HOUSE OF COMMONS

Science and Technology Committee

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

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Watch the meeting

Members present: Greg Clark (Chair); Aaron Bell; Dawn Butler; Chris Clarkson; Katherine Fletcher; Carol Monaghan; Graham Stringer.

Questions 1565 - 1635

Witnesses

I: Professor Peter Horby, Chair, New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG); Professor Wendy Barclay, Head of the Department of Infectious Disease, Imperial College London; and Professor Neil Ferguson OBE, Director, MRC Centre for Global Infectious Disease Analysis, Imperial College London.

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Examination of witnesses

Witnesses: Professor Horby, Professor Barclay and Professor Ferguson.

Q1565 **Chair:** Welcome to this special hearing of the House of Commons Science and Technology Committee. Throughout the pandemic, this Committee has been taking evidence weekly from scientists and policymakers for a number of reasons, including better to understand the scientific evidence and analysis that informs policy decisions that come before Parliament, and to capture a contemporary record of what is in the minds of advisers and decision makers at the time, so that future inquiries do not need to operate entirely through the filter of hindsight.

The evidence of a particularly infectious new variant of Covid-19 in recent days has big potential consequences for policy by the UK Government and, indeed, the Governments of other countries. We are particularly grateful to our three witnesses for their willingness to appear before Parliament today at short notice, and just two days before Christmas.

I welcome three members of the Government's New and Emerging Respiratory Virus Threats Advisory Group, known as NERVTAG, which itself feeds into Government through SAGE. The chair of NERVTAG, Professor Peter Horby, is the director of epidemic diseases research at the University of Oxford. Professor Wendy Barclay is a virologist and head of the Department of Infectious Disease at Imperial College London. Professor Neil Ferguson is professor of mathematical biology at Imperial College and director of the Medical Research Council Centre for Global Infectious Disease Analysis. All three are members of NERVTAG.

I will start with some questions to the chair of NERVTAG, Professor Horby. We know that Covid now has over 1,700 variants that have been isolated and made known. What is special about the one that has occupied the attention of you and your colleagues in recent days?

Professor Horby: Good morning, everyone. For a bit of background, as you said, viruses mutate. You see substitutions in the genetic code that can lead to changes in the proteins that can lead to changes in the behaviour of the virus, which is why we monitor the genetic code of viruses. Like all other viruses, this virus mutates. Over the year, we have seen many different variants arising.

The vast majority do not have any material change in the way the virus behaves, but we need to keep monitoring it. The UK probably has one of the best genomic monitoring systems in place, a system called COG-UK, just in case we refer to it later. It is a genomics consortium and it sequences about 10% of all positive samples in the UK.

This variant became of interest because there was an investigation of the increasing case numbers in Kent in early December, despite the national lockdown. When Public Health England went in to investigate why there was that increase, it looked at the genomic data and saw an unusual cluster of a previously not recognised variant of the virus. Professor Barclay can talk more about this, but it was unusual in that it had many mutations and

not just one or two; I believe there were 23 genetic mutations leading to quite a few changes in the proteins. Some of them were in what we call the receptor binding domain, which is where the virus binds to the cell to infect it, which could affect the behaviour of the virus.

As NERVTAG, we heard about it on 11 December. PHE first heard of it on 8 December, and it put in an ad hoc paper to a routinely scheduled NERVTAG meeting on 11 December about the variant that it had discovered and its concerns about it. At that stage, on 11 December, we said that it was of concern, and we endorsed all PHE's measures to find more information. At that stage there was considerable uncertainty, and the data was observational. There were increasing cases in south-east England and London, and there was an increase in the variant, but whether they were causally related was unclear.

One week later we looked at the emerging evidence. That was on 18 December. We looked at three strands of evidence. One was the epidemiology, which was clearly showing that, despite the national lockdown, cases had been increasing in Kent, London and the east of England, and that the increase was associated, both in time and place, with a rapid increase of the virus variant. It was overtaking all the other virus variants. It happened in a way that suggested that it started in Kent, probably from one person, and then expanded.

We have had other variants due to importations from overseas, with multiple importations from Spain in the summer. You see different hotspots lighting up, but this looked like it came from a point source. The fact that it was a point source and that even during lockdown it was increasing rapidly, and increasing much more rapidly than other viruses, suggested that it might have some biological advantage over the other viruses.

The second strand of evidence we used was biology, which Professor Barclay can talk about: the changes that suggest that it is biologically plausible that it has a fitness advantage over other viruses, and some preliminary data that the viral loads were higher in patients with this virus compared with other viruses. That data is still a bit uncertain because there can be various biases in how people are sampled, but it suggests that there may be higher virus loads, which might explain why it is transmitting more quickly.

The third strand of evidence was the analytic approach to the epidemiological data, which Professor Ferguson will talk about. At the first meeting, we saw two types of analysis. One was looking just at the genome change rate and the other was looking at the correlation between the rate of increase of cases and the rate of increase of this virus, both of which suggested that this particular variant was spreading faster than other viruses in the same time and place, which would imply that it had a biological advantage.

Since that review of data on 18 December, in which we looked at three types of analysis, we looked at it again on Monday. We had another group do an independent analysis, in which they confirmed pretty much the same

result. Yesterday, there was another look by one of the other committees, SPI-M. It looked at five different independent groups looking at this. They all reached the same conclusion: it is highly likely that the virus has some advantage and is spreading faster. The precise estimate of how big that difference is moves about a bit, depending on how you do the analysis, and is not exactly important. What is important is that all groups are seeing a consistent pattern and that the increase is probably substantial.

I will finish by saying that we do not yet know if there is any difference in the severity of disease, the age distribution of cases or, most importantly, whether there is any immune escape—whether this virus is able to escape immunity that is induced by prior infection, treatment with convalescent plasma monoclonal antibodies or vaccines. Obviously, that is a crucial piece of work that is ongoing at the moment. We do not have any information on that.

Q1566 **Chair:** Thank you very much indeed, Professor Horby. We will go into some detail on each of the points that you made. On a foundational point, you said that you thought that this new variant might have been found in one person. Could you tell us how a new variant can begin its mutation, its change, in one person? How does that happen?

Professor Horby: Viruses have poor fidelity copying systems; they make random errors. It is really an evolutionary process. The errors are generated randomly, but then they are selected by evolution. You get some mutations that are what we call neutral, in that they do not really make any change. They can continue or not continue, and it does not really make any difference to the virus. If you get introductions of viruses like that, they can grow just by chance at a particular variant.

You can also get what is called selection within a person. If a person is not mounting a very good immune response, they are not getting rid of the virus but selecting the fitter viruses. The viruses that are better able to evade the immune system will grow and out-compete the other viruses. That tends to happen in patients who have long-term infections. It often happens in patients who have chronic infection; we see that with other virus infections as well. The virus has quite a long chance to evolve over time. It can also be generated by treatments. With HIV, for example, and antibiotics, if you give a suboptimal treatment, you can select out a resistant strain, so you could feasibly get a new variant arising because of resistance to a treatment like convalescent plasma monoclonal antibodies.

Chair: Thank you; that is very helpful.

Professor Horby: You could get them under pressure from vaccines, but at the moment there is not enough vaccination to do that.

Q1567 **Chair:** To the point that you can rule that out, had it obviously occurred before the vaccines? I guess they were being trialled. Are you confident that it could not have been in response to a vaccine trial?

Professor Horby: The first identified sample was on 21 September, before there was any roll-out. I think Professor Barclay can talk more about this,

but the range of mutation is probably not consistent with a vaccine-related emergence.

Q1568 **Chair:** I want to go into one important aspect, which is the extent to which this variant is more transmissible than the standard form of Covid. Perhaps Professor Barclay may care to comment on this. The NERVTAG paper of last Friday, 18 December, that you referred to said that there was "moderate confidence" of "a substantial increase in transmissibility." We have just heard that you have had two further meetings since then. Is it still your assessment that there is moderate confidence, or has that changed?

Professor Barclay: On Monday, when we had a joint meeting between NERVTAG and SPI-M, there was general agreement that we now had high confidence that there was an increase in the transmissibility of this virus.

Q1569 **Chair:** It had increased from moderate to high. Obviously, these labels are well known to you, but for members of the public and Members of Parliament, can you put a percentage on high confidence? Can you give us some way of getting a feel for it?

Professor Barclay: I don't think I can put a percentage on it. That conclusion was reached by consensus opinion in the joint meeting of NERVTAG and SPI-M, where there was no dissent around the table, if you like. Everybody at the meeting was in agreement at that point that they could see evidence of increased transmissibility.

Professor Horby: It is not a very strict cut-off, but there is a framework where between 50% and 75% is moderate, and 75% and above is high confidence. Above 90% is almost certain. The SPI-M meeting yesterday, which Neil was at, concluded that it was at that, and moved it up to almost certain. Data has been accumulating since 18 December, and it has gone from moderate to high to almost certain.

Q1570 **Chair:** Almost certain is the current description. Perhaps, Professor Ferguson, you might comment on that, as you were at the meeting. Is that the latest level of confidence?

Professor Ferguson: Yes, but it should be said that SPI-M is a sub-group of SAGE, and SAGE is the committee that will finally determine the level of confidence and the evidence balancing everything. Undoubtedly, the evidence has strengthened while it is still associative, but I can talk through that in more detail.

Q1571 **Chair:** That is very helpful. I wanted to get the parameters. Professor Horby, I think you touched on this in your initial answer. How do you know that it is transmissible? Is it from the fact that it is transmitted more, or is it knowing something about the structure of the variant? I think, without putting words in your mouth, that in your first answer you said it was a combination of both. Is that right?

Professor Horby: What we are seeing is that this virus is spreading faster than other viruses occurring in the same timeframe and in the same place, which would imply that it has some kind of biological advantage to make it

spread faster. We are confident that it is spreading faster than other virus variants.

At the moment, the underlying mechanism is not fully clear. It could be that the virus replicates faster, so you get higher viral loads, which means you are more infectious. As I say, there is some preliminary data suggesting that that may be the case and there may be higher viral loads in patients infected with this virus; but we have to put caveats on that because in an outbreak people may be sampled in a different way. They may be sampled earlier in illness because there is more awareness, or there is increased testing, which could lead to a bias. That means you detect patients with higher viral loads just because of the timing, rather than the actual biology. It could be that it replicates faster.

It could be that there is a shorter time between infection and illness, or being exposed and being infectious. If that timeframe shortens, you get quicker transmission. It could be that the duration of infectiousness is longer. There are a number of potential biological explanations. We do not know which it is, but they would all lead to the same picture, which is a faster spread of this virus.

Q1572 **Chair:** Thank you. In terms of its faster spread and its transmissibility, you said that viruses mutate and change all the time, so could it be a possibility that the increased rate of transmission is not intrinsic to this variant, but is because, for example, adherence to lockdown measures may have been less strict than it was in the spring, and that is causing a more rapid transmission? Is that possible?

Professor Horby: That is why at the very first meeting, on 11 December, we said that it was of concern but that we did not have enough data to establish the difference between the two scenarios you set out, which is what we really wanted to do. Is this virus different, or is it just around more because people are not complying with control measures? During that week, more data came in and more analyses, specifically to look at that question: is it the virus or is it behaviours? Professor Ferguson can talk much more about that. As the analyses have come in, we have increased our confidence that the virus would seem to be behaving differently.

Professor Ferguson: As Peter says, in the original meeting, we saw data that showed that, in the area of the country that was seeing an increase in frequency of this variant, we also saw an increase in transmission. That could to some extent be coincidence, but a number of sources of data and analysis have accumulated since then that suggest it is not just coincidence. The first is independent of work we have done, although we corroborated it. The Joint Biosecurity Centre did an analysis of Google Mobility and other data, which showed a proxy for how much people are moving around. It showed nothing special about what was going on in Kent and in the south of England during lockdown in London, compared with other areas of the country.

The second thing is critically important and where a lot of the weight of the evidence comes from. We drilled down into the data and said, what is the pattern we are seeing in a particular week and in a particular place? The strength of evidence comes from the fact that in many places we saw an imbalance between the variant and non-variant. We saw the non-variant declining in a particular week and place, while the variant increased in that same week and place, in the same population. That was very statistically significant. Looking across all weeks and places, there was a big imbalance between places where we saw the variant increase but the non-variant decrease in the same population, compared with the opposite, for instance. That controls for a lot of the other factors—population behaviour, for instance, and place-to-place variation. It is a lot of the reason why confidence in the conclusions has risen.

Q1573 **Chair:** Obviously, there are important implications for policy in how transmissible it is and whether it has increased. A former editor of the *Financial Times* said on Monday, "It is pretty clear now that Johnson egged up the transmissibility of the new strain of the virus so much to justify belatedly cancelling Christmas." Does the evidence that you now have put to rest that speculation?

Professor Horby: Yes. I do not think there has been any egging up, as far as I can tell. This is a new variant, which is of concern. We have looked at it very carefully. We have taken a lot of care, but at speed, to try to assess whether it is biologically likely that this virus is behaving differently. The fact that all the analysis so far would support that, and that we saw exponential growth of this virus during lockdown, makes it a significant concern. We passed on those concerns from NERVTAG to the Government, and they acted.

Chair: Thank you. We will come on to the timeline.

Q1574 **Katherine Fletcher:** Professors, it is 23 December and I know we face a serious crisis, but your time is hugely appreciated, so I am going to dive into some of the details to make sure that your time and expertise is worth it. I am genuinely appreciative and, when we are out of lockdown, I'll very happily buy you all a pint, or whatever is your beverage of choice.

You touched on the mutations—the current hypothesis that something structurally has changed within this virus variant to make it more transmissible. For the benefit of the public and those outside the science community, when a base pair changes—when it stops being an A and starts being a T—that is a substitution, but there are also times when the A disappears. When the virus gets read and turns into a protein, it does it in threes. It is almost like taking a stair out. It means that all of the other stairs move along, and a deletion in the mutation can make a big difference to the shape of the protein coming out of the other end. I appreciate that I am teaching all three of you to suck eggs.

I would be interested, with these 23 identified mutations, to know how many are substitutions, and how many are deletions or insertions that can have a profound change on the shape. Perhaps Professor Barclay can start.

Professor Barclay: Yes, I am happy to take that question. Let us focus first of all on the spike protein. The spike is the part of the protein that is sticking out like the corona of the virus. That is the way that the virus attaches itself to the cell and enters the cell. Within that spike protein, there are both types of the mutation that you talk about, and there are both substitutions, where the triplet nucleotides, called the codon, that make one amino acid, have changed and now they direct that the virus makes a different amino acid.

While you are right to say that sometimes those can be quite subtle changes, at other times they can be quite profound changes. For example, if the amino acid goes from being a very small one to a very large one, the key does not fit in the lock so well because it is too bulky. If the protein changes from being negatively charged to positively charged, it can act like a magnet, repelling or latching on better.

We see that kind of change. For example, one of the more famous changes here is N501Y. It is a pretty big change because it is seen as a totally different type of amino acid. That particular mutation sits right at the interface between the spike protein and the ACE-2 receptor, which is the host cell protein that this virus latches on to. We already knew from work that came out, and was published by a group in the United States about four months ago, that this particular place in the interface was a key way that the virus attaches to the cell, and that this particular change was even highlighted as one that could increase the ability of the binding strength between the virus and the receptor.

We know from other viruses that we study that, when you get an increase in the strength with which the virus can attach to the receptor, that is often a way for the virus to speed up or become more fit. It is easier for the virus to latch on to the cell, get inside the cell and initiate infection. One way that we know you can increase transmissibility is if it is more likely that all the viruses floating around will latch on to the right cell and initiate infection.

Q1575 **Katherine Fletcher:** Do you have a number for the 23? What number are significant, either a deletion or a fundamental amino acid change?

Professor Barclay: Within the spike protein, there are seven changes altogether. There are three deletions. Three amino acids have been deleted and the others are substitutions. You are right to point out the importance of deletions. There is a particular pair of deletions where, in fact, two amino acids that sit side by side are deleted from this virus. We have seen that many times. Andrew Rambaut is a member of the COG-UK group that Professor Horby referred to, and in fact Andrew and I had been discussing, the previous week, the importance of that particular pair of deletions, in that they seemed to come along in a number of different viruses with mutations that alter the receptor binding site.

It seems that, when a virus has the combination of the deletion and the receptor binding site change, we see it emerging more frequently. Other lineages of the virus with changes like that have been seen to emerge in

the United Kingdom and elsewhere. This particular combination was something that really rang some alarm bells to begin with.

Finally, one of the other substitutions in the spike protein is a change in what we call the furin cleavage site. We know that is also an important part by which the virus fuses its membrane with the cell membrane. Altogether in this spike protein alone, of the seven mutations we can see, there are three combined for the first time. We have not seen those three come together before. They add up to a biologically plausible mechanism for enhanced entry and faster replication for this virus.

Q1576 **Katherine Fletcher:** Thank you; that is incredibly clear. I am sure we will return to transmissibility and the measures to counter it, but ultimately the $64,000 question is this. We have some fantastic scientists in Britain and around the world creating vaccines that require the shape of the spike protein to look a little bit more like a Christmas tree to allow for the lock-and-key hypothesis to work. We have heard Professor Vallance say that there is a theoretical risk to the shape of the current vaccines being rendered less effective or ineffective. Where are we with examining that? The vaccine is what gets us out of it; we know that the lockdown is just a holding measure until we can get a vaccine or a treatment.

Professor Barclay: I will make a start on that question. The first thing to say is that we do not yet have direct biological data to give the answer, but the experiments are set up and ongoing in several different laboratories in the UK. The key is that, even though the vaccines are all reliant on us making antibodies to one protein of the virus, it is the spike protein that is the key protein, and you need antibodies to block the spike receptor interaction. That is how the vaccine antibodies will work.

Most people will make what we call a polyclonal response to that protein, which means that they will make several different types of antibody that seek different parts of the spike. The mutations that we are talking about would throw off, potentially, antibodies that see one end of that receptor interaction. We are hopeful, because of the polyclonal response that we all naturally make when we make our immune response, that most people would make antibodies that seek other parts of the receptor ACE interaction and then, after natural infection or vaccination, they would still be there and still be able to block the virus receptor interaction.

It could be that the efficacy of the whole response was reduced, but it would be highly unlikely, with this particular set of mutations, that the entire vaccine response was useless. Everybody makes polyclonal responses, so it would be much more likely that the other parts of the antibodies would work.

Where it could be relevant is when we use monoclonal antibodies as therapies, because they are just one pure antibody that sees one piece of the interaction. If the interaction happened to throw that one off, that monoclonal antibody would not work any more. Usually, when monoclonal antibodies are given as therapies, they are given in pairs or in threes to overcome that issue.

Professor Horby: I think you raise an important point. Even if this variant does not significantly escape the current vaccines we have, future variants may. It is important that we have a system in place to rapidly assess new variants against immune sera raised against vaccines, and also have a process in place to rapidly generate new vaccine variants or new vaccines against the new variants. You can do that by having banks of variants made, and at least you have gone through some of the partial testing so that you can take them out and accelerate them much quicker than you would have done otherwise.

Katherine Fletcher: That may be something we want to come back to later. I am conscious that other colleagues want to come in.

Q1577 **Chair:** On the point about testing the new variant in conjunction with the new vaccines, do you have access to the data and the samples necessary to be able to carry out that assessment now? Is that happening now?

Professor Barclay: What many labs and Public Health England have at their disposal are sera that were banked during the past year from people who were infected and recovered. Those are what we would call convalescent sera. By trying out laboratory experiments with those sera and the new variant, we will very quickly and readily be able to answer the question as to whether or not the immune response that people have mounted from a previous infection will protect them against this new variant.

What we also need to do is to test sera from people who have received the vaccines, because that will be a slightly more focused immune response. It is only against spike protein. It is early days in terms of the people who have received the vaccine as part of the roll-out. Everybody so far has only received one dose, so it is probably too early to conduct those experiments. We would need to collect sera very quickly, and have a bank of sera to test, from people who, in the real world, have received the vaccine.

It would be good to have that sera available from the clinical trials that have been conducted of these vaccines. I think Public Health England and other bodies are going to conduct that, but it would be good to be reassured that vaccine manufacturers are going to make those sera available for the tests.

Q1578 **Chair:** That needs to be done very quickly, one would assume, both now and, for the reason that Professor Horby gave, for future variants. Just as we have accelerated the trials and the approvals, we need to be very agile in being able to test the new variants against the vaccines that are there. Professor Horby, do you know whether that work is being done, or does it require any approvals or releases of data or samples?

Professor Horby: It is being done. The virus is being grown and, as Wendy says, there are serum banks from natural infection. What concerns me slightly is that we want to test the new virus against the serum raised in the vaccine trials, and my understanding is that those sera belong to the pharmaceutical companies that sponsored the trials, and permission is needed from them to use those samples for this purpose. I think it is a

national priority to do that. If there is any sense that the companies are not immediately giving permission for that to happen, pressure should be put on them.

Q1579 **Chair:** Who is that pressure from? Obviously, public opinion will be very engaged, but is it the MHRA or the national public health authorities?

Professor Horby: I don't know. It is probably best to talk to the Vaccine Taskforce, but it might be from the Government, who have contracts with the vaccine manufacturers.

Chair: Thank you. We will follow that up after this meeting. It has been very helpful to hear that from you and Professor Barclay.

Q1580 **Carol Monaghan:** Professor Ferguson, you have hinted that there may be evidence that children are more susceptible to this particular strain. What evidence do you have for that?

Professor Ferguson: The data shows that we do not have a causal mechanism, but there is a hint, if you do what is called a case control study, and carefully match cases of this variant with location and time-matched cases of the non-variant and compare the age distribution, and bear in mind that that is mostly during the lockdown in November, you will see a statistically significant increased proportion of cases in under 15-year-olds for the variant compared with the non-variant. Beyond that we know nothing.

There could be a number of hypotheses as to why that might be the case. One is that maybe children are more susceptible to this variant. As Wendy said, for previous strains of this virus, we know that children were less likely to get infected and certainly much less likely to get symptoms than adults. That is unusual for a respiratory virus, in the sense that most respiratory viruses transmit most efficiently in children.

One possibility is that this virus has changed in some way that does not particularly target children but just makes children a bit more like adults, even in terms of symptoms, or viral replication or transmission, or both. Again, it is very early days. We have very little direct biological, never mind experimental, evidence that that is the case. At the moment, we have an observation that there is a slight shift in the age distribution, which would be consistent with any of those hypotheses. I emphasise that, while it is a significant shift, it is not a huge shift. It is relatively small.

Q1581 **Carol Monaghan:** When we are looking at this, and looking at these cases, are we seeing poorer outcomes for children compared with the previous strain?

Professor Ferguson: There is a lot of work under way at the moment trying to look at outcomes. You have to do that very carefully in what is called a case control design. PHE are undertaking that at the moment. Obviously, the outcomes we are most concerned with are with respect to hospitalisations. Hospitalisation is a very rare outcome for a childhood infection for this virus. The focus initially will be on comparing overall hospitalisation rates for this virus with overall mortality rates. Those data

will, hopefully, become available in the coming few weeks. It will take longer to resolve things like whether there is a variation in outcomes by age. We need much more data.

Q1582 **Carol Monaghan:** How are we going to get that evidence? How are we going to accumulate the data? You talked about hospital admissions. Are there other things that you are looking at?

Professor Ferguson: There are a lot of studies under way. We are working with PHE. Other universities and the London School are working with PHE, so there are a number of studies under way of coronavirus transmission. There has been a set of studies in schools. Of course schools are shut now, but there are residual samples that can be tested to see if they were variant or non-variant, to understand, for instance, if there is any association between this variant and more transmission in schools. There are anecdotal reports that the last few weeks have seen more explosive school outbreaks in London and in the south-east of England, but they are just anecdotes at the moment.

There are ongoing household transmission studies as part of the ONS national survey. Again, retrospectively, those samples are being tested to see if they are variant or non-variant and whether we can see a difference in the pattern of transmission in households. There is a hint that there may be greater household transmission in data literally gathered in the last day, but we do not know as yet whether that is related to age or has any age effect.

Going forward, those studies will collect data that allow us to distinguish between the variant and non-variant and to see whether there are differences in characteristics. There is an enormous amount of work under way. This is very early, and it will take some weeks before we properly understand the characteristics of this virus, both in the details of transmission and in clinical outcomes.

Q1583 **Carol Monaghan:** What would increase the infectiousness in children? What would the implications be for how we manage the virus?

Professor Ferguson: Increased infectiousness overall in the population, if it went up evenly across all age groups, poses a challenge for control, as we know. On its own—not if this virus was targeting children in any sense, but if it was just an overall increase—it would still increase the challenge of maintaining infection control in schools. Obviously, if there is a shift, and it is very much an "if" at the moment, such that children are now more like adults in their infectiousness than they were with the previous strain, it will pose greater risks of transmission involving children mixing with each other. Potentially, there are challenges for particular types of control measures and what we want to do with schools.

Q1584 **Carol Monaghan:** Professor Horby, you talked earlier about the virus mutations and the number of mutations that would have to happen in order for us to be where we are now. Is there any evidence that the virus is mutating more rapidly in the UK than in other countries?

Professor Horby: I do not have that data, but, to my knowledge, no. Lots of other countries also see virus mutations, but we have much better genomic coverage than most other countries, so we are much more likely to pick it up. It may be that other countries have experienced things like this, but they have not detected it because they are not sequencing the virus. We have recently seen that South Africa has a very similar problem. It has a new variant with multiple mutations that seems to be spreading very quickly there as well. It is slightly different from this one.

Professor Ferguson: This is really the work of Andrew Rambaut and people like Eric Foltz in the Imperial centre. There is no evidence, for instance, that this new variant lineage, as it would be called in a genetic perspective, is evolving any faster than previous variants. There is also no evidence of geographic variation in the rate of evolution of SARS-CoV-2 globally.

I emphasise that the South African variant, while it is also a variant with many changes—over 20 changes—to the genome, some of which overlap, is not related to the UK variant at all. It evolved independently.

Q1585 **Carol Monaghan:** So it is just unfortunate and bad luck that we have ended up with a more infectious strain.

Professor Ferguson: Yes.

Q1586 **Aaron Bell:** To follow up Carol's question, Bayesian probability would urge us to be quite sceptical of the idea that the country with the best genomic monitoring should happen to be the country where the most dramatic mutations occurred. You can see from the data that there has been a huge rise in cases and deaths particularly in south-eastern Europe, in countries like Czechia, Slovenia and so on, that happened before this period. In your view, what is the probability that we imported this variant rather than it developing in a mutation, whether in a patient or whatever, in Kent in the first place?

Professor Horby: Others can comment on this, but I will kick off by saying that we just do not know. You are right that there are other parts of the world that have high transmission rates and where they will not be doing good genomic surveillance. They may have had the strain that could be a single importation to Kent, or it could have been de novo from a person in Kent. We just do not know. Wendy or Neil might want to add to that.

Professor Ferguson: I can add a bit to what we know about the phylogeny of the virus. You are completely right that we disproportionately sequence. Of all global sequences of this virus, the UK conference contributed nearly half. We only have 10 in Denmark, a few in the Netherlands and two imported in Australia. There are only a handful of other detections of this virus's lineage elsewhere.

At the moment, if you look at the evolutionary tree of the virus—the phylogeny—the earliest known sample originates in the UK, in the east of England. Epidemiologically, it looks like a point source spreading out from a location, but we cannot completely rule out that it was an importation to

that part of the country from elsewhere in the world that is arising there. The only way we will be able to look at that is, as further examples are collected, by looking for viruses circulating now that appear to have an earlier evolutionary time point—obviously, we will not see the first virus; we have to infer it—that seems to predate the viruses we see in this variant in the UK. We have not seen that as yet, so at the moment the hypothesis is that it originated here, but we cannot be sure.

Q1587 **Aaron Bell:** Professor Barclay, do you want to add something? You were nodding.

Professor Barclay: Maybe a different way of looking at it is that there are so many unique mutations in this one single genome of the virus that the evidence is quite strong that it is what we call within-host accumulation; that a single person probably gave rise to at least many of those in that cluster. We know that there are reports of similar viruses arising in immunocompromised patients, both in the UK and elsewhere. There is a report of a particular patient in Cambridge hospital with a different cluster of mutations that does not seem to have given rise to a transmittable variance. It is important to realise that this kind of situation will give rise to those clusters in that type of patient, wherever they are.

Q1588 **Aaron Bell:** Is the cluster that we saw in south Wales in particular, which emerged a little bit before the London and Kent cluster took off, unrelated as far as you are concerned?

Professor Ferguson: We do not have as good sequence coverage data in Wales, so it is hard to tell, but there is a proxy for this variant that is called S-gene target failure. With the PCR testing, which is the commonplace pillar 2 testing—community testing—not all, but a lot of the testing we carry out targets three different genetic targets. I think it is N gene, ORF1 and spike protein. What we see with this variant is that, while two of those targets are still positive for PCR, one of them is negative because of that 69-70 deletion that Wendy referred to.

We have evidence from south Wales, from recently collected and collated data from the Lighthouse labs, that there is a reasonably high frequency of S-gene target failure cases in south Wales. I am talking to the Public Health Wales authorities, and they seem fairly convinced that at least part of the cause of the problems they are experiencing is this variant.

Q1589 **Chair:** I want to ask a question about the sequencing. I think I heard you say, Professor Ferguson, that we sequence 50% of the sequencing done in the world. Is that correct?

Professor Ferguson: About 45%.

Q1590 **Chair:** Professor Horby, is it the case that, if we are doing more sequencing than the rest of the world, we are going to expose more variants? There has been something of an international reaction, including closing the ports, that seems to be on the assumption that we are somehow more infectious in this country, if I can put it that way. It may be the case that actually we are being penalised, as it were, for being more rigorous and

more open about the sequencing. Is that a fair reflection?

Professor Horby: It is fair to say that countries that have more extensive and more rigorous science, and are very open and transparent, obviously expose themselves to important information being made available to others. It is a global public good. It is in our interest that we know about these viruses so that we can control the spread better and make sure that our counter-measures like vaccines and drugs are better targeted. It is a global public benefit that we make that available. What we should be doing is encouraging others to do that. I was on a call with European colleagues just yesterday, and their conclusion was that they need to replicate what is being done in the UK in their genomic surveillance coverage.

Professor Ferguson: Denmark does the most per capita sequencing at the moment, but it has far fewer cases than us, so it is easier. The fact that it has picked up 10 cases with sequencing of this new variant in a country as small as Denmark, with a relatively low infection rate, would almost certainly suggest, in my view, that this virus has been introduced into the great majority of European countries, if not all, at the current time.

Q1591 **Chair:** It is already there. Presumably, on the same basis, it is quite likely that there are other variants across the world—not just in European countries—that might also have high levels of infectiousness but where they are less likely to know about them because they have done less sequencing. Would that be right?

Professor Ferguson: The one of greatest concern, other than ours, at the moment is the South African one. It has much poorer epidemiological data, but certainly there are anecdotal reports of explosive outbreaks with that virus, and very steep increases in case numbers. Nigeria is showing a very sharp uptick in case numbers at the moment. We have no genetic data from there. There is benefit, as Peter said, globally in having better genetic surveillance.

Q1592 **Chair:** I want to follow up on a question that Carol asked about the age distribution of infections. Professor Ferguson, you were saying that we need more information on that. The NERVTAG paper of last Friday, 18 December, said in its minutes: "Better data on the age distribution of infections with this variant will be available next week"—in other words, this week. Have they been available? Have you had access to them yet? Have you seen them?

Professor Ferguson: All the university groups—Wendy's and mine, Edinburgh and others—are working very closely as part of the incident management team with PHE. The better data being referred to is the S-gene target failure data from the PCR testing, but because there is a lot of variation from lab to lab, and in which labs actually test the S gene, and depending on demand, as samples get routed to different labs, it is taking some time to get a finalised dataset. The results I talked about just now were in terms of the A shift. It is true in England and true in Wales with the data we have available, but we are trying to refine those datasets as a matter of urgency to allow us to do much more rigorous case control

studies. We are not in a position to do that right now, but we will be in the next week or so.

Professor Horby: It is reflected in the minutes of the meeting on the 21st that some information has come through on age distribution that shows a possible suggestion of slightly better transmission in children, but it is very preliminary. I think Professor Ferguson has already spoken a bit about that. It is too early to make any strong conclusions about the age distribution.

Q1593 **Dawn Butler:** I want to put on record my thanks to the professors for coming in today, two days before Christmas.

First of all, I want to ask a question on references to the old virus versus the new variant. In the beginning, when we discovered the virus in the UK, there were two different variants. One was from Europe and I think the other one was from the US. When we now talk about the new variant versus the old variant, what is the old variant? I am not sure which professor is best to answer that.

Chair: Perhaps Professor Horby, as chair of the group.

Professor Horby: I can start. It is very complicated. Even when you are infected with a virus, you are not actually infected with one pure strain; you are infected with a population of viruses. Even in one individual, when you sequence a virus, you are actually sequencing the dominant strain. If you do another type of analysis called deep sequencing, you find that even within one individual there is a population of viruses.

How you define virus A from virus B depends on how deep you want to go into the genome. It gets very complex in terms of naming the lineages. You are right that there is not an old virus and a new virus. There is certainly the new variant, which has the characteristic fingerprint of these mutations, but there is a whole basket of other viruses that seem mostly to behave the same. We have certainly had other variants. There was one that had a mutation that seemed to increase transmissibility a bit and has become widespread not just in the UK but internationally. That has become one of the dominant strains.

Wendy, as a virologist, is much better placed to explain the complexity than I am.

Professor Barclay: I think you have done a very good job, Peter. The new virus variant is called B1.1.7 because it tracks back to clade B of those. I think what you are referring to is that in the very early stages there were As and Bs, and then they branch out from there. If you track this new one, it originally derived from clade B, so it is one of the two that you are referring to.

I think that is such a long time ago in the history of these viruses that it is probably better to compare this new one against what was around in September and August, when it would appear that the new one acquired the cluster that is making it behave differently from the others around it.

Professor Horby: It is also difficult to compare timeframes because the level of intervention is different over time. The interventions in the summer were different from the first and second lockdowns and tiers 1, 2 and 3. That obviously confounds the transmission of the virus, which is why the work that is being done—Professor Ferguson has led a lot of it—is trying to compare the new variant with all the other viruses in the same time and place, when they are under the same kind of pressures.

Professor Ferguson: We have seen this before. We have seen new strains and variants of the virus arise and dominate. D614G was perhaps the most important. Peer-reviewed papers in reputable journals, including by Eric Foltz in the centre I head, have shown that that variant—we don't know quite where it arose—was associated with the European outbreak back in February and March, and quickly dominated over Asian lineages that originated in China. It is one of the hypotheses for why Europe saw a more explosive first wave of the epidemic than in, for instance, Wuhan, where transmissibility appears to have been slightly lower.

Similarly, in the summer, when infection levels were very low in England, we saw a new variant come in, probably imported from Spain or Europe, called A22V, which probably had less of a fitness advantage but rapidly went to a high frequency in the population. That is probably more of a founder effect—the fact that a lot of infection was introduced and then that changed the transmission, starting with infections from a background of lower levels of infection.

What we are seeing with this variant is quite different. We see it from a UK perspective as almost a point source at a time when we have lots of other virus around, but this one grew much more successfully in the population than all the others. It is more evidence for our concern about the transmissibility of this particular variant.

Q1594 **Dawn Butler:** The variant from Europe quickly dominated. We know that normally viruses mutate on average every two months. Picking up on something that Carol said earlier, did you say that it is mutating at a faster rate or not?

Professor Ferguson: I will obviously let Wendy answer this, but there is no evidence of any change in mutation rate. These viruses accumulate mutations down each of the evolutionary lineages, each of the strains we contract, even faster than that. The rate of accumulating very significant changes may be slower, but they are mutating all the time. As Peter said, within a single person who is infected, you can find a whole population of viruses that are genetically slightly different from each other. It is down to the error-prone nature of RNA viruses in how they copy, but maybe Wendy might like to add more.

Professor Barclay: To reiterate, there is no evidence that this virus is mutating more quickly.

Q1595 **Dawn Butler:** Professor Barclay, do we know yet the markers associated with long Covid?

Professor Barclay: Do you mean genetic markers or clinical? Long Covid is a consequence in some individuals of having been infected by the virus. There is no evidence that that is due to infection with a different variant of the virus. It is much more likely to be due to a difference in the host response that an individual mounts, which could be genetic or otherwise.

Q1596 **Dawn Butler:** Thank you. Professor Horby, you talked a little bit about bigging up the new variant. If we had cancelled Christmas at the beginning of December, would we have needed a tier 4?

Professor Horby: I don't know. That is a policy question and it would also require some modelling assumptions. The assumption is that cancelling Christmas would have had an effect on the transmission that was occurring in October/November, which is when this variant arose. What would have mattered is what was being done at that time. We saw this virus manage to expand very successfully, both in numbers and in space, during the national lockdown, which I think speaks to the fact that it is a very efficient virus, unfortunately.

Q1597 **Dawn Butler:** Did each of you in any way panic when you thought that three households were going to be mixing over Christmas? Did you hold your head in your hands and think, "Oh no, this is really a bad thing to do"? What were your thoughts? Would each of the professors answer, please?

Chair: Briefly please, and perhaps Professor Horby first as the chair.

Professor Horby: It is not the three households; it is the whole package of measures that matters. It is not just whether three households mix. It is also whether you had isolated before that, whether you had taken precautions before that; how intense your measures are, and whether before you mixed you had been careful with social distancing, hand hygiene and face masks.

Professor Barclay: I agree with Peter. The idea of three in itself is not the problem, but whether it was three on one day and then a different two on the next is the issue, and whether people really understood the logic behind the three is another question. It is about the whole before and after as well as on the day that matters.

Professor Ferguson: It was always a balancing act. I have said before, and it was the conclusion of all the scientific advisory bodies, that, clearly, any relaxation of mixing within households poses some risk. The three-household bubble was a way of mitigating that risk, but it is an increased risk. As background, contact rates generally in the population are lower over the Christmas holiday than just before and just after. We expected to see some increase but, hopefully, in a manageable way. That comes down to a political decision about balancing protecting health against people's freedom to socialise at an important time of year.

Dawn Butler: Thank you all very much.

Q1598 **Chair:** Professor Horby, to paraphrase, you said that the time when we

could have acted against this new variant was in September or October when it first appeared. Obviously, we did not know about it then. This has been quite a rush, and in the last few weeks there has been a lot of information, and decisive action taken. Was it possible to have discovered what we have discovered in recent days and weeks much earlier, at a time when we could have nipped it in the bud, so to speak?

Professor Horby: I think it has been detected pretty quickly. Once it was detected, I think the train of actions has been quick, quicker than in the past, and in a good way. PHE heard on 8 December. It told NERVTAG on 11 December. We requested some actions, and within a week we could make a decision that it was a serious concern. The next day measures were put in place. We are now here, and it has been a very quick turnaround. Whether it could have been detected prior to 8 December, I don't know. It is a question for PHE and the other surveillance networks as to whether they had access to data that would have allowed it to be detected a bit earlier.

Professor Ferguson: Most of the data that supports the conclusion that this is more transmissible is relatively recent; it is data from early December. In the sequencing of viruses, there is a two to three-week lag time between a PCR test happening and the sample being selected and sequenced. I do not think we would have had evidence much earlier. It might have been a few days earlier, with the wind behind us, but it would have been very difficult to have the same sort of level of confident conclusion that this really was associated with higher transmissibility very much earlier than we did.

Q1599 **Chair:** Thinking about the future, we want to learn lessons along the way, and if we have new variants appearing all the time, I guess the question is whether it is possible much more quickly to detect them and discern whether they are going to be particularly dangerous, rather than needing the look-back that exposed the dangers of this variant.

Professor Horby: There are a number of things. One is cluster investigation. Where you see unusual epidemiology—fast-rising rates, unusual clusters, unusual size and setting of clusters—it needs to be investigated very quickly, including with genomics, to see if it is a variant of the virus. That is how this variant was detected, through a PHE investigation of an unusual pattern of transmission in Kent.

The next stage is to understand the biology of the virus. I think that could be accelerated. Professor Barclay is leading some work in that area. We need to grow this virus quickly and see how it replicates in different cell lines, and then test it against drugs and vaccines, to see if the genetic difference makes a material difference in how the virus behaves. That is the crucial information that perhaps could be speeded up somewhat. Professor Barclay could speak to that.

Professor Barclay: As Peter was saying, once you detect a genetic variant using COG-UK and the surveillance system, what we perhaps have not done so much until now is to have a way to interpret what the genetic

changes mean. This is a very new virus and, in general, coronaviruses are understood as a group of viruses in comparison with a virus like influenza, for example, or HIV. There is still quite a steep learning curve to know how to interpret the genetic changes and what they will mean in the phenotype, the way the virus behaves.

There is a group of virologists coming together in the UK, and of course international work is intense in this area as well, to try to work very closely with Public Health England and COG-UK to be able to advise on and interpret all those changes and put in place the biological systems, the experimental systems and the various models that will be able to supplement the real-world epidemiological data, to give more confidence in which ones will make a meaningful phenotypic change.

Professor Ferguson: The COG-UK consortium has been very effective at monitoring lineages and ringing alarm bells before—for example, about D614G, as I mentioned. This is not the first time. It is the first time it has hit public health significance, but it is not the first time. On the virology side, we are learning lessons. We are learning lessons regarding rapidly linking the epidemiological data to the schematic data to be able to pick up potential changes earlier and earlier.

Q1600 **Graham Stringer:** May I follow up with Professor Horby Carol's earlier questions about understanding the biology of this mutation and determining whether it is just a strong correlation or whether it is causal? Are we testing in hospitals for the rate of infection and rate of deaths from this new variant as opposed to other variants?

Professor Horby: That is a good question. There are lots of things. We focused first on whether the correlation is causal, whether we think there is a biological difference in the way that the virus is growing in the population. Clearly, there are other important things. One is whether it is associated with outbreaks in particular settings, particularly in nursing homes and in hospitals. Work is ongoing looking into that. Certainly, it has caused some outbreaks. At the moment, it is unclear whether it has caused more outbreaks than other variants. Professor Ferguson probably has more data on that. At the moment, there is no indication that the disease severity is any different with this virus. These are all on the to-do list and are being done through studies that control for all the confounding factors.

As I said previously, we have to look at what is happening with this virus now and what is happening with other viruses now, because the situation is different from the past. The measures that are in place are different. The infection control measures are different and the testing regime is different. The treatment regime is different. You cannot compare the death rate now with one in March because they are lower now. We have to compare the death rates now in people with this variant and people without, and we do not yet have that data.

Professor Ferguson: PHE is conducting a lot of studies. First, and all important, is the case-control study Peter referred to, which controls for confounders and looks for whether there is any evidence in a change in

severity. There is no evidence as yet, and the power of the study is not strong enough to draw the conclusions as firmly as we would like.

Secondly, is it more likely to cause outbreaks in particular settings such as care homes and hospitals, and schools for that matter? There have been a lot of anecdotal reports in the last few weeks of increased explosive outbreaks in all those settings. We do not know, as Peter said, whether that is more associated with the variant or not. PHE is doing quite a lot of intensive work on sampling and sequencing from those outbreaks to look at whether there is any sort of signal.

Q1601 **Graham Stringer:** Does that study encompass looking at transmissibility within domestic settings and whether that is increasing or not?

Professor Ferguson: We have a hint of that already, and that is from the ONS survey. You will be aware that the Office for National Statistics has an infection survey that samples large numbers of people, tens of thousands people a week. That is a household-based design. They recruit entire households and swab everyone in the household every week. That allows us to track infection in households to some extent. They are now going back over what they have collected retrospectively, sequencing those viruses and determining which people were infected with the variant and the non-variant. That has provided powerful information because it is a truly random survey. It controls for a lot of biases.

There are hints in that data of the increase in viral load that Peter referred to, and early hints that there may be increased household transmission of this variant. I say hints. None of it is statistically significant. It is a trend in a certain direction. The numbers are low and the data will improve as time goes on.

Q1602 **Graham Stringer:** I have a very simple question I would like to get on to the record. In common debate and dialogue around this issue in the media, transmissibility and infectiousness are used interchangeably. Can you give precise definitions, so that there is clarity?

Professor Ferguson: I am not sure if there are completely precise definitions. Transmissibility is the thing we quantify by the R number, the reproduction number—how many secondary cases one person infects. Infectiousness is often used on a more individual level, as to whether someone is infectious right now or how infectious they are. You can perhaps think about transmissibility as being more on population level on average how well something transmits. I could be highly infectious right now and somebody also infected could be less infectious. Maybe Wendy could give her virologist view.

Professor Barclay: I think the words are used fairly interchangeably. Perhaps we should think of individuals as being infectious and the R being the average of all those infectious individuals. It is also important to bear in mind that there are many ways, as I think was alluded to earlier, in which the numbers can increase. For example, if an individual becomes infectious earlier during the course of their disease, what is called the serial interval will reduce and therefore the virus will spread from one person to

another more quickly. That kind of change could be underpinning what we see, as opposed to an individual shedding more virus and infecting more people at a given time. There are several different parameters that feed into the growth of the outbreak, but I think perhaps that infectiousness is on an individual basis and transmissibility for the whole is the better definition.

Q1603 **Graham Stringer:** Professor Barclay, Tony Blair has suggested that, if this mutation is more infectious, and more people are going to get infected, rather than waiting to give people in the queue two doses of the injection, more people should have one dose of the injection. What is your view on that?

Professor Barclay: The issue with that is that the vaccine is on the basis of giving two doses, and the efficacy that we are hoping for is on that basis. To change at this point, one would have to see a lot more analysis coming from the vaccine clinical trial data, if that is indeed available, about what the effects after one dose are. You would then have to go through a different process than we have currently done.

I think that kind of decision would require some modelling to answer the question. If you simply doubled the vaccine doses that we have available by going from two to one each, so you would vaccinate twice as many people, what effect would it have at this stage on the growth of this variant virus? At the moment, I think that is a question that modellers are looking at. If it did not give any benefit, and one was vaccinating in a different regime out of licence, it would not be ideal.

Q1604 **Graham Stringer:** May I paraphrase that? Are you saying that it is an interesting idea, but it is too risky at the present time without more evidence?

Professor Barclay: Yes.

Graham Stringer: Thank you.

Professor Ferguson: It would not be permitted. Our regulator, MHRA, is authorising vaccines on an emergency basis, given certain data provided by the trials, and on the basis that people will receive two doses. It would require an entirely different regulatory submission to authorise just a single dose.

Q1605 **Chair:** I read the article in the *New England Journal of Medicine* that I think that recommendation comes from. The conclusions of that article are that the study was not designed to test the efficacy of a single-dose regimen. Nevertheless, in the interval between the first and second doses, the observed vaccine efficiency against Covid was 52%, and in the first seven days after dose two it was 91%, reaching full efficacy against disease, with onset at least seven days after dose two. Presumably, that is why these things should be subjected to proper analysis. You repose confidence in the MHRA to prescribe the right regime for these vaccines, do you, Professor Horby?

Professor Horby: Yes, that is right. You cannot assume that one dose is as good or half as good, or whatever as good, as two doses because the data you have is on two doses. There are clearly the two points Wendy mentioned. One is that we do not know whether it will work or not. The other is whether it will achieve your objective. How much of the population would you need to immunise to have an effect on reducing transmission rates? That is very different from what we are currently doing, which is immunising those at higher risk to reduce the mortality rate.

Q1606 **Katherine Fletcher:** A slight change, Professors. I am conscious of our responsibility to get the public to understand the science. "We are following the science" is an oft-used phrase. When we talk about this being "much more" infectious, it can get lost in that it is not quantifiable. I was wondering whether we could make some benchmark analysis of the R. I confess that when I heard it could add 0.4 to 0.9 to the R rate, as a scientist I went, "Eek." Professor Horby, what was the R for Spanish flu, which was the last very serious global pandemic? What is the R for normal flu? How confident are you in that 0.4 to 0.9 increase? Does that take the R for this coronavirus variant to 4? Where do we get to—one person infects four other people? Could you talk around that?

Professor Horby: I will start and pass on to Neil, who is the R master. What is clear is that even during the second national lockdown we were seeing rapid growth of infections and people ending up in hospital and stress on the healthcare system. That is what really matters. Even with controls in place, we are still seeing increasing case numbers and pressures on the healthcare system. We know that, when the R is above 1, the case numbers keep increasing. Eventually, we would reach a point where we would far exceed the numbers in hospital from the first wave and we would exceed the pressures on the healthcare system in the first wave; therefore, action is needed if we are to avoid deaths. Neil is much better placed to talk about that.

Q1607 **Katherine Fletcher:** Professor Ferguson, I asked the wrong person, apologies. What is the Spanish flu R?

Professor Ferguson: We think the R0 for Spanish flu was about 2, maybe a little under, which is much less than the R0 for coronavirus. R0 is if you have no control measures in place—

Katherine Fletcher: Totally unmitigated.

Professor Ferguson: —before I get criticised for that. When coronavirus hit Europe, it was probably about 3. In that context, yes, a 50% increase would take it all the way up to 4.5, which is a very big increase. I want to emphasise that our estimates of how much more transmissible this new variant is compared with the pre-existing strains of coronavirus were all derived in a context where we had a lot of social distancing and control measures in place. It is not necessarily easy to extrapolate the increase in R we saw during the recent national lockdown.

I agree with Peter that the non-variant virus is the old viruses. During the recent national lockdown in England, the SPI-M groups, the multiple groups

coming together, were estimating an R of about 0.8 to 0.9. For this new variant, we were seeing an R of about 1.2, 1.3, maybe even a little higher. That is why we had that 0.4/0.5 difference, maybe even larger in some areas. One was going up and one was going down. We think that is about a 50% increase in R. To go from 0.8 to 1.2 is about a 50% increase, but it is all measured in a very particular setting, with very particular data. While we are confident in it in that setting, I urge caution in extrapolating wildly what it would be, for instance, if we relaxed all controls. There is more work needed on understanding that.

Q1608 **Katherine Fletcher:** But the context is that it is a big number, and it is a number that grabs your attention scientifically, whether it is 50% more with lockdown measures, or a whole load more unmitigated and just letting it run.

Professor Ferguson: As Peter highlighted, the conclusion from NERVTAG and the SAGE sub-group, NERVTAG and SPI-M, was that it was a substantial increase, and an increase that had public health consequences.

Katherine Fletcher: I have been listening intently to this session. It has been incredibly powerful. One of the things we were caught slightly with at the start of the pandemic was the levels of asymptomatic transmission, people not feeling poorly but being infectious and being able to transmit it. Is there any evidence at all that this new variant increases the period of asymptomatic transmission, or that it has differed? Can you asymptomatically transmit for five days as opposed to three? Do you have any data on that?

Professor Ferguson: I can talk to that a little bit. The answer is that we do not know at the moment. The ONS survey, which is a random survey of infection and which swabs people whether or not they have symptoms, may be able to start to address some of that question. Peter?

Professor Horby: Sorry, I was waving goodbye to my wife.

Katherine Fletcher: At least your priorities are in the correct order.

Professor Barclay: Coming back to the biological plausibility of that sort of explanation, one of the other mutations in the 23 in this cluster is that one of the whole open reading frames, one of the whole proteins of this virus, is lost. It is called ORF8.

Early in the pandemic, an outbreak in Singapore reported a virus that lost ORF8 and reported more asymptomatic or milder infections with that virus than symptomatic ones. There is a biological plausibility to what you are suggesting, in that we could have spread from people who experience milder symptoms. Again, it is very preliminary. We do not have any biology on the new variant to back that up, only to say that, very strangely, going all the way back to 2003-04 when we had SARS-1, during its circulation in humans, right towards the end before we finally got it under control, it also picked up an ORF8 deletion, which seemed to circulate rather well, in comparison with what had come before. That is another alarm bell that rang for us when we looked in COG-UK at the sequence here; there was

one more mutation somewhere else, even in the genome, which may be adding up to something we should think about.

Chair: Very briefly, Professor Horby, as we have a lot of other ground to cover.

Professor Horby: While we have confidence about the increase in growth rate, we do not know about disease severity or asymptomatic transmission. It could be less or it could be more. We should not make any assumptions.

Chair: Katherine, I think you are muted.

Katherine Fletcher: I detest Zoom with a passion. The message to the public is that it transmits more. If a test is offered to you, take it. There is a possibility that you could be asymptomatic and still spreading it.

Q1609 **Aaron Bell:** Thank you all three for your time today and for all your work on NERVTAG during the pandemic. Professor Horby, may I quickly go through the timelines? You have already set out quite a lot of what happened in the last week or two. When was the new variant first detected, as you understand it?

Professor Horby: When it first became an issue identified by Public Health England, I understand, was 8 December. It tried to understand the reasons for the increase in case numbers in Kent and identified a cluster of this virus variant. When it looked back through the data, the very earliest sample with this virus was 21 September.

Q1610 **Aaron Bell:** Some people have said, in criticising PHE, NERVTAG and the Government's response, that this new virus was "spotted" in September. Is that an unfair misrepresentation of what happened?

Professor Horby: It would have been present in September. That is when the first sequence was available. But, as we have said, there are thousands of variants, so to know which particular one is a problem requires epidemiological data.

Professor Ferguson: To put it in perspective, there is a two, three, sometimes four-week delay between someone being swabbed and the sequence becoming available. While the first identified case of this virus is from late September, that sequence was not available; I do not know the precise date, but I suspect it was not available until three weeks later. It takes much more than just one sequence. We need hundreds and hundreds of them showing growth of the lineage, before we can conclude anything about its significance. The data really comes from November, when it starts to show the correlation between transmission of this variant and increased transmissibility overall.

Q1611 **Aaron Bell:** To be clear, you do not think it is fair to say it was spotted in September. It was looked at later, but it was present in September. Thank you.

Professor Horby, the genomics consortium has been sequencing Covid samples throughout the pandemic, but it has only been identified

retrospectively, as we have just said. Is there any way it could have been identified earlier, given the growing numbers in Kent? We looked at the behavioural explanations first. Should we perhaps have been looking for the genomic explanations earlier?

Professor Horby: There is always a good case to be made for more genomic surveillance, but a case can also be made for investing in other things. We have demonstrated in the UK that that has proven to be very valuable, because we have identified a variant that has public health significance, not just for us but internationally, and we have been able to act on it.

It would probably be good to speak to people from the COG-UK consortium as to ways they think that might be improved. They have a certain methodology that is very robust, which is to take almost a random sample that allows you to avoid biases. There may also be value in more targeted surveillance of certain groups. We have been having discussions about whether we should be doing more surveillance in immunocompromised patients in hospital who may generate concerning variants, and that might be something that should be thought about more carefully.

Q1612 **Aaron Bell:** In your view, Professor Horby, have the Government acted in a timely way to respond to the emerging evidence?

Professor Horby: I think they have. We sent our first note to them raising a significant concern on the 18th, and on the 19th measures were put in place.

Aaron Bell: Thank you.

Q1613 **Carol Monaghan:** I am aware of the time, so I will try to be quick, and I would ask the witnesses to try to be quick in response. We have so much we want to ask but very little time with you.

How quickly might this new variant spread around the UK? We know that it is present all over the UK but that it is still highly concentrated in the south-east. How quickly could it spread further from the south-east?

Professor Ferguson: First of all, it is everywhere now. It is not so much about spread at the moment but about how quickly it grows from the level it is in every place in the country to a higher level. We are seeing growth of this variant. Certainly, there is a cluster in Cumbria and growth in the north-west now. As I said, the data is not completely clear, but we are seeing growth in south Wales. There is no reason to believe that it will behave differently in different places. The rate of growth is quite significant.

When you look at overall case numbers, of course, we see the very rapid rise in London, the south-east and the east of England. That is just because it is at a much higher level. Of all the viruses around, this virus is dominating. In other areas, it is still at a lower level and the old viruses are flat or even declining, but still everywhere we are seeing increases in this variant.

Schools are now shut. We are in a near lockdown situation across the country. Contact rates are low over Christmas. I hesitate to make any sort of prediction, but I expect that we will see a flattening of the curve in the next two weeks. We will see at least a slowing of growth, if not more constant case numbers over these quieter two weeks. The critical question is what happens in January, and the extent to which we then want to make public health measures more uniform across the country if the new variant is everywhere.

Q1614 **Carol Monaghan:** With talk of restricting travel between different parts of the UK, is there any point in that at this stage in containing what, as you have said, is all over the place at the moment anyway, or is continued travel around the country still going to be problematic for this?

Professor Ferguson: To some extent, every little helps. First, NERVTAG did not make policy recommendations; we presented the evidence. Christmas is associated with a lot of travel around the country, so it is an exceptional time of year. Restricting that helps prevent the situation of suddenly increasing the frequency of the virus across the whole country. It is everywhere now; we cannot stop it, but it is still beneficial to not let it jump up dramatically just because we are letting people move around.

Q1615 **Carol Monaghan:** Travel restrictions, in your opinion, are useful at this stage.

Professor Ferguson: Associated with the Christmas season, let's say. I think the rationale going forward needs to be examined more carefully.

Carol Monaghan: Thank you.

Q1616 **Aaron Bell:** I have a brief question about what the implications are for the PCR tests. I understand that the fact that the mutation has this deletion means that some of the redundancy in the tests is no longer there. That has been fortuitous and has helped us pick up and survey this. First, does that lead to a risk of more false negative tests? Secondly, does it mean that we need to redesign the tests? Professor Barclay or Professor Ferguson might want to answer that.

Professor Barclay: It is fantastic that we have that redundancy. We have the ORF1ab and the N still picking up the vast majority of cases that are out there. I think an analysis would show that the number of cases that are picked up on the positivity of the S gene alone is not significant. We are not missing tests based on this, because we built in that redundancy. As to whether we need to go back to having three tests to have the full redundancy that we had before, there is some analysis that could be done, but I suspect we are in a pretty good place with having two tests that work at a highly sensitive level to pick up these infections.

Professor Ferguson: Most countries in Europe do not test for the spike. They just have two targets.

Q1617 **Aaron Bell:** That spike test itself is obviously the modification; I think it is the N501Y we are most worried about with the vaccines, but I will leave it to the rest of my colleagues to ask about that.

Professor Barclay: The drop-out of positivity of the S-PCR is down to the deletion we talked about earlier, which is the 69-70, the two bits missing. The PCR itself does not necessarily tell you whether you have the 501Y there as well. There have been other variants that have emerged earlier during this pandemic that have the 69-70 deletion and do not have this particular cluster. Analyses of sequencing show that now 97% of the S-gene drop-outs are this cluster; therefore, it is a very good surrogate marker for the presence of the cluster. As you said, it was fortuitous, in a sense, because it helped Neil and others to trace how widespread the variant had become.

Q1618 **Dawn Butler:** May I ask Professor Barclay a quick question on the effectiveness of vaccinations and their ability to adapt to the new variant? The vaccines are developed differently by different companies. How are you able to assess which vaccines can be adapted quickly to be effective against the new variant?

Professor Barclay: As you said, there are several different platforms that are being used by different manufacturers to produce vaccines. The new platforms are the mRNA vaccines from Pfizer/BioNTech and Moderna. That is a piece of nucleic acid that is synthesised. One of the beauties of this novel technology is its simplicity and, in theory, its adaptability and agility to respond.

There is some talking to be done and some work to be done, but there is some optimism that that kind of vaccine platform will be able rapidly to insert a new sequence for the variant spikes as they emerge, to respond. That is not to say that the other vaccine platforms could not also do that. The other vaccine platforms—for example, the AstraZeneca and Oxford platform—use a recombinant virus, but one where again the spike gene gets inserted into the recombinant virus. It is a little more complicated than adapting the mRNA. Some of the others use protein expression vehicles as well. They are all flexible systems that can receive new sequencing information and adapt. There is an order of speed and agility that probably makes the mRNA vaccines a little more agile than the others.

Q1619 **Dawn Butler:** I see Katherine wants to come in, so this is my last question. Information is so vital in people understanding how to stay safe and how to keep their families safe. Should our priority be to reduce crowds as much as possible in whatever the scenario is, whether it be at train stations or supermarkets? Should that be our priority until we get the vaccine roll-out on a massive scale? I have an additional question on antibodies. How important is it for us to test antibodies in people?

Professor Horby: The principles have not changed because of this virus variant. The way it is transmitted will be the same; it will be through respiratory droplets, perhaps some aerosol transmission and contaminated surfaces. All the measures that have been recommended are the ones that will work. They just need to be enforced much more strongly. You are right; the risk of transmission is from person to person, and the closer and longer it is, and the more it is indoors in a poorly ventilated environment, the higher the risk of transmission. We need to keep reinforcing those

messages and make sure that we put in place measures to reduce that. Don't mix in households unless you really have to, especially if there is a vulnerable person in the household. Be very careful in crowded places, particularly places where you will spend a long time, such as the hospitality sector, and so on. The simple messages, "Hands, face, space," still apply. In fact, they become even more important with this new variant.

Q1620 **Dawn Butler:** And the antibodies?

Professor Horby: There are various reasons for testing the antibodies. The first thing you want to do is test whether the antibodies from people who have been infected and vaccinated neutralise this new virus, and any other new viruses that come along, because that will tell us what the risk of reinfection is in people, and what the likelihood is that the antibody-based therapies—convalescent plasma and monoclonal antibodies—work, and the vaccines work. That is the baseline for interpreting antibody tests that you might use, for example if somebody has some protection; if they are re-exposed, their risk of infection is low, so they can perhaps not self-isolate, but to have that kind of certification, you need to understand what level of protection the antibodies are providing.

Q1621 **Katherine Fletcher:** On the timeline for adapting existing virus technology, are we talking four weeks, four months, six months? Could we have one for the mRNA type and one for the more conventional type like the Oxford AstraZeneca?

Professor Barclay: Again, I think this needs verification from the Vaccine Taskforce, who have a much better idea, and I believe are in conversation with manufacturers about such a timeline. My understanding is that it will take a matter of weeks to make an mRNA that could be tested for immunogenicity. You are still talking perhaps months before you would have a vaccine that could be given at scale to the public.

Katherine Fletcher: Thank you.

Q1622 **Graham Stringer:** Does the latest information and data we have mean that the tier 4 restrictions are unlikely to get the R number below 1? I think that is for Professor Ferguson.

Professor Ferguson: In the context of the festive break and schools being closed, I think we have more confidence that it will than we would if schools were open. We will see what happens in the next two weeks, and that will be informative. Hopefully, if we see a significant decline in case numbers, both of the variant and the non-variant, it will offer us greater comfort going into the new year that tier 4 might be sufficient.

If we do not, of course we will have a more difficult situation. It is not about whether this variant affects children more or not. It is just that any increase in transmissibility, any increase in contacts in the population, poses a risk of transmission. The real question will be how we reduce the infection risk associated with schools. We will know much more in the coming two or

three weeks about the case trends we see there, and that will inform the decision making.

Q1623 **Graham Stringer:** Professor Ferguson, I and I am sure other members of the Committee are grateful for your input and that of all the academics we have had before us over the last eight or nine months. I am interested in the structural process. The Government told us that you were not going to be part of the structure. I am pleased that you are. Can you tell us what happened?

Professor Ferguson: I cannot comment on No. 10 comments. I agreed back in May that I would step aside from SAGE. I was never asked to step aside from anything else and I did not offer to. I am here now.

Graham Stringer: We are grateful for your contribution.

Professor Horby: As chair of NERVTAG, I decided that Professor Ferguson should stay on NERVTAG and I am very grateful that he agreed to.

Graham Stringer: Well done.

Q1624 **Aaron Bell:** Pursuant to what you just said about restrictions and the R rate, Professor Ferguson, I have seen this new variant characterised as moving us from a siege position to one where we are now in a race. What are the implications for the vaccine roll-out process, assuming that the MHRA approves the AstraZeneca? Should we be absolutely prioritising vaccination above all else and trying to roll it out even more quickly than we are?

Professor Ferguson: Knowing the people on the Vaccine Taskforce and in the NHS, I think it has been a top priority anyhow. Clearly, it adds extra urgency, and everything will be done to speed it up, to the extent possible. This is going to be an unprecedented vaccination campaign in its scale and speed, far greater than we do every year, say, for seasonal flu, which is rolled out over the course of a few months. There are huge logistic challenges. Clearly, this makes it an even more urgent priority.

Q1625 **Aaron Bell:** Would you agree with the assessment that we have moved from a siege situation, where we can hope to suppress the virus, to now just slowing its growth?

Professor Ferguson: If it turns out to be the case—it is a big "if", and we don't know—that it is quite difficult to keep schools open and keep control of this new variant, of course, that puts us in a much more difficult situation. We do not want children to lose out on education. It just adds to the urgency. We do not know whether that is going to be the case at the moment. Things like the mass use of lateral flow testing in schools might help as well.

Q1626 **Chair:** I have some final follow-up questions to clarify some points we have talked about. We know that you now have high confidence that this new variant is more transmissible. We do not know yet definitively whether it is more serious in terms of hospitalisations and deaths. Is it possible to predict or anticipate that? Is it the case that new variants tend to be over

time less serious, if I can put it that way, or would that not be a safe assessment to make?

Professor Horby: We don't know if it is more serious and we don't know if it is less serious. There are evolutionary arguments to be made; you have an evolutionary advantage if you are causing less severe disease as a virus. What you want is prolonged viral excretion from somebody who is relatively well, and then you will be very successful. Most people, even with the normal variant, do not get that sick. It is only a small proportion who get very unwell. There probably is not much water in that case for this, and we just have to wait and see.

You get compensatory mutations. They are trying to out-compete other viruses in their ability to infect cells. Whether it causes severe illness or not, is, to an extent, dependent on where it does that. If it replicates very efficiently in the upper respiratory tract but not in the lower respiratory tract, you may end up with less severe disease, but if it replicates equally well in both, it would be the same.

Q1627 **Chair:** We have been able to detect the presence of this new variant partly by seeing its spread across the country and detecting it that way. What we have also seen in recent weeks, compared with the first wave, is that the number of patients needing to be admitted to ICU facilities has fallen. Does that not give us the grounds to make a provisional judgment that it might be associated with the increasing dominance of this new virus, at least in Kent and the south-east of England?

Professor Horby: I think not, because we have seen a decline in case fatality rates since the start of the second wave, and across the country in areas where this variant was not there. It is much more likely to be due to both the transmission risks, with transmission happening more in younger people through the summer as they were mixing more, and the improvements in diagnosis and care of patients.

Q1628 **Chair:** That finding predated the existence of this strain.

Professor Horby: Yes.

Q1629 **Chair:** To follow up Aaron's question on vaccination and the race to get people vaccinated, does your work on this new strain of the virus have any implications for who should be vaccinated first? Should it be the most vulnerable or the people most likely to transmit the infection?

Professor Horby: At the moment, the priority chosen by the Joint Committee on Vaccination and Immunisation—JCVI—is to use the vaccine to protect the most vulnerable. That seems to me the most sensible approach, and I don't see any reason to change it.

Q1630 **Chair:** That was based on the knowledge of the virus at a certain level of infectivity. The findings of the last few days and weeks do not change your judgment as to that prioritisation.

Professor Ferguson: If we had huge amounts of stocks all available at once, such that we were able to vaccinate everybody, it might possibly

change things, but we are not in that position. We are going to be vaccinating people as we get stocks. An enormous amount of work from multiple groups has looked at the optimal strategy in such circumstances. It is always optimal to protect people most at risk and that is not affected by the level of transmissibility. We have looked at that.

Q1631 **Chair:** On the spread of the virus across the country, the figures that we get are, to a certain extent, lagged because people contract the infection before they test positive for it. Is it your view that it is now prevalent across the country to a significant degree, or can we still rely on local restrictions to contain it?

Professor Ferguson: I think it will be a moving target. At regional level, it is in every region, but at a very local level there will probably be some areas that do not have it and some areas that do. As I said, the pattern we are seeing in the data at the moment, using the S-gene drop-out data as a proxy, is that those case numbers are increasing everywhere, but in some areas they are only a small proportion of all cases. You do not see a big uptick among all cases, but those cases of the variant are increasing quite quickly. It will be a moving target. I think the Government prioritised the really high-risk areas with a high frequency of this variant first, based on the data available, but we will have to revisit those restrictions in the coming weeks.

Q1632 **Chair:** Should it be done on the fortnightly cycle of reviews or does it need to be done in a different way?

Professor Ferguson: I think in the current context everyone is tracking data day by day.

Professor Horby: I reinforce the point that it is the early stages. We have some early indications that were worrying about transmissibility and that warranted action. We still have quite a lot to learn about how the virus is behaving, both itself biologically and in areas where there are small numbers of cases and transmission rates are lower.

Q1633 **Chair:** Does what we have established about the fact that children are perhaps no more prone but equally prone as adults to transmit this virus have implications? Is a decision required before the beginning of the new term?

Professor Ferguson: First, may I slightly correct what you said?

Chair: Please do.

Professor Ferguson: We do not have evidence of any change in transmissibility in children. What we have is a slight shift in the age distribution. We do not know why that is. It could just be that they are slightly more likely to develop symptoms, whereas in the past children were quite unlikely compared with adults to develop symptoms. There is a hint and, going on with your question, if that pans out and it looks like transmission is enhanced in children, which we will not know immediately, potentially it will have consequences, yes, but it is too early to be definitive about a conclusion.

Q1634 **Chair:** That is very helpful and very clear. We cannot know yet. We do not have enough information to make that decision. Are you able to say when we might be in a position to do that? Obviously, the more notice that people—children, parents, teachers in schools—have of this the better.

Professor Ferguson: That is something we and multiple other groups are working on at pace, and data is being collected by PHE. I cannot easily give a timeline, partly because schools are now closed, so we have to rely on data collected in the past few weeks. Everybody is working as fast as they can. We will know more without doubt within a couple of weeks. Whether it is sufficient to be conclusive on the issue remains to be seen.

Q1635 **Chair:** In one of your earlier answers, you gave a look forward and you thought that, because of the measures that are in place now, and because of the change in patterns of movement over Christmas, you expected the increase in cases to fall off a bit. I do not want to put words in your mouth. Given that you are a very prominent modeller of this pandemic, could you give us your forward look over the next six weeks to two months, to give your best assessment, based on your modelling, of what we might expect for infection rates, hospitalisations and deaths?

Professor Ferguson: The SPI-M group brings together multiple modelling groups. Every week we generate the R numbers, which you hear reported each week, and we also generate medium-term projections. Those projections are saying: if nothing changes, what is the trajectory? Of course, the trajectory right now is a rather negative pessimistic one. Case numbers are increasing. The overall R is 1.2 or something, hiding a lot of regional variation.

My comment that I expect to see that flatten, that rate of growth at least to slow—whether we see case numbers decline remains to be seen—is based on our understanding that over the Christmas period contact rates in the population generally tend to be lower than either side of Christmas. People are generally not in work, schools are shut, and both of those things make a difference. Exactly what we will see is almost impossible to predict, partly because of the difficulty of quantifying precisely how transmissible this new variant is.

If we start to see significant decline over the next two weeks in case numbers overall, particularly case numbers of this variant, I would still not say we are in a great position; we are in a worse position than we were before, but it offers a little more optimism that maybe we can keep on top of it. If we see case numbers increase, which is not my expectation, we will be in a very difficult position, and I do not have any particular thoughts as to what we do at that point.

Chair: I am grateful for that. It is very clear, both in terms of the analysis of the data and keeping an eye on the level of infections and its patterns, as you put it, that this is a daily task. It is probably going to mean for you and your colleagues and the science community, as well as people in government and in the NHS, a pretty active season ahead.

On that note, I very warmly thank our witnesses for giving up their time to

appear today. It may be holiday time, but it is very clear that they are not on holiday, and they have a lot of important work to do. We wish you well, and please convey our thanks to your colleagues. I thank the people who make these meetings of the Committee possible—the Clerk, Danielle Nash, the broadcasting team and all the Clerks team. Arranging these meetings at short notice and having high-calibre witnesses and the ability to convey this to the public takes a lot of effort and logistics. I am very grateful to them for breaking into their time with their families. Thank you very much indeed. I wish everyone a very merry Christmas, and I call the meeting to an end.