



Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Monday 29 June 2020

3 pm

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

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Questions 101 – 108

Witnesses

Professor Peter Horby, Professor of Emerging Infectious Diseases and Global Health at Nuffield Department of Medicine, University of Oxford; **Dr Sir Michael Jacobs**, Clinical Director of Infection at Royal Free London NHS Foundation Trust; **Dr Sheuli Porkess**, Executive Director, Research, Medical and Innovation at Association of the British Pharmaceutical Industry.

USE OF THE TRANSCRIPT

This is a corrected transcript of evidence taken in public and webcast on www.parliamentlive.tv.

Examination of witnesses

Professor Peter Horby, Dr Sir Michael Jacobs and Dr Sheuli Porkess.

Q101 **The Chair:** Good afternoon, everyone, and welcome to this evidence session on therapeutics. Sir Michael Jacobs, Professor Horby and Dr Porkess are our first three witnesses. Viscount Ridley has sent his apologies. As well as lots of other people who might be watching on live stream, we have our clerk, Simon, Amy, Cerise, and our adviser, Professor Ibrahim Abubakar. Keeping me right is Jack Harty, and I think, but I do not know for sure, that Mr Nick Besly is joining us later. Welcome, all.

I will ask the first question. Could you outline, rather than give details of, the different kinds of therapeutic drugs that could be used for the treatment of Covid-19, such as antivirals, antibodies, and HIV or cancer drugs? Should we also look for novel therapies? What might they look like? Or might repurposed molecules help in the treatment of Covid-19?

Dr Sir Michael Jacobs: One way to frame this question is to say that, conceptually, there are two ways to treat this infection. The first is to target the replication of the virus itself, either directly or indirectly. The second is to ameliorate or prevent the effects of the virus on the body that cause the severe disease. Those are two very different things.

There are lots of different drugs that might play into either of those two mechanisms. There are a lot of repurposed drugs that are likely to be able to impact on the pathophysiology of the disease—the inflammation and other effects of the virus—but the drugs repurposed to act as antivirals are not very promising, so it seems likely that we will need new drugs for treatment, particularly in the antiviral space.

Professor Peter Horby: I agree entirely with Sir Mike. There are also different categories of host-directed therapies—the non-virus ones. There is a big range of anti-inflammatory drugs to choose from and many of them are being evaluated. There are other features of the disease that are slightly different from what we have seen before. We are seeing a lot of blood clotting in these patients, so there may also be a chance to improve survival by looking at anticoagulant drugs.

There are a number of ways to address the damage which the virus causes, as Sir Mike said, but the agents acting on the virus are less promising. Convalescent plasma, which is an old-fashioned treatment that is directed at the virus, may be a beneficial avenue to follow.

Dr Sheuli Porkess: I am here representing the research-based industry, which at the moment is working across the board on all types of therapeutics in a range of modalities, including antivirals, antibodies, and immune modulators, and looking at both repurposed and novel therapeutics. To give a sense of the scale, as of Friday 26 June, there were 432 drugs in the pipeline to treat or prevent Covid and over 2,000 ongoing clinical trials. The majority of those 432 are in the preclinical stage, not yet in clinical trials.

On the question about repurposed and novel therapies, repurposing medicines is a very helpful first step, but it needs to be complemented by developing specific therapies. As other panellists have alluded to, there is a range of health issues associated with Covid. We do not know what long-term health issues there will be for patients who have had Covid. As we learn more about it, we will need to develop more medicines so that we have the right selection of treatments to give to patients at the right time. Repurposed therapies can give us answers in the shorter term, but we also need to look at novel therapies that can give a more tailored response and the range of therapies that we will need.

The Chair: Are there any particular challenges with developing novel therapies for Covid-19?

Dr Sheuli Porkess: Some challenges are general to a medicine's development and some are specific to Covid. When developing a novel therapy, you are looking to answer three questions: does it work, is the safety profile acceptable, and can you manufacture a formulation that works for patients and keeps the quality the same dose after dose?

One of the key issues at the moment is matching the research to where the disease is. As the virus spreads and is suppressed in various countries and regions, how do you match the research to where the patients are? How do make sure that you have the highest patient safety standards while conducting the research and development at pace?

On the question of efficacy, this is a new disease, as I said, and we do not know all the effects yet, so how do we make sure that we really match the emerging science with the ongoing research?

On transparency, there is huge amount of research going on across the board into how to make sure results are available quickly.

Lastly, how do we make sure that we can make the formulation, manufacturing and distribution to patients at scale and at pace?

Professor Peter Horby: One needs to take a dual track on the repurposed drugs and the novel therapeutics. The beauty of the repurposed drugs is that we know a lot about them already. We pretty much know the safety profile of them. There might be slight anomalies in patients with Covid, but in general we know very well how they work and what the side-effect profile is. So we can do it at scale with less concern about safety than you would with a novel drug, where you would have to go much slower because you really do not understand the safety profile at that time.

As we have seen with dexamethasone, there is a benefit to be had from some of the repurposed drugs, but you need to do both in parallel. Slightly different development programmes are needed.

The Chair: Sir Michael, if I understood you correctly, you felt that developing antivirals might be a difficult task.

Dr Sir Michael Jacobs: It was not so much that it was difficult but that it was an essential task. The antiviral drugs that we have in the cabinet already are unlikely to be very effective for this disease. None of them

was designed specifically for it. The difference with the anti-inflammatory drugs and the antithrombotic drugs is that we have a vast panoply of drugs that work in that sort of way and it is very plausible that some of them will be beneficial in Covid.

One of the great difficulties is that we do not understand the pathophysiology well enough to make a good guess about which ones will be the best drugs to use. At the moment, a lot of the testing is somewhat empiric. Obviously, as knowledge evolves, we can get a bit more precise.

Two things are coming out clearly from this discussion. First, when you are dealing with a pandemic, time is new feature in drug development. Usually you are worried predominantly about whether a drug works and is safe, but here there is an issue of time if we are going to have an impact. So we need to use innovation to speed up the development of drugs. There are various ways of doing that, both in the preclinical phase and when it comes to human testing. It is very important that we look for new drugs as well.

The second thing that comes out clearly, even from the discussion so far, is that it is very unlikely that we are looking for a single, silver bullet here. We are talking about various drugs, maybe in combination, for different patients in different stages of disease, and we are going to need a toolkit to help us to treat these patients most effectively.

Q102 Baroness Young of Old Scone: I will ask about antiviral drugs and what mechanisms they target. Could you cast some light on how successful we have been at finding therapeutics to treat viral infections in the past? Are there any antivirals that are effective against more than one virus, and how do they work in particular? I take Sir Michael's point that this may be a very difficult task, and some of the pre-existing antivirals may not have efficacy in this case.

Professor Peter Horby: There are many different stages. If you take it through the life cycle, there is the attachment of the virus to the surface of the cell and then bringing the virus into the host cell, because the virus is a parasite—it replicates within human cells. Then there is the machinery within the cell to replicate the virus, and there are various enzymes in there which are involved in the replication process. Then there is the release of the virus from the infected cell, so it goes on to infect other cells.

There are various antivirals that act at different points. Some bind to the outside of the virus so that it can no longer bind to the cells—that is the way convalescent plasma or artificial antibodies work. Others will bind to the receptor on the surface of the cell to prevent the virus attaching to the cell. Then there are ones that interfere with the enzymes in the cell: protease and polymerase inhibitors. Some of those are being tested at the moment; remdesivir, a drug you may have heard of, is one of those, and one of the HIV drugs we have been testing works on the enzyme's replication. Then there is exit from the cell; with influenza, for example, there is a drug that works at that stage. So they can work at all sorts of different stages in the virus life cycle.

Some of the drugs may work across different viruses. If the viruses have similar enzymes—a similar polymerase or protease—an inhibitor of those enzymes may work for more than one virus. Some of the drugs work, say, on preventing the virus getting into the cell, like hydroxychloroquine or chloroquine, and because it changes the pH of that process that is a generic activity, so it may work for many different viruses. So some are highly targeted while others are more generic and may work across multiple viruses.

In general, there are some good antivirals against chronic and long-standing viral infections, where you have a long time to get the drug concentrations and to impact on the replication. But we have had far less success with acute viral infections: those that are very short and aggressive. They are much more difficult, because you have a narrower therapeutic window. We have not had much success with antivirals for acute infections. Sir Mike can also give insight on this side of things. For hepatitis, HIV and other things, the antivirals are good. For acute infections like influenza they are not so good, particularly when patients are already quite sick.

Baroness Young of Old Scone: So are you as pessimistic as Sir Michael about this approach?

Professor Peter Horby: No. What makes me less pessimistic is the experience with Ebola, which is a very acute, very severe viral infection. Some of the synthetic antibody products, which are effectively antivirals, surprisingly worked rather well. If you can do it in Ebola, you can do it in Covid.

Dr Sir Michael Jacobs: I think my pessimism has been misunderstood. Antivirals are absolutely the key to this. It is just that they will not be repurposed antivirals—things that were designed for other viral infections—which will unlock this. It will be new antiviral drugs that are designed specifically with Covid in mind and tested for SARS-CoV-2. I really would not want to give the impression that antivirals will not be helpful; they will be absolutely fundamental to the treatment of this.

All the antivirals that we use in the clinic have been designed for specific viruses. We use anti-HIV drugs for the treatment of HIV, anti-hepatitis C drugs for the treatment of hepatitis C, et cetera. We are only now entering an era where we are conceptually thinking about broad-spectrum antiviral agents that work across lots of different virus families that are unrelated to one another. Because those are relatively new, we do not have them in the clinic yet, so they are at a very early stage of testing.

That plays a little into the fact that we could have been a bit better prepared for this. One of the ways in which we could have prepared is to have developed a sort of antiviral toolbox, where we have a matrix of compounds that we know treat various virus families, such as coronaviruses or influenza viruses—all the things that we could have imagined would cause outbreaks—so that when they occurred we would then have been able to test them in humans and see whether they were

really effective in the treatment of disease. We were not that well prepared conceptually for this, but we can be in the future.

Baroness Young of Old Scone: Dr Porkess, what proportion of the list of trials and pre-trials that you summed up for us at the beginning of your evidence are in the area that Sir Michael just talked about: the novel therapies in the antiviral sphere?

Dr Sheuli Porkess: I do not have those figures to hand now; we can send something in later. I wanted to build on the comments made by the other two colleagues about lessons learned from other viruses that we have developed medicines for. HIV is an interesting one to look at. Obviously, it is a different type of virus and a different set of diseases and symptoms. But if you look at the history of how we have developed antivirals for it, over time they have got a lot better. The first sets of treatments had quite severe side effects and needed lots and lots of tablets and regimes, and over time that has become a lot better as the industry has refined what it does.

So there are lessons to be learned. There is certainly a body of expertise within the industry on developing agents for viruses, and we need to make sure that we build on that expertise and that industry and academia work together as effectively as possible.

Q103 **Lord Winston:** Dr Porkess, can you tell us what specific antivirals have been produced that are effective against SARS-CoV-2?

Dr Sheuli Porkess: I would highlight the example that Pfizer is building on. The research community is building on its learnings from Ebola, MERS and SARS, and Pfizer is building on its research effort against SARS in 2003 to identify a lead protease inhibitor that has shown antiviral activity against Covid-19. It needs to go through the research process and complete the preclinical testing, but then it will look to start a clinical trial of the lead molecule in quarter 3 of this year.

Lord Winston: What is the mechanism by which this particular antiviral works?

Dr Sheuli Porkess: It is a protease inhibitor. We can get more information to you on that.

Lord Winston: Would you be kind enough to give us some idea of the side effects that concern you with these sorts of drugs generally, and perhaps with protease inhibitors in particular?

Dr Sheuli Porkess: Understanding the side effects as a general concept absolutely needs to happen. I am sure that my colleagues on the panel can give some more insights from the clinical perspective as to specific things that they are looking out for in the research.

Lord Winston: Professor Horby, would you like to talk about the stage when we might give these drugs? How early can we expect to use them, and is earlier better than later?

Professor Peter Horby: It depends on what drugs you are talking about. With the antivirals, earlier is definitely better than later. Probably

the closest analogy is influenza, where the neuraminidase inhibitor class of drugs works very well for prophylaxis and pretty well in early treatment for mild cases. They do not work well at all in hospital, and that is likely to be the case with antivirals.

We see with Covid that there is a very clear stratification of risk by age. A really good approach would be an easy-to-take antiviral—a tablet—that has few side effects, can be used with lots of other drugs, and prevents people getting in to hospital. That is much better than trying to rescue someone once they are in hospital. Once people are in hospital, combination therapy would be the favoured approach, targeting the virus plus the inflammatory and other complications at the same time.

Lord Winston: Sir Michael, I am sure you have some things to add to this conversation. Could you also give us some indication of the strategy for designing a specific antiviral that might be effective against this? We have heard about protease inhibitors. Would you like to expand on that a bit?

Dr Sir Michael Jacobs: I do not work in the preclinical drug development space, so I am talking at a very conceptual level here. Going back to what Professor Horby said earlier, the vast majority of antiviral drugs directly target some critical function in the virus life cycle. The most common target is the replication of its genetic material, which requires specific mechanisms, separate from the cell mechanisms. That is where most antiviral drugs have worked in the past. As you have already heard, there are enzymes, such as proteases, that viruses need in order to function. They can be targeted as well, as can be some other functions such as entry of the virus into the cell or assembly of the virus, or release of the virus from the cell.

Those are all things that act directly on viral targets, but you could also design antiviral agents that affect the host functions which the virus subverts in order to replicate. That is a different group of drugs, much less common at the moment in use, but a big future field of research. Not least, that might answer some of the questions about getting broad-spectrum antiviral agents by targeting crucial host functions that a virus uses—for example, to enter the cell—which might be common to many different virus families.

Lastly, you can have an antiviral effect by stimulating and boosting the immune system. The traditional example of that is the use of interferon, which acts through the human immune system, as an antiviral.

Those are the fundamental ways. At the moment, most of the energy will go into looking for directly-acting antiviral agents. That is often done by screening lots and lots of compounds against the virus.

Lord Winston: One final question, if I might. What about the risks to these compounds when you might have a virus that is mutating, possibly like Covid?

Dr Sir Michael Jacobs: Resistance is always an issue with antiviral drug development, because viruses can mutate rapidly, particularly RNA viruses like SARS-CoV-2. When you develop drugs, you test them

rigorously in the preclinical development phase to see what the barrier to resistance is. You stress it, basically; you grow the virus in the presence of the drug, at subtherapeutic concentrations, time and time again, to see whether it can develop mutations to escape.

Resistance may be considerably more important in chronic viral infections like HIV and hepatitis C, where you are talking about much longer-term treatment and the virus being exposed to the drug for a long time. If we were to give people with SARS-CoV-2 an antiviral treatment, you might envisage treating them for three or five days early on in the illness. Whether that is important in creating resistance is less clear. Even if it does, we are not sure whether the viruses that have mutated can then pass on to other people and whether they are as fit as the virus you started with. If they are not, they will not survive in the population. It is a bit unknowable, and may be less of a problem than with things like HIV and hepatitis C.

Lord Winston: Those are all very useful answers. Thank you.

Q104 **Baroness Walmsley:** Thank you. Talking about host functions, what treatments are available that help boost the immune system's response to infections? On what immunological principles are such treatments based? For what conditions are they most commonly used?

Dr Sir Michael Jacobs: Boosting the immune system is very specific thing and not something that we really do in clinical medicine, with the one exception of using interferon for the treatment of virus infections. It is a bit of a blunderbuss treatment, and it is not clear how well it will work. The reason for that is that viruses have all evolved to escape from the interferon system. We all have interferon. It is a very powerful antiviral. In fact, you probably cannot be a successful virus unless you know how to get around that system. It is very unclear whether giving more and more is going to work.

Just to disaggregate something, we sometimes give people antibody treatment. Antibodies are part of the immune system, but they do not boost it; it is actually called passive immunisation. We are bringing forward a natural process that is going to occur, so that if you are infected with SARS-CoV-2 you will develop antibodies but you will do it much later, when you recover from the illness.

The question is whether giving the antibodies early in the illness speeds up the recovery or prevent serious complications. There are several ways of doing that. We have touched already on the idea of convalescent plasma, where you take blood from people who have recovered from infection, take the plasma fraction, which you think contains antibodies, and give it to infected individuals. Then, of course, you can engineer antibodies in the laboratory—they are usually called monoclonal antibodies—and give them to people.

The Chair: We will get on to that next.

Dr Sir Michael Jacobs: I will say nothing more about it for now, then.

Baroness Walmsley: Has there been any success in using these

treatments for Covid-19 patients? If so, at what stage of infection are they likely to be of most value?

Dr Sir Michael Jacobs: The straightforward answer is no, there has not yet been. They are an active area of investigation and we simply do not have the data yet to know whether they are effective. If we were guessing when they were likely to be effective, we would come back to the question of how they are working. They work by inhibiting viral replication. The corollary of that is that we assume they will work if you give them relatively early in the illness, but there will be a point later in the illness when they are less likely to be effective.

Professor Peter Horby: The host immune system is a bit of a double-edged sword in Covid-19, it would seem. You might want to boost the immune system early on, but there is also the associated inflammatory system; we are seeing quite severe inflammation, almost the cytokine storm picture, which we have also seen in other serious viral infections of the lung. So at a later stage you may want to dampen down the inflammatory system, not necessarily the immune system, and we have seen some success there.

Dr Sheuli Porkess: I will give examples of a couple of ongoing studies in the UK's urgent public health study portfolio. There are 48 studies in total. Eight of them are industry studies and two of them are phase 2 studies looking at cytokine therapies, but it is too early to tell whether the treatments will work or not.

Q105 **Baroness Sheehan:** Welcome to all our witnesses, especially Sir Michael. We met last year when you very kindly gave me a tour of the quite remarkable infectious diseases unit that you founded at the Royal Free.

You almost answered this question, which is about neutralising monoclonal antibodies. Can you tell us a little bit more about them and how they can be used to treat Covid-19 infection? At what stage of development are such treatments, and how important do you think they are likely to be?

Could all witnesses include in their answers the benefits of monoclonal antibodies over treatments such as convalescent plasma? What risks, if any, are associated with those treatments? That is a fairly comprehensive set of questions.

Dr Sir Michael Jacobs: It is a very comprehensive set. Shall I start with some of them? Forgive me if I missed some of the answers; others can fill in.

Monoclonal antibodies in a way are much more controllable than convalescent plasma, because convalescent plasma depends on harvesting the plasma from people who have recovered from the infection, and the response that individuals get with antibodies is very variable from one individual to another. Even if you pool them all together, you have some uncertainty about the level of antibody in the

sample and whether it is neutralising antibody or not. Monoclonal antibodies are engineered in the laboratory; they are very controllable, and you can give much higher concentrations than you can ever achieve with convalescent plasma.

Monoclonal antibodies therefore have tremendous potential as therapy, and this was shown very dramatically with Ebola, where monoclonal antibodies proved to be an extremely effective therapy. That was the first example of using them in modern times for an acute, severe infection. So one would imagine that you would use monoclonal antibodies as an antiviral quite early on in the course of the illness.

Monoclonal antibodies have some disadvantages in that they are relatively complex molecules to make, they are generally relatively expensive and they are rather harder to scale than other antiviral agents. After all, we are considering using them as a substitute for other types of antivirals. There is, at least theoretically, a risk of a phenomenon called immune enhancement, where the antibodies actually contribute to the disease getting more severe later on. That is only theoretical; it has been described in some animals and we have no idea whether it translates into human disease. There are also some technical steps one can take when making monoclonal antibodies to try to mitigate that risk.

How important monoclonal antibodies will be is a very difficult question to answer. If we were successful in developing a more conventional, small-molecule antiviral drug that was effective and powerful, that would supersede the use of monoclonal antibodies. If we are not, it is likely that monoclonal antibodies will be effective and play a role in this. Whether they are sufficiently scalable to have a big impact on the epidemic, and to treat people very early in the disease—they are relatively difficult to administer—is a different question.

Professor Peter Horby: Convalescent plasma is a good proof of concept, because it is available now and is being trialled in the UK and elsewhere. There is, as we have heard, the possibility of immune enhancement, but it is being given at quite large scales in the US. They have treated more than 30,000 patients with convalescent plasma in the US, but unfortunately outside a trial, so we do not know if it works. That is a good proof of concept while the monoclonal antibodies are being developed, which they are. They will go into healthy volunteers in clinics sometime, probably in July, at least in the US and the UK.

So there is something that we can do with convalescent plasma, and towards the end of the year, or even in the autumn, we may be in a position to try the monoclonals or polyclonals as well.

Dr Sheuli Porkess: There are also some immunomodulatory monoclonal antibodies in clinical trials at the moment that are being repurposed from other uses. They are in phase 2 and phase 3, and we can send details of those.

Dr Sir Michael Jacobs: I want to comment on the issue of convalescent plasma. Professor Horby is absolutely right that if convalescent plasma works, that is very good evidence that monoclonal antibodies may well

work as well. But I do not think that the converse is true, because you can give a lot more antibody, and very specific antibody, targeted at specific parts of the virus, with monoclonal antibodies. If convalescent plasma does not work, it does not mean that monoclonal antibodies will not. They still warrant testing.

The Chair: I thought you said, Professor Horby, that experience suggests that convalescent plasma is found to be effective in the United States, although it is in early treatment. Is that correct?

Professor Peter Horby: No. Well, it appears to be safe. There is concern about immune enhancement. It has been given to a lot of patients and there was no clear signal of immune enhancement, so it may well be safe, but we cannot say that it is effective.

The Chair: I understand.

Q106 **Baroness Rock:** I want to come back to the damage caused by Covid-19. Professor Horby mentioned inflammation and thrombosis. We have heard about damage to the tissues of lungs and other organs. Could you talk about the specific drugs that have been identified as effective for treating this? How do they work? What are the side effects of anti-inflammatories and antithrombotics, in the short and the long term?

Professor Peter Horby: The inflammatory system is very complex and there is lots of redundancy in it. There are lots of bits of the system that you can target. In the RECOVERY trial, we looked at dexamethasone—a steroid that is a bit of a blunderbuss anti-inflammatory, in the sense that it does not target a particular part of the inflammatory system as some of the newer drugs do. To our surprise, it was pretty effective in patients who were sick enough to require oxygen or mechanical ventilation. That shows that there is a significant inflammatory component and you can improve survival by targeting that process.

There are lots of other ways of targeting that. As we have heard from Dr Porkess, a number of monoclonal antibodies that target different parts of the immune system are being trialled. They may be more or less effective than dexamethasone, for example, because they are more targeted, but we will have to wait and see. The big difference is the price. You are talking about hundreds or thousands of pounds versus £5 for dexamethasone. These more targeted drugs would have to show significant benefits to beat that cost-effectiveness profile.

There is a lot of discussion about side effects. The risk-benefit balance changes a lot depending on which patient you are talking about. Patients in intensive care—

The Chair: We are coming on to a much more detailed question. I think Dr Porkess is trying to come in.

Dr Sheuli Porkess: We have talked already today about how our understanding of the disease is still growing. We are also thinking about the long-term effects. From an industry drug-development perspective, it is about understanding the science, the clinical need and integrating the

patient's lived experience—what will be needed when we get people who have had the disease and may be living with its long-term effects.

While we have some medicines that we can use now, if we think about developing future options and novel therapies, bringing those three things together will be crucial. We will need longitudinal healthcare datasets, for example, to understand what we are trying to do. What is the outcome? Is it treating the damage to lungs and other organs, or are there other things that we need to be aware of and develop medicines specifically to treat them?

Again, this absolutely needs industry, NHS and academic collaboration to agree the outcomes that we are trying to address.

The Chair: Sir Michael, were you trying to come in?

Dr Sir Michael Jacobs: No, but I can add a little bit to directly answer Baroness Rock's question about anti-inflammatories and antithrombotics. I reiterate that, when we first heard about this disease, this was not at all the direction of travel we expected. It was very unexpected to find such an inflammatory component late in the disease. All the thrombosis that we have been seeing, which is extraordinarily dangerous for patients, was also a great surprise. I think that we still do not know how to use the suite of drugs we have that treat inflammation and thrombosis. We already have a lot of medicines that will treat those things, but we are not quite sure when to use them in these patients, or which of the various anti-inflammatories and antithrombotics we have are most effective for this.

We still have a lot to unravel, and that goes back to what Dr Porkess was saying. Without understanding the science behind it, it is really difficult to be very precise in our targeting. A lot of the studies that are being undertaken at the moment are pretty empiric. They are broadly thinking about inflammation and thrombosis without really understanding the details of the mechanism. Some will succeed and some will not.

Of course, the triumph in all this is dexamethasone, which we will come on to in a bit. Its extraordinary effect is greater than very many people, including me, would have anticipated. It will be quite an impressive drug that does better than that in its effect size. It is a really big step forward in dealing with the inflammatory side of this illness.

The biggest risk with the anti-inflammatory drugs is if we give them to the wrong patients. Whatever the anti-inflammatory drug is, if we treat people too early, at a stage when viral replication is probably still a very big issue for them, we could make the disease worse rather than better. Again, we do not really understand the transition from the early stage of the disease, from which most people recover, to the later stage when they get the severe inflammation and thrombosis that has been described, which needs treating in its own right.

Nor are we very good at predicting, on an individual basis, who will go through that transition. The vast majority of people who are infected will recover from the illness without any severe complications. When we talk about early treatment of infection, we have to understand that we will

end up treating a lot of people who were never going to get ill with it. We understand the risk factors on a population basis: being older, diabetes, some ethnicities and so on. But it is not very granular and, certainly at an individual level, it is very hard to predict who is going to become severely ill and who is not. That plays into the early treatment group. That is the main worry with anti-inflammatories: that if we treat people too early, we could make things worse rather than better.

Baroness Rock: I would like to ask a supplementary on the issue of milder versus more severe damage. Sir Michael has already answered my question about whether the development of treatments is worth while for people who are experiencing milder illness and the implications of that. Can the other two witnesses expand on that? What is the status of therapies for people who experience the milder illness? Are treatments worth while, or should we not be going down that route? Do you want to come back first, Sir Michael?

Dr Sir Michael Jacobs: Do you mind, because I have given you one side of the coin, which is that you are going to be treating quite a lot of people who were never going to get ill, because we are not very good at predicting that yet.

The other side of the coin is the potential to have a huge impact on the epidemic on a population level, if we can treat people early. We can prevent them from going to hospital and ever developing these severe complications, at least in principle. That is the best possible intervention that we could have, so that is what we are weighing up. Particularly when we talk about scaling treatments to low and middle-income countries, which do not have high-resourced healthcare facilities, interrupting the disease very early on, and preventing severe illness, is even more crucial.

Having said what I said earlier, I am hugely supportive and in favour of the idea of searching as hard as we can for treatments for mild disease that are population-scalable, oral and affordable and that could have a real impact on the epidemic at a societal and population level, not just treating the people who are at risk of dying from this disease.

Baroness Rock: Sir Michael, thank you very much for that clarification. I appreciate it.

Dr Sheuli Porkess: The industry model for developing medicines tends to look across the different severities of a disease. In Covid research, around 700 of the 2,000 trials that I mentioned earlier are looking at Covid pneumonia, and 185 trials are looking at patients who are critically ill. Just over 500 are on patients with severe disease, over 300 are on patients with moderate disease, and 240 are on patients with mild disease. There are also 58 trials looking at asymptomatic patients. So they are looking across the range.

Key to the research is seeing whether treating these patients gives a clinically meaningful result that is acceptable for patients, and whether the benefit-risk profile from side effects is acceptable, and understanding the impact of giving treatment to the population with milder illness. The UK needs an overall strategy for what we want to research and how UK

research will link to what is being researched globally. As I said earlier, the patient population is changing as the disease spreads and is suppressed in different countries. How does our research get the answers we need in the context of a virus that is moving?

Professor Peter Horby: The best approach would be an antiviral in patients in the community who are at risk—the over-50s et cetera. At the moment, though, there really are not many antivirals of much promise on the horizon that would fit that bill, unfortunately.

Q107 **Lord Kakkar:** I turn now specifically to the RECOVERY trial. Can you take us through the principal results, and then perhaps we can explore some of them?

Professor Peter Horby: The RECOVERY trial was set up as a national trial of hospitalised patients, so it is open in more than 175 hospitals in all four nations across the UK. We focused initially on repurposed drugs, because we wanted to be able to look at things that are currently on the shelf that showed some promise, and either throw them in the bin so that we could get on and look at better stuff, or put them into routine care.

We started off with four drugs; at its peak there were six drugs in the trial. So far, we have recruited just over 11,800 patients, so it is a very big trial and it has the statistical power to show a benefit on deaths. We want to improve the death rate and have a really important effect. We have had results from three arms now; I will tell you the result that is going to come out later today—any minute now.

Hydroxychloroquine was one that was widely touted as an antiviral; it has antiviral effects in the lab. We have shown very clearly that it does not work in hospitalised patients. It may even be harmful. That has changed global practice, because it has been used in many countries as a first-line antiviral drug. Although that is a negative result, it is still important, because lots of people are getting that drug.

The second result was dexamethasone which, as Sir Mike said, surprised even me. I thought it might have an effect, but it would be marginal. It actually has a jaw-dropping effect in the right patient group, but it must be in that group. In early patients, it does not have an effect and may even be slightly harmful, but it seems to be very effective in those who require oxygen. I am particularly pleased that, of all the drugs, that is the one that has been shown to work because it is the cheapest and is available in every country. I could not have wished for a better result.

The third drug for which we have the results, which will be announced today, is lopinavir/ritonavir, an anti-HIV drug that interferes with one of the enzymes involved in replication. We have just looked at the results and they show that that is not effective either. That is another drug that has been recommended in the national guidelines of many countries. We have now shown clearly that it does not work either.

Currently we have three drugs left. Azithromycin is an antibiotic but also has anti-inflammatory properties. It would be great if that had some effect, because again it is also widely available and not that expensive.

There is convalescent plasma, and a drug called tocilizumab, which is a monoclonal antibody against part of the inflammatory process, which we are only using in the more severe patients.

So we have three drugs left in and we are currently looking at adding new drugs as we go into the winter.

Q108 Lord Kakkar: That is most helpful, and many congratulations on a remarkable clinical study. The trial specified, a priori, the three principal populations: those not requiring any oxygen, oxygen support, or mechanical ventilation. There is clearly a difference in the results for the three populations. What are the implications of that, specifically with regard to the first two groups, where the determination of those not requiring oxygen and those requiring it can be quite subjective and where the clinical outcomes of dexamethasone for those populations move in two different directions?

Professor Peter Horby: Yes, that is right. It clearly shows that you do not want to give it to people in the community who have mild disease. We have tried to be clear about that. The danger is that people in India or Africa start buying it over the counter and using it in the community. That will be either harmless or harmful, but not beneficial. That is very clear.

The other group is those requiring oxygen. The RECOVERY trial is designed to give answers quickly. We managed to find dexamethasone so that it could be used before we reached the global peak, which is fantastic. That required the trial to be very simple, which means that we have not collected lots of physiological or biological data. We do know the oxygen saturations at which it is recommended in the UK to give oxygen, so we can give guidance—to the WHO, for example—on what levels of oxygen saturation might indicate that you need dexamethasone, even in settings where there is no oxygen.

Lord Kakkar: That is very interesting. Another interesting feature is the duration of symptoms and, ultimately, the beneficial impact of dexamethasone. How would you put that into the broader context of clinical practice?

Professor Peter Horby: There are many interrelated issues: age, disease severity, time since illness onset. Time since illness onset and severity are highly correlated. In the first week, people are having mild replication and mild to moderate illness. They come to hospital in the second week when they have more severe disease, associated with poor oxygenation in the lungs.

It is difficult to tease apart that time window and the severity, because they are basically on the same causal pathway. In the end, we felt that it makes more biological sense to recommend treatment based on disease severity rather than time, because you could be seven days from illness onset and be convalescent. Rather than try to tease the two things apart, we wanted to give a clear message that this drug will work only in the more severe patients.

Lord Kakkar: More broadly, on the protocol itself, and having now had results from three of the interventions, are there ways in which you might develop the protocol and the platform to enhance capacity to deliver important answers to these clinical questions?

Professor Peter Horby: Now we are at the stage where we can move on to more experimental drugs, because they are now becoming available. We can start to build in what we call a phase 2 programme, where we do some of the early testing of a drug that does not yet have a clear safety profile. If we can see that it is safe, we can immediately move it straight into phase 3, the large-scale treatment of patients. We are currently in discussion with a drug company about putting one of the monoclonal antibodies into the RECOVERY trial.

Although we have recruited far more patients than any other trial in the world—nearly 12,000, which is the only way you can get definitive answers—that represents only 15% of all the patients who were admitted over the period when the trial was running. There is still scope to go even bigger and so get answers even faster.

Lord Kakkar: There is, of course, a very hard endpoint in mortality but, particularly in the setting of ITU, there are clearly circumstances in which there is a clinical decision to withdraw support. How could that impact on this type of open-label trial design, or are you confident that the treatment effect is so great that that need not be an anxiety?

Professor Peter Horby: We saw that the average age of those on ICU in the dexamethasone arm was 10 years less than those still on the ward on oxygen et cetera. You are seeing clinical decision-making that the very elderly are less likely to go into intensive care, so the average age on the ICUs is mid-50s to 60s. We do not think there is likely to be withdrawal of care for that group, unless it is absolutely necessary. Ideally, you would have a placebo-controlled trial, but doing that with six drugs across 176 hospitals is just not feasible.

Lord Kakkar: That is most helpful.

The Chair: I think Sir Michael was trying to come in.

Dr Sir Michael Jacobs: I must have that look. I do not think I was. I am happy, though, to say something about the impact of studies such as RECOVERY. I work clinically, and the results of RECOVERY have changed my clinical practice. We treated patients differently from the moment we saw the results. We will use dexamethasone in the patients who we believe fit the profile of those who benefited in the study. It translates very quickly into how we are treating patients across the NHS.

Lord Kakkar: It is a very impressive result.

Professor Peter Horby: The plan is to continue it, certainly for another year. We can get through a lot of drugs and either discard them or put them into clinical practice.

Dr Sheuli Porkess: I echo that it has been great to see the RECOVERY platform set up at speed and pace and delivering important results.

There are two reflections on my side. First, how do we take the learnings from the last three months, when we have done this research at pace and scale, and build it forward? That speaks to my previous point about the UK's strategy and how it links into the global strategy. If we are finding answers in the UK, how does that link to what is happening globally, and vice versa? Now that we have had the first three months, having that strategy will be important for where we go with this next.

Dr Sir Michael Jacobs: By design, large studies such as RECOVERY are suitable only for drugs when you have a good sense of their safety profile. They are late-phase studies. We talked earlier about developing completely new drugs. It is important that they start off in small-scale clinical studies but then get rapidly fed through into larger-scale ones. I emphasise that, because it may have been a bit neglected in the epidemic up to now, where there may have been a slight lack of focus compared with the phase 3 studies.

The Chair: Thank you. We are just in time to finish this session. I thank Sir Michael, Professor Horby, and Dr Porkess for coming today to help us. Thank you very much.