HOUSE OF LORDS

Select Committee on Science and Technology

Corrected oral evidence: The science of Covid-19

Tuesday 19 May 2020

10 am

Watch the meeting

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

Evidence Session No. 1 Heard in Public Questions 1 - 10

Witnesses

Professor Danny Altmann, Professor of Immunology, Imperial College London; Professor Jonathan Ball, Professor of Molecular Virology, University of Nottingham; Professor David Robertson, Head of Viral Genomics and Bioinformatics, University of Glasgow.

USE OF THE TRANSCRIPT

Examination of witnesses

Professor Danny Altmann, Professor Jonathan Ball and Professor David Robertson.

The Chair: Good morning all, and a particular welcome to our witnesses this morning for the first session of the Science and Technology Committee's current inquiry on the science related to Covid-19. May I ask Baroness Blackwood to start the first session, please?

Q1 **Baroness Blackwood of North Oxford:** May I thank the witnesses for joining us today? Would you start us off with some basics and give us an insight into how viruses are structured and classified and, in particular, how Covid-19 is structured?

Professor David Robertson: We look at the genome architecture and in particular gene structure. When you find a new virus, the big challenge is to find the homologous sequences that are available. What is really interesting with SARS-CoV-2 is that it is very closely related to the SARS-1 virus, or has a very similar genome structure, so very clearly it has emerged from the same part of that evolutionary tree, which includes lots of bat viruses.

Q2 **Baroness Blackwood of North Oxford:** That takes us to another question. Could you explain how this is a new and novel virus and what that has meant for the way it has had to be managed?

Professor David Robertson: Across its genome, on average it is about 24% different in sequence identity, which sounds high but for a virus is not that high. In China, there is a radiation of viruses in horseshoe bats. What is interesting about this virus is that it has emerged at the very extreme of that known radiation or known diversity in China. Lots of research was done after the first SARS virus, even identifying viruses in bats that can transmit to humans. What is interesting here is that there is what we call a sister lineage, which existed in the phylogenetic tree, and that is where SARS-CoV-2 has emerged. There were only fragments of that lineage previously known about.

Baroness Blackwood of North Oxford: What is its rate of mutation? Is it a fast-mutating virus or not?

Professor David Robertson: It is an RNA virus. Typically, RNA viruses are quite fast evolving, but these coronaviruses have some error correction, so it is a relatively slow-evolving RNA virus. Everything is relative, but it means that it is quite slow evolving. In some ways that is what is making it so interesting, because it has evolved to the human system within bats. Clearly we are going to have to discuss that.

Professor Jonathan Ball: To add to David's comment about the mutation rate, it is fairly stable as regards the errors incorporated as the virus replicates, but these viruses are well known to genetically recombine, so if you get an animal or a human infected with two different strains, they can swap gene sequences, and that contributes quite a lot to coronavirus genetic diversity.

Baroness Blackwood of North Oxford: And Professor Altmann.

Professor Danny Altmann: I have nothing to add.

The Chair: Professor Ball, in what way does this combining of genes lead to, for example, Covid-19?

Professor Jonathan Ball: There are certain genes within the virus which we think are less tolerant to these sorts of switches. Some of the genes involved in the replication of the virus are a lot more conserved, but if you look at the key protein on the surface of the virus, the spike proteins, which is what gives the virus its appearance and makes it look like a crown—hence "corona"—we know that those genes can acquire fragments from other viruses.

If we look at the coronavirus circulating at the moment, the SARS-2 virus, we know there are fragments of the spike that look very similar to coronaviruses found in an endangered species called the pangolin, in particular the region involved in receptor binding—the receptor on the surface of the cell to which the virus has to attach. That has great similarity to the viruses circulating in the pangolin. It may well be a natural recombinant between bat viruses, for example, and viruses that have been circulating in pangolin, but it still needs to be proved.

Professor David Robertson: To clarify, we have looked at that recombinant signal, and although there is a part of the pangolin virus, a very small part of the spike, that is closer to the human SARS-CoV-2 lineage, it looks very much like the RaTG13 bat virus has recombined. A different virus is thus the recombinant, and RATG13 has moved away, giving this artificial signal that SAR-CoV-2 and the pangolin virus are closer. The evidence is pointing to this important evolution, and these recombinant events, occurring in bats.

Viscount Ridley: Professor Robertson and I corresponded about this some weeks ago, and he was very helpful in explaining some of this, but may I pin him down on one thing? He is saying that the virus in the bat was already capable of infecting human beings, and that that is quite an important discovery which we did not appreciate. I know we are going to get on to the origin of it later in the session, but I think that is quite an important point to get on the record.

Professor David Robertson: Would you like me to comment on why I think that is the case?

Viscount Ridley: Yes, please.

Professor David Robertson: Essentially, what appears to have happened is that the virus that has evolved in the bats is a bit more of a generalist than usual. What is interesting about these coronaviruses is that they tend to transmit between these different horseshoe bat species, but because they are slower evolving that permits this normal jumping between bat species. By chance, the virus that has evolved in this lineage is more of a generalist. It is not pre-adapted to humans only. It is just a bit more of a generalist virus. That has been borne out by the finding that it replicates in ferrets and cats, and it has been found in pangolins as two

divergent lineages. Importantly, natural evolution in the bats seems to be happening.

The Chair: Does that mean that an intermediate host was not necessary for this virus to develop?

Professor David Robertson: That is the bit that is very hard to say. Although the closer RaTG13 virus in bats is only 4% different in sequence identity, when we do what we call molecular clock dating analysis it shows that the divergence of SARS-CoV-2 and RaTG13 is about 40 or 50 years in time, so there is quite a lot of evolutionary opportunity where a virus could have jumped to an intermediate species. However, the key point is the important evolution we believe is occurring in the bats, and if there was an intermediate species involved it was probably more of a carrier[1]. It could have been a species like the pangolin, which comes into contact with humans more often. The bit that we need to know urgently is what the transmission chain was into humans.

The Chair: Is there a general agreement among virologists about what you have just said?

Professor David Robertson: There has been an enormous amount of research done and an enormous number of preprints and published articles, and if you were to look at the average signal in that literature you would find quite a noisy signal, but for the people who have been looking very carefully at this, and the people who have tackled the idea that it is somehow non-natural, there is very much agreement between virologists that this is all consistent with natural evolution. If you look back into the first SARS literature, people like Ralph Baric have written articles that say that SARS virus is poised to jump from bats into humans. What has happened (the pandemic) was predicted by people who worked on these viruses previously.

The Chair: Do the other two witnesses want to comment on bat viruses generally?

Professor Danny Altmann: Could I endorse everything that has been said, with a bit of an overview? I speak uniquely among these witnesses as a professor of immunology, not a professor of virology, and I am an enthusiastic amateur when I read all these manuscripts. I see an enormous weight of manuscripts over the last decade or so cataloguing more and more sequences of more and more bat viruses in particular, and potential zoonoses, and people trying to get momentum behind the effort to track potential zoonoses, spot them on the horizon, and fill in the narrative of which intermediate species they may get to us through, and trying to raise the alarm over many years.

The Chair: Professor Altmann, you are not just an immunologist, you are the immunologist.

Professor Danny Altmann: That is very kind.

Q3 **Lord Borwick:** What are the properties of coronaviruses that make them

[1] i.e. a conduit for infection of humans, not a true reservoir based on current evidence.

a risk for pandemics, and how do they differ from influenza viruses?

Professor Jonathan Ball: On the question of why they are a potential risk for pandemics, we have just heard from David that some of these viruses are almost ready to go in humans. They do not have to acquire too many mutations, if any at all, to make the jump to be able to infect human cells. That is the first important step in being able to successfully infect humans, and some of them will go on to transmit in humans. Over the past two decades we have seen the appearance of SARS first in 2002 and the MERS coronavirus in 2012, both of which highlighted the potential that coronaviruses have to make that jump into humans.

The other key thing is that they have been around for millions of years, so if we think about the animals that we are most likely to interact with—rodents as well as bats; we must not overlook rodents—all these species have a lot of coronaviruses naturally infecting them, so there is a huge potential reservoir for these spillover viruses. They have similarities to influenza. They are respiratory viruses and they spread via the respiratory route, but in terms of the way they transmit we know that influenza has a more rapid incubation period. We know that with influenza you get what we call pre-symptomatic shedding—somebody can shed the virus before they show symptoms. We suspect that also happens with the novel coronavirus, but in their general behaviour they are very similar, so the sorts of risks for the transmission of virus are very similar.

Professor David Robertson: The coronaviruses are a particular problem, because they seem to be able to replicate so efficiently immediately on entry into the human population. Normally, we think of RNA viruses as being fast evolving and able to adapt quickly to new host species, whereas here the virus is getting in the human population and, as we have seen, is so transmissible so immediately. It is very terrifying.

Lord Borwick: That is a property of the CoV-2 virus that makes it more difficult to deal with. Are there any properties of the virus that make it less difficult to deal with? Are there any vulnerabilities?

Professor David Robertson: It has a very large genome of about 30,000 nucleotides. Because it has quite a slow mutation rate, it has the luxury of adding extra genes and functions to its system. This gives us lots of targets for drugs. There should be ways to interfere with this virus—hopefully—just because it is more complicated in terms of genome organisation than other RNA viruses.

Professor Jonathan Ball: May I also pick up on an important factor for the novel coronavirus? At the time of the outbreak, a lot of commentators and my colleagues were suggesting that this virus would turn out very much like SARS and that it would be easier to contain. Unfortunately, with this coronavirus, which has caught us off guard, the vast majority of infections are very mild, which has given the virus the opportunity to spread, to transmit in human populations, without people realising that it is around. Eighty per cent of people infected with SARS had very serious illness, and almost 100% of people had a fever, so it was very easy to identify people who were infected, to isolate those people and to contact

trace and bring the outbreak under control very quickly. This current coronavirus has caught us off guard because of that mild symptom presentation.

Lord Borwick: That is very interesting, thank you.

Professor Danny Altmann: The question was about the points of vulnerability and whether there was any good news. I feel that in the immunology of this the vaccine community has been very much to the fore and, in a way, quite gung-ho in rolling out strategies.

When we think about how and why that has been the case, there is perhaps a glimmer of good news. When I think about the recent history of vaccines, some diseases have been really intractable and we have had really slow progress. Diseases such as HIV, malaria and tuberculosis are very complex immunologies to narrate in terms of which are the antigens and which are the targets that need to be attacked by the immune system.

There is a gathering consensus around this infection that if we could identify really potent ways of blocking virus entry through the interaction of spike with the ACE2 receptor, by whatever means that is, or whatever kind of vaccine that is, with minimal adverse events, that might do the trick. I see that as a kind of vulnerability.

Professor David Robertson: I would add that it is an acute virus. This is so important and means that most of us naturally clear the virus/infection. Our immune response tackles it and gets rid of it, unlike HIV where there are no natural cures, (i.e., no immune clearance) and nobody ever clears the virus even when anti-viral drugs are used. That means that SARS-CoV-2 is inherently vulnerable merely through its life cycle as an acute virus.

Lord Winston: Professor Altmann, does the fact they go through animals make that an easier way of getting a target to affect the virus?

Professor Danny Altmann: Absolutely. I would be interested to hear what the virologists say about this, but I can remember many high-profile programmes going back many years, certainly in this country at the Wellcome Trust and the MRC, and in America through the NIHR, placing quite high emphasis on trying to track those zoonoses and those intermediate hosts, with precisely that kind of strategy in mind, because that is obviously the way to go. When we look back on this in years to come with the wisdom of hindsight, which is terribly easy to do, we will curse ourselves that we did not do more of it, but it is certainly the way to go.

Professor Jonathan Ball: The idea of being able to identify and track potential future pandemics sounds very appealing, and there are certainly areas where that is possible. The SARS cluster of viruses, for example, which David so eloquently described, is a group of viruses that are ready to go into humans, so they have to be monitored very closely, particularly those living in proximity to those viruses and the reservoir species.

We also have a fairly good idea of the sorts of groups of viruses that are likely to make future spillover events, and to have that kind of surveillance, not necessarily in the animals but certainly in populations that are most at risk from future pandemics. That is what we call sero-prevalence studies, which look for antibody evidence that people have been exposed to different viruses, as well as actively search for viruses.

We have fantastic genomic technology these days, which can trawl through the genetic sequences in a person and identify viruses very quickly. It is reasonably trivial work, but of course it is expensive, and you have to be in the right place at the right time to spot the virus in the reservoir host or in the people. It is a big thing in the United States to throw lots of dollars at these kinds of PREDICT or EcoHealth Alliance-type projects, where you go out surveying wildlife, but it has to be very well thought out to ensure that the money is well invested.

Professor David Robertson: I concur entirely. We have to get better at monitoring the animal-human interface. Some of these large studies that have tried to predict every possible virus in the world that might get into humans are very ambitious. This virus is so typical of the types of virus we need to monitor for. We knew it was probably going to re-emerge. People have even done serology studies. There are a few papers in the scientific literature where people living in proximity to bat caves were found to have evidence of 1% to 2% serology for antibodies linked SARS-like infections. That means that people were getting unsuccessful incidental infections. When you have an outbreak like this, it undoubtedly means that there were many times when the virus got into humans but did not take off.

We need to get much better at prioritising the identification of viruses that are getting into humans. MERS is a good example. Almost every case of MERS was from a camel to a human. We should be trying to control that, because if that virus became slightly less virulent and more transmissible, you would have a very dangerous virus on the scene very quickly.

The Chair: What do you do when you identify that a virus like Nipah has gone through a human population and is probably dangerous?

Professor David Robertson: You have to be very good at surveilling what makes people sick. You have to be working very closely with hospitals. If somebody is sick, you need to know what is making them ill. Even in this country people get sick with viruses all the time. They are not usually identified. We just assume it is flu or something. We need to get better at monitoring what viruses are in the human population, where they are circulating, how often they emerge. That is just resource. We need to do it routinely. I guess that before the pandemic it would have been seen as very expensive, but now it is clear that the cost of not doing it has been much higher than if we had been better at surveilling the animal-human interface.

Q4 **Lord Browne of Ladyton:** To some extent, perhaps even to a large extent, this question has been at least engaged with and may even have

been answered. I want to be very specific about what we have just been talking about, and I suppose this goes to the virologists, so I will ask you, Professor Robertson, to answer this question first and then Professor Ball and Professor Altmann may want to comment.

To what extent are virologists able to predict which viruses may become threats in the future? How do they make such predictions? To some degree you have suggested what we should do to do that. Should we expect other coronaviruses to become threats in the future? I know the answer to that is yes, but it is still quite interesting.

Professor David Robertson: As somebody relatively new to the SARS field, I was shocked after I started reading the literature to find papers saying that the SARS virus was poised to jump species from bats. That is not the exact paper title, but when SARS emerged research was done, over subsequent years, that showed that related viruses were found in bats. People took these bat viruses and showed that some could replicate in human cells. They absolutely nailed the risk. The science was done, the research was in, but it feels like there is a gap there between basic science and public health, where you have identification of a risk but no appropriate action. I guess that is typical of many systems where you do some kind of investigation into where things went wrong. Often the information is known but is just not acted on appropriately.

Going forward, it should be possible to set out a list of viruses. Coronaviruses are now top of the list perhaps, but we have to worry about lots of other viruses, and invest in finding out where they are circulating and getting ready with medicines that are perhaps targeting host molecules that would work in advance of a virus being identified. It is all within our capabilities. We can do all this type of research. It will just take time and effort to come up with strategies.

Baroness Manningham-Buller: Professor Robertson, are you aware of the work which the Coalition for Epidemic Preparedness Innovations has done on these vaccines, because before this pandemic quite a lot of work was done to look for vaccines against SARS and MERS and this emerging coronavirus threat? You are saying that not enough was done. A certain amount was done, but obviously it was not enough.

Professor David Robertson: We eradicated SARS. My understanding is that there was a lot of contact tracing and a real effort to get rid of SARS. What we should have done, even though it had been eradicated from the human population, is to have kept investing in SARS research. I am not an expert on this, but my understanding is some of the vaccine research that was in play was not continued. We did not follow through, because I think we thought that the threat had been lowered. I think that is the answer.

Baroness Manningham-Buller: Do you accept that they were working on SARS and MERS but had not got that far?

Professor David Robertson: There was a lot of research into SARS and a lot of concern about it, absolutely, yes.

Professor Jonathan Ball: To follow up some of the points that David raised, we suspect that the sorts of viruses that are likely to spill over are clearly those present in wildlife populations, potentially even domestic animals; in other words, animals that have a close interaction with humans. Of course, the way we lead our lives in the 21st century means that the human-animal interface is getting more intimate week by week and month by month. Humans are encroaching into what used to be very isolated habitats and populations of wild animals, and therefore increasing the risk. That is where these PREDICT projects stem from. They are trying to pre-empt where the viruses are likely to come from. We suspect that certain virus families have the potential to jump species. At the moment, the WHO's list focuses on species, and I think it would be well to broaden that out to think of larger groupings of those viruses, such as genera, or even families of virus.

If we can take that approach of looking for evidence of human spillover, we can also start to develop more broad strategies of trying to develop not only vaccine platforms but drugs that can act across various species of virus. We know, for example, that a drug called remdesivir is being trialled for the novel coronavirus. It was a drug that was originally developed for hepatitis C and it was then trialled for Ebola. It works against one of the enzymes that viruses have. All the enzymes in these families of viruses are potential targets for more broadly acting antiviral therapies. Hopefully, that would give us a bit more resilience against the next pandemic because, in truth, we have not been very good at predicting pandemic threats.

Lord Browne of Ladyton: I have a further question. This is an issue of some controversy at the moment, but it is not the controversy we are interested in, it is the science. Was the global community prepared for a coronavirus pandemic or was global planning focused on influenza? If that was the case, why?

The Chair: Was the global community focused on an influenza pandemic rather than a coronavirus pandemic? None of the witnesses has any comment.

Professor Danny Altmann: All I would add is that I think there was an overwhelming focus on influenza outbreaks. One of the lessons from all this will be to state the obvious, but sometimes it needs stating—that we had all our international surveillance platforms kind of in place. We had had all these discussions that I can remember through CDC, the World Health Organization, the Wellcome Trust and 'HIRO' – the heads of international research organisations.

There was lots of discussion about things like this being on the horizon. I saw a paper in *Nature* about the origins of coronaviruses, which stated that the resulting data would help prevention and control of emerging SARS-like diseases in the future. That was dated 10 December 2018, almost exactly 12 months before this outbreak, and whatever we did it just was not enough. To me it is an argument for more international, joined-up preparation on a grand scale.

Q5 **Baroness Hilton of Eggardon:** To turn to rather a different topic, in what way does the virus attack particular tissues and cells in the human body? Why is it so infectious? Why does it attack particular sections of the community like the elderly more than others?

Professor Jonathan Ball: I will start, but I will hand over very quickly to Danny, because a lot of the pathology around the novel coronavirus is around the immune response and how it might sometimes go wrong. The virus works by attaching to cells that express a particular molecule on the surface called ACE2. We find that through the respiratory tract, particularly down in the lungs, and in other tissues such as the gastrointestinal tract. Once the virus locks on to that receptor, it can gain entry into that cell and start to replicate.

One of the unusual features with the current novel coronavirus is that it has in its spike protein—the surface protein that locks on to the receptor—an inserted genetic sequence which we think increases its efficiency to use that receptor. There is some evidence that it might increase its ability to do that. That might in turn have allowed the virus to replicate to a very large extent in the nose and throat of people who are infected, and that hugely increases its potential to spread, whereas SARS was predominantly a virus that was infecting deep in the lungs, and it was a lot more difficult for that virus to spread. It has to spread through coughing. Something replicated in the nose and throat is more easily transmitted. That is also a key difference between SARS as was in 2002 and the current strain of the virus.

Professor Danny Altmann: I would endorse all that. A simple point is that viruses that can attach and enter via the upper airways have a head start, because they are going to be much more infectious. That has been a big difference, for example, from the MERS story, and it caught people off guard.

To tell the story of this infection and this pandemic, when you consider that this sequence has been known now for four months, the learning curve has been very steep. The tendency is to start with generalisations and analogies because you have nothing else and then to drill down more on the details and differences. That has very much been the case here. The more we have learned—and we have had to do it in terribly rapid time—the more we have realised that, like any infection, the depth and details are rather different from stuff we have seen before. Sure, there is the pneumonia, the capillary congestion, the strokes, and what people call the cytokine storm—the overexuberant immune response. But it is not quite a typical overexuberant immune response or one I have ever seen before, so even that analogy does not work well.

The immune mediators talked about here are cytokines, the immune molecules in your blood, but the ones that are dysregulated here are not ones that I have seen specifically in a dysregulated pattern before—mediators like interleukin-1, interleukin-6 and tumour necrosis factor. It is a unique story that is being told in real time in emergency conditions by really talented people.

I am amazed at the papers I see coming out more or less on an hourly basis. Part of the story it tells about the ACE2 receptor for the virus is by looking at which parts of the body it most lives in. That gives you an answer. It says we should be looking in the lungs, then the kidney, and then the heart. That is what has happened. If you look at sick people on ITU, those are the bits that have packed up and gone wrong, because that is where it has attacked. It is not just a lung story.

The Chair: Professor Ball, do you want to come in?

Professor Jonathan Ball: No, I think essentially that is it. It is obviously a lot more complex disease presentation than a lot of my clinical colleagues who are working and dealing with these patients in ICU have seen before. Patients are presenting with very unusual pathologies, particularly with the amount of clotting that they are seeing in the pulmonary system, which is adversely impacting on a patient's ability to get oxygen into their blood. Unfortunately, it was very much a case of learning from the start, because what we knew from SARS and what we knew from influenza did not help to a large degree.

Professor David Robertson: It is very important to appreciate that this is about how people are responding to the same virus. There is a very strong age response and comorbidity response, which seems to be linked to immune dysregulation, so the virus is causing the immune system to go out of control, and those kinds of pathologies in your immune system are associated with ageing.

Also, ACE2 has very important protective functions in the lung. If the virus is knocking that receptor down, it is potentially being directly pathological, in addition to having an immune pathology, which many viruses cause. But it is the body's response that is being bad for the infected individual's health, this virus is also taking down this important molecule (ACE2). There is some evidence that in older people you have less ACE2 and there are some potential interactions going on there. The virus attacks on many fronts.

The Chair: Are you suggesting that we have not come across a virus that behaves in the way this SARS-2 behaves in its cytopathology and that we are having to learn a completely different science?

Professor David Robertson: It is very close to the SARS virus in its biology. It is using the same receptors as the first SARS virus. The first SARS virus caused lots of pneumonia and ARDS and a lot of these different syndromes, but it did not infect so many people. The first SARS virus infected over 8,000 people, so it was a much smaller sample set. In China it did not seem to infect as many old people, but that was probably just because of how it manifested epidemiologically. I would be a little cautious about saying that this is very different from SARS-1, but from the emerging data it seems it is much more than just a respiratory virus; the way it is affecting the gut and other parts of the body seems to be new.

The Chair: Professor Altmann, do you agree that the immune responses are completely different from other viruses, or are they the same?

Professor Danny Altmann: I think it is completely different, but as a professor of immunology I think all immune responses to all viruses are different from all other viruses. That is what keeps us in a job. Whenever we try to make generalisations about this virus based on what we already know, it has come back to bite us because it has so many special and exotic features. One of the interviews that I enjoyed very much was with the Italian Minister of Health, who is also a doctor, who described it in his English as a 'very deceitful virus'. I loved that expression. I think this is a deceitful virus and it does strange things when you least expect it. All bets are off and we simply have to do very good research to work out the rules of this virus, not especially by comparison with other viruses.

The Chair: Our Prime Minister described it as an invisible mugger.

Professor Danny Altmann: I prefer deceitful virus, but anything goes.

Q6 **Lord Hollick:** To what extent do we understand the origin of this virus? How do we know whether it is a naturally occurring virus? That view is contested by no less a person than President Trump, who, based on his researches and his advice, has asserted that it was in fact made in a laboratory in Wuhan. Would you like to comment on that, Professor Ball?

Professor Jonathan Ball: I will certainly comment on it, but I suspect David will have a lot closer understanding of the genetic evidence against that. Put quite simply, if you were to ask a virologist to design a SARS-like coronavirus, there are potential recipes out there, but the current virus is not one they would have produced. From what we knew of the previous SARS coronavirus, and what we knew of related circulating coronaviruses in those horseshoe bats, and everything that we know about what the virus needs to have to be able to infect humans, it would not be the one that we would come up with. I will hand over to David, because he will be able to explain the nuances in there, particularly around things like receptor binding, et cetera.

Professor David Robertson: This virus has been surprising. It behaves in ways that are different from the first SARS virus. Despite having a very good sample of the related viruses in bats, it has emerged as a sister lineage to that group. Interestingly, in some of the recombinants in the bats we talked about earlier, there are elements of fragments of that lineage, but they would probably have been ignored. That is what happened with the RaTG13 virus. They had this virus in a lab, but it had been ignored, presumably because it was seen as low value, being so divergent from the first SARS virus. It is unpredictably different, and we are not clever enough to have designed this virus. It is far too unique.

Although in terms of evolutionary history the evidence is absolutely solid that there are viruses in bats that are highly related to SARS-CoV-2, there is evidence now of related viruses, probably through direct transmission from bats, circulating in pangolins. There is a highly complicated recombination history that goes very deep into the evolutionary tree, so these viruses are essentially churning over in the bats due to them evolving in the bat species presumably due to pressure from the bat immune response.

Lord Hollick: By what mechanisms do viruses such as this pass to humans from animals?

Professor David Robertson: Using the same receptor, ACE2. Because of our evolutionary history with other animals, we are sharing receptors with them, and the virus (SARS-CoV-2) has to be able to evolve to use our receptor in a similar way. It is not that the virus in the bats evolves specifically to use human receptors. It seems that, either through compartment change or through some kind of evolution of bats, it has become a bit more of a generalist, so it is able to use the receptor in more diverse species, and we have just fallen into that range. In some ways, it is just bad luck that this has happened.

Lord Hollick: But if this transfer mechanism is so well known and understood, why have steps not been taken to address the source of it, such as wet markets in China?

Professor David Robertson: That is a very good question. It is incredible that these wild-animal markets exist, given the risk. If we think there are viruses circulating in animals that have these highly transmissible SARS-like viruses, you would think we would be better at containing that. It is important to appreciate that most viruses are quite adaptive to the species they use. The viruses are very dependent on the cells in the host, so jumping species is quite a significant thing. What is unusual here is this absolutely incredible fast-forward evolution in a new host species without the need for much evolution. That is a very unusual circumstance.

Lord Hollick: Has the Chinese scientific community made clear that these wet markets are a breeding ground for this sort of virus? Have they recommended any changes to these wet markets?

Professor David Robertson: The international scientific community has pointed this out. I am not able to comment specifically on the influence Chinese scientists would have on politics. I do not know.

Lord Hollick: That is another topic. Are the viruses that originate in animals becoming more common? Are we going to see more of these types of transmissions, in your view?

Professor David Robertson: It is very important to appreciate that these kinds of spillovers of viruses moving between species are very natural, and it happens all the time. The other four human coronaviruses, that are non-pathogenic, will have spilled over in the past at some time. These kinds of events will have gone on in our evolutionary history, but as the world has become more connected and there are more humans, and as we encroach on wildlife, there are perhaps more events occurring where people are coming into contact with exotic viruses.

Professor Jonathan Ball: To reiterate that, and going back to the point about wet markets, unusually this virus seems to have been primed and ready to be able to reasonably efficiently—in fact, very efficiently—infect humans and be transmitted. Sometimes these viruses have to acquire some adaptive and evolutionary changes, and sometimes that occurs in an intermediate host. With SARS, for example, we think that it jumped

via a civet cat. We know that MERS was probably a bat virus that got into camels and then spilled over into humans.

Wherever you have a large mixture of different wild animals being kept close together, alive, there is always the chance a virus can jump from one to another and acquire some mutations, and those mutations might then enable it to infect humans and onwardly transmit. It is a lottery for the viruses. It is a game of chance, but you stack the odds in the favour of the virus if you have lots of these wild animals being kept cheek by jowl in these sorts of markets.

Lord Hollick: Professor Altmann, do you have any sympathy with President Trump's view?

Professor Danny Altmann: I am not sure where President Trump has drawn his science from, but carrying on from what David and Jonathan have said, coronaviruses have probably been crossing over for the last 1,500 years or so—that we know of—because it is something they do.

I feel there is a warning in the fact that the common cold viruses came across somewhere between 1,500 and 500 years ago and have never really left us. In the space of the last few years we have had three very devastating crossovers of SARS and MERS and now this one. I think that is trying to teach us something about the way we are living on this planet, and the way we are eroding our boundaries with the animal kingdom by the way we are living on this planet, and it ought to make us address this in some way, if we do not want that spillover to keep increasing.

The Chair: Do RNA viruses behave differently from DNA viruses in terms of jumping species?

Professor Jonathan Ball: We know that the genomes for DNA viruses are a lot more stable, so if a virus has to acquire mutations to be able to infect humans and transmit easily, it is more difficult for those DNA viruses in general to acquire that. It is a property of RNA viruses, because they are much more rapidly mutating, even though this coronavirus does not mutate quite as much as a lot of other RNA viruses out there.

Q7 **Viscount Ridley:** May I ask a supplementary here? I can accept that the evidence for the deliberate creation of this virus is extremely thin, if not absent, but there is evidence that there might have been samples handled in laboratories, the Institute of Virology and the Center for Disease Control and Prevention, in Wuhan, both of which we know were catching bats and handling their blood samples, that might have leaked to the wet market and got amplified. Can one rule that out or not?

Professor David Robertson: It seems unlikely, given that it emerged in an animal market. If you have virus that you think comes from an exotic species and you have a wildlife market, that seems the most parsimonious explanation. It is much more likely that somebody got infected and travelled on a train to get to the market. The train stations in Wuhan are probably as likely to be the source as the lab. Without

evidence, there is no way to support a leak from a lab. While it is possible, you would need evidence to support that, of which there is none at the moment.

Viscount Ridley: May I quickly ask a supplementary on that? Professor Robertson, you have said that the RaTG13 sample which they found this virus in five or six years ago is 40 or 50 years different, so it could not have been that sample that gave it to us. Is that correct?

Professor David Robertson: Absolutely not. What has driven some of these conspiracy theories is speculation about the chances of them having had this virus in the lab. Although close in sequence, it is not close in time and it would have been a low-value virus. It would have been a divergent virus and you might have said, "That's not very close to SARS-1. I'm just not going to look at that any more".

Viscount Ridley: We have reports that other scientists were collecting bats closer to Wuhan, looking for viruses, including horseshoe bats.

Professor David Robertson: There is a new one, RmYN02, published quite recently, which is close in some of the genome and is a recombinant. Again, it supports bats being the natural host, and there is really no evidence for a leak. We can all enjoy a conspiracy theory, but you need to have evidence.

Q8 **Lord Winston:** This question has partly been asked. The thing that concerns me is that we have two functions in this Select Committee, one of which of course is to help inform the public about some of the issues that worry them. Listening to this conversation, one of the concerns the public may have—not unreasonably—is about domestic animals. We have talked about wild animals, but what about domestic animals? For example, there are a huge number of dogs that interface very closely with the human population. Do we think there is risk there and, if so, should we be doing something about it?

Professor Jonathan Ball: We know that domestic animals, particularly livestock, have been the source of spillover viruses in the past. We suspect that measles, for example, came from a cattle ancestor. For truly domestic animals like cats and dogs, because they have been living with us for so long you would expect spillover events to have already occurred because they have been domesticated for quite some time.

The big question is whether they could act as intermediates for the future. As human populations expand, and as domestic animals expand their range with them, they might in theory act as an intermediate. I do not like to use influenza as an example in this case, but we know that dogs get influenza, and there is no evidence that those viruses can pass on to humans. But you can never discount it. You have to be realistic about the fact that any animal could be a potential source of viruses or act as an intermediate host.

Professor David Robertson: I would be more worried about my cat bringing a rat into the house and the danger there, because although we have talked a lot about bats it is very important to appreciate that bats

tend to have a lot of viruses because they are very successful and are very well spread geographically, but rats also carry lots of interesting viruses.

The Chair: Please do not talk to parliamentarians about vermin risks. May I pass on to Baroness Walmsley, please?

Q9 **Baroness Walmsley:** One has to wonder whether if human beings had not been eating pangolins, which is an endangered species, all this might not have happened.

We have heard a fair bit about the virus's evolutionary history in answer to previous questions and about the relatively low rate of mutation, but of course there are many mutations. Have any of those mutations directly affected transmission or even severity of disease? Do future mutations of this particular virus pose a potential risk?

Professor Jonathan Ball: Could I very quickly butt in and then I will allow David, as the evolutionary biologist, to explain it in a bit more detail? We did some work on Ebola during the outbreak, which showed that certain genetic changes in the surface proteins of that virus increased infectivity in human cells, but we do not know how that relates to human disease pathogenesis or indeed human transmission, so it is very difficult to tie changes of the virus to behaviours in humans.

We know that these viruses are likely to mutate and change, but at the moment there is no evidence that they are particularly altering their behaviour. There have been some preliminary reports showing a variety of mutations. We are very interested in what they might do to the virus, but you have to do the laboratory work, and even when you have done that you cannot be sure that it is impacting on human transmission or disease. I shall hand over to David.

Professor David Robertson: I guess the most important point is that it has already been such a successful virus from the get-go that it is highly transmissible, so even changes in transmissibility are not going to make a massive impact on its success. Wherever the virus turns up the human population is susceptible, so the virus is successful. Even a less transmissible virus in a new population would have nothing to compete with, and the population it is affecting is also highly susceptible, so it will be successful.

When we track the mutations so far, we see many. We see amino acid replacements, and we see lots of change, but no evidence of any functional change, as it were. There are some reports of a few amino acid replacements in the Spike protein, for example, which might have some effect. I guess one hypothesis is that they are changing how well the virus can latch on to the human receptor.

At the moment, these are hypotheticals. I am aware that labs are looking into this and I suspect that in the next month we will have an answer to this question. The most important thing is that SARS-CoV-2 is so transmissible and so successful, and we are so susceptible, that it is a bit

of a red herring to worry about it getting worse, because it could not be much worse in terms of the numbers of cases.

Baroness Walmsley: To clarify, you regard it as being successful, because on the whole it does not kill the host and is very infectious.

Professor David Robertson: If you contrast it with Ebola, which has a high virulence and kills very many people, which makes it very controllable as you can readily identify the infected people, this virus is infecting so many people with asymptomatic to mild symptoms that it is almost uncontrollable. We have to be clear that we are not going to be able to eradicate this virus. It is going to settle into the human population and over several years it will become a normal virus.

If anything, we are accommodating to it. Our immune systems, if we are infected, will give us some protection. We will use vaccines to mimic normal immunity. We have already changed our behaviour to accommodate the virus. It will be interesting now to see the effects of our behaviour changes on this virus, and other viruses, and to see what happens to other respiratory viruses driven down in terms of their replicative success.

Q10 **Baroness Young of Old Scone:** This question is not particularly to do with mutation but perhaps to do with a previous question of Baroness Hilton's. What makes different groups of people experience this virus in different ways and have different degrees of severity of response? We talked a bit about people with underlying health conditions, but how about minority ethnic groups?

Professor Danny Altmann: It is a discussion that has been raised many times and it includes black and minority ethnic groups. It is really important. It will be a very complex answer to do with all the obvious aspects you might imagine, such as differences in exposure and differences in comorbidities—things like hypertension, obesity, vascular disease in different ethnic groups. Then there will be genetic polymorphisms, such as differences in ACE2 receptor expression. There is a whole range of things that we will need to look at, including differences in the immune response with ageing, to try to build a composite picture of differential susceptibility.

Baroness Sheehan: How many genomes are there, as a stab? Is that number dependent on the number of people infected? I suppose what is concerning me is the importance of ensuring that it does not get a hold in a continent like Africa.

The Chair: I presume the question is whether the genomic differences in different populations have an effect on transmission. Is that right?

Baroness Sheehan: It is purely about the number of genomes and how dependent that is on the number of people infected.

The Chair: The number of genomes of what, of humans or the virus?

Baroness Walmsley: Of the SARS CoV-2 virus.

Professor David Robertson: There are about 27,000 genomes available in the public database. The UK has already generated nearly 20,000 genomes, so there is a sampling bias at the moment. The UK has sampled its population very heavily, but that sampling should not reflect anything more than if you sample more from one location you will find the more viruses there, essentially. That is the same with testing. The places that have the most cases often test the most. We have to be careful not to be misled by sampling biases.

The Chair: But we know that the virus has 30,000 nucleotides.

Professor David Robertson: Yes.

The Chair: So we know the complete map.

Professor David Robertson: We have 30,000. There has been an unprecedented effort to sequence the genome since this virus has emerged. For a virus with so little variation we have never had so much data, but it has been a real challenge. There is barely enough information to track the history as the virus moves around the world. It has been quite a challenge to study evolutionarily.

The Chair: Are there any RNA viruses with an equal or greater threat than the SARS-2 virus currently circulating in humans and domestic animals?

Professor David Robertson: I think the re-emergence of this virus (SARS-CoV-2) is the biggest threat because of the high transmissibility and high numbers of asymptomatic/mild cases. Other viruses could emerge that are probably deadlier but more containable. This one is the bad one, because it gets in to so many people, and we have high death rates just because of that equation.

Professor Jonathan Ball: An important factor in the re-emergence of this particular group of viruses is how closely related they are and how much immunity there might be in the population. There are problems with long-term immunity to these coronaviruses. In truth, we cannot easily predict what virus will be the next pandemic, but we have to be concerned about a virus with this kind of profile, which is easily transmitted, causes mild symptoms and is transmitted via the respiratory route; in other words, something that will enable the virus to spread very quickly through a very interconnected world.

The Chair: Thank you very much to all three professors. It has been a most interesting session. We have learned a lot, and clearly we have a lot to learn. It has been extremely informative. Thank you.