or other parts of the population?

Professor Peter Openshaw: We are considering a paper at NERVTAG this week, which is about targeting different subpopulations with vaccines. Sometimes it is possible to protect a vulnerable group by targeting another group. This is being done with influenza, for example. Over the past few years, the UK has been at the forefront of rolling out the live attenuated vaccine for children, because schoolchildren amplify the distribution of the virus in the community. It is possible to see that grandparents are being protected by the vaccination of children that are in school using this very benign, nasally delivered vaccine that causes good protection in the nose and in the respiratory tract. Even though children themselves do not always suffer from severe flu, that is a very simple non-injectable form of vaccine that causes wider protection in the community. So you can get indirect protection using that type of community-based approach to limit the spread.

I absolutely agree with Professor Akbar that different vaccines may be appropriate for different age groups within society, some of which might be high-dose injectable, perhaps with adjuvant to provide direct protection to those most vulnerable, in whom it is most difficult to induce immune response, but also getting secondary protection by identifying groups of people who are amplifying the responses, which in the case of coronavirus might be healthcare workers, people in front-line occupations, or people doing public-facing jobs, for example. They might be particularly important people to target to limit the spread within society.

Baroness Hilton of Eggardon: Thank you. That sounds a very subtle strategy.

Professor Ultan Power: I want to come back to what Professor Akbar was talking about: the possibility that we could bring antibodies not as vaccines but as prophylaxis in highly vulnerable people. A number of strategies are being studied at the moment—in fact, they are in clinical trials already—looking at the possibility that antibodies might be able to act as prophylaxis in very high-risk individuals such as the elderly, who have difficulty mounting good responses.

More recently, there has been a development of technology that enhances the half-life of antibodies so that an single injection, for example, could last for quite a long period of time within individuals without having to reinject people regularly. This kind of technology could be of significant use in the arena of susceptibility in the elderly, who are compromised in developing really good, strong responses to vaccines.

Professor Arne Akbar: To understand the impact of vaccination and decreased immunity we really have to understand what goes wrong with the immune system as you get older. Without going into great detail, one thing that is apparent even in healthy older people is that more inflammation is happening all around the body. We need to understand

where that inflammation is coming from. The very fact that there is increased inflammation suggests that older people do not handle inflammatory responses very well—they sneak through and create problems.

This baseline of inflammation in older people is linked to frailty and many negative outcomes as you get older. This seems to be exacerbated when you get a severe infection like Covid-19. If you have individuals who already have a compromised system where inflammation is always leaking through, they cannot control it well. If you get very overt inflammation like we do with the virus, it is devastating.

What is the source of the inflammation in the first place? That is something that we really need to get to grips with, even before we try to understand what happens in the disease. Why is the inflammation there? Should we look at inflammation and how to treat it even before the infection starts appearing in the older group?

Q85 **Lord Hollick:** Can we return to the question of mutation? Professor Openshaw described this particular virus as a rather mature and well-developed one, so what are the dangers that the efficacy of any vaccine would be undermined by the ability of the virus to mutate?

As an allied question, over what timeframe could this take place?

Professor Peter Openshaw: I think Professor Power might also have views on this. I come back to saying that this virus has only recently come into the human population. We need to watch in real time as it evolves. We have never had the power to do this before. We have never had the techniques to allow us to watch the evolution of a virus as it enters the human population in quite this same dramatic fashion.

We can speculate that there might have been incidents going right back to, say, ancient Athens—the plague in Athens described in antiquity probably represented the first introduction of some virus of this sort—but trying to unpick the history of virus entry into the human population is very, very difficult.

Because of the regular way in which coronaviruses evolve and mutate, we can speculate about how long the common-cold coronaviruses, of which there are roughly four, have been in the human population. This ranges from about half a millennium to sometime in the 1950s. We think these viruses have been separately evolving mainly in humankind.

As I say, certain areas of the virus surface proteins are essential for them to gain entry via the receptors that they are adapted to bind to. By targeting those areas with vaccines, we should be able to develop vaccines that confer some immunity from which the virus cannot easily escape. I would be very interested in Professor Power's view on this.

Lord Hollick: Do you share that optimism, Professor Power?

Professor Ultan Power: I share a lot of it. The virus does seem to be evolving rather slowly so far, but it is very early days. We are only six months into the pandemic. We have only known the virus for a very short

period of time. In general, the history of viruses tells us that viruses tend to mutate towards symbiosis with their host. They become less pathogenic as they develop over time, because it is not in the virus's interest to cause a lot of mayhem and destruction. If it did that, it would not be able to pass from one person to another or one host to another. It would defeat its own raison d'être if it was not capable of transmitting easily from one person to another.

Having said that, it takes only one slight mutation to make a devastating change, positively or negatively, either for the host or for the virus. As Professor Openshaw said, we are in a position to look at that in detail as it happens, as it unfolds. From a virological point of view, it is extremely exciting to be able to see that happen.

Professor Arne Akbar: When we think about mutations of viruses, we always assume the worst: that they will cause even more devastating consequences than they are causing already. I am not saying that I totally agree with the data, because I have not seen the detail, but there are a couple of groups, one in Italy, saying that the viruses may be mutating into a less pathogenic form. Somebody in Italy has said this twice now, backed up by somebody else. There is another group also saying this elsewhere; I cannot remember exactly where. Mutations could go both ways. Yes, they could be even worse than they are now and cause disease, but they could also mean that the virus will become less virulent at some stage. We do not know yet.

Lord Hollick: To what extent can the developers of a vaccine mitigate the risk of mutation? Can they get a step ahead of the virus?

Professor Peter Openshaw: We try to do this with influenza. Trying to predict where a virus will go next is a great skill—an art and partly a science. Some very sophisticated people look at the antigenic map, the landscape, in the population to see where the weak spots are and where the virus might have to go next to find fresh territory. This is done twice a year for the northern and the southern hemispheres to try to anticipate where the virus will move according to the immunological susceptibilities of the population.

We do not know that that will be the case with the coronaviruses because, as I said, they are not driven so much by the immunological susceptibility of the population, as far as we can tell. Watching the mutations is very helpful in trying to study the epidemiology of the virus and to work out which strain or sub-strain has caused a particular little outbreak locally or whether an outbreak in, say, a care home is due to several different introductions. That is very useful information, but it does not usually have much impact on the immunological responses.

Professor Ultan Power: One of the big disadvantages of influenza is that it mutates very, very frequently, but one of the big advantages is that we know what the correlates of protection are. For this coronavirus, for SARS-CoV-2, we do not yet know what the correlates of protection are—is it a certain level of virus-neutralising antibodies, et cetera?

If and when we get that information, with the technology that is currently being used to develop vaccines we could be in a position, like we are with influenza, whereby new vaccines can be prepared rapidly if we know what the correlates of protection are and we can develop the vaccines in a much shorter period of time than we have for this original virus vaccine.

It remains to be seen how that will pan out in terms of biomarkers and markers of protection, but if we understand those, the possibility of developing and mitigating any new strain that might develop will be greatly enhanced.

Professor Arne Akbar: Professor Power touched on this, but the speed at which vaccines are now being developed is unprecedented—we know that. This is much quicker than a vaccine that has been produced for anything else. That is an example of the community coming together and working together to try to build knowledge.

I think you have heard that the immune system is very complicated, with many different aspects. Not one person can be an expert in all the different areas. There are things that I do not know about which Professor Openshaw and Professor Power are much better versed on. There are also many other subtypes of immunity which none of us knows all the details of.

That is why it is great that the Academy of Medical Sciences and the British Society for Immunology brought together a group of scientists with different expertise to discuss the immunology of Covid-19. This has come together very quickly. We produced a paper for SAGE, which you may have seen, on the immunology of Covid-19, which I had the great pleasure to chair. This was people from the immunological community, with different expertise, all coming together. This will surely be a prototype or blueprint for the future of how we should work together to try to solve the problem quickly and effectively, with a range of different expertise.

Lord Hollick: Is that collaboration also happening on an international scale?

Professor Arne Akbar: There is some dialogue going on, but I think the general feeling right now is that we need to get our own house in order before we start looking at other people's areas of expertise and the way they are dealing with different problems in their own way.

Q86 **Lord Kakkar:** I turn to the issue of antibody-dependent enhancement. First, perhaps Professor Akbar, Professor Openshaw or Professor Power might be able to explain to us the mechanisms by which antibody-dependent enhancement occurs, and then turn to the question of whether there is a risk for this with any of the vaccination strategies that are currently being proposed for SARS-CoV-2.

Professor Peter Openshaw: It has been a concern for a number of viruses. The most obvious example is Dengue. With any of the four strains of Dengue virus that are circulating in different parts of the world, the first infection is often relatively mild and causes a low-level, flu-like

illness. The great fear is that, on encounter with another strain of Dengue virus, there will be some cross-reactive antibody that does not neutralise but causes enhanced uptake of the new Dengue virus into cells, particularly into antigen-presenting cells like macrophages.

It is a sort of Trojan-horse mechanism that allows the virus to gain augmented entry into the very citadel of defence. The virus can then multiply within those cells, having gained entry via this Trojan-horse effect. Then there is a higher risk of what we call Dengue haemorrhagic fever, where there is a massive release of cytokine mediators, blood pressure drops and platelets become depleted, and there is quite high mortality. That is the classic example.

In the field in which Professor Power and I work, which is immunity to childhood viruses, there are examples of vaccine-augmented immunity with RSV. The mechanism is a little different there; the role of immune complexes in RSV augmented disease is rather controversial, but it has been seen. One of the reasons why we usually proceed with such caution in developing vaccines is that we do not want to see this happen.

There are examples of immune augmentation with coronaviruses, particularly in feline peritonitis—peritonitis in cats. It is quite a common disease, for which vaccines were attempted. That caused an augmented progression of the peritonitis. Another clear example within coronaviruses is that there can be augmentation due to prior immunity.

A really intriguing study done in Kilifi, Kenya, followed natural coronavirus colds. It found that there was limited protection that lasted about 80 days. Then, in people who became re-infected with the same coronavirus which they had previously been exposed to, the virus replication was increased. That was a concerning study but a very intriguing one.

So it is a live question. We are really hoping that it will not be a problem with this coronavirus, but we are keeping an eye on it. It is a very important immunological question.

Lord Kakkar: Have antibodies that are typical of an antibody-dependent enhancement been seen in samples from patients who have been infected with the SARS-CoV-2 virus?

Professor Peter Openshaw: It is difficult to know how to measure those antibodies. There are studies that can be done in vitro, where the antibody is diluted progressively until you get into a zone where the antibody is not sufficient to cause neutralisation but can cause some enhancement in cell culture. It is not clear really whether those are a true corollate of antibody enhancement, or how much they are in-vitro artefacts.

Lord Kakkar: How might antibody-dependent enhancement manifest itself in this particular infection? You gave the example a moment ago of uptake for a different virus into macrophages. Here—I think you have spoken about this elsewhere—there is the capacity for the virus to be taken up by endothelial cells and for the spike protein to be expressed on the endothelial surface. This might represent in some way the thrombosis phenotype that is seen in these patients, with more vessel expression of

spike protein and interaction with platelets.

What might the implications be for ADE of enhanced uptake into the endothelial cells as a consequence of vaccination?

Professor Peter Openshaw: These are unknown but quite important questions. We are kept awake at night worrying how to explain the more systemic pathology that is seen in some of the more severe cases. Whether this is fragments of virus that are being released into the circulation and which then become adherent to the vascular endothelium during recirculation is not really clear.

A lot of the pathology in the lung is on the pulmonary arterial side, rather than on the pulmonary venous side. You have to wonder how the mechanism works. Is it that, whatever it is that is triggering this response, is coming out and then going back via the arterial circulation into the pulmonary arterial supply? It is very intriguing, but as yet I do not think there is any great clarity about exactly what that immunothrombosis is triggered by and how we can best interfere with it.

Lord Kakkar: I turn to Professor Power and Professor Akbar with regard to the potential concern about ADE.

Professor Arne Akbar: One cell type that has been shown to cause a lot of inflammation in Covid-19 is the monocytes that infiltrate the lung. Following on from what was said by you and Professor Openshaw, if macrophages have been infected by the virus, are they causing a lot of inflammation? The virus might be getting into the macrophages through ADE, but is that creating an inflammatory macrophage or not? Unfortunately, we do not know yet, but these are things that need to be looked at. Hopefully, before too long we will be able to understand this.

One thing that is really lacking, as I think Professor Openshaw has hinted at already, is that we really do not know much about what is happening in the lung itself. We are guessing, from animal studies and previous experience, but essentially we cannot look very easily in the lungs of patients with severe Covid-19.

Where material is available, we can look immunohistologically at what cells are present, which cells harbour the virus, which cells are in close proximity to each other, and, more importantly, which cells are close to the blood vessels that are causing all the micro blood vessel issues. But until we know more about that, we cannot get a full picture of what is going on.

There is no easy way around this. On the one hand, you could work on cadaveric tissue from people who have unfortunately succumbed to the virus. Here, with consent, you might be able to take part of the lungs to actually see what is going on in there. With other techniques which clinicians use, to put in ventilators et cetera, you can get hold of small bits of lung tissue; Professor Openshaw knows much more about this than I do.

Each group that works on this in different hospitals will have access to a few samples only. What we really need is a consolidated effort, where

people with these small numbers of samples get together and share the material. If you share the material around the country, instead of having five or six samples you suddenly have 30, 40 or 50. We are now trying to work towards having an integrated consortium of immunology researchers who will share material, for the greater good, so that we all understand together what is going on. While each group will not produce enough to have a definitive answer, collectively you might be able to do so.

Professor Ultan Power: This is a very intriguing area, not just from the point of view of a vaccine but from the point of view of the immunopathogenesis of the virus, where it remains poorly understand exactly what is happening. I find very intriguing that those who get the most severe diseases have, in many cases, the earliest seroconversion and the highest antibody titres.

That begs the question whether they are producing the wrong kind of antibodies that are not resulting in good protective immunity to block the infection and are poorly co-ordinated with their innate immune response that dampens down the virus infection, or whether those antibodies are enhancing the pathogenesis, facilitating the virus entering cells that it might not normally enter. That remains to be studied. It is a big and very intriguing area that requires a lot more study

Lord Kakkar: Is there a greater risk for an individual who is prone to ADE of having a very high exposure to the virus in, say, their second run? If this were to be an important but unpredictable problem, and we were to start vaccinating lots of front-line workers as an immediate priority, might individuals who have a very high exposure to the virus subsequently be at greater risk?

Professor Peter Openshaw: That is such a difficult question to answer. My own hope and expectation is that the ADE problem will not prove to be major. It is so difficult to predict at present. We immunologists worry about it a lot. I am hopeful that at least one of the many vaccine approaches that are being developed, and which you will hear more about later today, will produce some good, solid, protective immunity and will not cause this immune enhancement. That is my optimistic view: that this will be effective.

To follow up on what Professor Akbar said about the collaborative approach being taken in this country, it is great to see people working across barriers. Professor Dame Sally Davies, for example, has deliberately enhanced this country's infrastructure for doing clinical research. That has flowed through to the collaborative approach that we, as a nation of scientists, have taken in our response to this. I would like to highlight that, and the role of NIHR in particular, in promoting really good translational research.

In the ISARIC-4C study, centred in in Liverpool and Edinburgh, which I am a co-lead for, we have managed to recruit 45% of all the patients with Covid coming into hospital. That is unprecedented; they could not do it in any other country. We are world leaders because of that collaborative approach, which is wonderful to see.

Lord Kakkar: I have two questions about something Professor Akbar said about the ageing immune system. First, is there any particular anxiety about some of the adverse toxicities of vaccination, such as ADE? Secondly, for those who have autoimmune disease, is there anything about the behaviour of the cellular immune system that might give us cause for greater concern?

Professor Arne Akbar: I know of no evidence that ADE is enhanced in older people, especially with Covid-19. That is not to say that it might not appear in due course. The problem with Covid-19 from the perspective of patients with rheumatoid arthritis is that, if you have a full-blown inflammatory syndrome, which appears after the infection in some patients, it will cause more inflammation in every other situation as well. We need to tackle the inflammation. What is the source of it—where it is coming from? When do you dampen it down in older people: early or only when it becomes a problem? We do not know the answer to these questions yet.

Q87 **Viscount Ridley:** I want to press you a little more on the question of the virus being pre-adapted to human beings. Nikolai Petrovsky in Australia has shown that the virus has greater affinity to human receptors than any other species he has tested. This has led him and others to argue—

The Chair: Professor Openshaw, is it pre-adapted to humans?

Professor Peter Openshaw: We could have a very long discussion on this. It is important to point out that the virus has no intent: it just mutates at random, as Lord Ridley will know. It just happens to be very avid in its binding to that particular receptor.

Viscount Ridley: I was going to ask whether this does not suggest that it has been in human beings for a long time, either in a subclinical manifestation in a rural area or perhaps in cell lines in a laboratory. That is the debate that is occurring.

Professor Peter Openshaw: Right. As Jacques Monod would say, chance and necessity. I think this is chance.

Professor Ultan Power: I agree. I think this is totally haphazard.

Q88 **Baroness Blackwood of North Oxford:** I just wanted to follow up on the questions from Lord Hollick and Lord Borwick on the longer-term mutation of the virus. There are contradictory theories about whether infectivity is increasing and severity is decreasing. I wonder if you could comment on that.

Professor Arne Akbar: I think Professor Power is better placed to answer that question.

Professor Ultan Power: Again, this is the part of the evolution of the virus that is happening in real time, and we need to follow it carefully. I do not think the evidence is clear at this stage that there is more infection with less severity. There is probably more testing at the moment, so we are picking up more virus than we did before.

The evidence for evolution is not clear at this stage. I think the virus is evolving very, very slowly so far—thankfully, from a vaccine point of view—but I am not convinced that there is a lessening of severity at this stage.

Q89 **Lord Winston:** Can you give us some indication of the lifespan of memory T-cells? Why is it so short?

Professor Arne Akbar: Memory T-cells divide a lot when they encounter their cognate antigen, and when they divide they shorten their telomeres to a point where they stop growing. So memory T-cells have a finite lifespan in general. If you exhaust all your very important cells through continuous simulation, you will be left with more and more cells that have less and less specificity as you go on with the infection. This applies especially to persistent viruses like cytomegalovirus. We do not know about Covid-19 yet, and this is data that I will be really excited to hear about when it actually appears.

The Chair: Thank you very much, all three of you, for a most interesting session. We very much appreciate you making time today to speak to us. We have learned a lot.

The Committee suspended for a minute's silence.