HOUSE OF COMMONS

Science and Technology Committee

Oral evidence: UK Science, Research and Technology Capability and Influence in Global Disease Outbreaks, HC 136

Wednesday 1 July 2020

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Watch the meeting

Members present: Greg Clark (Chair); Aaron Bell; Dawn Butler; Katherine Fletcher; Andrew Griffith; Mark Logan; Graham Stringer; Zarah Sultana.

Questions 906 - 998

Witnesses

I: Professor Sarah Gilbert, Professor of Vaccinology, University of Oxford; Professor Sir John Bell, Regius Professor of Medicine, University of Oxford; and Kate Bingham, Chair, UK Government Vaccine Taskforce.

II: Professor Jonathan Van-Tam, Deputy Chief Medical Officer and Lead, Therapeutics Taskforce, Department of Health and Social Care; and Dr Jonathan Sheffield, Covid-19 Research Operations Director, National Institute for Health Research.

Written evidence from witnesses:

– [Add names of witnesses and hyperlink to submissions]

Examination of witnesses

Witnesses: Professor Gilbert, Professor Sir John Bell and Kate Bingham.

Q906 **Chair:** The Committee will be hearing evidence today on the latest developments in vaccines against Covid-19, and later on this afternoon on the development of therapeutic treatments.

I am delighted to welcome our first panel of witnesses. They are Professor Sarah Gilbert, who is professor of vaccinology at the University of Oxford and leads the Jenner Institute vaccine and emerging pathogens programme; Professor Sir John Bell, who is the Regius Professor of medicine at the University of Oxford and, among many other distinguished appointments, is a former president of the Academy of Medical Sciences; and Kate Bingham, who is the relatively new chair of the UK's relatively new Vaccine Taskforce. Thank you all very much for joining us.

Perhaps I can kick off with some questions to Kate Bingham. Could you describe the main activities and accomplishments to date—in so far as they are at this early stage—of the vaccines taskforce?

Kate Bingham: I cannot tell you too much about accomplishments yet because some of it is commercially confidential, but the goal of the Vaccine Taskforce is to protect the UK population through vaccination against Covid as soon as possible, and to help distribute any successful vaccines internationally.

Specifically, we are building a diverse portfolio of the most promising vaccines, recognising that many of them are based on unproven platforms. We invest both in manufacturing and in clinical trials before we know whether or not the vaccines will work. We want to maximise the chance of success, by having a vaccine available if and when the vaccine is proven to be both safe and effective.

It is an uphill struggle. It has not been done before. We do not know coronavirus well. In examples like HIV and malaria, we know those diseases well, yet we do not have vaccines against them. We may never get a vaccine, or we may only get a vaccine that modifies the severity of the disease. Our long-term goal obviously is to get a sterilising vaccine that prevents infection.

We have worked quite quickly. I think this is my seventh week. We have assembled a private sector expert team that we have embedded within Government. In addition, we have seconded people from NIHR, which is the national institute in the UK that runs clinical studies, and MHRA, which is the regulator that decides whether or not vaccines and drugs are safe and effective. That means we are getting realtime top advice, which is fab.

In terms of progress, we have had money from manufacturing, and there is a lot more that I cannot talk about, but that is all in train. We have been working very closely with the UK's clinical trial network, which John

knows all about, and that has been evidenced by the phenomenal result with dexamethasone. The nimbleness of our small team has enabled us to move quite quickly. We are assembling an attractive portfolio. We are off to a good start, but it is a heroic task.

Q907 **Chair:** Thank you. It is great to have that energy behind it. You have a lifetime of experience in the life science sector; you do not come to it from a position of lack of familiarity. What assessment do you make of the prospect of us having a vaccine, eventually, for Covid?

Kate Bingham: I am relatively optimistic that we will find a vaccine that will be able to treat the population. The caveat is the point I made. Is it a full sterilising vaccine, which means you cannot get infected, or is it one that basically just takes the edge off the symptoms so that it reduces mortality? Clearly, we would like to get to a sterilising vaccine so that people are prevented from being infected. In the near term, we may just have to satisfy ourselves with a vaccine that reduces the severity of the disease, and I am pretty optimistic that we will get that. As to how quickly we can get a sterilising vaccine, I do not have a strong view yet.

Q908 **Chair:** Are there different vaccine candidates in the choice between full sterilising and ones that help alleviate the symptoms? Do the same candidate vaccines do both, and it is just a question of how well they work, or are there completely different approaches depending on what they aim to do?

Kate Bingham: All of them aim ultimately to prevent the infection, and there are different types of vaccine that work in different ways. Actually, until we run the clinical studies, we do not know. There is nothing fundamentally to say that one could be a sterilising vaccine and one could not be. We are exploring all the different vaccines: the adenoviruses, which Sarah will talk about; mRNA, which is what we are doing with Imperial and others; and then the more established ones. Those are more advanced formats, and they are the ones where we are likely to see the earliest clinical data, but they are the least proven. The more proven vaccine format would be the adjuvanted protein format. That is what we standardly get. Those are coming a bit further behind, but they are better understood in terms of how the vaccines work.

Q909 **Chair:** I see. Is it possible to say which is likely to be available first? Is your implication that a symptom-alleviating vaccine is the most likely to be available for deployment, followed by a sterilising one? Is that the case?

Kate Bingham: We have Sarah Gilbert on the line, and she will talk about Oxford. Oxford will be highly likely to read out first. If it is fully sterilising, fantastic. I am just conscious that we may not deliver that immediately.

Q910 **Chair:** I see. We have lots of questions for Professor Gilbert and Sir John as well. On this theme, to understand the potential contribution of vaccines, there is a phenomenon, I understand, known as disease enhancement or antibody-induced, or vaccine-induced, enhancement,

where it is possible that a vaccine—obviously inadvertently, which is why you need to do the testing—can make conditions worse. Can you say a bit about that and how we can make sure that it does not happen?

Kate Bingham: I will give an answer and then let in the two experts, who know much more about that. What you are describing is called ADE, antibody enhancement of disease. It happens when an immune response to a vaccine is not strong enough to build up a high level of neutralising antibodies, so you may end up with antibodies against the virus that enable the virus to actually enter the cells and infect them rather than eliminate them. You can mitigate by doing a lot of work on whether you are generating a sufficiently potent immune response to the vaccine that would then eliminate the likelihood of that happening.

There has been a lot of work done on that, and one of the reasons we have the MHRA embedded in our team is so that we can work every step of the way with the regulator to make sure that anything we do, or the companies with whom we are working do, is ensuring against that. John might want to comment on ADE.

Q911 **Chair:** Sir John, perhaps you might comment.

Professor Bell: Kate has accurately described it. It is a risk. There are some vaccines like the RSV vaccine that were held up for 20 years while people tried to sort out the ADE issues. There is a little bit of encouraging noise. You might imagine, if there was an issue, that you might find enhancement using convalescent sera. It was not really a trial; it was an observational study in the US of convalescent sera in 9,000 patients. I think it is just reading out. As far as I understand it, there is no evidence of enhancement in that population. That does not prove we will not see a problem, but it is encouraging news. Sarah probably also has some data from the pre-clinical studies.

Q912 **Chair:** Professor Gilbert, would you like to amplify the answers that we have heard?

Professor Gilbert: One way we can look at this is by doing animal studies where we vaccinate them with the same vaccine that we plan to use in humans and then expose the animals to very large amounts of the virus. That is not so much to look at the effectiveness of the vaccine; it is to look at the safety of the vaccine in the face of a very high dose of viral infection and to see if there is any chance that the vaccination, prior to the exposure to the virus, makes the disease worse.

We have been doing four pre-clinical studies with three different collaborators in different parts of the world to look at that. We had data from the first of those studies before we started our first phase one trial. Before any people were vaccinated in our clinical trials, we had evidence from a study in non-human primates, which was made public on bioRxiv, that there was no evidence of disease enhancement after vaccination and then exposure to the virus. Subsequently, we have had data come through from three similar studies in two different animal species with, again, no evidence of disease enhancement at all.

We also have a better understanding now of what type of vaccine is likely to produce that kind of response. The RSV vaccine in the 1960s was an inactivated RSV virus. You take a large amount of the virus itself, inactivate it with formalin so that it cannot cause an infection, and then use that with an alum adjuvant to strengthen the immune response. That is the type of vaccine that seems to be most associated with causing that type of enhanced disease after exposure to the virus. That was seen in some early development of SARS vaccines—the original SARS, not SARS-CoV-2—again with inactivated virus vaccines with an alum adjuvant, whereas it has not been seen with different types of vaccines, and we now understand better that they are inducing a different type of immune response.

As well as doing studies where we vaccinate and then deliberately infect animals, we can look at the type of immune response they are generating and make sure it is the type that we associate with a good response and not with a bad response. We have seen that in all the pre-clinical studies we have done in the animal testing; and in other uses of that type of adenovirus vector in the 12 clinical trials we did before we started the coronavirus trial, we see the right type of immune response. We are very happy that we are seeing the right sort of immune response, that will give protection, and not the wrong sort, that might cause enhanced disease.

Only time will tell if we have problems caused by vaccination that are very rare events. If you remember, in the H1N1 swine flu pandemic in 2009, one of the vaccines caused narcolepsy in a very small percentage of the people who were vaccinated. The number was so small that, although it is a real effect of vaccination, it is not something you see until you start to do not just very large trials but have widespread use of the vaccine. We cannot rule out a very rare side effect of vaccination. Nobody can ever do that. But we can say that we are getting the type of immune response that leads to protection and not to enhancement of disease.

Q913 **Chair:** That is very clear, and I am grateful for that. Given what you have seen, and what you have drawn on in your career, when would you expect a vaccine could be available at the earliest reasonable opportunity?

Kate Bingham: Again, I will let Sarah answer for the Oxford one. Outside Oxford, it is likely that we will start seeing vaccines at the tail end of this year or early next year. We will have some phase three efficacy readouts coming through by the end of the year. Of course, they have to go through the regulatory process to get approved before they would be ready to actually launch.

The issue we have in the UK is that social distancing has been very effective, so we are operating in the declining pandemic. Maybe we are seeing a bit of a spike coming up in the last day or so. Trying to demonstrate a clinically effective response, a protective response, in a declining pandemic is challenging. Our options are that we either expand the size of the studies, or we go abroad, where we can focus the studies

on the epicentres. The caution in terms of being able to show a definitive result is that we actually have to have some disease. I think the message would be early next year.

Q914 **Chair:** The implication of its being early next year is that we might have to face what some people foresee as a winter resurgence without a vaccine. We should be preparing for that, in other words.

Kate Bingham: I have excluded Oxford. I will let Sarah talk about her timelines at Oxford. She is well ahead of the world.

Q915 **Chair:** If we take out Oxford, we ought to be preparing to face the winter without a vaccine, before we come on to Oxford.

Kate Bingham: I think that would be a reasonable assumption, yes.

Q916 **Chair:** Professor Gilbert, how is Oxford in terms of the timeline?

Professor Gilbert: I hope we can improve on those timelines and come to your rescue. Obviously, the thing we have to do is show that the vaccine works. As Kate said, we cannot show that the vaccine works unless we have infections in the group receiving the control vaccine so we know that people were being exposed and that the vaccine has protected them.

With transmission dropping so much in the UK, we now have trials going on in both Brazil and South Africa. We have currently vaccinated a few hundred people in Brazil, but within weeks that should be up to 4,000. In South Africa, we are aiming for 2,000 people. Those are both areas of high transmission at the moment. It is very dependent on getting people vaccinated and being able to follow them up and record cases in the control group, and of course we do not know which group they are in in real time. We just know there are a certain number of cases being recorded, and then the statisticians, when there are enough cases, look at them and determine if the vaccine is working.

We are still continuing in the UK as well. We now have 8,000 people vaccinated in the phase three trial in the UK, and that is very good going. Apart from the ability to test efficacy if there is any increase in virus transmission, that also gives us the safety database that we need, because we are looking at the vaccine in older adults as well as younger adults. We need safety data and we need to look at the immune response in people of different ages as well, so that, when we eventually get a result of vaccine efficacy, we can start to make judgments about whether it is likely to work as well in older people as it would in younger people. It is really important to know about that.

As to when we get the efficacy result, I cannot give you a precise answer, because it depends on what happens in the different trials that are running. We are now partnered with AstraZeneca, as I am sure you know, and they will be starting a very large study in the US in August. They will be vaccinating, aiming for 30,000 people, in areas where there is high transmission. We are maximising our opportunity to determine

vaccine efficacy, but we have to get that result before we can decide that the vaccine is ready to be used.

In parallel with that, manufacturing is scaling up. Manufacturing is increasing every week. We are getting improvements in the ability of more companies to manufacture the vaccine, and the aim is by the autumn to have a large amount of vaccine ready to use. As soon as we have the efficacy result and can go through the emergency use licence process, we would be able to start vaccinating people.

Q917 **Chair:** We will come on to the manufacturing in a bit more detail. We are grateful for that. Kate Bingham said early next year, outside your study. You said you could be earlier than that. Can you home in a bit on a kind of timeframe?

Professor Gilbert: It is completely dependent on the results of the efficacy studies. We have to show it works before we can be ready to use it. When we started our phase one trial, we were told by the modellers in the UK that, if we could get 1,000 people vaccinated by the end of April, we would have a result of vaccine efficacy during May, because transmission at the time was predicted to be such that we would have been able to get that result. Clearly that did not happen; transmission was probably higher than the modellers thought it was at that particular time, so the country went into lockdown and now transmission has reduced a lot. These things are very unpredictable, and that is why I cannot give you a firm timeline. I can just tell you that we are vaccinating in multiple countries where there is high transmission, so we are increasing the chances of getting the efficacy results early.

Kate Bingham: We are working with the NIHR to think about how we can maximise the effect so that we can enrich for places where there are hotspots, where the disease transmission is highest. We have activities in place that allow us to use realtime swab data to then send our research nurses to particular hotspot sites, so that we can enrol in those centres and maximise the likelihood that people in the trial will be exposed to disease. Then we will be able to show whether or not a vaccine has a protective effect.

Q918 **Chair:** Thank you. Sir John?

Professor Bell: My only comment is that the development of vaccines is a world that historically has gone very slowly. It normally takes years and years and years. To the credit of Sarah's group and the Jenner, they have really changed the way people think about the speed at which these vaccine trials can be done. We all remember when Tony Fauci, who was brought in to help the Americans with their vaccine efforts, said in April, "Oh, don't expect anything till mid-2021."

The reality is that the way Sarah and Andy Pollard, who is helping to run the clinical trials in Oxford, have approached this has rewritten the book on how quickly you can do vaccine studies. We now find that many of the other big commercial players are trying to mimic the Oxford approach, and I think that is a great credit to the UK in terms of setting the style in

which you can get these things done, but retaining very close attention to the safety issues, which is obviously the thing that we need to pay attention to. Many companies are now interested—Kate can probably comment on that—in potentially doing some of their trials in the UK because we know how to do it, and we know how to do it because Sarah and Andy have shown us the way.

Q919 **Chair:** Do you think we need to be preparing for the winter without a vaccine, or should we be confident that we can have one to help us through the winter?

Professor Bell: This whole epidemic has relied too heavily on assumptions that have turned out not to be true. My strong advice is to be prepared for the worst.

Chair: That is very helpful.

Kate Bingham: I have one quick statistic. The Oxford study will have likely vaccinated all their efficacy subjects before any of the other vaccines actually start their big efficacy trials. That gives you the scale of how far ahead they are versus the other companies.

Chair: Thank you.

Q920 **Aaron Bell:** I would like to try to get a bit more of a handle on our current understanding of immunity in general—obviously it is going to be speculative—and what we might think about the immunity that might be conferred by a coronavirus vaccine.

Professor Bell, three areas in particular seem to be up for debate. One is the length of any immune response—how long that is likely to be. Another is the effect on different populations, which I think Professor Gilbert already touched on. Vaccines are not always as efficacious with older people. You have covered disease enhancement already. The other one would be viral mutations. Would a vaccine still confer some immunity even if the virus itself evolved? On those three issues, do you have any general comments, Professor?

Professor Bell: What we know based on other viruses generally, and in particular other coronaviruses, is that the longevity of natural immune responses to the normal endemic coronaviruses does not appear to be that long. But in the case of SARS there was still evidence of antibody-based immunity a couple of years out in infected people, and some evidence in SARS and MERS that cellular immunity continued a great deal longer than that—six or seven years in some cases. It is possible that you get a more long-lived immune response with either natural infection or the vaccine in those cases. How well a vaccine works and how long the immunity it generates lasts is an open question. Again, it is one of those things that we will not know until we have been able to measure it. I would be optimistic that you might well get a year and maybe a couple of years of pretty safe immune responses.

On the mutation issue, the virus mutates, but it mutates pretty slowly. It will be interesting to see whether you get a lot of mutation against, for

example, neutralising antibodies. There are programmes, as you know, in pharma to generate monoclonal antibodies that are specifically neutralising. There are programmes in two or three pharma companies to do that. They will be targeted at particular epitopes, or a small set of epitopes, and that will provide a pretty strong selective pressure. It will be interesting to see whether the virus is able to avoid those antibodies by mutating to avoid them.

It turns out that most of the neutralising antibodies are just spikes, and they do not always occur in the places where you would imagine them. Some of them have rather complex mechanisms of action. I think that is an open question but it is an important one. As Sarah will describe in a minute or two, other vaccines in this space tend to use a much larger protein and will generate a much wider set of antibodies and, hopefully, a wider set of neutralising antibodies, which will make them less prone to escape than one sees with a monoclonal antibody that is specific to a single epitope.

Q921 **Aaron Bell:** Professor Gilbert, do you want to add anything?

Professor Gilbert: Before we started work on this particular coronavirus vaccine, we had been working on a different coronavirus vaccine against Middle East respiratory syndrome. We had vaccinated people in the clinical trial and taken their serum, which contains the neutralising antibodies, and tested the serum to see if it would neutralise different isolates of the MERS virus and accumulated mutations over the time. In fact, we looked at the most diverse MERS viruses that we could, and we found that the neutralising antibodies neutralised all of them. That is a different coronavirus, but MERS also mutates quite slowly. The mutations take a long time to accumulate, and we were not seeing any escape from the neutralising antibodies that we were generating by vaccination.

On the question of duration of immunity, as Professor Bell said, it does not seem to be very long-lived. Naturally acquired immunity to other human coronavirus infections is relatively short-lived, and we know that people get reinfected, sometimes quite quickly. That does not necessarily mean that we will see the same thing with the vaccine, because the vaccines have a different way of engaging with the immune system.

We followed people in our vaccine studies using the same type of technology to make vaccines for several years, and we still see strong immune responses. Again, it is something we have to test and follow over time. We cannot know until we actually have the data, but we are optimistic, based on earlier studies, that we will see a good duration of immunity, for several years at least, and probably better than naturally acquired immunity, based on what we know so far.

On immunity in different populations and different ages, we have previously vaccinated people against flu with this type of vaccine technology, and seen very good immune responses in older adults, people in their 80s. We are looking at that now for the new coronavirus vaccine. It will be a question of determining not whether it works at all

but whether the immune response is significantly less in older people. If it turns out that it is, you might be able to mitigate that by giving a higher dose or by giving an extra dose to try to bring their immune response up to the same level that you see in younger people.

As soon as we have some vaccine efficacy data from any of the vaccine programmes, and we have a better understanding of what level of immunity you need to get protection, we can start to tailor the vaccination schedule for older people, to make sure that we can achieve it in them, hopefully, as well as we do in younger people.

Kate Bingham: Sarah just brought up the point that we could add an extra dose. It is important to understand that these vaccines may not be a single shot. In many cases, they are already predicted to require two dosages in order to generate immunity. That is another aspect we have to think about as we are selecting and building up the vaccine portfolio and then thinking about deployment. What is the likely dosing regime that these vaccines are going to require in order to get that level of protection?

Q922 **Aaron Bell:** Thank you very much. In fact, that speaks to what I wanted to ask as well. Do we need to develop vaccines that might need to be administered in different ways, whether injections or nasal sprays or whatever? Is that something the programme is looking at?

Kate Bingham: Our priority focus is on vaccines going into the clinic this year that will generate clinical data, possibly this year or early next year. At the moment, that does not include intranasal or oral, although both are absolutely in our sights and things that I think we are continuing to explore for a second wave. The focus we have is speed. We want to get hold of the vaccines that are most likely to generate efficacy data and safety data as soon as possible.

Q923 **Aaron Bell:** Thank you; that is very clear. Finally, do you have any comment on the reports coming out of the Karolinska Institute that twice as many people showed a T-cell response rather than an antibody response? It is obviously a small sample, and it is pre-peer review and so on. Do you have any comments on that, and does it have any implications for a vaccine programme?

Professor Bell: There are a number of other papers in that space. There is quite a bit of publication going on in that space at the moment. What seems clear is that you have cross-reaction from T-cells that are activated by standard endemic coronavirus peptides from viruses with peptides from the Covid virus. I think a number of people made those observations.

They are present in quite a significant number of people. There is probably a background level of T-cell immunity in people before they receive the Covid virus, and that may be relevant to the fact that many people get a pretty asymptomatic disease. There is also a concept called T-cell senescence, where your T-cells get a bit tired once you are beyond the age of 65 and may not be as effective at removing the virus.

The T-cell may explain a number of the different features of the disease. There is quite a bit of work on T-cells in the UK at the moment, and we have an opportunity to see whether immunity to the virus is wholly dependent on antibodies or more likely dependent on antibodies and T-cells. I think Sarah can comment a little bit on her vaccine and its ability to generate those types of responses.

Q924 **Aaron Bell:** I will go to Professor Gilbert in a moment. To clarify, we have heard a figure of 60% thrown about for what herd immunity would look like, or potentially numbers a bit higher than that. If it is the case that some people have a T-cell response without an antibody response, prevalence studies would suggest we would get to a herd immunity position before 60% of the population was showing antibodies. Is that correct?

Professor Bell: That is definitely a confounding factor for the modellers who were trying to think about herd immunity and R0. I think it is a complicated problem. Because—

Chair: I think we have lost the connection to Sir John.

Q925 **Aaron Bell:** I will go to Professor Gilbert. Could you comment on both my initial question and the follow-up?

Professor Gilbert: T-cell immunity is very important in immunity to viruses. It is often overlooked because it is rather difficult to measure. It is more complicated to measure, and there are lots of different ways of measuring that give you different kinds of readouts. What we know is that our vaccine is very good at inducing T-cell responses as well as antibody responses. In the paper coming out of the Karolinska Institute, a lot of the T-cell responses were to the spike protein, which is the protein that is in our vaccine. We would expect to get T-cell responses as well as antibody responses to the vaccine. We saw that with the MERS coronavirus vaccine.

In terms of vaccine development, it means that if you have something like a protein adjuvant vaccine, a more traditional style of vaccine that is not very good at inducing T-cell responses but induces antibodies and potentially neutralising antibodies, you may need a much higher level of antibody induction than you do with the viral vector vaccines and the RNA vaccines that induce T-cell responses as well. Because you have two components that are contributing to immunity, you may not need such a high level of antibodies to get full protection if you also have a strong T-cell response that adds to that protection.

Seroprevalence may possibly underestimate naturally or already acquired immunity to the virus. That is something we need to keep an eye on; there is certainly evidence that people infected with SARS-CoV-2 have not developed antibodies but have a T-cell response, and that will be likely to protect them against another infection. It is not massively more than the people who have antibodies, and it depends on which assay you use to measure the antibody responses. If the assay is not very sensitive, you will not see an antibody response. If you use a different assay, you

may see an antibody response. We need to keep an open mind about whether there are large numbers of people who have protective T-cells in the complete absence of antibodies.

Chair: Thank you very much indeed.

Q926 **Mark Logan:** I want to follow up Aaron's questions about immune response. This is a bit of a layman's question, but if we had vaccination in place by the winter, does the fact that we, every year, nationally roll out flu injections for people in advance of the winter have an impact on people's immune response system, or on those who have compromised immune systems? Should we be thinking of rolling out the flu vaccination much earlier this time around?

Kate Bingham: The Joint Committee on Vaccination and Immunisation will advise the Government on the right way to think about who should be vaccinated and when. That is the starting point. We have expert people who will advise, and they have already issued their first advice on the likely vaccine prioritisation.

The second point is that none of the trials at the moment is being co-administered with the flu vaccine. It is not likely initially that people coming for flu vaccines will be able to have a Covid vaccine at the same time. There will be a separate deployment process to think about how you vaccinate different sub-populations. The advice that has come from JCVI is that it is likely that the expanded flu cohort—people who have been recommended to have annual flu vaccinations—are likely to be the same people, initially, who will be recommended for Covid vaccines.

Professor Bell: It is a pretty important question. One of the things that clinical staff in hospitals worry about is that, if we have a significant flu season, we are going to have a bit of a clinical problem if we have Covid running alongside. You will get people with severe pneumonias arriving with fever and all the usual things, and it will be pandemonium in the A&E departments. I am rather hoping that, first of all, ideally, we expand the number of people getting flu vaccines so that we get better coverage, and, secondly, we push quite hard to make sure that people are compliant and participate in flu vaccine programmes. The uptake is lamentably small in some sectors. We are not messing around any more. It could be really serious if people do not get their vaccine.

Q927 **Chair:** To do that, to emphasise Mark's point, do we need to start earlier? Do we need to be doing it in the early autumn rather than the later autumn?

Professor Bell: Some of it has to do with the availability of the vaccines. As you know, they take some time to make and they have to be made every year. Also, being able to predict exactly the sub-type of flu that is going to be used is not an easy game. I see that a new H1N1 has just popped up in China. We should start when they are ready, and get going. That would be my view. More importantly, it is surprising how many people who are eligible for flu vaccines do not get them. We have to

enforce the idea—not enforce, but encourage people to participate as widely as possible.

Q928 **Mark Logan:** It sounds as if being prepared for the first wave will not be the same as being prepared for the second wave. Is that what you are implying? We will have different conditions.

Professor Bell: It is exactly what I am implying. Whatever happens is likely to happen through the autumn getting into the winter, and we will have a whole new set of other respiratory viruses floating around. If we happen to have a bad flu season, it will cause lots of trouble and there will be a real challenge doing diagnostics, separating the flu from the Covid patients, and doing all that kind of stuff. We need to be on the front foot and prepared for that come the autumn and the winter.

Q929 **Mark Logan:** Ms Bingham, what potential stalling points in the vaccine development process has the taskforce identified, and what action has been taken to remedy them?

Kate Bingham: There are all aspects of vaccine development. You have the manufacturing supply chains: can you actually make the vaccines? What we have done there is to put in place two vaccine supply chains; one for adenoviral vaccines and one for mRNA vaccines, and they are currently supporting Oxford and Imperial. Those are generic supply chains. Should those two vaccines fall over, we would then be able to use those manufacturing capabilities for alternative vaccines.

We have plans in place that I cannot talk about today to expand capability and capacity in the UK. What is public is VMIC. VMIC is the Vaccine Manufacturing and Innovation Centre, which is being opened in Harwell. We have now expanded both the capability of the different kinds of vaccines it can make as well as the capacity. The capacity of VMIC when it comes on stream will, at surge capacity, make 70 million doses of vaccine in four months. We are shoring up the supply chain so that we can manufacture vaccines as and when they look promising and we want to bring them into the portfolio.

The second thing is around the clinical trials. We have talked a little bit about how you prove that a vaccine is both safe and efficient. We need to be able to ramp up the clinical trials very quickly. As soon as a company is ready to go into efficacy studies, we need to be able to turn on those studies in a dime. In addition to using the realtime transmission data, where we can send research teams out around the country, to Leicester or wherever the hotspots are, we have assembled a group of pre-existing clinical trial cohorts. They are people who have already signed up to say they are willing to be approached for clinical trials, and we are focusing on the cohorts we think are relevant for the coronavirus vaccine. That includes cohorts that have ethnic minorities.

We are working with a Genes & Health cohort, managed by Barts, which combines people from east London and Bradford. We already have 47,000 British Bangladeshi and British Pakistani volunteers we will approach in due course for vaccine trials. We have other pre-assembled

cohorts dealing with elderly people so that, again, there is another likely high priority population for vaccination that we can include in clinical trials.

The two key things we have focused on are how we can be sure we can make enough vaccine quickly so that we have sufficient supplies for the UK, and how we can be sure that we can demonstrate that those vaccines are safe and effective and do it as quickly as we possibly can. I have never seen trials get started as quickly. An example, as I said, is the RECOVERY study, which is phenomenal. It has rewritten the rulebook about how you get clinical trials up and running and controlled, and end up with a very definitive result. What we need to get out of it in the UK is to show that we can be the place in the world to do those sorts of high-quality and nimble clinical trials with definitive data coming out.

Mark Logan: To link that to something Professor Gilbert was saying earlier about how the transmission rate decreased—*[Inaudible]*

Chair: We have lost the sound, Mark. We will try to come back to you later when we have a better connection.

Q930 **Andrew Griffith:** Thank you for everything you are doing Kate, Sir John Bell and Sarah Gilbert. This is a really good, positive, upbeat session, if I may say so. I want to talk briefly about funding. We had evidence from Phil Duffy back at the beginning of June, who talked about around £114 million of funding.

Chair: Mr Duffy is from the Treasury. Perhaps the witnesses might need to know.

Andrew Griffith: It is always good to know exactly the name of where your money is coming from.

Could our witnesses give us an update? Has all of that money flown to your programmes? Do you need more money? Perhaps you can give us an update.

Kate Bingham: I absolutely know who Phil Duffy is. He is excellent and has been highly co-operative and helpful. I am afraid £114 million is not going to be sufficient. We have a funding plan submitted with the Treasury now, and a full business case. I cannot give you the details; suffice it to say that the teams are working very well. It is coming up for approval—or not—and we have not had pushback on anything we have requested to date.

Q931 **Andrew Griffith:** To that point, the vaccines taskforce originally said to SAGE that you were going to develop a funding and operational plan for everything we have talked about today, for procurement and delivery of vaccines. Has that plan been submitted, and would you be willing to publish it when you submit it?

Kate Bingham: The plan has gone through the BEIS process and is being considered at the programme board coming up. I do not know the political aspects of whether it gets published or not. I just do not know the answer. We will have to come back to you.

Q932 **Andrew Griffith:** It exists. You have pushed it up into the system.

Kate Bingham: Yes. We are very clear on the funding costs, the milestones, the key value inflection points, and the point at which we say, yes, this is working or, no, this is not working. I am a venture capitalist. One of the things I am very, very sensitive to is not spending money if you do not need to. If it is very clear that something is not going to work, you turn the lights off and move on. You focus your funding and your resources on the candidates that are most likely to work. Yes, we have a very clear plan of what we are doing.

Q933 **Andrew Griffith:** Where would you spend now if the magic money fairy came along? Where do you think we would get to? John is always full of ideas, so I might direct this to Sir John. Where would be the best place to put incremental funding, should we want to try to move further or faster?

Professor Bell: The game is to place lots of bets. Hopefully, Sarah gets a tail wind and she gets across the finish line. That would be terrific. I do not think we can assume that is the case. We want to be prepared and, ideally, be ready to manufacture at risk for a number of other vaccines. As you know, there are 170 vaccines on the list; we do not want to do them all, but to give Kate the elbow room to do a significant number will be important.

Because our vaccine manufacturing infrastructure in the UK was allowed to drift, and was pretty lamentable, to be honest, at the beginning of this activity, we may need to think about putting money into infrastructure to allow us to do the things we need to do between now and next summer. I strongly encourage that, because we do not want to be left relying on importing vaccine from the US. I promise you, you will not get it until a long way down the line. We need to be self-sufficient in this space.

Kate Bingham: Just to be clear, that is what our plan includes. First of all, our plan has funding for a portfolio of vaccines. Second of all, it has funding to run clinical trials for those vaccines, and then it has funding to do the bulk manufacture and the fill-and-finish manufacture of those, both in the short term using CDMOs—contract development organisations—and building permanent manufacturing capability and capacity.

Q934 **Andrew Griffith:** Orders of magnitude. I did not think you would say that £114 million was enough, but orders of magnitude.

Kate Bingham: We have not disclosed it.

Q935 **Andrew Griffith:** One billion? Two billion?

Kate Bingham: It is more than a billion. But until we have the sign-off, I should not say where we are.

Q936 **Andrew Griffith:** I fully understand. I was not trying to overly press you.

Kate Bingham: We have to do this properly. We cannot do a half-committed plan. We are doing it properly.

Q937 **Andrew Griffith:** The status is that the plan exists. The plan you have put together does what you think we need to do as a country, not just for the short term, but—John's point—to create long-term capability in this space, potentially to create future economic opportunities for the country as well. That is going through the process at the moment.

Kate Bingham: Yes. And skills. As we build up the advanced manufacturing capability, we need to include the people who are actually going to be making it and doing it. Something we are obviously investing in as well is how we make sure that we can build those jobs and build the skills workforce to deal with the advanced manufacturing.

Q938 **Andrew Griffith:** It sounds like the sort of thing you want to wrap into a new deal.

Professor Bell: Andrew, there is a really important point, which is that, to be honest, we were pretty complacent about our abilities to manufacture these kinds of health security-type products. As you probably know, we have very little onshore antibody manufacturing capability. If neutralising antibodies are the answer, we are going to be stuck with that as well.

I have made the argument, and fortunately when Greg was Secretary of State in BEIS he listened. The VMIC was entirely the result of an effort to build out some activity in the vaccine manufacturing space. People need to remember that this is not a one-off, where we are going to wait 100 years for another one. Since 2000, we have had eight close calls, which should have made us wake up. We have had three flu epidemics, or near-flu epidemics, two SARS episodes, one MERS episode, Zika and Ebola. Any one of those could have blown up to be exactly what we have now. This now needs to become part of our national health security infrastructure. It is really important.

Kate Bingham: We need to make sure that we come out of this stronger as a result of the pandemic than we went in. That is a very clear mandate for us to deliver.

Chair: Sir John's role in this should be recorded. He was self-effacing, but he proposed in the life science and industrial strategy the Vaccine Manufacturing and Innovation Centre. I was pleased to support it, but it was Sir John's idea. Can we go to Dawn Butler if that is okay, Andrew?

Q939 **Andrew Griffith:** That's fine, unless there is anything Sarah wants to say. I do not want to discriminate when the money is being talked about.

Professor Gilbert: This is something we need to do more of, but it is also something we are very good at, and we should not just make one vaccine, stop, and then think that it is all behind us. As Sir John says, we need to do more of it, and we can do more. We need support to continue and do it faster next time.

Q940 **Dawn Butler:** Thank you all for all the work that you are doing. Can I pick up on something that was said earlier in regard to two vaccinations being needed? Is that two vaccinations straightaway, or does there need

to be some time lag between vaccinations?

Kate Bingham: The vaccines that we are looking at that have two different vaccinations are between 21 days and 28 days apart.

Q941 **Dawn Butler:** You would need to see the person you vaccinated twice. That is interesting.

Kate, you talked earlier about how fast we have been able to develop, and we are moving quite speedily as opposed to what normally would be the case. What would have been the normal hurdles that would have slowed down the process that are no longer there?

Kate Bingham: The two strands. One is the manufacturing. To take Sarah's vaccine as an example, growing up modified virus in cells, you start off in a test tube and then you slowly take it in a step-wise way and scale it up to thousands of litres. We are now doing that incredibly quickly rather than making sure that each step is completely validated and every single aspect is checked in terms of optimising the processes and the reagents and the conditions. We are accelerating that process.

There will be bumps along the way because we simply cannot predict how the cells will perform in different quantities, effectively. One aspect is that we are doing it much faster, but there will be some unknowns, and things will get in the way.

The other aspect is the clinical trials. We are absolutely compressing the clinical trial process, which is why we have MHRA embedded with us. MHRA is universally known to be an incredibly flexible and thoughtful regulator. We hear very good comments from the different companies we talk to around the world; they now preferentially want to come to the UK because they know that the MHRA is willing to talk to them at a very early stage, and look at the data and the documents before they have even got beyond a draft stage, so that they can give input along the way and therefore be able to turn it around quickly.

Those are the two aspects that are being compressed. Inevitably, we will have some unknowns and some bumps. Don't think that it is all going to work perfectly. As John said, we will come out of this stronger, because the streamlined ways of working that we have had to develop as part of Covid absolutely set the pace for how we should be doing things in the future.

Q942 **Dawn Butler:** Professor Bell, what do you think those bumps will look like? Do you have any idea in your modelling of what you think the bumps will look like?

Professor Bell: There is a whole set of potential things that may get in the way. One of the things is that the vaccines may not show the efficacy we need. That will push the issue further down the road. There is a massive issue about manufacturing at scale. Sometimes, the scale-up does not work. Getting material in place is going to be complicated.

There is also a set of wider bumps that relate not just to the UK, but to the world getting access to the vaccine. Whatever vaccine comes through, I think we all hope that it will be made available globally as quickly as possible. That is a mammoth exercise, and certainly Sarah's partner, in the form of AstraZeneca, has been focused on trying to make sure there is supply for the developing world; for example, low and middle-income countries that may not be able to produce it themselves.

This is a situation where we are not safe until we are all safe. There is no point in saying we will just vaccinate the UK and everybody else can worry about themselves. There is a corporate responsibility to make sure that everybody gets vaccinated as soon as possible.

Q943 **Dawn Butler:** As a follow-up to that, can I ask about international working? Are there any countries that are ahead of us in regard to development of the vaccine? I also want to ask Professor Gilbert about the trials and the selection process for the trials and people signing up for the trials. How exactly is that decided? Are people signing on the dotted line and are they fully informed that there could be complications? How does that work?

Professor Gilbert: No country is further ahead of us in development. In terms of recruitment of the trials, we publicise the trials on the website. People are invited to register and receive information. They are sent an information package. They have to be within a particular age range for different components of the trials. There are things that would rule them out, such as severe pre-existing disease.

We then invite people to come forward for what we call a screening visit where they get the opportunity to discuss the trials and the information they have received. They see a video presentation to explain everything to them in that way. Then they have a one-to-one session with a doctor where they can ask questions; they have blood taken to check their health before they enter the trial, and then they have a consent form that they can choose to sign to say that they have understood all the information and that they want to be part of the trial.

There will be a gap between the screening visit, when they have all the information, and the vaccination visit when they return, so they have time to read everything, discuss it with family if they want to, and think about it. Then they are invited back for a vaccination visit, and, before they are vaccinated, obviously they need to sign the consent form. It is not a rushed process, and they have plenty of opportunity to receive information that is all approved by the ethical committee and to ask questions about it before they decide if they want to go ahead.

Q944 **Dawn Butler:** Is it all done in different languages?

Professor Gilbert: In the UK, it is not done in different languages. Obviously in different countries, all the public-facing information has to be translated into the local language, and, depending on what country it is and how many local languages there are, there will be multiple language documents provided. When we do trials in Gambia, for

example, or Kenya, there may be more than one language the documents need to be in.

Q945 **Chair:** In a sentence, could Kate Bingham or Sir John Bell say whether there were any countries ahead of us in the race to develop and manufacture vaccines?

Kate Bingham: Oxford is ahead of the world in that it is the most advanced vaccine anywhere in the world.

Q946 **Chair:** I am sure the Regius Professor of medicine at Oxford is going to agree with that.

Professor Bell: Yes, but can I add something? I know everybody thinks that we have had a bumpy pandemic. This is stuff that the UK does unbelievably well, much better than anybody else; it is not just Oxford. It is the Vaccine Taskforce; it is the clinical trials. It is amazing, and we should be very proud of that.

Chair: Thank you. We are.

Q947 **Katherine Fletcher:** You have given such a rousing account. I have been trying to explain the unbelievable efforts that have been going on in this space to friends that perhaps are not close to the detail. I have been describing the vaccine effort, should it come off, as something not far off going into a shed and coming out with a jet engine. I see nodding. It is pipe cleaner stuff. I want to take this opportunity to say a big thank you for the women-led science that is going on. I was trying to explain to my niece when we heard private evidence from Professor Gilbert way back when. It all went in, and about three weeks ago she said, "How is the very clever lady with the camels getting on?" In all seriousness, your leadership is an inspiration to a generation, and I want to put that on record. Thank you.

I was going to talk about a UK vaccination strategy, but we have actually started to cover it off slightly. If I understand correctly, we have a strategy if this vaccine candidate is brilliant. We have a slightly different strategy if that vaccine candidate is brilliant, but the nuances require the clinical evidence. We have manufacturing capability for a range of different vaccines should they be required. That is correct, isn't it?

Are there any concerns that the Committee needs to be aware of about a strategy for UK vaccination? Sir John, I know you are correct about the need to make sure that the world is safe, so perhaps I could start with you. Is there anything we need to worry about in a UK vaccination strategy or anything the Committee needs to focus on?

Professor Bell: Kate and her team at the Vaccine Taskforce have covered off almost all of the key risks that we had. To be clear, I was on the taskforce before Kate ever joined it, and the list of risks was very long. As far as I can see, they have looked after most of the things that would make me anxious.

Kate Bingham: The one key risk is the fact that some of the vaccine candidates we are looking at, specifically the mRNA vaccine candidates,

require a very challenging cold chain. Some of these vaccines have to be kept at minus 80 degrees. People are obviously working very hard to say what level of degradation they get if you warm them up to minus 40, minus 20 or minus 2. That, I think, is a challenge. It is not a challenge specific to the UK, but it is a massive deployment challenge, and it will be much harder to distribute vaccines internationally until we have a solution as to how we can stabilise them at temperatures that are not quite so heroic.

Q948 **Katherine Fletcher:** Do you have any concerns about the behavioural side in terms of adoption of the vaccine? It is not an area that is without controversies, as in childhood vaccination, for example. Is there anything that suggests it is something we need to think about?

Kate Bingham: There is a very active anti-vaccination lobby, and we need to recognise that it is out there. John said earlier that not everyone is necessarily keen to get vaccinated. What is important is that we work within the regulatory framework and make sure that what ultimately comes out of this process—if anything comes out—is safe and is approved by regulators. Yes, I absolutely think we need to work on the communications, and work on being clear about what the vaccines can and cannot do.

Katherine Fletcher: I repeat my thanks to all three of you.

Q949 **Chair:** Thank you, Katherine. Finally, there are a couple of questions to Sir John from me and my colleague Graham Stringer. Sir John, you are a professor of medicine and you have taken a very authoritative view through the whole pandemic, advising very wisely bodies and Governments.

There was a study in *Nature,* published yesterday, that found in one of the hotspots in Italy that over 42% of people with Covid infections were asymptomatic; they showed no symptoms at all. Does one draw from that that the next phase of the response has to be routine testing of people who are not displaying symptoms?

Professor Bell: The data from the ONS survey that I helped to set up here, as you know, which is doing a representative sample around the UK, comes up with a number that is higher than 40%. In the ONS survey, it looks like it is 70%. Because people are revisited every week, we can know not only that they do not have symptoms today but that they do not have them next week or the week after. I think that number is probably pretty robust.

This is largely an asymptomatic disease, which means you have to be careful about a track, trace and isolate strategy that relies on symptoms because you will miss 70% of the people. My view, which I have certainly expressed before and I continue to do so, is that we need much more extensive testing across the community, not just the big labs, which have been terrifically successful, as you know, but distributed testing now at point-of-care level. We need new technology to help us, but I have seen in the last week or two a couple of examples of tests that might well be

of the standard we need to produce a result in a few minutes. That would be transformative, because we could all test ourselves regularly and test our kids after they have been off to the rave and all that stuff. That is where we need to get to.

Q950 **Chair:** Would it be fair to say that the priority for regular tests of the asymptomatic should be in NHS settings and care homes?

Professor Bell: In a curious way, the NHS should be able to deal with regular testing, because they have the big PCR capability in the labs. I think they can saturate tests as much as they want. They got off to a slow start, as you know, and I am not entirely sure why that was. They really should have been testing all their staff from the get-go. Care homes are the same; they got off to a slow start. Obviously, the more widespread the testing innovation becomes, the easier it will be for care homes, for example, to test regularly.

Q951 **Chair:** We have, we are told, plenty of capacity in testing. Can you think of any reason why you would not test regularly and routinely in hospitals and care homes?

Professor Bell: No, I cannot think of any reason, if we want to manage this infection. As we know from the Italian experience, and to some extent the UK experience, when this thing gets away on you, it often gets away on you in hospitals. Saturation testing in hospitals should be an absolute requirement. I am not talking about antibody testing. I am talking about real PCR virus testing because that is what tells you who has got what.

Chair: Thank you; that is very clear.

Q952 **Graham Stringer:** If I can take you back, Professor Bell, to something you said before, you painted a pretty horrific picture of next winter if there is a major flu epidemic. I have not seen any statistics—I assume they exist somewhere—about the last flu season, from the winter that has gone by. Do we know what impact the last flu season had on the epidemic? Has there been any contamination of the statistics from that, and can we learn from that about any potential flu epidemic interacting with the continuing Covid epidemic next winter?

Professor Bell: The answer is that last winter was not a bad winter for flu, which was really fortunate because, if bad flu had tailed into February and March, we would have had a real problem. We were lucky. It does not appear that Australia, at the moment, is having a particular issue with flu. Usually, the two go hand in hand. You get a bad winter for them and you then get a bad winter for us.

There are reports coming out of China about a new flu strain that is a swine flu strain, which always worries us. Many of these strains emerge out of China, and if that got going over the course of the next four or five months, we would have a big problem.

Q953 **Graham Stringer:** Thank you. You referred to the NHS getting off to a slow start, which was I think a bit of a euphemism. Listening to you as

witnesses today—I do not know if this is the 11th or 12th session we have had—I cannot as a member of this Committee think anything but that the UK is a scientific superpower; we have seen absolutely first-rate scientists before us. When it comes to testing and tracing, we seem to have been second or third-rate, potentially over-centralised. Do you agree with that, and as a close observer of events can you give any reasons why that might be?

Professor Bell: Can I paint a general picture? I do not think we had particularly competent or extensive planning for any pandemic before this, to be honest. The plans for pandemics were not very well developed. People occasionally talked about flu, but very little was done. I think we were not really ready for a pandemic in the UK, and that is something we need to pay very close attention to, as I said before, going forward.

Where we have shone, and I think you identified a couple of areas, is in doing clinical trials at scale with remarkable ability, to produce vaccines that are well ahead of the rest of the world. They did not come from a pandemic planning strategy held by PHE. They came from strong academic science and have been allowed to flourish in that environment. Without them, we would be in real trouble.

We have to go back and think about how our healthcare system and our public health system thinks much more strategically about how we get ready for pandemics, rather than trying to react after they have arrived on the doorstep. I think that is where the problem was.

Q954 **Graham Stringer:** Professor Bell, that was a very diplomatic and, in one sense, clear answer. There have been a lot of press comparisons—in the academic press as well—of how this country has dealt with the epidemic and how other countries around the world have dealt with the epidemic. There have been difficult comparisons with what has happened with the epidemic in Japan, South Korea and Taiwan. Do you think the differences are down primarily to their ability to test and track very quickly? Or are there other factors at work that would help us understand the very different infection rates in those countries?

Professor Bell: I am not persuaded that the infection rate or death rates in those countries can be attributed to the testing regimes. They have often had better testing regimes, but South Korea has not necessarily done that much testing. Where South Korea has been rather good is contact tracing and identifying people who have been in contact with others who were infected.

Similarly, I do not think you can attribute the German experience—the exceptional experience—to the testing in Germany either. The testing in Germany was very distributed. A lot of it was done in primary care. It was not clear to me that the data was centralised or handled in a way that would allow them to make strategic decisions on the back of it. There have been some countries that have been lucky and others that have been unlucky. That would be my view.

Q955 **Graham Stringer:** That does not sound like a very scientific answer, if

you don't mind my saying so.

Professor Bell: No, it doesn't, but I cannot produce a scientific explanation. As you can see, now that we get to the second wave, Germany has its own problems. It is not entirely clear why it avoided the first wave. It is not clear that the testing itself was going to reduce the death rate to such an extent. Testing people, unless you follow it up with extensive contact tracing, will not reduce the death rate at all. We cannot alter the course of the disease, at least not until we discovered dexamethasone two weeks ago.

Q956 **Graham Stringer:** You do not have a hunch about what the difference might be.

Professor Bell: I have a lot of hunches. Some of it may be due to immunity, but I do not want to go any further than that because I have no data.

Chair: Thank you. I am sure we will have a chance to talk about these things again.

I reiterate the remarks of all colleagues about how much we appreciate your expertise being deployed throughout this pandemic in the public interest. You have a very important task ahead of you. We wish you well in it, and we are very grateful for your very clear evidence today. Thank you very much indeed.

Examination of witnesses

Witnesses: Professor Van-Tam and Dr Sheffield.

Q957 **Chair:** I am delighted to welcome our second panel, to discuss some of the therapeutic innovations that are under development. Professor Jonathan Van-Tam has become a famous face throughout the pandemic; he is the deputy chief medical officer and is also professor of health protection at the University of Nottingham. Dr Jonathan Sheffield is the Covid-19 research operations director at the National Institute for Health Research. Thank you both very much indeed for joining us today.

Professor Van-Tam, could you summarise the purpose of the UK Therapeutics Taskforce and what you regard as its achievements to date, recognising that it is still early?

Professor Van-Tam: I could summarise the purpose of the Therapeutics Taskforce very easily by saying that we started this pandemic with no known effective treatments, and the mission of the Therapeutics Taskforce is to get as fast as possible to discoveries. That does not necessarily mean new drugs but discoveries of medicines that are safe and at least partially effective, and are accessible to UK patients primarily, but with one eye further afield on their accessibility across the world. It is about discovery, safe and effective UK patient access, and incorporation into UK clinical practice as rapidly as possible.

Q958 **Chair:** Thank you. That is very clear and succinct. Would it be fair to say

that dexamethasone would conform to that? Could you say a bit about that?

Professor Van-Tam: Yes. The big achievements so far of the Therapeutics Taskforce are, first of all, to identify the very first medicine in the world that is proven to reduce mortality from Covid-19. I understand that there are also discoveries around remdesivir—an antiviral drug—for example, but the data on mortality are not clear in that particular space. But the data are very clear from the UK effort that dexamethasone reduces mortality. On top of that, dexamethasone, in comparative terms, is an extremely cheap and widely available drug. That is extremely solid and important news for UK patients and for global public health.

There are additional discoveries already about a couple of medicines widely touted as being important for the treatment of Covid-19; you will have seen yourselves the headlines around the world. Hydroxychloroquine—the antimalarial drug—and Kaletra, which is a combination of two HIV drugs, have both been claimed to probably be of benefit to patients. Our efforts in the UK, through the Therapeutics Taskforce, have conclusively arrived at the conclusion that they are not beneficial. The really important piece about the clinical trials that we have done is that they have established for and against certain drugs.

Q959 **Chair:** That is very helpful and important information. Can you say why the taskforce that you lead in this country has been able to do that ahead of the world? What do you do differently?

Professor Van-Tam: First of all, I do not agree with the previous speaker that we were not well prepared and were not one of the best prepared countries on the planet for the advent of an influenza pandemic. I personally think we were, but that is probably a discussion for another day. It is contextually important to say that to you now because after the 2009 swine flu pandemic, as it was known, there was a very important reflection exercise in the Government. I was not part of Government at that time, but I was one of their advisers, and the reflection was that, in 2009, we had to get an awful lot of research going very fast, from a blank sheet of paper.

After that, the mentality changed. There is a long list of studies on pandemic influenza that were prepared, rehearsed, funded and then mothballed, ready for an influenza pandemic. We did not get an influenza pandemic—we got a coronavirus pandemic—but that thinking had happened. First of all, it was getting research moving much, much faster, and indeed repurposing some of the studies that had been prepared for pandemic flu to mobilise them for a new purpose to the coronavirus pandemic.

The first part of the answer, and the most important part, is that the culture had changed between 2009 and now, and we were ready to move very fast indeed to start research. One of the earliest conversations I had

with the chief medical officer, when it became clear that there was going to be a pandemic, was about how we would get moving on it.

Q960 **Chair:** In the example of dexamethasone, do you think the early progress you were able to make with that draws on the experience since 2009?

Professor Van-Tam: It draws on the mentality, yes, absolutely, and the culture that we had to get things moving very fast indeed. As you know, the dexamethasone discovery was part of the now celebrated RECOVERY platform trial in the UK. I will ask Dr Sheffield to give absolute chapter and verse, but it was a matter of a couple of weeks from concept through to the first patient being recruited to that study. It has been the most dramatic success, in terms of activation and rapid recruitment, that I have ever seen—that I think anyone has seen internationally.

Q961 **Chair:** Thank you. We will come to some more detailed questions on this. Clearly, we have an enormous appetite to make these discoveries and to establish the safety and the effectiveness of them as soon as possible.

In the case of dexamethasone, the pre-print that was published on 22 June did carry the standard warning that it was a pre-print and should not be used to guide clinical practice. How did you form the conclusion that, notwithstanding that early stage in terms of the publication cycle, it was nevertheless safe to be deployed?

Professor Van-Tam: We were informed about the dexamethasone result. We had a discussion with the principal investigator on, I think, 14 June, and it was very clear from them that they intended to independently announce the result on 16 June. We understood the RECOVERY trial from the word go. We had seen the protocols clearly. We had approved them because it was a UK Government-funded trial at the end of the day. We understood the absolutely enormous patient numbers in the treatment arms, and we understood from that perspective that the size of the result they got and the statistical significance of their findings meant that the probability that this was a result that had arisen by chance was so incredibly low.

We still have a very high confidence in the absolute quality of the RECOVERY team, so much so that we felt it just was not the right thing to do to wait more than another day to allow UK patients to begin to access that. It was a collective system judgment, and collective system taking of risk, that we were prepared to operationalise that two days later with a letter to all clinicians in the NHS, advising them, with the caveat that this was pre-peer-reviewed research, as it still is unless things have changed sometime today, that we should go ahead immediately. I am glad about that. I make no apologies for that at all—for allowing UK patients access as quickly as possible.

In the same tone, I make no apology for the fact that we took a decision, many weeks before that, to put the UK in the best possible position that, if one of these medicines was going to prove to be effective and important, then we had to have supplies ready to use, and we do.

Q962 **Chair:** One of the things we are keen to do is to document and analyse, and commend if necessary, innovations that take place. Speed, we know, is of the essence here. When you referred, Professor Van-Tam, to "we" in this, what was the approving body? Who is the "we" in the decision to approve the treatment?

Professor Van-Tam: That decision was taken at the highest level, by the chief medical officer. It was entirely a clinical decision, and it was informed by an expert senior clinical group, but ultimately the decision is with the chief medical officer.

Q963 **Chair:** It comes from the clinical side of his work rather than the SAGE side, as it were.

Professor Van-Tam: Yes, it does. It comes from the clinical side. SAGE really would concern itself primarily with the science.

Q964 **Chair:** I have just one final thing before I turn to my colleagues. Remdesivir has been in the news today, and we understand that it is likely to be the first treatment approved at the European level. Have you made an assessment of its prospects over the last few weeks?

Professor Van-Tam: We have been keeping a very close eye on remdesivir indeed. I do understand that the CHMP, the European Approval Committee, has made a provisional recommendation in favour of remdesivir. It will take a period of time, usually a matter of a few weeks—it is mainly procedural—before there would be a European licence for remdesivir.

The decision has been made on the basis of the US clinical trial data, which shows that, for patients who are hospitalised with moderate severity with Covid-19, their length of stay in hospital is reduced. There is a suggestion—I would call it no more than that—in the data that mortality may also be reduced, but that is not a clear or statistically significant signal.

The size of that trial is completely dwarfed by the kind of trial size and comparison size that RECOVERY can make. I am cautious at the moment about whether there will be or will not be—there may be—a mortality signal with remdesivir, but that is a bit different from dexamethasone. It is an unlicensed product in the European area until licensed by the EMA, and it is a medicine that is, as I understand it, relatively difficult to manufacture. Because it is not yet licensed, it will be in much less plentiful quantities or less easy to obtain than dexamethasone.

Q965 **Chair:** I understand. Will you make a separate assessment of it, or will you draw on the US trial data and/or the European assessment?

Professor Van-Tam: In a sense, the assessment has already been made in that the company concerned has applied for the Early Access to Medicines Scheme run by the MHRA. That has been granted, and, already, patients in the UK healthcare system—the NHS—can obtain remdesivir. There is a protocol for that; it has been available now for several weeks and stocks are available.

Q966 **Chair:** So it is open to any NHS physician treating people with Covid to prescribe it.

Professor Van-Tam: Yes. Subject to certain conditions and in hospitalised patients, yes.

Q967 **Chair:** Finally, you will have read today that the US has announced that it has bought up the prospective production of remdesivir: 100% of the production for July, and 90% for August and September. Germany has said that it has secured enough supplies. Do you have a concern that it is not going to be available to UK patients?

Professor Van-Tam: Right now, there are stocks in the UK, and I judge us to have adequate stocks of pre-licensed—as in unlicensed—clinical trial stocks of remdesivir that are available to be used through the emergency access protocol that I talked about. It illustrates the point that, depending on which medicine you discover works for Covid-19, if it is one of the ones already licensed for something else that one can repurpose, then it tends to be plentifully available, and if it is an old drug, there are many manufacturers often making generic versions of the same drug. If it is something brand-spanking new, as it were, from a new developer, it is likely to be in relatively short supply in the first instance, but I do know that the commercial teams in the Department of Health and Social Care are working extremely hard in this area.

Q968 **Chair:** Is it a function of the taskforce to secure the supplies of therapeutic treatments for the UK that are manufactured overseas like this?

Professor Van-Tam: The taskforce concerns itself really with the end-to-end journey from identification of medicines that require evaluation in case they are effective in the treatment of patients with Covid-19, through to colleagues within the taskforce, within the DHSC commercial teams, who will take responsibility for acquiring those medicines for the UK. I am sure you will understand that it is a very fine balance between Professor Sir So-and-So saying, "This is a very important drug that you need to evaluate," through to full proof of concept through a large trial such as RECOVERY. It is a finely balanced judgment about when or if—well, first of all, if and, secondly, when—to obtain those medicines in quantities that may be needed for patients.

Unlike a vaccine, we are never talking about needing 50 million courses for the whole of the UK population. Each of these medicines will have potentially a point in the course of the illness when it is most beneficial to give it, a point in the course of the illness when it becomes futile to give it, and there may well be medicines that work in certain sub-groups but not in others. Typically, that is going to be divided into the antiviral drugs such as remdesivir, where we know with antiviral medicines, because of the nature of the way that viruses multiply in the body, that the earlier the treatment, the likelihood is you are going to get a better outcome. We know with Covid-19 that you have this vicious tail end in the illness, which is essentially a hyperimmune response, where damping down that response is the most important thing. That is where dexamethasone

comes in and plays its role, so there are almost different horses for different courses along the course of the patient pathway.

Q969 **Chair:** For that early treatment, if it proves to be the case that remdesivir turns out to be a useful therapy, do you believe that you can obtain it in the quantities that we would need in this country, given what the US has done in terms of buying up the stock of the future production?

Professor Van-Tam: The answer to that lies in two parts. No, I do not think it will be as easy or as straightforward to obtain as the measures we took for dexamethasone, by virtue of its scarcity and by virtue of the fact it is a new medicine with a relatively long manufacturing time. So, no, I do not think it is going to be as easy. I could not say otherwise.

By the same token, it will not be suitable for all patients. It is an intravenous medicine given through a vein. Until there is an oral formulation, it would never be suitable for use as early as we might like to give it—for example, in primary care or patients at least at home with it. That is just not a reality in any healthcare system in the world for a medicine that is given through a vein, so there will always be these limitations according to the formulation that the company has developed so far.

Chair: Thank you. That is very clear.

Q970 **Graham Stringer:** I would like to ask you some questions on clinical trials, but, before I do, can I take you back to the point you made in response to the previous panel? You said we were as well prepared as, if not better prepared than, any country in the world for a flu epidemic and we will use that experience. If that is the case, why do our statistics on infection rates and deaths look so bad in comparison to other countries?

Professor Van-Tam: This is not flu; this is a coronavirus. The point I was trying to make, I think—well, I am sure I was—is that, for example, listening to the previous discussion, we had to start from scratch, or nearly from scratch, to make a coronavirus vaccine.

I am part of the Vaccine Taskforce; you have seen the amazing work that is happening there. Were that to have been pandemic influenza, for example, the UK still has and has had for many years an advance purchase agreement with vaccine manufacturers who make flu vaccine, to have very rapid access indeed to a pandemic flu vaccine, as fast as any other country on the planet. The advantage there, of course, is that we already make seasonal flu vaccines, and, effectively, what you do is you change the formulation and turn your seasonal flu production capacity towards making a pandemic flu vaccine.

The point I am making is that, actually, we are very well prepared indeed for a flu pandemic, but the whole world has been very unfortunate that this has been a coronavirus pandemic instead.

Q971 **Graham Stringer:** How effective has the process for awarding clinical trials national priority been, and how much has it speeded things up?

Professor Van-Tam: There was a very rapid response. I am just going to look for the precise timelines for you. There was a very rapid response to funding clinical trials in the UK. This is really down to the hard work of the NIHR and the UKRI together, who launched a research call for Covid-19 on 4 February. That, I think you will agree, is very, very early indeed. That was originally badged to be a £20 million research fund but grew to £24.6 million.

The first applications closed on 13 February, so you can see the timeframes were very compressed, but we already had 58 applications in that space. The second part of the call closed on 27 February, and there were 212 further applications in that space.

A rapid response assessment panel met to consider the first bids on 2 March. By 23 March there had been another meeting and the first six projects had been formally announced. What we were looking for in those projects, and Dr Sheffield will be able to give you more detail again, were research projects that could lead to changing or influencing the UK's response within 12 months. In other words, we were looking for very rapid impact studies. That was not the only focus, but the majority focus was, "What is going to get us something useful quickly?"

Since 17 April there has been a rolling call, which closed yesterday in fact, and has been ongoing ever since in that space, funding to a much larger amount than the initial £24.6 million.

That tells you two things; one, that the UKRI/NIHR research system, the Government-funded system, responded incredibly quickly—4 February is very early to put out a call if you think about the timelines of what we knew about China and how it was happening. The response from UK researchers has also been overwhelmingly large and swift.

Q972 **Graham Stringer:** This was all done under the European clinical directive, was it?

Professor Van-Tam: I beg your pardon? I did not catch that one.

Q973 **Graham Stringer:** Were the clinical trials carried out under the European clinical trials directive?

Professor Van-Tam: All clinical trials are carried out under existing EU clinical trials directives, yes.

Q974 **Graham Stringer:** Has it been difficult getting patient participation in the clinical trials, and what has been done to increase that participation?

Professor Van-Tam: I have an amazing story to tell you, really, on that one. The RECOVERY trial, since it started, has recruited perhaps just shy of 12,000 patients. That is really the most unprecedented and astonishing speed. As of 3 June, in the SOLIDARITY trial, which is relatively similar, run by the World Health Organisation across multiple countries across the globe, 35 countries together have recruited 3,500 patients. One country, the UK, has recruited almost 12,000 patients. Almost 200 UK hospital centres have taken part in that amazing effort.

So, yes, the world is looking at us and saying the UK clearly can mobilise its physicians through a national Government-funded research platform, and those physicians in turn can mobilise the altruism of UK patients to take part and help the world get answers.

Q975 **Graham Stringer:** That is extraordinarily impressive. Apart from people's altruism, are there any procedural organisational lessons to be learned and recorded from that process?

Professor Van-Tam: Yes. At this point you should really, with respect, ask Dr Sheffield to elucidate on the might and the organisation of the NIHR and the clinical research networks. I would pay particular tribute to the four UK chief medical officers, who responded very quickly when we asked them for a national letter to clinicians that would really spell it out to everybody working on the frontline that this was a national effort and that it was very important that as many patients as possible were recruited into the RECOVERY trial, which, at its peak, when unfortunately we had lots of Covid-19 patients, was recruiting well over 200 patients per day across the UK. If you compare that, for example, to the size of the remdesivir pivotal studies of under 1,000 patients, we were recruiting at over 200 a day.

Q976 **Graham Stringer:** Dr Sheffield?

Dr Sheffield: I would like to reiterate the massive effort that went in across the whole of the UK to deliver these trials. Just to give you some more close facts on RECOVERY, we set up 176 sites, so 176 hospitals across the country started to deliver the RECOVERY study. It was given an urgent public health badge on 11 March, following its funding. The HRA— the Health Research Authority—approved it four days later. The Medicines and Healthcare Products Regulatory Agency also approved it in four days, so there was amazing synergy between the Medicines and Healthcare Products Regulatory Agency and the Health Research Authority. The trial opened on 18 March, and the first patients were recruited on 19 March. In actual fact, at its peak, during April and May, over 400 patients a day were being recruited.

What I would like to say is that this was an effort carried out by all the research networks across the NHS. NHS staff were highly committed in this, but, most of all, patients volunteered to be involved in this research in their most desperate hours. If you look at the results from the RECOVERY trial, many patients did not survive that, but they still committed themselves to be involved in research. In fact, in total over 120,000 patients have been recruited into clinical studies across the whole of this epidemic; that is a massive achievement by the UK.

Q977 **Graham Stringer:** Thank you. A final question from me: at the start of June there were 720 proposals for research funding. How many are there at the present time, and do you have a view on how many of those are likely to lead to positive therapeutic processes for Covid-19? That was a clumsy question.

Chair: Who is that to?

Graham Stringer: It was to Dr Sheffield.

Dr Sheffield: I am not an expert on the actual grant aid side of the NIHR, but we have had an enormous number of research grant applications. We have prioritised those that were already funded, because that will make it a lot easier for us to be able to deliver them. We are still going through a process of sifting and sorting through these studies. The studies are highly variable in the quality they come to and in their state of preparedness. The whole point about that urgent public health process was to make sure that those studies were ready to go so that we could get them delivered quickly, efficiently and effectively. Our aim was to make sure that these studies were completed within the year, which is exceptional, again, in terms of the way that we deliver research.

Q978 **Aaron Bell:** We have already heard about the achievements and the successes that we have seen, especially dexamethasone here, but also what is going on with remdesivir. There have been a couple of controversies along the way, obviously, and Professor Van-Tam has already mentioned hydroxychloroquine. How did we handle that here? What lessons have we learned about what happened with that around data integrity and peer review processes? Was it a major issue for us, or is it essentially something that played out in the academic sphere rather than your area, Dr Sheffield?

Dr Sheffield: It absolutely played out in my area. The issue that we had with clinical trials was actually about global supply of drugs. Even simple drugs like hydroxychloroquine were very difficult to source for clinical trials. It was only the fact that we had a system with the Department of Health procurement systems that we had those supplies available, working with Public Heath England, for us to conduct those trials. What was really interesting, from our point of view, was that a lot of countries, I would say, panicked before the science evidence was available. We know that there was permission given in France to prescribe hydroxychloroquine, with no scientific evidence of effect. The FDA also allowed hydroxychloroquine to be prescribed, again with no scientific evidence.

What was remarkable was the fact that the chief medical officers really made that statement very early on in the epidemic, stating quite clearly that there was not any scientific evidence of appropriate treatments for Covid and that the doctors and nurses—those people caring for people with Covid—needed to be involved in research. Research was going to provide the answers.

When we had all the issues with hydroxychloroquine and the safety issues and our trials were suspended, it was the fact that we had recruited a large number of patients already into the RECOVERY trial, with hydroxychloroquine, that we were able to submit that evidence to the MHRA to demonstrate quite clearly—that was, again, the RECOVERY team doing that—that there was not the same level of safety issues in the context of our clinical trial that we were seeing in the paper that was

published in *The Lancet* and was subsequently withdrawn. That was a useful exercise to demonstrate why the science base was so important.

Secondly, because the RECOVERY trial continued, we were able, a fortnight later, to publish evidence that demonstrated that hydroxychloroquine had no effect on mortality on patients who were hospitalised, so in actual fact we drew a close on that piece of research. To me, that was as important a discovery as was the fact that dexamethasone worked. There had been a lot of hype about hydroxychloroquine and its effect, and what we had demonstrated was that, in hospitalised patients with Covid, hydroxychloroquine does not work.

Q979 **Aaron Bell:** You are absolutely right, of course, that negative results are equally valuable in terms of moving us forward and determining what the truth is. I was struck by your use of the word "panic" there, among the international response, because that speaks to what happened with the lockdown in the first place. The countries who panicked locked down earlier and that seems to have played in their favour.

When dealing with a pandemic, is there not a case for sometimes taking a more precipitate approach, shall we call it, rather than necessarily waiting to play it out like you normally would do? Is that something you would consider?

Dr Sheffield: As an ex-medical director of a large teaching hospital, I believe that the way we practise medicine has to be on an evidence base. So I believe very clearly that there is a tripartite agenda in healthcare. First, we need to deliver the highest-quality clinical care; secondly, we make sure that the education and training of the staff is of the highest level; and, thirdly, we continue to deliver research that gives us the actual definitive answers as to how we treat people with their diseases. I would be very uncomfortable if we moved to an area where we listen to what was going out on Twitter feeds, or a whole range of fake news about products that may have an effect. The fact is that we have to base our medical care on the best scientific evidence available at the time.

Q980 **Aaron Bell:** I completely agree with that. It is more a question of whether we have the stocks of something that might prove successful.

Can I just also ask you briefly about ibuprofen? Have you done clinical trials around that, because there was controversy over whether that was contraindicated earlier in the term? I know that has been resolved to some extent, but have there been trials about the effect of ibuprofen and other anti-inflammatories?

Dr Sheffield: There is a trial being conducted at the moment on a liquid format of ibuprofen. It started late because of the controversy, so we do not have the evidence based on that trial. It did not receive urgent public health badging, because it was not allowed to start until towards the end of the first wave of the pandemic.

Aaron Bell: That is great. Thank you very much.

Chair: Thank you very much indeed. Can I come to Katherine Fletcher, please?

Q981 **Katherine Fletcher:** Thank you. I just want to understand what else could be coming, but, before I do that, can I add my voice to the record and say what an amazing response this has been? Genuinely, it is remarkable, and it is testimony to the British public—they are marvellous—as well as our structures and scientists.

Is there anything else coming? We have done a remarkable thing. Is the indication that dexamethasone is something that works sending people off to look at other drugs that interfere with the immune system? What are your thoughts? I can see Professor Van-Tam waving his learned finger at me.

Professor Van-Tam: Thank you for the question. Obviously, that is a very pertinent question for you to ask. By way of a bit of context before I answer your question, I will say that, now, we are pretty sure that dexamethasone is pretty important, or at least, shall we say, a corticosteroid is pretty important, in patients who are admitted to hospital who require oxygen—they are at that stage of severity. The new standard of care is therefore dexamethasone or an alternative.

From that perspective, the comparison now becomes: what else can you add where dexamethasone is part of the supportive care or standard care arm? The question has now altered. It is: what is the incremental benefit of adding something on top of dexamethasone?

Q982 **Katherine Fletcher:** So you don't mean adding prednisolone on top of dex, for example.

Professor Van-Tam: No.

Q983 **Katherine Fletcher:** You mean a complementary—

Professor Van-Tam: Dex is a constant now as the underpinning therapy, so it is kind of, "What else do you get back?"

RECOVERY has not finished; it is not finished by a long chalk. If, regrettably, as Professor Bell said in the previous session, there is a resurgence of disease this autumn/winter, RECOVERY will again be busy and continuing to do its work.

I am expecting RECOVERY to be able to give us a readout fairly soon on another of its arms, which is azithromycin. I recognise that that is an antibiotic, and the listeners—not the Committee but the listeners—will be saying, "That sounds very bizarre for a virus." Azithromycin, as you know, has a very potent anti-inflammatory effect in the lung, and that is the reason why it was chosen as a potential arm. On top of that, of course, it is widely and easily available. That is also important to us, because we can discover anything wonderful we like, but if we cannot actually get it and give it to NHS patients, what does it mean?

From that perspective, I expect the azithromycin RECOVERY triallists to be able to give us some pronouncement on that fairly soon. They are also evaluating an IL-6 inhibitor called tocilizumab—

Q984 **Katherine Fletcher:** I am sorry to interrupt you. Forgive me for being nerdy. We probably should explain what an interleukin is, for the benefit of the tape.

Professor Van-Tam: In other words, it is a sophisticated drug that damps down the immune response in those very severely ill patients. Again, the phenomenal success of RECOVERY is that there are many hundreds of patients already randomised to that treatment, and it is likely to be, when it reports—it is not ready to report yet—the largest study of an IL-6 inhibitor in the world and, therefore, most likely to give the most solid signal.

That is not the end of the story. RECOVERY is also now evaluating convalescent plasma, which is the plasma from patients who have had proven Covid-19, have recovered and therefore have antibodies in their blood. The plasma will contain the antibodies; that can be infused back into other patients who are notably unwell with Covid-19, and may be of benefit. There is certainly quite a historical literature that convalescent plasma may be important and may reduce mortality in severe respiratory virus infections, although obviously not proven yet with Covid-19. That is another readout that I would expect from RECOVERY in due course.

Beyond that, the Therapeutics Taskforce has a committee that is looking deeper and further afield for novel medicines, either repurposed or completely new, which might have a role to play in the treatment of Covid-19, even though they were not initially intended or designed for that. Those trials have started in very small scale. We plan to try to incorporate more of them into RECOVERY, to use that national branding and national footprint to get them going a bit more. That is going to require the patient numbers. Of course, at the moment, disease activity is thankfully low in almost all parts of the UK.

Just to give you and the Committee a flavour of the kinds of things that are going to be looked at there, there is a novel antiviral called bemcentinib—we can send on this list to the Committee afterwards.

Chair: Thank you; we would be very grateful.

Professor Van-Tam: There are a range of different monoclonal antibodies; there are some tyrosine kinase inhibitors and a protease inhibitor. There is a common drug called spironolactone that reduces ACE-2 receptor expression in the lung and therefore may be important in preventing the virus from binding in the lung. There are some anticoagulants in there, both parenteral and inhaled or nebulised.

There is quite a lot there trying to target, without going into the detail, multiple different pathways in the pathogenesis of Covid-19. We do not fully understand those pathogenic pathways yet. That would be tough

going for a virus that we only first knew about five or six months ago, so, from that perspective, that is a voyage of discovery too.

Q985 **Katherine Fletcher:** What we are worried about is a second spike coming in winter as people start spending more time indoors, and the wonderful efforts that have gone in to stop the NHS getting overwhelmed by very sick people. A lot of what you were talking about there is about reduction in mortality and helping people spend less time in hospital. Are any tests going on to stop the disease progressing from the point where you need to get admitted to hospitals, in other words, to minimise its—I have forgotten the proper word—but to minimise how awful it is? Maybe, Dr Sheffield, you could help.

Dr Sheffield: We have run, also, the PRINCIPLE trial. That was incredibly fraught with difficulties, mainly because it was aimed in primary care, with the specific purpose of hopefully stopping patients from getting to the state where they are admitted into hospital. We had enormous problems delivering that trial, because of the lockdown of general practice. We had to continually adapt the design of the trial and how we got the supplies to people who were in lockdown. There was a whole chain of really complex logistical problems in delivering that trial. So what we have done over the last two months is to try to redesign that trial in a way that will be much more effective if there is a second wave, because we are going to have to expect that patients will only be seen remotely by primary care.

We set up a call centre with the NHS 111 system so that when patients were reporting their symptoms, which was more common than reporting them through that route than through their own primary care practices, we could put them in touch with the central primary care research team in order that they could be recruited into the study. What we are looking at, at the moment, is what products we would be interested in in aiming at that group of people.

Q986 **Katherine Fletcher:** Where are you in that process, just in terms of understanding what we could be evaluating?

Dr Sheffield: One of the things that we are looking at, at the moment, is convalescent plasma. We already have the study going on in RECOVERY and in REMAP-CAP, our ITU-based platform study. What at the moment is being written up by the National Health Service Blood Transfusion Service is a model for taking that convalescent plasma study out into the community when people are infected early. We feel that that might have a much bigger and more profound effect because you are treating the virus at an earlier stage, but the logistical problems of delivering a trial in those circumstances, clearly identifying that the people have Covid and then the testing, is something that we will really have to work hard at to make sure we have all the systems and processes in place in preparation for that.

Q987 **Katherine Fletcher:** Never mind getting the volume of convalescent plasma available.

Dr Sheffield: Great progress has been made on that. That was the initial problem. When we started the convalescent plasma trials back in May, supply was the problem. You have to wait 28 days for the convalescent plasma to have the levels of antibody. What we were finding was that it is the sickest patients who produce the most antibodies, and at 20 days post infection, even if they have recovered, they are still very ill, so 40% of the people who were donating their plasma were not fit to donate their plasma. We have had to make all sorts of adjustments, and the National Health Service Blood Transfusion Service will be able to explain that in much more detail than I can. There are over 9,000 units at the moment in storage, and that collection is continuing.

The advantage of the convalescent plasma is that it is a local resource and also it can store for up to three years, so we are building stocks of that at the moment. The really interesting question will be: does it work in recovery? Also, does it work in early disease in the community?

Q988 **Katherine Fletcher:** I have one more, if I may. That is really, first, scientifically interesting and, secondly, good luck. I would love to see the results. However, that is not going to be something that is made available to everybody that has not had Covid, by volume. It does not matter if the answer is no, but is there any indication at all of a test where we can all pop a pill if we get it and that helps us to minimise the worst side-effects?

Professor Van-Tam: You are illustrating a tension here that the lower you go, if you like, in the patient pyramid, the much greater numbers you have in primary care, and so anything that you are going to discover that works at that early stage, which can be given to patients while they are still a bit poorly but not very poorly in the community, you, first of all, have to be able to deliver at scale—real scale—which means very high volumes of supply. On top of that, it has to be safe enough that it can be administered in a relatively unsupervised community setting, which is very different from the 24/7 staffing on even a general hospital ward. From that perspective, it is a different challenge altogether.

Right now, even if you were to discover something that was highly safe but completely new and orally administered—pop a pill, as you say, just once, or, to coin a military analogy, fire and forget—from that perspective, if it was a new medicine, you would have to be secure on supply as well as manufacture; and that is another headache that comes with this whole area.

Katherine Fletcher: We are a long way off. Thank you, gentlemen.

Q989 **Chair:** Thank you. Finally from me, just on that point of manufacturing, you might have heard in the previous session that we were talking about vaccine manufacturing and the establishment of the vaccine manufacturing centre. Is your taskforce thinking in similar terms about the need for a therapeutics manufacturing centre, or is the vaccine centre able to cover both, as it were?

Professor Van-Tam: On the final question, "Is it able to cover both?", no. I am the former UK medical director of a vaccines company, many years ago. The manufacture of vaccines versus the manufacture of medicines is really very different indeed. The manufacture of medicines is very diverse indeed, from the typical kind of dry active powder that can be compressed into a pill and placed into a foil sheet, through to many of the medicines I talked about that we want to evaluate next, which are complex, monoclonal antibodies. For a start, they are proprietary and patented. For another thing, they are incredibly complex and difficult to manufacture. Trying to find a generic solution to drug manufacture is very different indeed from finding a generic solution for vaccine manufacture. Even that is not straightforward, but, for example, if you have a chemical or a cell culture bioreactor, if you have both of those, you can in theory make a lot of vaccine.

The different chemical processes involved in all these very diverse medicines are really so difficult, so you cannot just have one or two industrial options and one size fits all or two sizes fit all. That is not to say that the UK would not be perfectly prepared to look at manufacture of a medicine that could be manufactured if it had to, but, really, it is not in the same space where you can invest in the facilities and then wait for which vaccine makes it, if you like. This is a different space, where you have to know what is going to make it through the clinical trials process and then say, "How do we manufacture it, and can we even do so in terms of its patent status?"

Q990 **Chair:** Indeed. Obviously, we have talked extensively about the benefits in taking therapies that are familiar and have been tested and produced for other things. If there are some therapies that are new and require manufacturing facilities to be built up, is the UK a contender for that, and is there anything we can do to make ourselves so?

Professor Van-Tam: I don't really have the answer to that question, personally. I would not want to just speculate and give you some kind of waffle, so I won't answer.

Q991 **Chair:** Obviously, the Vaccine Taskforce very much has this in its scope.

Professor Van-Tam: Yes.

Q992 **Chair:** That is not part of the remit of your taskforce.

Professor Van-Tam: The Therapeutics Taskforce very much has that within its scope and within its remit. It is currently reporting in through BEIS, so it is reporting in through the right piece of Government to have that ambition for manufacture, but what I am saying to you is that, right now, there is nothing obvious in that target space, where we need to be working at the same pace or intensity that we have had to work from day one in the vaccine space.

Q993 **Chair:** I understand. Then, perhaps conversely, there may be a need for commercial negotiators to negotiate supplies from other manufacturers around the world for therapies that might be licensed elsewhere.

Professor Van-Tam: Yes, indeed. Yes, absolutely. *[Interruption.]*

Q994 **Chair:** We have a Division; that explains the bell. Just perhaps a final question if you can still hear me, Professor Van-Tam, above the din.

Professor Van-Tam: Yes.

Q995 **Chair:** We talked a bit with Professor Bell—Sir John—about what we discovered through the pandemic. We know much more now than we did at the beginning. One of the things we know is that asymptomatic transmission is a pretty common feature of most countries in the world and therefore practice should develop in response to that. What are your reflections on the implications, perhaps as deputy CMO, for the testing regime in NHS settings, given that we know that upwards of 42% of people may be asymptomatic?

Professor Van-Tam: As I understand it, and having checked recently with NHS colleagues, there is now plenty of capacity for testing, and every single patient that is admitted either for elective surgery or as an emergency admission, whether for Covid-19 suspicious symptoms or for something else like a broken leg, is tested for Covid-19. I think that is really important. The programme of testing and having a low threshold for testing in staff is important, but I do think there are limitations to what you get back from testing.

Let me be clear on this. The incubation period for Covid-19 may be typically five days but is described as up to 14 days. If you were an individual, sir, who was infected, and it is ordained by a higher power that your incubation period is going to be 10 days, and you were infected yesterday, I can test you on every day for the next eight days and your test will be negative. I will only hit the bullseye, if you like, on day eight, two days before your symptoms begin. So you can see the problem you have in terms of false reassurance of negative tests unless you are testing extremely frequently indeed. You have to think very carefully, with 2.5 million workers in our health and care sectors, how you could do that in an extremely frequent way right across the piece. That is just a word of caution. Yes, testing is incredibly important. Yes, we are now in a place where we can do a great deal of it, but there are limitations to what you can get back, in terms of reassurance or management tactics, from a negative test.

Q996 **Chair:** I understand that, but that applies to every negative test result from anyone.

Professor Van-Tam: Indeed. Indeed, at the moment, because we have a very low level of disease, you will get false positives too, and so this is not magic science, if you like.

Q997 **Chair:** In general, we now have enough testing capacity to have the option of testing people. Is that your assessment?

Professor Van-Tam: My understanding is we have a lot of testing capacity now, and that may well be important if we get a resurgence of disease in the autumn. It is very important for our test and trace facility

going forwards, and it is very important for testing all our patients who are admitted to hospital for other reasons.

Q998 **Chair:** Just a final point in terms of the false assurance of a negative result that may be before the disease is detectable. Is it not the case that, if you do not have tests at all, then, in effect, you are drawing that same false assurance through not having symptoms? If you continue to work in a setting in which you are with vulnerable people, are you not at least giving some more useful information? You are closing down the level of—

Professor Van-Tam: I am absolutely not arguing for no testing—absolutely not. I am just making, I hope, a very clear point that testing is extremely important, but it is not without its limitations.

Chair: We are very grateful to you both, not just for your evidence today but, as my colleagues have said, for your extremely important and extraordinary work. We are very grateful for everything you are doing on behalf of the country, and indeed the rest of the world, when it comes to some of these discoveries. We are very grateful for you giving evidence to us today. We want to make sure that we learn the lessons, so that we can make sure that we apply them and do all the things that we have done well during this pandemic deliberately in future and can build on the successes and, if there are learnings to be made as to how to do things differently, we can do those together. That is our purpose, and we are very grateful for your assistance with that endeavour today.