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THE BMJ INTERVIEW

How the Oxford-AstraZeneca covid-19 vaccine was made

Andrew Pollard has been leading the Oxford vaccine clinical trials in the UK, Brazil, and South Africa. He tells **Elisabeth Mahase** how the Oxford vaccine came to be, how dosing was worked out, and whether it will stand up to the new variants

Elisabeth Mahase *clinical reporter*

Andrew Pollard was in a French taxi when he realised what was coming.

On his way to a meeting to present his group's research on typhoid, he happened to share a ride to the airport with John Edmunds of the UK Scientific Advisory Group for Emergencies, and they discussed a new virus emerging in China.

"He had a fairly catastrophic view of what was likely to happen to the world from that point," says Pollard. "That was an incredibly chilling moment because I realised that our lives were going to change completely during 2020. Straight away I was thinking that we needed a vaccine."

A multi-award winner, Pollard has become one of the faces of the world's pandemic vaccine effort. As chair of the UK's Joint Committee on Vaccination and Immunisation and the European Medicines Agency's scientific advisory group on vaccines, he knew better than anyone the size of the task ahead. But, as an experienced climber (he was deputy leader of the successful 1994 British Mount Everest Medical Expedition), he knows that mountains are there to be conquered.

The world is obviously worried about the new variants that have emerged in the UK and South Africa. How much would the virus need to mutate to make a vaccine ineffective?

The vaccines that are currently in late stage development, or that are authorised for use, use a large part of this spike protein, which is a very big protein. So, the immune response is against lots of different bits of that protein. This means that, to completely escape, the virus has to mutate quite a lot—so this may give some advantages against escape happening in the short term.

Mutants can arise that escape from the vaccine when there's a lot of pressure on the virus to change. At this moment hardly anyone in the world has been vaccinated and hardly anyone in the world has had disease, even though it feels like a huge impact. Most people have not had an infection yet. And so, the virus is not under huge immune selection.

When lots of people have had disease or been vaccinated, the virus is going to come under a lot of pressure, and when that happens some viruses just can't compete against that immunity.

Will it mutate instead? With this coronavirus we don't know the answer to that question yet, and that's why

surveillance is going to be critical in the year ahead to make sure that we're not in a position where, at the point of population immunity, the virus escapes. And if it does, we need to know that, so that we can redesign the vaccines.

How easy would it be to redesign a vaccine?

For the RNA vaccines and the viral vectors it's relatively straightforward, because you just have to synthesise a new bit of DNA in our case—or RNA in [the Pfizer and Moderna] cases—and then insert that into the new vaccine. Then there's a bit of work to do to manufacture the new vaccine, which is a reasonably heavy lift. But the same processes would be used.

The second component is that there will almost certainly need to be some testing, whether it's in animals or humans, to show that you can still generate immune responses, and then the regulator would have to approve that new product.

SARS-CoV-2 is new to us, but it's from a known family of viruses. Was this helpful in getting the vaccine effort off the ground?

This has been the great thing about this being a coronavirus, because we know so much about the biology of these viruses and particularly how to make vaccines against them.

Over the past 20 years we've had two huge outbreaks of coronaviruses: one back in 2002, which was the SARS coronavirus with about an 11% mortality, and then about eight years ago the MERS coronavirus, which had a 35% mortality. Because those were so horrific and there were around a thousand cases on each occasion, lots of efforts went into making vaccines, which were mostly tested in animals.

We found out from those studies that making immune responses against spike protein could result in protection. My colleague Sarah Gilbert was already working on a MERS coronavirus vaccine just before the [current] pandemic. It was essentially switching the spike protein from the MERS coronavirus to the spike protein of SARS-CoV-2.

All currently available vaccines are two dose regimens, and the interval between doses has been intensely debated. Is there a case

for a one dose strategy or, alternatively, two half doses? Why is two doses the default?

The two dose strategy for our vaccine is actually a change. We originally planned a one dose strategy, and that was really going back to those discussions with the modellers back in February, where it looked as if the UK would be struck by a huge first wave of disease that was devastating. My thinking then was that, if you waited for two doses, we'd have enormous numbers of inpatients and deaths—whereas, if you got one dose, we might be in a much better position to manage.

So, the original strategy when we set out in our trials was just a single dose. But we had a subgroup where we gave two doses, and we found in that group that we ended up with much better immune responses. We went back to the regulators and agreed that we'd move to a two dose strategy, with the idea that you hopefully get some protection from the first dose but that the second dose would give better and perhaps more sustained protection.

As a result, we had to then manufacture enough doses to give the second dose, and that inevitably led to a delay in having the second dose available. That's given us this really interesting phenomenon in our trial, which wasn't intended at the beginning, where we [now] have some people who were vaccinated a month after the first dose and some people, because they'd been vaccinated before the manufacturing happened, who had to wait almost three months for their second dose.

So, we've got this spectrum of people between four and 12 weeks who were vaccinated, and the regulator has approved that interval because there's a lot of data over those different intervals. Absolutely fascinatingly, and perhaps predictably, those who had a longer interval actually make much better immune responses after the second dose. We see that with other vaccines, such as the cervical cancer vaccine.

The half dose has an advantage of dose sparing, but the vast majority of the data that we have is around two full doses. For the regulator, that's the compelling data package. The downside [to a half dose strategy] is that it's a bit more complicated to deliver for a practitioner who has to decide whether this is a half dose person or a full dose person.

Why does a longer dose interval seem to provide a better immune response?

It's almost certainly because the immune response matures after you give a first dose, and, if you give it long enough to mature, you get a very good memory booster response to the second dose. If you have the second dose too early the immune response hasn't matured fully: there's a bit of negative feedback so it doesn't overshoot the mark, and you get a much smaller response to the second dose.

Are more data being collected on these different dosing regimens?

The analysis that has led to the UK authorisation of the [Oxford-AstraZeneca] vaccine was an interim analysis, and so we still have 23 000 people being observed in my trials in the UK, Brazil, and South Africa. We're accumulating more data, and that may be very important because we'll have data on the new variant and hopefully efficacy against the new variants, both here and in South Africa.

We don't have any new trials planned to look at different regimens here in the UK, but we're moving on to new trials to evaluate different age groups—for example, children.

Why did your group wait longer than the other trials, such as those run by Pfizer, AstraZeneca, and Moderna, to release its phase III protocol?

All the way through I think we've followed the normal processes, and actually, for our studies, we've got five publications on the clinical trials. All of the data are out there for people to see. And it's a bit perplexing that there's this constant accusation of a lack of transparency. It's actually something that, as a university, we're absolutely committed to and have been doing all the way through.

What we normally do with our research projects is write a protocol paper, and *BMJ Open* is one of the places we usually launch those. I have to say that, in this pandemic, we've just been a bit busy. We didn't focus on publishing a protocol paper as we've gone along; we just said that we'll put it in the publications when we get there. But I think it's just the scale of what we've been doing as a small university research group: we just couldn't do everything that maybe the big pharmaceutical companies could.

What has it been like to have the spotlight on you, with every small action scrutinised and every event making international headlines?

To be honest, the year has been in many ways not exceptional . . . we've been doing the mundane stuff we normally do—it's the day job. And yet you step into the outside world, and suddenly you realise that everyone's watching you and wants to know exactly what you're going to do next and why you did what you did yesterday.

I think in many ways it's been a completely normal year in vaccine development. What's been different about it has been much longer hours and then immense pressure on the team, because of that external spotlight on us and the urgency of a pandemic.

What can the UK learn from the covid-19 vaccine development?

We could be better set up in the UK than we are, and we're one of the best countries in terms of being able to stand up multiple trial sites. In the UK we have 19 trial sites helping run the trials, and they were set up in about three weeks. They've done an amazing job in setting up, but they didn't have a dedicated infrastructure already in place. It required a lot of work to get that up and running.

There are multiple vaccine centres already established in the US, where they're doing vaccine development, vaccine research and evaluation, and laboratory work on testing immune responses. We have very little of that in the UK, so [one thing is] having more of this established, well funded, and running so that capacity is there on the research side.

And then there's the clinical delivery side. I think that one of the real stresses for everyone was being able to find the staff, to find the space and the training required to stand up a large scale study. If we were doing more of this day to day, I think we could do even more than we were able to do—and more quickly.

Andrew Pollard has recused himself from the Joint Committee on Vaccination and Immunisation's meetings and discussions on covid-19 to prevent any conflict of interest.

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