Covid-19: What does the future of vaccination look like now?

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(Sponsored podcast) Citywire's Gavin Lumsden talks to Paul Major, fund manager of **BB Healthcare** (BBH) investment trust; Dr Annalisa Jenkins, former chief executive of Dimension Therapeutics; and Professor Justin Stebbing, professor of cancer medicine and oncology at Imperial College London and a non-executive director of BBH, about the scientific, political and societal challenges in keeping coronavirus at bay.

This is the second in a series of three Funds Fanatic podcasts in association with BB Healthcare. The first looked at the 'global collaboration that will help us defeat Covid-19'.

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Gavin Lumsden: Hello, welcome to the Citywire Funds Fanatic podcast. My name is Gavin Lumsden. Today, I'm presenting the second in a series of three programmes, in association with BB Healthcare Investment Trust. The aim of our series is to bring to wider attention, some of the important topics around healthcare the investment trust board and its fund manager

regularly consider. With me is Paul Major, BB Healthcare's fund manager. Paul, good to see you again.

Paul Major: Hello, Gavin.

Gavin Lumsden: Last time we discussed the incredible international collaboration between scientists and doctors that led to the successful development of Covid-19 vaccines in record time last year. Today, we're recording this on the anniversary of the UK's first lockdown and we're going to take a closer look at the vaccines and how they might need to develop, but before I introduce our two guests, Paul, I'd ask you, what are you hoping to find out from our conversation?

Paul Major: Sure, as you touched on, I think it's great that we've developed these vaccinations against Sars-CoV-2, but it's worth bearing in mind, there's a whole planet that we have to vaccinate and there's clearly a long way to go before that's complete. Along the way, issues such as production capacity, distribution logistics and of course, the emergence of these variants could weigh on the future outlook and success of that programme. So, it begs the question, what does the future of vaccination of Sars-CoV-2 look like and what do we need to be thinking about as investors, in terms of that and hopefully, around the timing of a return to normal in the coming months to years?

Gavin Lumsden: Thanks, Paul. Time to introduce our two guests to answer your question. I'm very pleased to welcome Dr Annalisa Jenkins, who describes herself as a life scientist thought leader, which might sound a little abstract, but is in fact, a totally apt description for someone like herself, a fully qualified medical doctor, who spent over 25 years working in senior research and development roles in big pharma, culminated as chief executive of Dimension Therapeutics. Annalisa is, nowadays, a committee member of the science board to the US Food & Drug Administration, chair of the court of the London School of Hygiene & Tropical Medicine and also sits on advisory groups at Genomics England, looking into Covid-19. Annalisa, it's very good to meet you.

Annalisa Jenkins: Hi, Gavin. Good to be here, thank you.

Gavin Lumsden: Our second guest is Professor Justin Stebbing. Justin is a non-executive director on the board of BB Healthcare, but his main job is professor of cancer medicine and oncology at Imperial College London, where he focuses on immunotherapies for breast, lung and gastrointestinal cancers. In the past year, he's probably become best known for leading a team of researchers that used artificial intelligence to identify an already approved drug, Baricitinib, a rheumatoid arthritis treatment, as a potential treatment for Covid, as well. Justin, good to see you again.

Justin Stebbing: Good to be with you, Gavin.

Gavin Lumsden: It seems likely, judging from the prime minister's warning today, that there will be a third or fourth wave of Covid in the coming months, unfortunately. Hopefully, later rather than sooner so we can work on vaccinations. Annalisa, I'll start with you, what are your thoughts on the probability of the next wave?

Annalisa Jenkins: Well, Gavin, of course the nature of an infection like Covid is that there inevitably will be a next wave. Of course, one has to define what a wave really means and what we should really be focusing on is how do we get prepared to manage and navigate through the inevitable next wave and in order to decrease the impact that that will have, not only at the individual level, but of course, as we've heard over the last year, the impact that will have will all be on our healthcare system and also, of course, just generally our society and our economy.

Justin, let's take that forward a little bit. Is there any chance it could be silent? With infections, but low morbidity and mortality.

Justin Stebbing: I think we don't know yet. I think the key question for the upcoming winter is, what will the excess mortality from Covid-19 be? I think for a fourth wave and we're already seeing this in Minnesota, Michigan and Florida and perhaps, around Europe, is that it's not going to

be accompanied by a similar pattern of hospitalisations and deaths because of the vaccines. That will create a slight political dilemma, what do you do with the surge in case numbers, but because of the vaccinations, what restrictions may you apply or may you just say, the reality is, by September I think there'll be a realisation that this will be endemic. The probability of having a Covid-19 zero society I think is very low. By September we're going to have data from kids' vaccination programmes, as well, which is an ethical debate in its own right, considering the number of children you need to vaccinate with the arm pains and fevers, to save one child's life. Obviously, there's the argument about transmission in schools and so forth, but I think the concept of herd immunity as we've seen in Manaus in Brazil, where they had a very vicious further wave, despite huge zero prevalence rates, means that we might not ever achieve herd immunity and we're going to get used to living with it. In terms of future vaccination strategies, as you hinted on and as Annalisa has said, it's going to be different.

Pfizer are banking on a third booster shot, Moderna have changed the sequence to match the E484K mutation in the South African and the Brazilian variants and we just don't know the durability of vaccinations, which raises the issue of vaccine passports and so forth. So, all these things raise more questions than they do answers. I think the future will be learning to live with it and I think it will cause a lot less alarm going forwards, but it's possible, with the variants, as Paul mentioned, that the story isn't fully written yet. We've had the highly transmissible B117 variant, which may be associated with more deaths because it lasts longer in you. We've had the vaccine-resistant variants in Brazil and South Africa. Are we going to have a combination of highly transmissible vaccine resistant, we don't know, but one's tempted to say right now, that with the pace of vaccinations in America, UK and Israel, we can see that things are going to get better and we're waiting for Europe and the rest of the world to catch up.

Annalisa Jenkins: I think that last point is so important. It's tempting, sometimes, to be overly parochial and focus on what has been a

remarkable effort here in the UK and clearly, in Israel, the Emirates and now, we're seeing obviously, in the US, but we have to remind ourselves that the virus knows no boundaries and really, this is a global issue, a global problem and we need to find a global solution. I think throughout this discussion, again, when talking about an endemic virus and its impact on our society here, that's going to be, to a certain extent, determined by how the rest of the world and other countries are able to implement their public health goals and priorities and over time, we again should come back to that because whilst we're living in unprecedented times, vaccinating an entire population over such a short space of time, which we've never done before, okay, then the question arises as we're thinking about future waves and exposure, potentially, to new variants, how do we sustain that and build an ecosystem within our public health system and our general health system to be able to navigate that sequentially over the years to come?

Gavin Lumsden: I think people would like to know, there's a lot of uncertainty around the variants, but you and Justin are talking about it being endemic and never going away, how serious, how severe could be the following waves? Will they be as bad as what we've had so far?

Justin Stebbing: Up until now it's been a race hasn't it, between a pathogen and vaccination. That's what's been happening this year. Some people call it a molecular arms race, but I don't think the future waves will be as bad. My first point, Gavin, was what will the excess mortality look like in the future? I just saw a Daily Mail article, obviously, I obtain all my medical knowledge from the Daily Mail, saying that in the last couple of weeks there has been zero excess mortality in the UK, which is hugely encouraging, but in all seriousness, there are a lot of unknowns. Who would have thought that 2020 would turn out the way it did and I suspect, the story isn't written yet? Crucially, we don't understand the role of previous-, how long vaccines are going to last for and it's not an all or nothing thing. So, we saw from Novavax and Johnson & Johnson that they just worked less well against Brazilian and South African variants. It wasn't like they did work against the classical wild-type USA strain and didn't

work against South Africa and Brazilian variants and maybe, we should be a bit careful not to use the name of origin as there's a bit of controversy there, but that's what I do so, sorry. It's not an all or nothing thing. So even if we have a vaccine that prevents hospitalisation and deaths, it may not prevent asymptomatic infection, for example. It may not prevent asymptomatic transmission, as well. There are a lot of unknowns.

Annalisa Jenkins: Having been in drug development over so many years, it's remarkable to think that we're now taking actions and trying to make predictions with datasets that are remarkably small and are really datasets that will mature over time. The two questions that really, at the moment are unknown, as Justin has just mentioned are, one, the durability. The durability of the vaccine is a critical dataset and we will start to get some data on that, emerging data, I think, as the summer progresses into the second half of the year, of course and the second beyond the durability, is really this issue of transmissibility. Those with mild-, particularly, the asymptomatic, do the vaccines prevent that or to a certain degree suppress that because that will of course determine, as Justin was saying, whether we are able to get to herd immunity and what that might look like. Personally, I feel it's going to be challenging to get to herd immunity and if we assume that that's the case, by definition we're in a situation of an endemic disease and we have many endemic viruses that circulate seasonally through our population. So, the question then just becomes, how do we take actions, whether those be vaccine, therapeutic prophylaxis and just public health measures, non-pharmaceutical interventions, to be able to minimise the impact on society?

Gavin Lumsden: We've talked about the next wave, let's think about vaccine developments. Justin, the question is, do we need multivalent vaccines, immunising against two or more strains? Could that be as easy as it has been for the flu, for example?

Justin Stebbing: It's not been very easy for the flu. Flu vaccinations work 50% to 60% of the time. Fortunately, this virus is less mutable than the flu, but there are real mutations and as I mentioned earlier, different

vaccine developers have different approaches. So, if you have a vaccine that produces an efficacy, say 50% top 60% efficacy, to me, that's still meaningful. Provided enough people are vaccinated, albeit with our herd immunity, my overriding view is, I think we'll be okay and by September, Covid will largely be off the front pages, but it will probably still be on pages two and three.

Gavin Lumsden: Annalisa, in terms of some of the practicalities, you were mentioning, could we combine flu and Covid jabs in one shot moving forward?

Annalisa Jenkins: I actually am not necessarily of the view that that makes sense, to be honest. I think that we are used to having vaccinations for different diseases, different vaccines for different diseases. I suspect it's going to be rather complicated and in the world of drug development it's usually good to try and keep things simple. Interestingly, as you know and I'm sure you've spoken about this on previous episodes, that we've seen no flu this year and I think one of the interesting questions—.

Justin Stebbing: In the southern hemisphere, right.

Annalisa Jenkins: Yes, in the southern hemisphere. I think it's going to be fascinating to see what we see coming up next winter and again, I think many of us last summer were very concerned about the combination of flu and Covid and it didn't really turn out as we thought, actually. So, my view to summarise, is I suspect we will not primarily, head in the direction of a single vaccine to cover both, I think technically it will be challenging from a regulatory point of view, it will be challenging from a scientific-, just generally, clinical studies it will be challenging. We might see it one day, but I don't think that's the scenario we're going to be in, in the next year or two.

Justin Stebbing: I agree with that, completely. There'll probably be joint testing this winter for Sars and influenza, but not joint vaccinations.

Gavin Lumsden: Paul, I wanted to bring you in if I can. Speaking to you

before, you wanted to ask about the Hoskins effect and antigenic sin, which sounds terrible. Can you explain what they are, first of all, before you put your question?

Paul Major: Sure, very simply, the immune system prioritises speed over everything else. So, if it looks at a previous immunological memory and exposure-, so simply put, if your body thinks it's seen something before, it will produce the same antibodies that were successful the last time around. So, one of the challenges around these variants-, Justin touched upon the point, these variants of Covid, they're actually small changes in sequence. So, I guess it would be interesting to hear the participants thoughts on whether it might be challenging to get variant boosters to actually create new antibodies or if, in fact, the body is going to say, it's another Sars-CoV-2, I'll just churn out the antibodies I churned out in response to the first vaccination that I got?

Gavin Lumsden: That does sound problematic, Justin, do you want to tackle that first?

Justin Stebbing: Paul, it's a great question. We know that infection with the 2002, 2003 Sars, perhaps, MERS gives some protection against Sars-CoV-2, as does infection with routine seasonal coronaviruses, as well. We know that one type of flu or one type of flu vaccine can confer some cross-immunity, although not complete cross-immunity with others, as well. So, there's many, many layers to your question. With this virus, it has no aim, it has no desire other than to reproduce its genetic material and it's very good at that because of it's viral load during the asymptomatic period, when no one knows when they're infected, but in terms of the immune response to it and whether we need new vaccines, I suspect that we will do. I think it's become clear that we will need boosters, just from the Imperial College React zero prevalence study showing the decline in antibodies, but at the same time, the nightmare scenario, that will need another booster say, every three-to-six months doesn't look applicable or appropriate. One thing we will hear about, just purely based on numbers, is that people who have been vaccinated, will

become infected and some of them will become sick. Now, the reason for that-, maybe the vaccine doesn't work in them or the vaccine durability wears off and sometimes, the vaccines don't work, but the reality is, if you've got six people around you and they all have umbrellas up, even if yours isn't working, you're going to have some protection from the rain, right?

Annalisa Jenkins: I would reiterate and I think, support the fact that my going-in hypothesis was that annual, annual booster. Obviously, I was concerned that it would be more frequent. I think we're coming to realise that's not going to be the case. Annual. Having said that, we shouldn't underestimate the enormity of an annual booster for Covid and not only just in the UK, but globally. If you think about how long it's taking and how long we predict it's going to take to get sufficient coverage on a global basis. So, for me, really, the bigger question is, could this perhaps, be spaced out to every couple of years and could we get there and I think that is something that we just don't have enough data on at the moment? To Justin's point, as well-, the other point, I think, we have to really work through is, really, what are we trying to achieve here? If this is going to be endemic, what is it that we will be prepared to accept as a society and that balance between health of our people and the functioning of our society. I do think that that debate is very much still ongoing, obviously, in countries around the world and some coming to very different views on that point, frankly. So that's going to be really interesting as it plays out and I believe, that governments, today, almost haven't yet come to that grand master plan. They're still so busy in the near term, what's the plan over the next few months, that I don't think we've seen all that much yet. What do we think the next two years might look like and what is it that we think, as a society, we would be willing to live with on account of Covid?

Gavin Lumsden: Annalisa, help me and them, the governments, the politicians, what are the implications that you're identifying there?

Annalisa Jenkins: Well, you know, we're very familiar with the flu. Interestingly, the Covid pandemic has really amplified and perhaps, shone

a light on data that much of the population didn't realise. The mortality, the sickness and the deaths on an annual basis that we, as a society, seem to be comfortable to live with each year, even with the availability of vaccines and vaccination programmes in our very sophisticated public health system. So, are we going to apply the same lens and believe that actually, having this virus circulating through the population as we, perhaps, put in place some public health measures? Will we still be wearing masks, will we still be socially distancing a little bit and will we, therefore, be accepting that we're able to-, there will be some excess deaths. However, the healthcare system and our hospital systems are able to cope on an annual basis. These are the sorts of questions that, I think, are going to be very important, not only for the healthcare leaders and public health system, but of course, for our financial communities, who are really trying to work through what our economies are going to look like and our societies are going to look like in the next two to three years.

Gavin Lumsden: Justin, just going back to Paul's question around the Hoskins effect, is it possible to develop a new, universal Covid vaccine, working against all the strains?

Justin Stebbing: People have been talking about that for flu, for a long, long time and it's never been possible for flu. For Covid, I think that it shouldn't necessarily even be an aim because I think we'll be able to adapt our science on a very regular basis. If you think about the fact that the first sequence, first Sars-CoV-2 was published in mid-January and by April, people were being dosed in phase one immunogenicity studies, we can do things very rapidly. More rapidly now, than then. I don't think that should necessarily, even be an aim of ours. I think there needs to be an understanding that it will be endemic, unless there's mandatory vaccination of all children. In every society, there's going to be at least 15% to 25% of people who will refuse vaccination for whatever reason. I don't think anyone's really thinking about a universal Covid vaccine at this point in time. That's just my view.

Annalisa Jenkins: No, I don't think that that really is the scientific

community's goal at this point. I do think the scientific community is really focused on doubling down on the evolution of these new platforms. I mean, we should remember that the MRNA vaccine from Moderna and Pfizer that we're all so familiar with now, is a fundamentally new platform in this space. I think the second point is that I believe that the peptide platform, the NovaVax and the like, I think will become an important part of the armamentarium and let's not forget, there's over 100 novel vaccines. There's not a day that goes by, I saw today there was an announcement in Japan, I think, that they're developing a novel MRNA platform. So, I think what really, you're seeing now, is people doubling down on optimising these platforms so that they will be flexible and quick enough to adapt on an ongoing basis and that therefore, it becomes one of adaptation.

Gavin Lumsden: You referred to the pipeline of other novel vaccine technologies, what are the issues around running new trials to test them?

Justin Stebbing: There's about four different issues. We have vaccines that work so, is it ethical to perform placebo-controlled trials, number one? Number two, because hospitalisations and deaths are going, having an endpoint of preventing severe hospitalisation and sickness is very difficult to measure because it's going away. Number three, we have technologies that we know work, even though they have side effects. Messenger RNA has entered real-time, we have viral vaccines, we have, as Annalisa said, Novavax's protein subunit vaccine which is adjuvanted and we have others as well. So, is it worth introducing a totally new technology when we have therapies that work?

Annalisa Jenkins: I agree. I think this speaks to again, learning more about the science of this infection so that potentially in the future, we can develop biomarkers or measures that are the surrogates for the clinical effect that we want to achieve. I think you'll see more of that as companies and academics start to explore how they're going to innovate in this space. One thing I'm encouraged about, actually, is that it does seem that some of our preclinical models, both cell-based models and animal-based models, in vivo pharmacology, seem to be reasonably predictive, actually.

They've panned out reasonably well in the translation between preclinical and what we've seen in the human setting. So that's useful. So, I do feel that the approach that we've seen in the last 12 months, I think this is the message, these massive studies with a primary endpoint of death in hospitals, I don't think that's going to be the future. So, the question, what does innovation in new vaccine development for Covid look like in the next few years and I do believe that will come to, basically, surrogate markets, biomarkers, just an evolution of that, but for now, I think everyone has to feel that we have what we have. We have five or six, obviously, we mustn't forget those that have come out of China and Russia and other parts of the world. Frankly, although we're still living in this scarcity on a global basis, one would hope that those will become the workhorses that will be able to serve large parts of the population, certainly, for the next 12 to 18 months.

Justin Stebbing: Just to take that further, we also know that we'd like a one-shot fridge stable, as well. We've learnt that, just from a practical point of view.

Annalisa Jenkins: Clearly. Which, by the way is why I suspect that the US is doubling down and focusing on the J&J vaccine as their workhorse for this space.

Justin Stebbing: Absolutely correct.

Gavin Lumsden: Justin, we've seen companies like AstraZeneca, you've alluded to, struggle to optimise production at some plants. How complex is it to make these vaccines?

Justin Stebbing: I don't think the production issues are the main issue, necessarily, with AstraZeneca. I think there's been one or two political issues there. Pfizer had problems at their Puurs plant in Belgium. Moderna have issues with Lonza. Everyone's had issues. The Serum Institute of India's had issues. It's very difficult to do this properly, but manufacturing practice of GMP, is well recognised to be left in the hands of very specialised companies that do it day-in day-out, where you need vertical

integration, a supply chain, the finish and fill, the syringes, the glass vials and everything automated. Now this is something that's well-known to the companies in the space, but of course, there are always going to be teething problems with it. I refer to them as growing pains. We've got seven billion people in the world. We're still travelling more than anyone's ever travelled. That's seven billion viral reservoirs, if you like, some of whom are immunosuppressed or on chemotherapy where the virus can mutate more easily. You've got the issue of pets and animals, which is a whole other subject, but there's probably going to be a big oversupply of vaccines, as well, which people haven't really talked about and in terms of manufacturing, there's always going to be growing problems and teething problems, but they're bumps in the road.

Gavin Lumsden: Annalisa, I introduced you at the beginning, you've worked for big pharma companies. What's your view on the production realities which the public at large barely know about?

Annalisa Jenkins: I think the message is, it's a complex process and as Justin said, before Covid, people really weren't aware of the fact that there were about four or five companies in the world who really, over the last 20 to 30 years have been responsible for the majority, really, of the innovation in vaccines and have developed long-standing capabilities in manufacturing global supply chains. There weren't that many companies, as opposed to other parts of our sector. So that's the first thing. The second is that this is a biological process. So, it has many steps. It often involves supply chains that are complicated and absolutely, as we discovered, cross national boundaries. So, whether that be flying vials or stoppers or packaging or even just the basic ingredients of the biological process, it is complicated, that's the second thing. The third thing that I'd like to say is that with these biological processes, if you run them over and over and over again, you will get errors because it's the nature of the process. So, to make that really simple, if you run a process and it's called a batch, those batches are tested on a continuous basis as you're making vaccine and if they fall out of spec, one of the little assays and measures is out of spec, you are required under good manufacturing process to throw

it away because we're held to very tight standards.

This is really a game of probabilities because over time, if you run it enough times, things will go out of spec. So, we've heard this issue around the yield out of the cells wasn't quite up to the expectation or there've been some assay issues or out of spec issues, it happens. It's not a surprise to the industry. I think why it's been an issue-, the reason it's been an issue is because we're under pressure to do this at volume, very quickly and the last thing I'll say is, a company like AstraZeneca that wasn't traditionally in the business of manufacturing vaccines so, couldn't really just bring one of its facilities online or a few of them globally, like some of the other companies, they had to go out and work with many, many third-party manufacturing facilities on a global basis and put that all in place over a period of nine months. That is an enormously complex procedure and operation. So, it's not surprising, as Justin has said, that it's going to take time to bed that down, for that team, globally, to really get to be a highly functioning, predictable organisation. I was not surprised at all and I don't think our industry was that surprised, but it will get better over time. It will clearly get better over time and I think the other thing it will do is focus not only on our industry and it has focused governments and the investment community on the need for more capacity. More national capacity and for building a long-term capabilitiy around manufacturing of these critical and essential medicines and vaccines on an ongoing basis and that can only be a good thing.

Justin Stebbing: Just to mention, well-known established vaccine manufacturers such as Glaxo, Sanofi and Merck have not succeeded in making Covid vaccines here, as well. They're well-known vaccine manufacturers. Just to highlight how difficult it is.

Annalisa Jenkins: That's right.

Gavin Lumsden: Justin, you've referred to the political pressure that Astra has come under. The onset of vaccine wars and the threat of export bans and that sort of thing, is that just inevitable in a situation like this or is it actually, something that's going to be quite damaging to preventing the

Justin Stebbing: I think of it as a global phenomenon. There's no question that China-, for example, if you look at the speech President Xi gave in Colombia yesterday, is using its vaccine for diplomacy. Russia as well. Hungary is giving it in Europe before any EU approval. I think there's an inevitability to it and people are using it as part of the diplomacy effort and it's being used as a pawn amongst political games between people, but it's not really my area. What I would say on the subject of China, is that I've been very surprised that we saw their animal data, their phase one and phase two data published in good journals like JAMA, Science, The Lancet. We've seen no phase three China vaccine data published. I don't really understand why that is still, despite seeing their data released a long time ago. Considering they published all their earlier data and early on in the pandemic, they published negative treatment data on remdesivir and lopinavir/ritonavir showing that in their populations it didn't work well. So, I've been very surprised by that, but there's no question that it's being used as part of a political process, but I'm not the best person to speak to about that.

Gavin Lumsden: One of the big issues and Paul, I'd like to bring you in here, but in terms of distribution and getting the vaccines and getting the vaccines distributed across the world and ensuring there's fair global access. It looks like there should be plenty of vaccines to do it, what are the issues of making sure everybody gets access to it?

Paul Major: From my point of view, looking at this from an investor's perspective, it's clearly the challenge, as both Annalisa and Justin have pointed to, is scaling up production. Everybody's frantically trying to do that, but there probably will come a point where we cross over and there's too much capacity, which is great because that then drives down prices, which is a secondary issue with regard to ensuring everybody can get fair and reasonable access to these things in less developed parts of the world. If you look at ultimately, what's happened with things like Gavi [the vaccine alliance], over time, driving down the prices are vaccines, I think

all of this points to ultimately commoditisation of these things. The WHO is probably going to decide what an acceptable vaccine is, specification wise, the ones we've got, efficacy looks incredible across the vast majority of them. So, they're all good enough. So, I guess it comes down to the points that Justin talked about, it has to be stable at a temperature that is suitable to the developed status and environment of the country you're shipping it to and it's a question of, what price and how much can you ship? If we think about the challenge of needing everybody to be vaccinated for life to truly return to normal, then that's actually a great position to be in, especially, as was discussed earlier as well, that we don't actually need new vaccines every single year, that maybe we have multiyear durability or that the variants that are emerging can be dealt with reasonably well with the vaccines that exist today. So, I think all of that is very exciting, but we're obviously going to have this painful process where the countries that paid for the research are going to want first dibs and there's not going to be enough to go around, at least initially.

Gavin Lumsden: Where does all this leave us and what are the priorities for action?

Annalisa Jenkins: Obviously, we've got an urgent and then, we've got an important. In the urgent, it's clear that we need to get on top of the current waves, both in the UK-, we've got to get an many people vaccinated as possible, we've got to get people out and about, we've got to get our economies going. We've got to start rebuilding trust that our people have, both in their ability to get access to vaccines, access to good standards of care, access to a system that's going to support them and then, obviously, access back into an economy that's working for them. So, for me, in the short-term, it's about public health. Vaccination, public health measures and getting ourselves back into a society that's confident. I think in the medium-term I mentioned earlier, I would love to see a joined-up thinking around what does a public health response look like for the next two years? What are we, in the UK, going to do to invest in vaccinations, therapeutics, diagnostics and how are we going to navigate the inevitable waves or perhaps, it will continue to be seasonal to a certain

extent, what does that look like? I think the third thing that we really need to focus on and Paul was just mentioning it, which is that this is a global issue.

I just continue to be, not frustrated, but anxious around the intersection of global health with these geopolitical issues and I do feel hopeful that the G7, hopefully, can come together and start to make progress on this. I hope that the WHO and other multinational organisations can perhaps, bring some sensibility to the fact that we do need to focus, globally and I'm hopeful that some of these inevitable geopolitical issues that we will have to live with, will not delay progress and will not become a drag on the next wave of innovation that we have in our hands to move forward. So, at the end of the day, it's all about leadership isn't it, really. So that's really where I'm at, at the moment.

Justin Stebbing: I'd echo what Annalisa and Paul said, it's very easy to get bogged down in the day-to-day minutia, everything happens at such rapid speed, but one thing I like about what Annalisa said is, you have to have a long-term perspective and for me, the long-term perspective has been that although I discovered a treatment and led global clinical trials on it, I'd have to say the treatments for Covid, once you have the pneumonia, aren't very good. Vaccines, on the other hand, seem excellent, our way out of the pandemic. So, we've been led by science out of the pandemic and focusing on a more humanised society, it's intersection with other things like climate change, geopolitics, stuff that I don't know very much about, I think it's going to become increasingly important and the relationship we have with each other and with the planet that we live on. To have a longer-term perspective, such as the one Annalisa just articulated, is the most important thing for me.

Gavin Lumsden: Paul, you posed the question at the beginning, are you satisfied with the answers that you've been hearing.

Paul Major: I think as ever, thank you both, a fascinating debate. I think it's very hard to come away from a call like this and not feel actually, more optimistic than you did before it started for the simple reason that we

know there are many things we don't know, but what's been expressed today is confidence that actually, the science we have around the existing vaccines is robust and that some of the challenges we're having around logistics and production of things are probably, shorter-term. So, if we just focus on that for a moment, the vaccines we have are incredibly good. So, if they don't work quite as well for some of these variants, they're still probably good enough and as Justin said, certainly better than the flu, for example. We've already reduced mortality significantly and we're beginning to talk about ways to bring life back to normal. So, there's been a lot over the last year to be worried about and to be pessimistic about, the overriding message from this is one of positivity and hope that actually, we are in the beginning of the end, which is a great way to mark the anniversary of the first lockdown here in the UK.

Gavin Lumsden: The scientific achievements have been admirable and very exciting to see. Thank you, Paul. Justin and Annalisa thank you too, very much, for joining us today, it's been a very interesting discussion and I'll look forward to our next episode in the series.