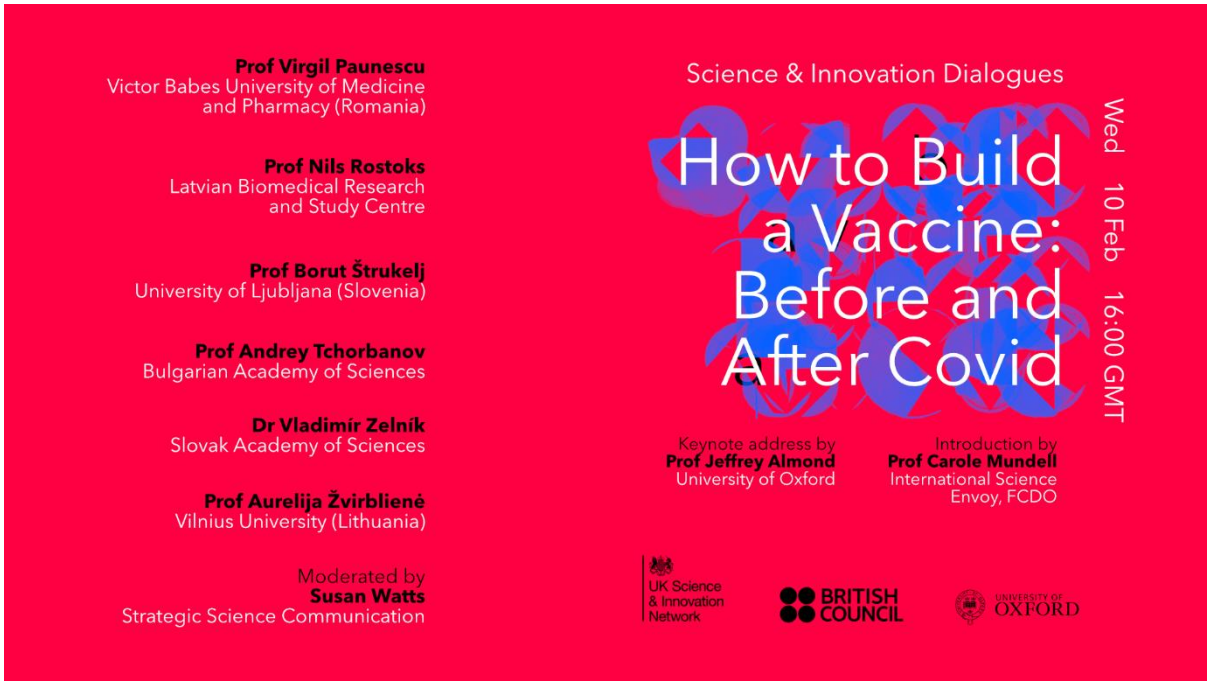

Nearly a year since it all began, the Covid-19 Dialogues mark a suitable point for reflection.

The first of these three discussion events: "**How to Build a Vaccine: Before and After Covid"**, came just as vaccine rollouts were uppermost in the priorities of Governments everywhere, and in the thoughts of the global population.

That we have reached this point is still surprising, even to those who have followed every twist and turn of getting here. "We really had no idea what we were about to deal with, and the thought of having a vaccine just 12 months on, let alone many vaccine options, was really like science fiction to us at that point," **Professor Carole Mundell**, Chief International Science Envoy , Chief International Science Envoy at the UK's Foreign, Commonwealth and Development Office (FCDO), told the online audience as she opened the discussion event, convened by the Science and Innovation Network of the FCDO, alongside the British Council.

Professor Mundell is Professor of Extragalactic Astronomy, and Head of Astrophysics at the University of Bath. She described the huge pace of vaccine development in the UK, and the networks and processes that made that possible, from her perspective as one of the team of science advisers funnelling advice into the UK Government over this past year. She said she hoped the vast mobilisation of expertise she had witnessed was one she hopes will remain on standby, to better equip us in coping with future challenges of this scale.

Her sense of awe at vaccine success, in the face of a seemingly impossible demand for speed, was clearly shared by the keynote speaker for the evening, **Professor Jeffrey Almond**: "I felt immensely proud…of my colleagues in Oxford, in Pfizer and in Moderna, and everywhere else that has chalked up success, that they were able to move so incredibly quickly, and get such an impressive result. And now we're in good shape," he said.

Professor Almond is a virologist and vaccinologist, and visiting professor at both the University of Oxford and the University of Reading in the UK. He switched from an early career in academia to a senior role in industry in 1999, joining Sanofi Pasteur, the vaccine division of the Sanofi group. He has advised on some 30 vaccine projects. He whizzed through the incredible success story of vaccination, with Covid vaccines notching us up to 25 viral and bacterial diseases against which we now have vaccines. He is clearly relieved at the Covid vaccine outcome, but said success was by no means guaranteed.

His biggest worry, even if a vaccine could be devised, was how to scale up manufacturing processes to produce the billions of doses the world would need. He showed a slide of a site built to produce a vaccine by one of the major companies. “I knew one of the guys involved in building this factory. I spoke to him in the early part of last year, and he said to me: ‘Jeffrey I've never built a factory to make any vaccine in less than three years… and when I built such a factory it might have a capacity of a few tens of millions and possibly up to 100 million doses. You’re now asking me for a Covid vaccine, and you want a billion doses by Christmas? Well good luck’, is what he said to me.”

Professor Almond described the challenges in creating a vaccine that works and is consistent in quality from multiple batches of living cells. “You've got to keep them in suspension, so you’ve got to stir them. If you put them in a huge vessel of 2000 or 5000 litres, you’ve got to stir them so hard you start to break them… and you're going to deliver oxygen and nutrients so you bubble in the gas and it turns foamy and it becomes an awful mess. Then you’ve got to add your virus to grow, and synchronize infection of all the cells in that huge vessel. And then you have a hell of a mess and some get infected, some cells break. Everything goes gloopy because the DNA is released… it starts to foam because of the oxygen you're trying to put in… it's a nightmare. So scaling up is really tricky.”

“Over the years, the vessel design, the speed of the stirring, the shape of the paddles to stir the cells, have been worked on and we’ve made big improvements, but it is surprisingly difficult. I joined the industry as an academic and I thought that stuff was easy. Then you see how complicated it is and it becomes amazingly impressive.” A key element of the success of scale-up, he said, was the multi-pronged approach of the Vaccine Task Force, which focussed not on a single site, but on establishing multiple active production sites and improving their output.

The evening included a roundtable discussion with six experts in their field: **Virgil Paunescu**, Professor of Immunology at the University of Medicine and Pharmacy in Timișoara, in Romania; **Professor Nils Rostoks**, director of the Latvian Biomedical Research and Study Centre; **Professor Borut Štrukelj**, who leads the group for Pharmaceutical Biotechnology at the Faculty of Pharmacy, University of Ljubljana, in Slovenia; **Andrey Tchorbanov**, Professor of immunology at the Institute of Microbiology of the Bulgarian Academy of Sciences; **Dr Vladimír Zelník**, head of the Biotechnology Laboratories at the Biomedical Research Centre of the Slovak Academy of Sciences; and **Aurelija Zvirblienė**, professor of Immunology at the Faculty of Medicine of Vilnius University.

Discussions ranged across the variety of technological approaches to developing a Covid vaccine, from those based on nanoparticles, or on cellular rather than antibody immunity, to others that might be administered as a nasal spray, or a pill. They also discussed the wisdom of using multiple vaccine types in a single individual, and why the focus on the spike protein…it turns out past experience of success, with polio for example, is just one reason.

Professor Almond described the cascade of demands of early 2020. “Those experienced in the field thought right, how do we start? What approach do we take? How long is it going to take? Can we realistically get a vaccine out there in the double quick time that it's needed? We've got to invent it first, we've got to choose the right process, the right design. And then we’ve got to think about how that is manufactured.”

He pointed to experience with Ebola as crucial to rapid progress. “Ebola triggered international action because we saw a rapid, emerging and potentially catastrophic event in Western Africa. The massive increase in cases in the early weeks of 2014 provoked a response from the world which almost acted as a little blueprint for what the world has done with Covid-19.”

Professor Mundell cited three elements without which success for the UK would have been far less likely. The first was sustained investment over many years in medical research infrastructure and the creation of networks between government, academia and industry. The second is the Medical Research Council, part of UK Research and Innovation, its funding agency, which supports leading medical research institutes, including in partnership with leading UK universities. Finally, the UK Vaccine Network, of which Professor Almond is a member, which brings together industry, academia and funding bodies to target investments in specific vaccine technologies.

Professor Mundell also pointed to rapid investment in genomics research, expertise in clinical trials, and the fact that the Vaccine Task Force secured access to promising vaccine candidates for the UK population as quickly as possible with a ‘portfolio’ approach. The final important elements were to make provision for international distribution of vaccines, and to ensure efficient, but sound, regulation. “This was a very important piece…to ensure that everybody understands that the safety data are robust, and make that publicly available.”

Professor Almond’s fears over scale-up have been allayed. “As of yesterday [9th February] 138 million shots have already been given around the world, according to the Bloomberg Tracker of vaccination. That’s an incredible effort. Well done to everyone involved. It's not the end of the story we have to maintain vigilance.”

He asked us to reflect on what the natural biology of SARS-Cov-2 might be. Is coronavirus going to behave like measles? he asked, where one vaccination or infection gives you immunity that more or less last you for life. Is it going to evolve into multiple different types, each of which require a different vaccine so that we have to mix the vaccines together? Are we going to see all of these types circulating at once? Could each of those types behave like flu and vary seasonally, so we've got multiple serotypes, all varying?

He cited moves already underway by manufacturers to “tweak” their vaccines to cope with emerging variants, and the need to retain this rigour. “We've been euphoric in welcoming the

vaccines, but we've got to apply them properly, we've got to apply them quickly and we've got to keep a very close eye on this virus and see how it evolves in the months ahead to know how to get on top of it."

"If corona virus behaves like measles, we're in good shape. If it behaves like flu, it's a bigger challenge. If it behaves like rhinoviruses, hell we're in bad shape, and it may even be like rhinoviruses and flu with multiple serotypes, all varying like crazy on a seasonal basis. Then we're going to need a good T-cell vaccine, and really a much bigger effort."

But he remains optimistic. He said that he wasn't expecting this sort of worst case scenario. "I don't expect it to go like that, and even if it does, we might argue that the second time round this disease might not be as severe. I just remind you that the pandemics of the 20th century, in 1918 and 1957 Asian Flu, 1968 with Hong Kong Flu and again in 2009, the first wave of those viruses caused a lot of problems, a lot of deaths. But in subsequent years the disease was not as severe." He puts some of this down to residual immunity. "And so it might be that with this corona, it's severe this first time round, but if it does vary and you get it again, it may be that it's just a common cold… mild enough that we don't really have to worry too much about vaccinating everyone… it might not be the catastrophic scenario that it would be if these are more virulent strains and they're really rapidly varying. So we're in dangerous waters, and it's interesting."

Questions from the audience were just as intriguing. What about treatments for Covid-19, in tandem with vaccines? On this, Professor Almond lit up with enthusiasm, citing drugs that prevent virus replication. "That might be an excellent first step… and yes, we shouldn't just focus on vaccines."

By Susan Watts

Moderator, Covid-19 Dialogue events 2021