HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Tuesday 23 June 2020

11 am

Watch the meeting

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

Evidence Session No. 10 Heard in Public Questions 90 – 100

Witnesses

Professor Sarah Gilbert, Professor of Vaccinology, Jenner Institute and Nuffield Department of Clinical Medicine, University of Oxford; Dr Ian Gray, Head of Medical (UK & Ireland), Sanofi Pasteur; Professor Robin Shattock, Chair in Mucosal Infection and Immunity, Department of Infectious Disease, Imperial College London.

Examination of witnesses

Professor Sarah Gilbert, Dr Ian Gray and Professor Robin Shattock.

Q90 **The Chair:** I welcome our witnesses to the next session: Professor Gilbert, Professor Shattock and Dr Gray. Thank you all for coming today to help us with our session on vaccines. We are extremely excited to hear what you have to say. Lord Mair will ask the first question.

Q91 **Lord Mair:** How successful have we been historically at developing vaccines for viruses?

Professor Sarah Gilbert: There are many viruses for which we have successful vaccines. We use them and we barely think about them; we do not need to think about the diseases they cause any more. Smallpox has been eradicated and, in veterinary vaccinology, rinderpest has been eradicated—in both cases through the very careful use of vaccines. Polio is on the verge of eradication, and we control measles, mumps and rubella very effectively through the use of a vaccine that deals with all three diseases at the same time. We have a newer vaccine against human papilloma virus, which can cause cancer as a result of chronic infection. That is also very effective. So for many viruses we have very effective vaccines.

But there are other viruses that are more likely to cause chronic infections against which we do not necessarily have vaccines. HIV is the example that first comes to mind—a disease that emerged only in the last century. It was felt that a vaccine would be developed very quickly, but it has turned out that because it is a chronic infection it mutates very rapidly within each individual person, and we still do not have a vaccine against HIV. Some of the other viruses that cause chronic infections—cytomegalovirus, for example—we do not have vaccines against either.

Coronavirus causes an acute infection. It is generally fairly short-lived. It is not highly polymorphic; it is not like flu, which changes its code all the time and keeps coming back in different versions. In general, the prospects for generating a vaccine against the coronavirus are very good.

Lord Mair: What are the factors that make it difficult to develop a vaccine? Do any of those apply to SARS-CoV-2?

Professor Sarah Gilbert: The difficulty with influenza, where we do have vaccines but they are not highly effective, is the very rapid mutation of the surface proteins of the influenza virus and the fact that it can exist in so many different forms. There are many, many different influenza viruses out there, particularly in wild bird populations. So it will never be possible to eradicate influenza A viruses because they will continually spill over into human populations from the zoonotic reservoirs.

This novel coronavirus emerged from the zoonotic reservoir, but that seems to have happened once and is not likely to happen repeatedly. Any virus where there is no zoonotic reservoir could be eradicated if we have a good enough vaccine, but if we have a large zoonotic reservoir, as in

the case of influenza A, it is not possible to eradicate it and we need a good vaccine to deal with it.

Influenza also has the problem of very rapid mutation and surface proteins in many different forms, which means that if you vaccinate with a vaccine that is effective against one of those forms, it will not be effective against all the other ones. So you have to keep revaccinating with a slightly different version of the vaccine. That is not a problem that we are seeing with the novel coronavirus.

Professor Robin Shattock: Professor Gilbert summarises the exact problem very elegantly. We see real difficulties with developing vaccines where natural infection is hard to clear. The classic example is HIV—a field that I have worked in for the past 30 years. Nobody has managed to eliminate the infection naturally themselves, so there is no correlate of protection, no immune example that we can follow.

We clearly see with Covid-19 that the majority of individuals evoke a rapid immune response and naturally clear the infection. With regard to being able to do that with a vaccine, that makes it much more tractable.

Dr Ian Gray: The challenge we have is that the mapping of the structure of the virus can be very complicated, especially if the structure is different from the other viruses that we have already studied. SARS-CoV-2 is such a virus. Added to the challenge is the need to understand which parts of the antigen expressed by the virus stimulate the greatest immune response.

Regarding the difficulties of developing a vaccine, especially for SARS-CoV-2, it is not only understanding how kind of virus works but bringing the vaccine through its development and into the manufacturing phase, where we can produce to scale enough doses to vaccinate all those who need it globally. In essence, it is a complicated process with a lot of challenges.

Lord Mair: Different vaccines give different levels of protection. Can you say why?

Professor Sarah Gilbert: It depends on the virus and the natural immunity that we have to the virus. With some viruses, such as measles, we know that a very low level of neutralising antibodies, which can be induced by a single measles infection, can give very long-lasting immunity. Only a small amount of antibody is required, and if that is present the measles virus cannot reinfect.

We know that with the live attenuated measles virus that we use in vaccines—it is still a live measles virus, but it is safer to use and it induces that immune response without causing disease—the antibodies that are generated by that vaccine are not quite so long lasting as they are by natural infection. If we needed to generate higher levels of neutralising antibodies, that approach would not be appropriate. It is an approach that works for measles.

Nipah virus is another virus and emerging pathogen that causes a highly fatal haemorrhagic disease, but a very low level of neutralising antibodies

against Nipah virus will give complete protection, so that will not be a difficult virus to develop vaccines against.

With some other viruses, it is more difficult to get the level of immunity to get the required protection. For each new virus we need to understand what the immune system needs to do to prevent infection or to rapidly control infection—those are slightly different questions. Ideally, we would like to have sterilising immunity, so that somebody who is exposed to the virus has absolutely no infection at all—the virus does not even start to cause an infection in the body.

What also works is having rapid immune response from the cytotoxic T-cell that responds, so in the first few days after infection we can control that infection and prevent it from spreading through the body before it becomes a serious disseminated infection causing serious disease. We know that that happens in natural immunity to influenza. People can have a very mild, asymptomatic infection without knowing that they have been infected. That kind of protection, if it can be mediated by a vaccine, is also useful. For each disease that we want to make a vaccine against we need to understand what we need the immune system to do to control that disease.

Professor Robin Shattock: There are two issues here. One is potency—the level of immune response that is needed to provide protection. The other is durability—how long will an immune response protect you for? Typically, the vaccines that give very long levels of immunity are attenuated vaccines where the virus can persist for a prolonged period of time. When they are non-replicating vaccines, they often require booster immunisations to maintain that level of immunity.

Covid-19 is a respiratory pathogen, so it potentially requires mucosal antibody responses. It is not just the level of systemic antibodies that may be important; it may be dependent on how much antibody or cellular response gets to mucosal surfaces in order to provide protection.

Dr Ian Gray: I do not have anything to add to what has already been said.

Q92 **Viscount Ridley:** How long does vaccine development usually take? Why have we not been able to speed it up more, and in what ways is this process being expedited in the current situation?

Dr Ian Gray: The classical process for vaccine development can take in excess of 14 years. The process goes through various steps. It starts off at the exploratory stage, where scientists are trying to understand how the virus or bacterium actually works, how it enters the body and how it elicits an immune response. Once the vaccine candidate is identified, we enter the preclinical phase, where its safety is tested in animals. Following that, it goes into clinical phases 1, 2 and 3, where it is tested on humans. Phase 1 looks at safety, phase 2 at how the vaccine works, and phase 3 looks at the efficacy of the vaccine in the human population which the vaccine has been identified for.

This preclinical and clinical process can take up to nine years. Once that occurs, it goes into the regulatory process in which the five modules that make up the dossier are submitted to the regulatory authorities, which then have to test the quality, safety and efficacy of the vaccine before it is licensed. When it is licensed, it then goes into the manufacturing stage. Manufacturing is a very complex process, of course, because vaccines are biologics. This leads to a number of quality control steps; in fact, 70% of the normal production cycle relates to quality control checks. Once it has gone through those checks and is ready for release, we have to get the different countries to approve it.

In essence, the classical approach to vaccine development is long, because of the processes that are in place to ensure the safety, efficacy and quality of the vaccine once it is delivered. In these unprecedented times, we have to deliver a vaccine in 18 or 12 months. This has to take on board the global effort to bring various stakeholders together to work in parallel to be able to do in 12 to 18 months what is normally done in 14 years.

This requires a lot of parallel working across the different phases that I mentioned. While we are working on phase 1, we are starting phases 2 and 3, with manufacturing processes working in parallel while we are coming out of phase 1. This will change how we look at vaccine manufacturing and development in future, but right now the most important thing is to try to make the vaccine available for use in the populations that need it.

Viscount Ridley: Would one of the others like to comment on why we have not been able to speed this up? In the 1930s, whooping cough vaccine went from nothing to distribution in about four years. Is it a failure of investment, or are there physical limits in the time it takes to do these trials that cannot be shortened, although, as you said, we are now trying to shorten them by doing them in parallel?

Professor Sarah Gilbert: We are now speeding these things up a lot by doing a lot of work not only in parallel but in advance. Professor Shattock and I are using what are called platform technologies to make vaccines against the novel coronavirus. This is an approach to making a vaccine that you can then apply to lots of different diseases. The huge advantage of this is that we can know so much about the individual platform technologies—we are using different ones—but we know how to manufacture them before we need to manufacture a Sars-CoV-2 vaccine. We know what the likely dose is in humans; we know what the likely reactogenicity or safety of the vaccination is going to be. We know something about the types of immune responses that can be generated and whether it will be appropriate for the type of virus that we now want to make a vaccine against.

In the past, we used to start on vaccine development by using a pathogen itself, then either making an inactivated vaccine or a live attenuated vaccine from it. Those were both quite slow processes. Because it was new every time and you were starting from a pathogen,

an enormous amount of time was required to be spent on safety testing before you could start to do anything else.

The approaches we are taking now, with platform technologies, only use one of the genes to make one of the proteins in the pathogen. The rest of the technology is already well known. The safety testing does not have to take as long, because we are not looking for all the potential effects of the pathogen itself. The means of manufacture is known. In our case, that was accelerated in the spring of this year. The clinical trials can be accelerated, because we have already seen, from using these technologies to make vaccines against other diseases, what they can do and how they perform in people of different ages and, in some cases, in people with compromised immune systems.

There will still be the need to make a specific vaccine against a new pathogen, which then needs to go through the phases of testing, and we need to do the preclinical testing and look for safety and any possible evidence of enhanced disease after vaccination when the animals have been exposed to high doses of the virus. We still have to do that before we start clinical studies, but we can do it much more quickly than we used to be able to.

Viscount Ridley: Am I right in thinking that CEPI, the Coalition for Epidemic Preparedness Innovations, is focusing exactly on the platforms that Professor Gilbert mentioned? Perhaps we could have done that 10 years earlier.

Professor Robin Shattock: Yes, CEPI has been looking at platform technology. It is unfortunate that we have to respond so early, because it will be a very different world for these technologies in five years' time. This is partly because many of them are very new, so there is not a lot of clinical experience with some of them. That has meant that their entry into clinical testing has been slower.

We also need to recognise that this is an unprecedented event. Classically, vaccines take that long period to develop because they are commercially driven. A commercial company is obviously risk averse and wants to make sure that there will be a return on its investment. There is a very high risk of failure for any individual vaccine approach. What is different here is that, as a global community, over 100—maybe 150—vaccine candidates are being developed. That is like a mini pharmaceutical company but spread across the world, so the risk of failure is being spread by having multiple approaches being developed at the same time.

It is probably not appropriate to compare it to the past. This is an unprecedented situation and there is an unprecedented effort. I suspect that if we have another pandemic in five years' time, we may well be able to do this much faster, based on the lessons that are learned as we do something that has never been done before in responding to Covid-19.

Q93 **Baroness Rock:** I want to come on to the specific types of vaccine that are currently in development for Covid-19. How does each type of vaccine stimulate an immune response? What are the relative merits of

each of the different approaches?

Professor Sarah Gilbert: All the different possible technologies are being used by a company or research institute somewhere in the world. We are throwing everything at it. Among the platform technologies, the one that I am working on is an adenoviral vector vaccine. That uses a replication-deficient adenovirus—an adenovirus that has had some of its genes removed, so that although it will infect the first cell it gets to after vaccination, it cannot then spread through the body and cause an infection. It is very safe to use

It is a feature of the platform technologies that they do not generally spread through the body, so they are very safe, even for people with a weakened immune system. They cannot themselves cause an infection, which is a concern with the live attenuated vaccines developed from the pathogens themselves. They may not be safe in people with some degree of compromised immune systems.

For the replication-deficient viral vector vaccines—I am using adenovirus—we take the gene from the spike protein out of the coronavirus and put it into the adenovirus, and the adenovirus will then make that protein. After you vaccinate somebody, the adenovirus goes inside a human cell. It makes the spike protein from the human coronavirus, but at the same time it is causing an infection in the first cell that it got to.

So it alerts the immune system to the fact that something is going on here, something is not right, something foreign is happening, and look—here is a large quantity of spike protein from the coronavirus. This is what the immune system needs to respond to. This is what it sees as the enemy. That alerts the immune system to make an antibody response and a T-cell response that is directed against the spike protein in the coronavirus, and when that person encounters the coronavirus in future they have antibodies and a cytotoxic T-cell response that can recognise the virus and neutralise it, recognise the first cells that have been infected with coronavirus, destroy those cells, and prevent the infection from spreading any further.

Apart from the adenovirus, people are using poxviruses in a similar way, and we have nucleic acid vaccines—DNA vaccines and RNA vaccines. All those technologies are using the same spike gene to produce the spike protein from the coronavirus inside the human body after vaccination and use that to signal to the immune system that an immune response against this particular protein is required.

We are also seeing the more traditional forms of vaccine development being applied, such as the inactivated virus, which is being done by a Chinese company. That is where you produce large quantities of SARS-CoV-2—under high biological containment; you have to be careful that it cannot escape the production facility—and you use chemicals to inactivate it, check that it is completely inactivated and cannot in itself cause an infection, and then use that as a vaccine, typically with an adjuvant, to strengthen the immune response. There you are using the whole virus, but because the spike protein is on the surface of the

coronavirus, you will get antibodies to the spike protein, again by using that type of vaccine. With the live attenuated vaccine, you make a weakened version of SARS-CoV-2 itself and then use that as a vaccine.

Baroness Rock: Would anyone like to add to that? Could you perhaps also discuss whether previous research into the SARS and MERS vaccines has helped to rapidly expedite the vaccine development for SARS-CoV-2?

Professor Robin Shattock: The previous research into MERS and SARS was extremely important and gave the vaccine effort a real kickstart, because we knew so much about the spike protein on those viruses thanks to previous vaccine attempts, including Professor Gilbert's work on MERS.

We know a great deal about the structural biology of the surface protein and that has allowed many modifications to that protein to lock it in a prefusion conformation, which may be very important for inducing the right sort of neutralising antibodies.

That has been one of the reasons why we have probably been able to move faster than if this were a virus that had never been seen before and was not related to any other virus.

Baroness Rock: Do you have anything to add, Dr Gray?

Dr Ian Gray: Nothing that has not already been said, except that Sanofi is using two of those technologies that Professor Gilbert mentioned, the recombinant approach and the mRNA approach.

To add to what was said about the work that has been done previously on SARS, this has really escalated following the advancements, especially at Sanofi when working on its recombinant vaccine, from the work that has been done previously with BARDA in the US.

Q94 **Baroness Sheehan:** We have heard quite a lot about the different vaccine approaches that your various groups have undertaken and the reasons why some of these approaches were chosen.

Could you say a little bit about the main challenges that you have had to overcome so far? What is the risk that mutations of the virus will affect the efficacy of any vaccine that you develop? You are all vastly experienced in developing vaccines. What promises do your various approaches indicate at the moment?

Professor Sarah Gilbert: One thing that gives us some uncertainty still is that although there are a number of coronaviruses that have infected humans in the past—we have heard about four that cause the common cold, as well as SARS and MERS—we still do not actually know what the immune system needs to do to stop infection by any of these viruses. So we do not know what we call the correlates of protection. For a hepatitis B vaccine, we know that if you immunise someone with the vaccine, you measure the antibodies in their blood and if they have a particular level of antibodies, that person will be protected against hepatitis B, they are safe and they will not be at risk of that infection. We do not have the same information about any of the human coronaviruses.

We are now in a phase 3 trial, and we have started a second one in Brazil, where we are hoping to increase our chance of determining vaccination, because there is much more virus transmission in Brazil now than there is in the UK. As we move through vaccine development and the first vaccines go into efficacy studies, as soon as one of these vaccines is able to demonstrate some level of efficacy—it does not even need to have complete efficacy; it could have a relatively low level of protective efficacy—and we have the answer to what level of immune response is being generated by one of those vaccines and what level of protection that correlates to, that will really help us to understand whether all the other vaccines in development also have a chance and are likely to be protective. If the first efficacy result is that we have a really high level of protection with quite a low-level antibody response, that is really good news, because it means that we can take that piece of knowledge and apply it to all the other vaccines in development.

With regard to concerns about the virus mutating and escaping from the immune response, most of the technologies being used are not employing just a small region of the SARS coronavirus; it is quite a large protein that is being used. We are also seeing, as we have seen in our MERS vaccine development, that when we vaccinate people and generate antibodies and then test those antibodies in their serum against all the different MERS viruses that are out there, it works against all of them.

The number of mutations is really quite small. In addition to the antibody response we are generating a cytotoxic T-cell response, so even if there is less effect of the neutralising antibodies we still have the cytotoxic T-cell response that can recognise other parts of the protein. Coronaviruses do not mutate very rapidly, and so far we have not seen any evidence that this is really going to cause a problem in vaccine development.

Professor Robin Shattock: In terms of mutations, as Professor Gilbert has already pointed out, we do not see evidence that the Covid virus is changing very significantly, which is very promising. If it changes, some of the technologies, such as those that we are using with self-amplifying RNA, are genetic code, so it is very simple just to change that code to take account of any changes that might occur in future.

You also asked about the difficulties that we face. Thinking specifically of the UK, one thing that has been a challenge is UK manufacturing capacity for these vaccines. You are probably aware that the Government have now invested and increased the funding for the Vaccine Manufacturing Innovation Centre that is being built in Harlow in Oxfordshire. Once that is in position, and as long as it is maintained so that it can respond more quickly, in future epidemics or pandemics the UK will be able to get up and running in a much faster fashion. That is promising.

Baroness Sheehan: Dr Gray, I think you were the first person to bring up the issue of advanced preparation for manufacture once the vaccine is developed. Do you want to give your views on whether we are ready to hit the ground running as soon as we get the go-ahead? To what extent do you think ownership of the vaccine, the intellectual property, might hamper those efforts?

Dr Ian Gray: That is a good question. I should state first that the challenge that we are facing is that this is a novel virus, which means that its structure and weaknesses are being discovered in real time and the epidemiological data are limited.

Expediting the development process, including sourcing and securing funding and conducting clinical trials, is also a challenge that we need to overcome. To achieve that, we are collaborating across industry and engaging with regulatory bodies.

You mentioned upscaling. The upscaling of manufacturing has to happen in a limited timeframe. Our aim at Sanofi is to start initial production in parallel with the first clinical study. We have moved from preclinical to clinical studies for our recombinant-based vaccine, and we expect to start phase 1 and 2 in September this year at the earliest, with full approval hopefully in the first half of 2021. The capacity that we are looking to bring from this manufacturing of a recombinant protein-based vaccine is 1 billion doses a year.

We are also working on an mRNA candidate alongside Translate Bio, a messenger RNA technology specialist. Again, we expect to move to phase 1 studies at the start of next year if the data is positive. We will look for approval at the earliest in the second half of 2021. The capacity that we are looking to produce of this mRNA vaccine is in the region of 90 million to 360 million doses.

With regard to scaling up and producing our vaccine, Sanofi, alongside GSK and BARDA for a recombinant-based protein, have the infrastructure in place as big pharma with multiple distribution sites and centres across the world to be able to deliver a vaccine. But, like I said, we have to get through the various clinical phases before we have the vaccine available.

Ownership is a conversation that you need to have later on in the process.

Q95 **Baroness Walmsley:** What type of immune response do you expect the successful candidate vaccine to stimulate? Secondly, we heard in the first session that it is possible that vaccines will be able to confer a greater level or duration of immunity than natural immunity. What effect do you think that should have on our vaccination strategy? Do you agree with that?

Professor Sarah Gilbert: The type of immune response we want to stimulate by vaccination and what we expect to stimulate comes back to correlates of protection again, as I was just saying. As soon as we can understand what type and what level of immune response will protect against the virus, that will help all of us in vaccine development.

With many of the technologies in development we will get both the neutralising antibody response and a binding antibody response, plus a cytotoxic T-cell response and a helper T-cell response that helps to maintain the antibody response.

The best type of immune response, in my view, is one that replicates natural immunity using both arms of the immune system. If you use

some technologies like the inactivated vaccine with an adjuvant, you tend to stimulate the antibody response more than T-cell response. That unbalanced type of response may not be beneficial, but it might also be protective. It will be tested and we will find out.

Sorry, what was the second part of your question?

Baroness Walmsley: It was about whether vaccines would be able to confer a greater level of immunity or a greater duration.

Professor Sarah Gilbert: Coronavirus natural infection does not seem to give very long-lasting immunity. We heard in the first session about the common cold coronaviruses giving very short-lived immunity. In other studies we have done, for MERS in particular, we have measured the immune response up to a year after vaccination and seen that it is very well maintained, which is not what we see with antibody responses or T-cell responses to the coronavirus infections themselves.

So there are grounds for optimism that when we use a different technology to produce an immune response against the same antigen, the same protein from the novel coronavirus, we will have better maintained immunity. It is something that we can know only by testing, but what we have seen from using the platform technologies so far is that they can give long-lasting immune responses and therefore may do better than natural infection.

Baroness Walmsley: Do we know why that is? What is it about the vaccine that provides better immunity than natural protection?

Professor Sarah Gilbert: We do not know in detail. We are beginning to understand that the coronavirus has some mechanisms for evading human immunity and not leaving a lasting signature, if you like, of its infection. The technologies we are using as vaccines do not do that. It is absolutely fascinating to understand exactly what that is, but we do not really need to understand how the coronavirus is evading immunity to use a technology that will give lasting immunity. That might be something that we understand later on.

Baroness Walmsley: Professor Shattock, do you want to add to that? Can you also say how effective at providing immunity a vaccine should be before we roll it out to the population?

Professor Robin Shattock: Professor Gilbert makes a very good point that we want balanced immunity. Most licensed vaccines are actually licensed on the antibody response. With our approach, we are more focused on having high levels of neutralising antibodies. It is unclear what level is required for protection. We know that the response to natural infection is very mixed, so some individuals make quite good neutralising antibodies, some make none at all. Obviously, we think that a vaccine needs to be at least as good as the best responses we see to natural infection.

Another issue is durability. We do not know how high the immune response needs to remain to be protective. It will be very important to have strategies that will allow a booster vaccination if that needs to be

done annually or every five years, particularly for vulnerable groups. That is something that the vaccine community is looking at very actively. It is not just rushing out the first wave of vaccination; it is also having a strategy that might be able to maintain it if that is required—we do not know whether that will be required.

Baroness Walmsley: Dr Gray, do you agree?

Dr Ian Gray: Yes, I concur with both the witnesses.

Q96 **Lord Winston:** I want to ask a very straightforward and simple question but a very important one about the mode of delivery of the vaccine and the various reasons for this.

Professor Robin Shattock: At the moment, most of the vaccines are being delivered by conventional intramuscular injection, because it is the easiest and fastest to get off the starting blocks and into clinical studies.

A number of us are interested in looking at mucosal immunisation as well. Professor Gilbert and I are already in discussion as to how we might be able to move that as a second wave of clinical study. Mucosal vaccination is great if you have replicating pathogens, because they maintain mucosal stimulation. Mucosal antibody responses are often not long lived. We do not really understand how well these approaches will work with mucosal administration. It is important for us to look at that. It might be that mucosal administration only is effective, or it may require a combination of parenteral administration with a mucosal boost. Those are all things that we need to do, but they are slightly behind this first wave of accelerating things into clinical study.

Lord Winston: Dr Gray, from your point of view, looking at the market of vaccines and the ease of administration, clearly an oral or a nasal vaccine might be quite simple to get round and cheaper to administer. Do you want to talk about that?

Dr Ian Gray: As has been mentioned, for speed and purposes of development we too could look at intramuscular injections for our vaccines. Time is of the essence, and we have to use what we have and try to deliver what we can in the space of time that we have. In the future, of course, technology and time will permit us to look at different administrative methods for the potential Covid-19 vaccine, but right now we have to use what we have to get the vaccine available as soon as possible. If that is through intramuscular injection, so be it. If an alternative was available to us more quickly and sooner, of course we would look at that too, but right now we have to work with what we have to get the vaccine available as soon as possible.

Lord Winston: Professor Gilbert, what about the type of immune response with an oral vaccine compared with one given intramuscularly or subcutaneously?

Professor Sarah Gilbert: With an oral vaccine, or particularly with an aerosol or intranasal vaccine, you would expect a much stronger mucosal response, as Professor Openshaw said earlier. That is probably really important in protection against respiratory pathogens. It is also difficult

to study. We are not very good at measuring it. It is hard to get the samples; measuring secretory IgA, for example, is quite difficult, because in taking the sample you tend to dilute the sample and it is hard to know how much of it there was in the first place.

So, as Professor Shattock said, we are interested in looking at delivery to the respiratory tract, by either intranasal delivery or aerosol delivery, which takes the vaccine right down into the lungs where it can access the same tissues that are reached by the virus infection itself. We have to proceed with caution, because it is a fairly new thing to be done with this type of vaccine, and we need to make sure that it is safe.

Some small studies have been done so far with vaccines delivered by aerosol, and of course we have intranasal delivery of the LAIV flu vaccine used in children. Delivering a virus to the nose gets very close to the brain, so we have to make sure that it is safe. By putting it down into the lungs, we are exposing a very large surface area to this new entity. Again, caution is needed in following the initial, very healthy patients whom we hope to study in the coming months to make sure that the method is safe as well as giving us a good immune response.

As the type of immune response that one generates will be somewhat different from that as given by intramuscular injection, it makes it more difficult to understand exactly what we are achieving by this and whether it is more likely to be protective. In one study of a viral-vectored TB vaccine delivered by aerosol into the lungs, it was found that T-cell responses were generated in the lungs and they could also be measured in the blood.

You could also use a lower amount of the vaccine and still get a strong response in the blood—but that did not look at IgA responses, because they are not considered to be particularly important in TB vaccination but they are in respiratory pathogens. We also have to build that part of the study into the clinical trials that we want to do and understand how the different types of antibodies that we might find in the respiratory tract could be generated by vaccination. It may mean that we could have a more effective vaccine by delivering to the respiratory tract, or indeed orally.

Giving vaccines orally is problematic, because we have to get them through the stomach, so they have to be specially prepared, and they then need to induce a response in the respiratory tract. What has been seen with flu vaccines delivered orally, particularly in adenovirus in an enteric capsule, is that they induce an immune response, a secretory IgA response, but a very high dose of vaccine is needed to get that level of antibody induction as compared to intramuscular injection or possibly intranasal injection.

Although oral is very simple for delivery, it may not be the most effective way of inducing immune responses against respiratory pathogens. All these things are possible and there is a lot of work to be done.

Lord Winston: That is a very comprehensive answer. There is some interesting stuff coming out about different genotypes. Could we

speculate briefly? Do you think there may be different vaccines for particular people with a different kind of genotype?

Professor Sarah Gilbert: I do not think we will need to be that specialised. We are starting to see evidence of different outcomes of diseases, but as yet I do not think that we will need to go down the route of different types of vaccine. Across the population and different age groups, we may need different formulations of vaccines. Older people's immune systems do not respond so well, so we may need higher doses or more doses, and for children we might be interested in giving nasal spray vaccines, for example, but I do not think that will need to be controlled for different genotypes.

Q97 **Baroness Young of Old Scone:** How can the effectiveness of a vaccine be established, particularly when case numbers in the population are decreasing?

Professor Robin Shattock: That is a challenge both for me and for Professor Gilbert in doing large-scale efficacy trials in the UK. If the incidence is low, getting the numbers to show that the vaccine works against a placebo will be challenging. You have heard that Professor Gilbert is already running a trial in Brazil, precisely because the number of transmissions is much higher, and we hope to do the same.

It is really about getting those numbers to be able to show whether a vaccine works and to what extent it works: that is, what the level of protection is. We think that a vaccine should be at least 70% protective, ideally higher, for it to be useful in terms of being rolled out.

That is always a nuanced conversation, because, in the absence of any vaccine, something that has low efficacy might have a good role to play. I suspect that some vaccines may be introduced early on, but as we understand how different vaccines work, the level of protection and the duration of protection, there may a change from one type of vaccine to others as we improve on potency and durability.

Baroness Young of Old Scone: Professor Gilbert, how easy has it been to get big populations elsewhere involved?

Professor Sarah Gilbert: When we started planning our vaccine trials in February and March, we were assured by the modellers that if we could get 1,000 people in the UK vaccinated by the end of April, we would be able to demonstrate vaccine efficacy within a month, because virus transmission was low at that time but increasing rapidly.

Of course, because it increased much more rapidly than anyone expected, we had the lockdown, which fortunately reduced transmission but was not so fortunate for those of us trying to develop vaccines in the UK. We now have essentially a very large safety and immunogenicity study running in the UK with little chance, frankly, of determining efficacy.

We have had offers from many countries around the world wanting to conduct vaccine efficacy studies with us. In many of those countries, there is increasing virus transmission. We require a country where there

is a very good, well-established clinical trials unit. We do not need just a hospital with a lot of coronavirus cases; we need investigators who are experienced in running clinical vaccine studies—there are those at the sites that we are choosing to work with—as well as an increasing level of transmission and little prospect of containing it.

There has been no lack of countries wanting to partner with us. We have chosen to work with Brazil because of previous experience of working with the clinical trials team there; we know that they can do a very good job—a high-quality study. We have another couple of studies likely to be announced in Africa—in fact, I think South Africa will start vaccinating tomorrow—and there is another African country also with high transmission or increasing transmission where we will begin trials. Now that our vaccine is licensed to AstraZeneca, it will initiate a clinical study in the US in the coming months. It is aiming for a study of 30,000 individuals. It will decide precisely where in the US based on virus transmission as they get closer to starting that study.

The problem for us is not knowing where virus transmission is now; it is knowing where it will be in four to six weeks, by the time we could have started a study, recruited people, vaccinated them and given them a couple of weeks for their antibodies and T-cell response to develop after vaccination. We need to know where virus transmission will be at that point.

It is very difficult to predict because of changing circumstances around the world. Our approach is to work with multiple countries in different settings to give us the best chance of seeing efficacy in at least one of them. As I said before, as soon as we get a signal of efficacy and can compare that to the level of immunity that we are generating, it gives all vaccine developers really helpful information in establishing whether their vaccines are likely to work as well, whether it would be one dose or two doses, and in older and younger people.

The first efficacy signal will be really important. As yet, we do not know which country will generate that.

Baroness Young of Old Scone: Is there a risk that the whole development and deployment process is moving so fast that there is not enough time to conduct efficacy studies?

Professor Sarah Gilbert: We have to have an efficacy result and we will get it from somewhere. No vaccine will be licensed even for emergency use until efficacy has been demonstrated.

Dr Ian Gray: A challenge we have is that, as of Monday, we had more than 140 vaccine candidates being assessed—going into preclinical and then, one hopes, into clinical trials. It is about co-ordinating the trials globally to ensure that they are all in place and can generate the data required. It is about managing the clinical trials in accordance with the epidemiology and the rate of change that we are seeing every day across the globe and trying to ascertain the data that is best suited and best available for us to bring the vaccine candidates forward.

Baroness Young of Old Scone: Is that being done? Who should be

doing that?

Dr Ian Gray: It is being done. As I say, it is a collaborative effort across the globe. In these unprecedented times, everyone is working together to try to establish the best way to proceed to ensure that we can have our trials conducted in collaboration with relevant authorities and groups, but at the same making sure that we can proceed at speed to get the efficacy data that can then support a licence of the vaccine for use.

Baroness Young of Old Scone: Is there any point in this process at which it would be okay to conduct a deliberate challenge on people who had been vaccinated, just to test that the efficacy results were right—or is that ethically dodgy?

Professor Robin Shattock: My understanding is that there will be a position paper from the WHO on human challenge studies. Of course, the ethical dilemma is that there is no effective treatment for Covid-19. You could argue that it is a low risk in young individuals, but those are not necessarily the individuals we need to protect anyway. There is a theoretical risk that an enhanced disease could occur—that cannot be dismissed—and it is not completely clear that, even if you showed protection against mild disease in young individuals, that would allow you to license a vaccine.

It will not be a short cut; we still have to do the efficacy trial to get the data to be able to license the vaccine. It might allow us to dismiss vaccines that have no chance of working. Even if that was embraced, I do not see that it would provide a step change for us in getting a vaccine licensed and made available globally.

Professor Sarah Gilbert: Human challenge studies will come, but we definitely need the effective therapy. Even if we are testing vaccines and then challenging—deliberately infecting healthy young individuals—there is some risk. They may have a serious infection, and before we start to do that kind of study we need to be sure that if that were the case we would have an effective therapy to treat them. That will come, and this time next year human challenge studies will probably be well under way.

Q98 **The Chair:** Thank you. I move on to a much trickier question. As I understood it—if I have made a mistake, Professor Gilbert, correct me—you feel pretty confident from the trials conducted so far that the vaccine you are developing is pretty safe.

Professor Sarah Gilbert: We are certainly confident that it is safe. There are two aspects to the safety. One is the vaccine technology itself, and we know the type of technology we are using to be safe. We tested it in 12 clinical studies before we started working on SARS-CoV-2. We have seen very good safety results in people vaccinated since 2014; we have been following people who have had the vaccine.

The other aspect is the safety of the immune response that we are generating; we cannot guarantee that it will be completely safe. You may remember the H1N1 flu pandemic, in which there was a widely used vaccine and then reports of narcolepsy in northern Europe. That turned

out to be a real but very rare side-effect of vaccination. It was a very rare autoimmune response generated in a particular subset of the population. That is not the kind of thing you can pick up in early-phase vaccine development, because you have to have millions of people vaccinated before you see any sign of that.

There always remains the risk that there will be some very rare effect of the immune response that we are generating against the coronavirus spike protein, which in a very small section of the population could induce this type of autoimmunity. Unfortunately, there is nothing we can do about that until very large numbers of people are vaccinated. That is where pharmacovigilance comes in. Post marketing, once the vaccination is used on a wide scale, it is important to continue to look for these rare adverse effects just in case they occur, but that cannot be known until we get into vaccinating millions of people.

Professor Robin Shattock: I have nothing to add. We have less clinical experience with our vaccine candidate, because it is a very new approach, but essentially it just uses genetic material, so we think it is likely to have a very good safety profile because it is produced by a fully synthetic process; there are no animal products or cellular processes involved. But as Professor Gilbert said, it is really when you move into the millions that you may see something very rare. You can never predict that.

Dr Ian Gray: As we all know, before any vaccine is licensed for use it has to go through a very rigorous testing process. As Professor Gilbert mentioned, the post-marketing surveillance is of the utmost importance post the licensing and availability of the vaccines. That is when you will start seeing some of the potential adverse effects to the vaccines, if any are present.

Q99 **The Chair:** Let us move on to the population aspect of the vaccination. What do you think is the level of vaccination required to get to herd immunity—knowing, of course, that herd immunity has natural immunity, too?

Professor Sarah Gilbert: We need to know more about the level of efficacy that we are going to get from the vaccines. We all hope it will be very high, in which case the population coverage could be slightly lower. Even if we have a vaccine initially with quite low efficacy, it may still be useful.

We also need to think about which sections of the population we are targeting. The first targeted group will be healthcare workers—not only to protect them, but because it is widely known that, in pathogen outbreaks, healthcare workers becoming infected even asymptomatically can transmit the virus to their colleagues and to patients. There is a lot of virus transmission in hospitals, which is really problematic, so that is probably the first group. People working in hospitals with coronavirus patients need to be protected for their own safety and to stop the spread.

We obviously want to protect the older population, who are most at risk of a fatal or very severe infection, but, as we know, vaccines do not

always work so well in older people. We will assess that with each of the vaccines as they go into clinical development. Once we understand what level of immunity is required for protection in a young person, we can see whether we can achieve that level of immunity in an older person without necessarily having to do all the efficacy studies in the older population before the vaccine is licensed for use. Again, that will continue to be assessed post licensure.

Ideally, you would have a highly effective vaccine that works very well in all age groups, and you would start by targeting healthcare workers and the older population. If it does not work so well in the older population, you would vaccinate more of the public-facing population, who are likely to be responsible for transmission, and possibly children, who often spread viruses around even if they do not become severely ill themselves. We have seen that in flu: vaccinating children against flu protects the older population in the area against flu as well.

There is still a lot to understand before we can plan the best vaccination strategy, and it may be different in different countries and with different types of vaccines.

The Chair: The media have hyped up quite a bit that we will have an effective vaccine, particularly from the two of you, Professor Gilbert and Professor Shattock. How confident are you?

Professor Robin Shattock: You have to balance optimism about our different approaches—we would not be working on them if we were not optimistic about their potential—against the known risk of failure. Vaccine success rates tend to be about 10% once you start clinical testing.

It is important to recognise that we need the global vaccine field; I think a number of vaccines will come through. As Professor Gilbert pointed out earlier, we do not know what level of immune response is required. If it is a very low level of immune response, I suspect we will see most of the vaccines working. If it requires a very high level of immunity or a specialised type of immunity, far fewer may come through and be successful.

In the UK, we are very lucky that we have two candidates already in clinical evaluation. We think that both will probably work individually. We also have the opportunity to look at them in combination; probably nobody else globally is currently thinking about combined vaccine approaches. I think our chances are high, but we should not overhype the potential success.

Professor Sarah Gilbert: I agree. We are both very optimistic about the technologies that we are using, based on all the things that we know in preclinical studies and in other studies, and about adenovirus technology in particular.

We obviously have to measure it, but what do we mean by success? What is the ultimate aim? The aim is to protect the population. That does not mean that the vaccination has to be 100% effective; even with 50% efficacy we could go a long way to protecting the population.

So we are optimistic that we will have something, and if necessary we can combine the vaccines to get something that works even better.

Q100 **Lord Kakkar:** I want to touch on the issue of antibody-dependent enhancement. Do Professor Gilbert or Professor Shattock have a view about that, bearing in mind what we heard in the first session?

Professor Robin Shattock: It is clearly a theoretical risk and one that we cannot dismiss. It faces all vaccine developers, so we are all looking at it very carefully. Obviously, if you have a strong immune response that prevents infection, you will not see ADE.

We are very focused on trying to induce particularly the right type of antibody response. One approach that we have used to de-risk things slightly is to make sure that the spike protein that we use is locked in prefusion conformation, because we think that gives us a better ratio of neutralising and non-neutralising antibodies.

Ultimately, however, we do not know. We are not seeing a high level of concern in natural infection, where you get a very broad profile of antibody responses. At the moment, there is no evidence that re-infection is causing problems with ADE, so we may gain some level of comfort from that.

It is a theoretical risk. We all have to be acutely aware and look for that, so that if it occurs we can stop any vaccine that may induce that type of response.

Professor Sarah Gilbert: We have done four preclinical studies in which we have vaccinated animals and then exposed them to a very high dose of the coronavirus, and in none of those have we seen any evidence of ADE.

The Chair: That is good information. Thank you very much. We have run slightly over time. The broadcast will be cut off in a moment, so may I thank you most sincerely, Professor Gilbert, Professor Shattock and Dr Gray, for coming to help us today? It has been a most interesting session. We wish you good luck.