The Oxford/AstraZeneca Covid-19 Vaccine:

An innovation ecosystems analysis and its policy implications

AstraZeneca

A Report to the Broman Foundation

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Executive Summary

In response to a global pandemic, the Oxford University/AstraZeneca vaccine against Covid-19 was developed exceptionally quickly, has been delivered in over 3 billion doses in 180 countries, and is estimated to have saved over 6 million lives so far. Based on interviews with key contributors at Oxford University, reviews of the literature, especially first-hand accounts, and media and company annual reports, this study reports on the vaccine's development, manufacture, regulation, and distribution, using the analytical framework of innovation ecosystems. Such ecosystems comprise the connections between research, government, large and small firms, and various other contributors.

The report is essentially in two parts. The first part tells the story of the development of the vaccine from the perspective of the main players in Oxford and a range of organisations involved. The second part considers what can be learned from the case, arguing it reveals three issues about innovation ecosystems and crises: latency, animation, and intensification.

- Latency includes deep and wide scientific expertise and research capability, and manufacturing and distribution capacity and agility, which can be drawn upon if and when necessary: a kind of insurance policy for crises.
- Animation of the innovation ecosystem results from recognition of crisis and involves extensive research collaboration and coordination, higher than usual levels of risk tolerance on the part of researchers and business, an astute approach to regulation, the presence of key leaders and individuals skilled at 'boundary spanning' to connect and convene disparate parties, all assisted by the existence of interpersonal and interorganizational trust built over many years.
- Intensification is driven by a sense of crisis properly informed by effective communications, concurrent rather than sequential decision making and operational processes, and the presence of extraordinary, circuit breaking, decision-making bodies with resources and authority.

From an innovation and research policy perspective, the report contends that Donald Stokes' analysis of 'Pasteur's Quadrant', of research concerned with both fundamental understanding and use can be enriched by emphasising its dynamics allied to evolving innovation ecosystems. It suggests a more useful concept is that of 'Pasteur's Space', and considers its implications for much greater flexibility in research funding and management. Essentially, while funding for 'basic' and 'applied' research in Pasteur's Quadrant is necessary and valuable, the ability for both kinds of research to flex into Pasteur's Space in response to the demands of a developing innovation ecosystem is crucial for effective responses to crises.

The report uses extensive quotations from respondents, giving voice to their knowledge and experience that was marshalled to great effect during the worst of times. As well as the quality of their science, and personal tenacity, there is so much to admire in their unwavering commitment to public health. Their efforts teach us how important it is to learn as much as possible from the Covid-19 pandemic in order to prepare for the next threat to global health. As a chronicler of the 1918 Spanish Flu pandemic reminds us "memory is an active process. Details have to be rehearsed to be retained" (Spinney, 2017:292).

Acknowledgements

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I wish to thank Professor Maureen McKelvey for her help and support for this project. Its conduct and progress depended, as it has for much of my work over the past 35 years, on collaboration with Professor David Gann, Oxford's Pro-Vice-Chancellor Development and External Affairs. I am grateful for the seminar groups at the Science Policy Research Unit, University of Sussex, and the Centre on Knowledge-Intensive Innovation Ecosystems, University of Gothenburg, for their feedback on presentations of the study. The Science Museum's exhibition: *Injecting Hope: The race for a Covid 19 vaccine*, met its usual high standard of being informative and insightful. The report could not have been written without the research and editorial support of Kate Dodgson who somehow found time for it amongst managing demanding projects for the UN and NHS. All errors are the author's alone.

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Introduction

On the 30th December, 2019 cases of 'pneumonia of unknown cause' in Wuhan, China were reported in ProMED, a publicly-available surveillance system reporting on global outbreaks of infectious diseases. In the course of the next three years this disease, which became known as Covid-19, killed over 6.5 million people around the world.[1] Despite extraordinary medical advances in prevention and treatment, and massive social efforts such as social distancing and travel restrictions, such was its virulence that three years later, on 26th December 2022, the World Health Organization reported that over 25,000 people had died from the disease on that day alone. Covid-19 immediately and profoundly changed the world and, like the global Spanish Flu pandemic of 1918-20, will continue to do so in unpredictable ways that will emerge and evolve over future decades (Spinney, 2017).

This is an account of the development of a vaccine for Covid-19 by Oxford University and AstraZeneca, the pharmaceutical firm (hereafter the OAZ vaccine). It is not an account of the seismic changes brought about by Covid-19, and the geo-political tensions and economic and social distress it caused, but these difficult and painful conditions provide the context in which the OAZ vaccine was developed. These circumstances framed the extraordinary pressures of the need to quickly develop an effective and safe vaccine in the face of massive scientific, commercial, and political challenges and uncertainties.

Work began in Oxford University on the development of the Covid-19 vaccine on 9th January, 2020 and it was given an emergency use licensure by the UK's medical regulator on 30th December, 2020. Five days later, at Oxford University Hospital, 82-year old Brian Pinker became the first person to receive the vaccine outside of its clinical trials. By the end of 2021 AstraZeneca reported that it and its global partners had supplied around 2.5 billion doses of the vaccine to more than 180 countries.[2] By July 2022 the OAZ vaccine was estimated to have saved 6.3 million lives - more than any other vaccine.[3] The number of doses delivered around the world increased to over 3 billion by October, 2022.[4] Prior to the development of the OAZ vaccine the fastest vaccine developed, from viral sampling to approval, was for mumps, taking four years in the 1960s.[5] It was not uncommon for the development of vaccines to take ten years or more. The speed of the development surrounding Covid-19 vaccines led Jeremy Farrar, then Director of the Wellcome Trust, to say in his book about the pandemic published in July 2021 that: "There's never been a year of progress scientifically like this in my lifetime." (Farrer and Ahuja, 2022).

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[1] *WHO Coronavirus (COVID-19) Dashboard*. Available from: https://covid19.who.int/.

[2] *AstraZeneca Annual Report 2021*, p8. Available from: https://www.astrazeneca.com/content/dam/az/Investor_Relations/annual-report-2021/pdf/AstraZeneca_AR_2021.pdf

[3] *AstraZeneca and Pfizer/BioNTech saved over 12 million lives in the first year of vaccination* (2022) Airfinity, Available from: https://www.airfinity.com/articles/astrazeneca-and-pfizer-biontech-saved-over-12-million-lives-in-the-first

[4] *Vice-Chancellor's Oration 2022* (2022), University of Oxford. Available from: https://www.ox.ac.uk/news/2022-10-04-vice-chancellors-oration-2022

[5] Offit, P. *Vaccinated: One Man's Quest to Defeat the World's Deadliest Diseases* (2008) Harper Perennial. For a history of vaccines, see: https://www.who.int/news-room/spotlight/history-of-vaccination. For a guide to the challenges of vaccinology see: https://www.nature.com/articles/s41577-020-00479-7.pdf.

Providing an account of this remarkable achievement requires consideration of a number of key issues, such as designing, resourcing, testing, approving, manufacturing, and distributing the vaccine, and this is complicated by the way in real time some of these occurred concurrently and iteratively rather than sequentially. The process was more organic than linear, and so while following sections address particular issues, they are often inseparable from others, and their timelines overlap. The account also needs to extend beyond Oxford University and AstraZeneca to the whole 'innovation ecosystem' of researchers, large and small businesses, governments as policy-makers, funders, and regulators of public health, and a variety of non-governmental organisations. It also involves innovative new organisations, such as the UK's Vaccine Task Force (VTF), whose existence would be inconceivable outside of a health crisis. The ecosystem was international and embedded in a society facing disruption and trauma that revealed the very best of humankind, and some instances the worst.

The policy and political responses to Covid-19 in the UK are contentious and fraught and are subject to a public inquiry.[6] Some decisions were remarkably prescient and valuable, such as the rapid focus on vaccines and the creation of a task force to hasten their development and use. Other decisions were ill-judged, occasionally reflecting political and personal advantage over considerations of public health.[7] The public inquiry will hopefully expose what went right and what went wrong in order to learn lessons for the future, but that remit extends well beyond the aim of this report which is to examine the case of the Oxford/AstraZeneca Covid-19 vaccine using an innovation ecosystems framework of analysis, including some reflections on the lessons it holds. This may, of course, help inform lessons from the pandemic.

'Pneumonia-like' symptoms

The scientific effort to identify Covid-19 began in earnest on 3rd January, 2020 when a sample of the 'pneumonia-like' virus found in Wuhan was received for testing by the virologist Professor Yong-Zhen Zhang at Fudan University in Shanghai. After a 40-hour shift, and using advanced scientific equipment, Professor Zhang's team identified the 30,000-letter-long genetic sequence of a novel coronavirus. Aware of its danger, Professor Zhang immediately notified the Chinese Ministry of Health about the need to take precautions (Farrer and Ahuja, 2022).

The threat of coronaviruses was well known. The coronaviruses SARS (2002-3) and MERS (2012), as well as the outbreak of Ebola (2014), had alerted the international public health community of the possibilities of a virally created pandemic. Responses to the threat included the creation in 2011 of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) which allows standardised clinical data to be collected and shared in public health emergencies, and the Coalition for Epidemic Preparedness and Innovation (CEPI) in 2017. They also led the World Health Organization (WHO) in 2019 adding an as yet

[6] *UK Covid-19 Inquiry*. See: https://covid19.public-inquiry.uk/

[7] Clearly revealed in a lengthy series of WhatsApp correspondence leaked to the Daily Telegraph in March 2023. As well as contention during the pandemic, polarised debate about the contribution of some individuals continues to be rancorous and this report will pay no attention to it.

unknown 'Disease X' in its list of ten prioritised diseases. The emergence of a dangerous viral disease was seen as inevitable.

The ProMED news was seen on the first day of January, 2020 by Professor Sarah Gilbert, Professor of Vaccinology at Oxford University, who made a mental note of it and decided to keep an eye on developments. Over the next few days Gilbert began emailing colleagues at the US National Institutes of Health's Rocky Mountain Laboratory about the outbreak. ProMED updated the spread of the disease on 3rd January and on the 8th January confirmed it was caused by a coronavirus, named because of its protruding crown-like spikes of protein that became so familiar in visual representations of the virus. The virus was identified as SARS-CoV-2. Professor Gilbert remembers the sequence:

> The way I remember it was reports of pneumonia of unknown cause. And then finding out that it wasn't. Then there was ruling out of various things we knew about, so it wasn't influenza. It wasn't SARS1. It was a Coronavirus. Then it was a novel Coronavirus.

Professor Zhang was ordered not to publish his research, but on 10th January a colleague of his, Edward Holmes at the University of Sydney, published an online article on his behalf entitled: "Novel 2019 coronavirus genome", which said that the genetic sequence of the respiratory disease had been deposited at GenBank[8] and would be released as soon as possible. In a note, the authors said "Please feel free to download, share, use, and analyse this data".[9] Scientific efforts to understand, cure, and prevent the disease could begin.

And the need was desperate as the disease was spreading fast. The first recorded case was in Wuhan on the 8th December, 2019. By 3rd January, 2020 cases were reported in Hong Kong, and by the 23rd January the disease had reached Singapore. Germany reported its first case on 27th January and the UK four days later. The WHO requested more information from China on the illness on the last day of 2019. On the 5th January it ruled out SARS, influenza, and bacterial causes of the disease, and based on information from China it reported no significant human-to-human transmission. Between 22-23rd January it held an emergency meeting to establish whether the Wuhan outbreak constituted a Public Health Emergency of International Concern (PHEIC) - the WHO's highest level health alert. On the 22nd it was reported divided on the issue and the following day declared the virus was not a PHEIC, but it was to convene again in a week. It wasn't until 30th January that a PHEIC was declared (the word pandemic was not used); meaning countries were required to notify WHO of cases. On 11th and 12th February, 500 people met in Geneva to set the scientific agenda for dealing with the disease in its first R&D Blueprint meeting. The WHO named the disease Covid-19 on 11th February, and characterised it as a pandemic for the first time.[10]

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[8] An open access, annotated collection of all publicly available nucleotide sequences and their protein translations.

[9] Holmes, E. *Novel 2019 coronavirus genome* (2020), Virological.org. Available from: https://virological.org/t/novel-2019-coronavirus-genome/319

[10] The WHO's role during the pandemic is subject to considerable controversy, often related to geo-political tensions, especially between the USA and China. Given its precarious position in such a crisis based on its funding model and political reticence to elevate public health over economic concerns in the face of what could be construed by some as ambiguous analysis, the WHO was in an invidious position throughout the pandemic.

The challenges the virus posed were summarised by Jeremy Farrar and Anjana Ahuja:

> The new decade had recorded its first highly transmissible viral respiratory disease, which could kill some and yet leave others untouched. Carriers could be both asymptomatic and infectious. The world had no natural immunity to this novel virus, and no diagnostic tests, vaccines or treatments. The virus had all the makings of a nightmare." (Farrar and Ahuja, 2022)

Developing the vaccine

On the 9th January, Sarah Gilbert decided, along with Teresa (Tess) Lambe - a fellow Professor of Vaccinology at Oxford - that the disease had pandemic potential and once the sequence of the virus became available, they should address it using the platform technology – a kind of template - they had developed that could be used to produce many different vaccines, and had shown promise in addressing MERS.[11]

The challenges were enormous, but as Katie Ewer, Professor of Vaccine Immunology at the University of Oxford's Jenner Institute, says of developing the vaccine: "There was never any guarantee that we were going to be successful with this. But we had to try."[12] And Tess Lambe says of her contribution: "This wasn't really a choice. This is what I do. I had to do it".[13] As well as scientific uncertainties, there was also uncertainty about the extent to which a vaccine was needed. Sarah Gilbert describes these circumstances:

> When we started making it we didn't even know whether we were going to carry on as far as a first clinical trial because the outbreak could have been controlled in a week or a month, but we thought we'd start anyway. It was literally starting to see if we needed to do anything, but if it was needed it needed to be done as quickly as possible so we thought we'll start and see how far we need to go and that was kind of the attitude the whole way through: that we don't know how far we need to go but whatever's needed is needed fast.
>
> Remember that pre-pandemic we weren't planning for a pandemic, we were planning for outbreaks. So the thinking had been that a few hundred thousand doses may be more than is needed to control an outbreak and that's still true, but we then had to actually manufacture for a pandemic.

The platform technology used was based on the common cold ChAdOx1 adenovirus virus, found in chimpanzees, which could be engineered to be harmless and to incorporate new genetic sequences to induce immune responses. The very next day after the sequence was

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[11] The principle behind this type of vaccine is to introduce into the body, or induce that body to make, something which the immune system can learn to recognise and attack if the real target virus presents itself. The spike of protein on the virus latches on to cells in people's airways, fusing the virus and cell together, and thereafter the virus quickly replicates. An alternative method of vaccine design was used in the fight against Covid-19 by firms such as BioNTech and Moderna which involved using mRNA to instruct cells to create the protein spike to induce immune response. Sarah Gilbert says: "They were different technologies, which I think was useful. Because if everybody had been trying to use the same raw materials in the same manufacturing sites, we would have had fewer numbers of doses available".

[12] Horizon Special: The Vaccine (2021) BBC. Available from: https://www.bbc.co.uk/programmes/m000x2tf

[13] ibid

published it was sent by Gilbert to her colleague Sarah Sebastian at Vaccitech, a local biotechnology company Gilbert had co-founded with Professor Adrian Hill, Director of the Jenner Institute, to use specialised equipment to do the final work on designing the genetic sequence encoding the SARS-CoV-2 spike protein.[14] Within 48 hours of the coronavirus genome being released, Lambe and Sebastian chose the exact protein sequence they wanted to encode and the precise DNA sequence that they needed: The vaccine had essentially been designed and was named ChAdOx1 nCoV-19. Tess Lambe says that:

> The reason that we could do it over the weekend is because we've done so much in that area before. We knew how to approach the problem.

The processes for its development included a 'classic' and a more experimental 'rapid' process. Sue Morris - an expert on manufacturing adenoviral vectored vaccines - began work at the Jenner Institute on the classic method in Sarah Gilbert's lab, and supervising the rapid method at the CBF on the 28th January. It was clear within a couple of weeks that the rapid method would not work and on the 20th February a revised, faster 'classic plus' process began.[15] This method was fast, automatable, scalable and reproducible, and also yielded double or triple the amount of vaccine.

The new vaccine, when injected, was designed to trigger host cells into making the Covid-19 spike protein, stimulating the production of antibodies and T-cells to produce short and longer-term resistance to the disease. Having been designed, it needed to be made and the new piece of DNA was sent off to be reproduced by ThermoFisher, a manufacturer of custom-made synthetic DNA.

The University's response was widespread. Richard Cornell, Head of Oxford's Nuffield Department of Medicine, convened the first meeting of a wide range of researchers with the potential to contribute on the 20th January, 2020. The group was large and included vaccinologists, immunologists, and structural biologists. John Bell describes the meeting as a powerful group of people all wanting to do something if things got out of control. John Bell says of the meeting:

> it was really obvious at that point that we, as an institution, had a lot to potentially contribute to what we thought was likely to be quite a significant human health crisis. What became really clear as we went around the room was the breadth and depth of the expertise. And what was really clear is that we could do a lot to help, but there was no structure. And that actually turns out in this circumstance to be a big asset, because the Oxford decision making structure is very flat, which makes it a very difficult place to manage, but as there aren't 15 committees you gotta go to, it makes a great place if you want to innovate and be agile, because people are not constrained except by money, but nothing else. (The meeting) gave profile to the breadth and depth of our capabilities.

By the 27th January, Oxford University's Clinical BioManufacturing Facility (CBF) had also agreed to make the 'starting materials' for the vaccine of the modified virus that would deliver the fragment of genetic code for the vaccine. As a certified vaccine-manufacturing facility, the

[14] Vaccitech was established to develop commercial applications of vaccines for viruses such as HPV and Hepatitis B using the platform developed by Sarah Gilbert and Adrian Hill.

[15] For a description of the classic and rapid method, see Appendix B in Gilbert and Green (2021).

CBF is an unusual resource in a university, and proved invaluable. Professor Catherine (Cath) Green, Head of the CBF, writes that:

> When we started to work on our vaccine, across the whole team we were drawing on years of experience in vaccine design, production, clinical trials and regulatory affairs. (Gilbert and Green, 2021).

The CBF had the advantage of being able to draw on the experiences of developing a rabies vaccine, using the platform technology, undertaken a couple of years earlier. Green says that:

> the work done on this project, successfully implementing a new purification process, laid the foundation for all of the large-scale manufacturing that was to come. (Gilbert and Green, 2021).

Risks were taken, however. The CBF time-compressed and did not wait for results to emerge sequentially, but pushed through work knowing that if adverse findings emerged the whole process would have to start again. Furthermore, CBF could only take on four projects at a time, and this project meant delaying others that had already been paid for. CBF operates like a small business and needs to cover its costs, so taking on this project was a financial and operational risk. (Gilbert and Green, 2021).

Sarah Gilbert describes the important infrastructure capability of the CBF:

> We have our own small pilot plant in the University, which we used. And that does really great work, particularly in the first step of manufacture of a new vaccine, where you actually need to put quite a lot of thought into the process, because you have to, even if it's very similar to something that's been done before, there will always be parts that are different and we need the experts who work on that, we can then pass that on to somebody else. They only have the capacity to manufacture small batches of vaccine and that's what they're there for. They should be manufacturing multiple different small batches of vaccine to facilitate early research.

By 17th March the first batch of starting material from CBF was ready, and six days later it was inoculated into a culture to grow: the “bread was in the oven”, as it was described. (Gilbert and Green, 2021).

The funding for Sarah Gilbert’s research and that of her group was entirely based on winning research grants. Foreseeing the need for a rapid response to outbreaks, she had applied for a grant to speed up the development process in 2018, but the application was rejected.[16] She says, however:

> But at least we'd done a bit of thinking and discussion about how we might achieve that [rapid response]. And then we had to try out the rapid method at the beginning of 2020, for the first time ever, and it didn't work. We'd always got multiple plans in progress. So then we tried what we call the classic method, and it always has been

[16] She ruefully says: “We knew we weren't prepared and had an application for funding to get prepared turned down”.

> really slow before, but it turns out, if you just get the right people making the right decision at the right time, you can speed that up.

There were additional difficulties to compound the scientific challenges, especially during periods of national lock downs with rules on social distancing. It was hard to access Personal Protective Equipment (PPE). Cath Green started making hand sanitiser in her lab, and there was also a shortage of thermometers to measure the temperature of volunteers. Professor Andrew (Andy) Pollard, Professor of Paediatric Infection and Immunity at Oxford, who led the trials for the vaccine, reports the process was a logistical nightmare. Despite these challenges the vaccine went from DNA construct to clinical trial in sixty-five days.

A parallel process was followed, with one stream focusing on manufacturing. This involved seeing if the vaccine could be made in a high enough concentration with a good yield and quality high enough to put into humans. This test aims to provide data for the regulator to know that what is claimed in a vial of the vaccine is actually in there, uncontaminated, with the right concentration. The parallel work is to see whether the vaccine made in the laboratory could ever be put into humans. This was checked on small animals to find an immune response and in the Rocky Mountain Laboratory to vaccinate non-human primates. Both of these were essential before trials in humans, because of the confidence it provided that the vaccine was safe and protective. Andy Pollard remembers:

> There was quite a lot of confidence here that the vaccine would work because of MERS work in the last 20 years: other vaccines with the spike protein worked out. And as long as you can make it, it should work in humans, the only thing we didn't know is how well it would work… But I think we were fairly confident that it should work because it was doing exactly what it should do.

A small research team in January grew to over 300 by July. International collaboration was crucially important. Gilbert says:

> As other work was deprioritised we gained access to a huge pool of skilled scientists who would usually have been working on other trials or research. And scientists and other experts from around the world were more willing than ever before to cooperate and collaborate". (Gilbert and Green:154).[17]

Tess Lambe says researchers were united by the desire "to make vaccines and make a difference and help people in low and middle income countries". People working on the development of the vaccine were working very long hours under intense strain. Letters of support and thanks from the public made a big difference, Lambe says, and they were particularly appreciative of:

> philanthropic donors, who gifted us funds quickly and could really help the speed of delivery, in particular one donation gifted us money to buy lunches and dinners. So at the time when the UK was locked down, we could eat while we were in the lab the whole time.

[17] Sarah Gilbert refers to the important specialisms in other universities with which she collaborates, including Glasgow university in virology research, Imperial College on animal models for disease and transmission studies, and the Royal Veterinary College studying the pathology and use of vaccines in animals.

Testing the vaccine

The original plan was for CBF to create starting materials to be sent to Advent, an Italian adenovirus vaccine contract manufacturer, to produce at larger scale. But CBF realised it could make them quicker than Advent, so they made batch 1, and then sent starting material to Advent to make batch 2. This was not usual practice, but it was believed that as much material would be needed as possible. Alex Spencer, a senior immunologist at the Jenner Institute, tested both batches to see if there were different immune responses at different concentration levels.

In addition to tests undertaken at the Jenner Institute, the further testing undertaken at the Rocky Mountain Laboratory reported on 21st April that its animal test results showed no adverse effects of the vaccine. The following day the batch of the vaccine was certified as ready to use, and the day after that, the 23rd April, Elisa Granato, a microbiologist, and Edward O'Neill, a cancer researcher, were the first volunteers to test the vaccine, one injected with the vaccine, one with a placebo. As a stark example of the malicious disinformation that was to surround all Covid-19 vaccines, parts of social media reported Granato died three days after the injection, one of the many instances of false news that plagued public health efforts in the fight against the disease.

Bringing the vaccines from Advent in Italy was crucial as trials had been planned in 19 non-Oxford sites in the UK, and there was not enough vaccine to distribute to them. As there were no commercial flights operating between Italy and the UK at this point, Omar El-Muhanna, Operations Manager at CBF, suggested chartering a private plane to bring the material to Oxford.[18] Andy Pollard recalls the Italian-made vaccine arriving on a Sunday and the demanding efforts to distribute it for the trials to begin on the Monday.

> [We had] a situation on a Sunday afternoon where I had 19 non-Oxford sites around the country. And we got the system set up so we could see how many volunteers they were going to vaccinate that week. And they had an extraordinary response. We needed 3000 doses that week. And when we looked at our inventory, because bizarrely, as a university, we were dealing with all of the distribution of vaccines to all of those sites, which is I can tell you something we'll never do again, and we didn't have enough doses. I couldn't really think how else we could do it, but we had just made them in Italy, so I just took the decision to hire a private jet from Italy to fly them over, and then sort out that distribution on Monday morning, and it cost about £25,000. And I phoned my head of department the next morning and I said I've just spent £25,000. I don't have it. But we've spent the money.

By late May, 1000 volunteers had been selected and enrolled in Oxford's phase I trial - a blinded Randomised Controlled Trial (RCT) – where half were injected with the vaccine, half with a placebo, with neither volunteer nor researcher knowing which had been received. The aim of this trial was to test the vaccine's safety and ability to produce an immune response in young healthy adults. To help enrol the larger and more diverse number of volunteers needed

[18] Anyone with experience of claiming travel costs in a university will know this to be a remarkably entrepreneurial, and brave, decision.

for the combined phase II and III trials,[19] and to increase volunteer numbers for other types of Covid-19 vaccines, the world's first Covid-19 National Citizens Registry on the NHS website was launched, enabling anyone to express interest in being part of a vaccine clinical trial, and some 10,000 people volunteered using this innovative approach in a matter of hours.[20] One of the problems ironically encountered during the trials was not having enough vaccinated people getting exposed and infected after their jab as fewer people caught Covid-19 towards the end of the first spike of the pandemic in the UK due to social distancing practices. Such exposure and infection was needed to test the vaccine's efficacy.

As Chief Investigator of the clinical trials for the vaccine, Andy Pollard, had impeccable credentials. He became Chair of the UK's Joint Committee on Vaccination and Immunisation (JCVI) in 2013, stepping down as his work on the OAZ vaccine began. Sarah Gilbert lauds Pollard's "huge experience (and) his unwavering commitment to public health and capacity for doing whatever it takes to make a difference." (Gilbert and Green, 2021). He also had extensive international contacts with groups expert at conducting trials, which were essential for increasing the number of volunteers necessary for later stage trials of a new vaccine, which eventually numbered 24,000. He says the trials he had already conducted in Bangladesh, Nepal, and Brazil involving 300,000 people had provided the skills and capabilities to run a Covid-19 trial. Gilbert reports on the importance of these pre-existing relationships in establishing the trials:

> We had a huge network of trusted colleagues all over the world. When we wanted to set up trials in Brazil or South Africa, Andy [Pollard] wasn't just pitching up unannounced at a hospital in Rio or Johannesburg. We had existing relationships, we knew all the people already, and we knew they would be able to conduct high-quality clinical trials because they already had the infrastructure and experience. (Gilbert and Green, 2022:150).

Andy Pollard outlines the process followed:

> I built a team with incredible expertise, to be able to go to far corners of the world simultaneously, and run high quality trials to a regulatory standard… So we had this coalescence of knowledge about the platform (technology) and the clinical trial experience and getting that meant that when we started the trials, we could see all the way to the end... [As for] the skills that they require, they need to be able to keep things clean, they need to be able to inject well, keep records. Well, actually, in some ways, the clinical bit is in a sense, the easy bit, you know, to ask for medical history, take some bloods, and then stick a needle in someone, and you've installed the vaccine, it's the same as giving routine immunisation. So the technical bit, that's fine. But you do need to work with sites that are used to doing it under regulatory control. So they have to be very good at documentation and training and so on, so that they can do all of those steps of the process. So that's clearly a very important component of it. But actually, it's the system underneath that matters: What's your database integrity? Is there an audit trail - so you can see no one's tampered with it, that it meets regulatory

[19] Phase II trials test for safety and immune response in a wider range of age groups than phase 1 (healthy adults). Phase III trials test vaccine efficacy. Oxford ran a combined phase II and phase III trials, starting on 22 May 2020.

[20] By September, 2020 more than 250,000 people had volunteered through the NHS Vaccines Registry to take part in various Covid-19 vaccine trials.

> standards? So that's the IT system, you have to have a statistical team that is able to crunch these enormous databases and extract the data, and we have to have a quality assurance system in place. And all the project management is rather complex for the large international standards involved in putting on trials particularly rapidly.

As is often the case, progress in the trials was not smooth. They stopped on 6th September when a participant developed a rare neurological condition. In trials of thousands of people, inevitably unrelated health conditions emerge, and the ultra-cautiousness of the trial process requires that these are examined to check whether there is any connection to the vaccine or new drug being tested. There wasn't in this case and trials in the UK, South Africa and Brazil restarted in a few days, but there was a seven-week delay in the USA.

The risks around the success of the vaccine were not to be under-estimated. At its first meeting of the Vaccine Task Force (VTF: discussed below)) Expert Advisory Committee meeting, on 30th April, its Chair Kate Bingham, asked the vaccine experts for their assessment of the likeliness of success of any Covid-19 vaccine. They said it was only 15 per cent likely in each case that any vaccine would prove effective, and then only if the vaccine was already in clinical trials. In all other cases, it shrunk to 10 per cent or lower (Bingham and Hames, 2022:75).

This faith shown by AstraZeneca in deciding to partner with Oxford proved to be well-founded. On the 21st November, Pollard reported the results of the trial to the team: The vaccine had an overall efficacy of 70 per cent, but groups with a half dose followed by a full dose got 90 per cent immunity.[21] Jeremy Farrar assumed the vaccine would be 40-60 per cent effective, and he was staggered when he saw 90 per cent (Farrar and Ahuja, 2022). Vaccines are considered useful if they achieve 50 per cent efficacy, and some commentators had warned that the OAZ vaccine would achieve 30 per cent. Academics usually publish their full results in peer-reviewed publications, clearly setting out their methodology and findings, but as a publicly listed company, AstraZeneca was legally obliged to disclose information that may affect its share price, and it had to reveal these findings immediately. After verifying these findings they were made public on the 23rd November. Under the headline: "AstraZeneca's Coronavirus Vaccine, Easy and Cheap to Produce, Appears Effective", the *New York Times* reported that: "While the overall efficacy of the vaccine remains unclear, the encouraging preliminary results indicate that it has the potential to become a powerful new weapon in the war on the pandemic".[22]

Resourcing the development of the vaccine

The ChAdOx technology platform upon which the OAZ Covid-19 vaccine was developed was funded almost entirely by public and charitable financing, with one study estimating such

[21] The half dose finding resulted from a group of volunteers mistakenly given a half rather than a full dose. Despite the UK regulator, the MHRA, being fully informed, this perceived confusion in undertaking the trial and reporting it provided fuel for critics, and took time and energy to explain.

[22] *AstraZeneca's Coronavirus Vaccine, Easy and Cheap to Produce, Appears Effective* (2020), New York Times. Available at: https://www.nytimes.com/2020/11/23/business/astrazeneca-oxford-coronavirus-vaccine.html

funding accounted for 97-99 per cent of the platform's development.[23] But finding the funds to develop and test the vaccine was a major challenge. As John Bell puts it:

> One of the things that was really obvious was if we were going to move at pace, we were going to have to have some money. It was clear to me that funding from the government wasn't going to be immediately accessible. So the money had to come from somewhere else. The university itself was not a rich institution, but they did have some flexible resources. The department had some money. People had little pots of money here and there. So we patched little bits of money together.

Finding the resources to develop the Covid vaccine was a primary concern for Sarah Gilbert at the beginning of 2020. She had already been engaged in lengthy and ultimately unsuccessful negotiations with CEPI over the platform technology she had co-developed. A small amount of money had been used in the early days of the vaccine's development from a flexible funding pot at VaxHub at University College London.[24]

Her main targets for funding were CEPI and UK Research and Innovation (UKRI),[25] and negotiations with CEPI began on 13th January. Along with colleagues she lobbied the government through the UK BioIndustry Association (the BIA - a network of companies that work to manufacture or support the manufacture of biological medicines), and started looking for a "commercial pharmaceuticals partner who would be able to manufacture our vaccine at the large scale that it was now obvious would be necessary." (Gilbert and Green, 2022:90-91). She refers to the notorious 'funding valley of death' of the gap between promising experimental results in universities and proven commercial opportunities for firms. She describes it as an issue Oxford University had been trying to address:

> We took the view that we needed to be able not only to research a vaccine candidate in the lab, but also to manufacture it for clinical trials, and conduct at least the phase I safety trials ourselves. (Gilbert and Green, 2022:152).

At an early stage, when access was needed to Advent's facilities and capabilities, a contract was needed with the company, and Gilbert received a promise that Oxford University would assume the risk of its underwriting before promised external funding was received. Following a rapid response call in February from UKRI, £2.5 million was awarded. Most of this money had already been expended: Sarah Gilbert had taken the risk of spending money they did not yet have. The Department of Health awarded £20 million to support expansion of

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[23] Cross S, Rho Y, Reddy H, Pepperrell T, Rodgers F, Osborne R, Eni-Olotu A, Banerjee R, Wimmer S, Keestra S. *Who funded the research behind the Oxford-AstraZeneca COVID-19 vaccine?* (2021) BMJ Glob Health. Dec;6(12):e007321. doi: 10.113bmjgh-2021. The extent of this funding contradicts the claim allegedly made by then Prime Minister, Boris Johnson, that the vaccine resulted from capitalist greed: Covid: 'greed' and capitalism behind vaccine success, Johnson tells MPs (2021) The Guardian. Available from: https://www.theguardian.com/politics/2021/mar/23/greed-and-capitalism-behind-jab-success-boris-johnson-tells-mps

[24] VaxHub was funded by the UK government's Development Assistance budget aiming to improve vaccine manufacturing methods and engage with manufacturers from low-and middle-income countries.

[25] UKRI is the UK's national funding agency investing in science and research in the UK, bringing together seven research councils.

manufacturing and clinical trials on 21st April, and this was subsequently increased to £31 million.

Funding from the VTF, which was so essential, was signed off by a panel of four Ministers (from Business, Health and Social Care, Treasury and Cabinet): a process ordinarily bound to lead to contention, risk-avoidance and delay. That decisions could be made quickly undoubtedly resulted from the position of Kate Bingham as VTF Chair. With her venture capital background she wanted a risk-tolerant investment committee model and to ensure there was money for vaccines upfront before it was clear if any of them worked. She also had a direct reporting line to the Prime Minister, established as a condition for her taking the job.

The UK government funded the vaccine's clinical trials in the UK; the Brazilian trials were funded by the Lemann Foundation, and the Gates Foundation funded the South African trial.

The Oxford/AstraZeneca partnership

The difficulties in quickly attracting a large pharmaceutical company to produce Covid-19 vaccines were expressed on February 11th, 2020 by Dr. Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases, who complained that no major drug company had committed to "step up" to make a coronavirus vaccine, calling the situation "very difficult and frustrating."[26]

The need for Oxford to partner in order to develop the vaccine was obvious; as John Bell puts it:

> We as a university had no real capacity to scale manufacturing, to do all the regulatory things that need to be done across multiple jurisdictions, and actually get this out to people at scale.[27] and
>
> We're a university. We cannot do a vaccine development program. It will need global regulatory approval. It'll need manufacturing at scale, distributed globally. And there's only one type of entity that can do that. And that's a pharmaceutical company.

He says this view was widely accepted across the university. Tess Lambe, for example, talks of the risks involved in getting licensure:

> And that's why we absolutely need to partner with pharma because we are a University and these institutions don't typically have the ability to license drugs or vaccine products.

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[26] *They Pledged to Donate Rights to Their COVID Vaccine, Then Sold Them to Pharma* (2020) KFF Health News. Available from: https://khn.org/news/rather-than-give-away-its-covid-vaccine-oxford-makes-a-deal-with-drugmaker/

[27] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell. John Bell adds that there was additional pressure at the time as it was possible that the OAZ vaccine was the only one that would work.

Discussions in Oxford were held with a number of large pharma firms, including Merck and GSK.[28] And they began with AstraZeneca, a company not known as a vaccine producer, although it acquired MedImmune, a biologics and vaccines business based in the US in 2007 and its 2019 annual report refers to a HPV vaccine. Covid-19 provided AstraZeneca an opportunity to move into vaccines along with the big five pharma companies that make vaccines: Sanofi, GSK, Merck, Janssen and Pfizer. While AstraZeneca was not the obvious choice - it only had one vaccine at the time - it did have expertise in biologics and international manufacturing networks. A team, including Sarah Gilbert and Adrian Hill, visited Mene Pangalos and Pascal Soriot, respectively Head of Research and CEO of AstraZeneca, and had a positive conversation. John Bell had previously been a colleague with Soriot, and spent a lot of time with him, and says he is one of the most thoughtful and insightful people he has met in pharma. He says Soriot was capable of doing the unconventional and he was going to be asked to do unconventional things.[29] The firm agreed not to make a profit from the vaccine during the pandemic, and afterwards sell it at cost price in low- and middle-income countries. As John Bell relates:

> Pascal Soriot is an old friend of mine because I was on the Roche Board for 20 years, and he ran pharma and Genentech at Roche and so I knew him very, very well. The team came back from AstraZeneca and called me up and said we think they might be interested. So I thought, okay, they're not a vaccine company, they do a little bit of vaccines, but boy, they do biologics really well. And Pascal is a very smart operator. So I think it was a Saturday afternoon. I called Pascal or he called me and I spent about two hours on the phone with him and we talked it through and he said I think we'd like to have a go with this with you guys, are you willing to do that? And I said I gotta get everybody to agree, but you know, from my perspective, you'd be a great partner. And we understand that this won't be straightforward for you, but provided you make a good effort, it'll be fine.

Sarah Gilbert reports that AstraZeneca became the choice because:

> They were prepared to take the risk that it wasn't going to work. Because we couldn't work with a company who would just make enough vaccine for the clinical trials and wait and see if we got good efficacy before deciding whether to invest in manufacturing because that would be too slow. So we needed somebody who could take the financial risk.[30]

Andy Pollard, who attended early meetings with AstraZeneca and got to know Pascal Soriot and understand the company, explains the discussions:

> I think they were interested to hear what we had to offer. And I think we were very clear that we know we had a vaccine, and we're sort of starting Phase I trials. And it should work because it works with animals, so there's quite a lot of competence. And I think they felt that in the pandemic, they should be in the game. And, of course, at that moment, all the other big

[28] According to John Bell, discussions with Merck were conducted as the firm was uncertain about whether to develop its own vaccine or to partner. The Health Minister, Matt Hancock, reportedly was concerned that Merck had no manufacturing capacity in the UK and US laws may prevent export from US manufacturing plants. GSK wanted to develop its own vaccine.

[29] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

[30] *Panorama - The Race for a Vaccine* (2020) BBC Documentary 2020. Available from: https://www.youtube.com/watch?v=d6MUey5lD4c

> companies were just getting started. Sinofi made a partnership. Pfizer was in the game, Merck was in the game. AstraZeneca, who only really had their flu business in vaccines, I think felt they should be in the game. Subsequently, in talking with Pascal, I think he wasn't sure if it was the right thing to do, but he says that his kids said to him, no, of course, you've got to do this. And there's two aspects of it. The thing that really burned them was the nonprofit part, which didn't seem right from a big pharma perspective. But it was a red line for the university. The Vice Chancellor's view was, we can't be seen to be profiteering in the pandemic. I heard her say that over and over again. And so I think what was critical for the AstraZeneca deal was that Pascal was prepared to go with that. I don't think joining with Oxford was such a big risk. The bigger risk was one around the not for profit. And I do think it was his force of personality that allowed that to move forwards. Because I do know he had to face down the investors over it.

John Bell describes the negotiations:

> I went around the houses with the team here, including Adrian, Sarah, Andy, and Sandy Douglas. And they all said, okay, let's go. The Vice Chancellor said, can you sit down and do the deal? So, with the university lawyers and an external counsel to help us we sat down and wrote a term sheet over the course of the next week, where we laid out all the principles as best we could. It wasn't perfect, but we signed that and then, over the course of the next two to three weeks, we did the definitive agreement and got it over the line and that was that was that and must be the fastest turnaround of any pharma deal I have ever seen. I have done many pharma deals over many years. That was by far the fastest and they were good and there was a lot of good will and good faith in the room. That was really impressive.

Negotiations on the partnership were not widely publicised, as its announcement surprised key players such as Kate Bingham and Cath Green.

In its press release about the partnership, to give him his full title, Sir Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said:

> The University of Oxford and AstraZeneca have a longstanding relationship to advance basic research and we are hugely excited to be working with them on advancing a vaccine to prevent Covid-19 around the world. We are looking forward to working with the University of Oxford and innovative companies such as Vaccitech, as part of our new partnership.[31]

Price and access were crucial considerations for Oxford academics, with their concern for the vaccine to be available at cost and to be just as available in poor countries as rich ones. AstraZeneca charged £3 a dose, at least 5 times cheaper than other vaccines. In her Vice Chancellor's Oration in October, 2022, Professor Louise Richardson, said this of the vaccine:

> The Oxford vaccine has had such an enormous impact in part because it was developed, not for profit, but to be distributed at cost. That was a heroic agreement on AstraZeneca's part and one I will always champion.[32]

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[31] *AstraZeneca and Oxford University announce landmark agreement for COVID-19 vaccine* (2020) AstraZeneca press release. Available from: https://www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-and-oxford-university-announce-landmark-agreement-for-covid-19-vaccine.html#

[32] https://www.ox.ac.uk/news/2022-10-04-vice-chancellors-oration-2022

The initial understanding between the UK government and AstraZeneca was that it was to buy 100 million vaccines, including 30 million by September 2021. This would cost just under £500 million, and AstraZeneca would receive an up front payment of £130 million. This cost did not cover the logistics of getting the vaccines into arms which would cost the government the same again. VTF provided upfront funding to reimburse AstraZeneca's costs and those of the various contractors working for them. Funding would not be recoverable if the vaccine was ineffective. (Bingham and Hames, 2022). To an extent, therefore, AstraZeneca's exposure was not as high as it would be in a commercial project as much investment was provided by governments and charities.[33]

In its 2020 Annual Report, AstraZeneca reported it had concluded an Advance Purchase Agreement with Gavi - the Vaccines Alliance - to supply 170 million doses of OAZ to COVAX for countries around the world.[34] In the following year's Annual Report it stated it supplied about 2.5 billion vaccine doses to more than 180 countries during the year. Of these, approximately two-thirds went to low- and lower-middle-income countries, and more than 247 million were delivered to 130 countries through COVAX in 2021.

AstraZeneca's journey can perhaps be simply encapsulated in the way the word "vaccine" was mentioned 18 times in its 2019 Annual Report, increasing to 136 times in its 2020 Report.In November 2021, AstraZeneca established a vaccines division.[35]

Kate Bingham refers to AstraZeneca's 'triumph', but it was triumph at a cost. In a BBC documentary Mene Pangalos talks about the pressures he faced:

> Everyone is doing this because they're trying to do some good for the world and when you get a lot of negative press and the criticism it's actually really, really tough and this has been for me probably the toughest thing I've ever worked on in terms of the goldfish bowl environment that you're in where every single thing is scrutinised, politicised, turned around, misrepresented.[36]

The challenge facing CEO Pascal Soriot in deciding to back the Oxford vaccine is summarised in an article in the *Financial Times*, in that it:

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[33] It is also the case for all businesses during a pandemic, of course, that unless it is controlled there is no business. The pressing question for all business leaders is how to save the business in the face of an existential crisis.

[34] Gavi is a public–private global health partnership with the goal of increasing access to immunisation in poor countries. COVID-19 Vaccines Global Access, abbreviated as COVAX, is a vaccine sharing scheme designed to assist poor countries access vaccines.

[35] *AstraZeneca to set up division for vaccines and antibody therapies* (2021) Reuters. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/astrazeneca-create-separate-division-vaccines-antibody-therapies-2021-11-09/

[36] *Panorama - The Race for a Vaccine* (2020) BBC Documentary 2020. Available from: https://www.youtube.com/watch?v=d6MUey5lD4c

could be Soriot's defining accomplishment or a symbol of over-reach that will permanently diminish his achievement in turning AstraZeneca into one of the pharma industry's global powerhouses."[37]

The article also illustrates Soriot's priorities in that on his first day at AstraZeneca he ended his predecessors' policy of share buybacks and promised to rebuild the R&D operation.[38] It quotes Samuel Johar, Chair of Buchanan Harvey (a board advisory firm), saying most leaders would never have agreed to partner with Oxford University in the first place, and:

> Any normal FTSE 100 company, deciding by committee, would have thought 'we're not going to make much money so we don't want to get involved.' It's only because of this mercurial leadership style of Pascal that he managed to roll all the obstacles away and make it happen.

Added to his list of motives, as John Bell recalls, was his belief that: "my kids would kill me if they thought we were making a lot of money out of this", a point also recalled by Andy Pollard.

As for working with AstraZeneca, Tess Lambe says:

> They were phenomenal. I remember meeting a counterpart in April 2020. And she was so eager, wanting to help so much. And I now consider her a very good friend. They went through the trenches with us. They gave us, in my opinion, the freedom to deliver those phase I, II and III trials. They allowed Andy to drive those trials and for me with others to drive the immunology; they helped where they could and without them, we wouldn't have got the licensure.

Sarah Gilbert says of the AstraZeneca partnership:

> The overwhelming result was that we got a vaccine that AstraZeneca agreed to make in very large quantities, when they could have only made 100,000 doses and said, well, we're not making any profit so this is as far as we can go. But that's not what they did. They made 3 billion doses. I think that was really down to AstraZeneca. Because the contract didn't say you have to make 3 billion doses… AstraZeneca were not the most obvious vaccine manufacturing partner. But they did really well for us.

Andy Pollard refers to the importance of the decision AstraZeneca made to trust Oxford's trials:

> On their vaccine side, the people there made one really important decision. They said to me, we're not going to take over the trials, because we'll hold you up. And I think that sort of understanding that Big Pharma can't do things rapidly, they've got lots of bureaucracy and process to go through, (whereas) you have this huge flexibility in the command and control you have in a university structure that you don't have in industry. And so that meant that we could make decisions on the hoof very rapidly, with just a small group of us to take us through, and had a direct line to be able to talk to regulators and ethics committees, and for them to expedite the process.

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[37] *Pascal Soriot; the Pharma CEO navigating a vaccine storm* (2021) Financial Times. Available from: https://www.ft.com/content/2ce008f2-b5d2-4578-802d-d69b89d7036c

[38] Of AstraZeneca's 80,000 employees, 13,000 work exclusively on R&D.

He adds:

> They helped provide some of the monitoring support for the trials, which they did in the UK and in Brazil, to check the quality of what's going on. And that was very useful, because obviously, we don't have an army in Brazil, where we could send people around who speak Portuguese to go check on the quality. And AstraZeneca did some of that. And then the last mile they were amazing, which was, okay, we've done the trials, we've got the data, we know the vaccine is safe and it works. How do you get it licensed? And then it's taking all this data and putting it into the format that the regulator needs to review. And we've never done that before. And AstraZeneca can do it because they're so huge. For example, just on data management, they had 80 people employed all over the world, working with our data team coordinating it. And so there were people in Australia who were working and when they went to bed, the people in Europe started working, and it just went right back in. So in less than a month, the database that we put together at the beginning, not really properly thinking about a regulatory submission, they put it together in a format, which could then get licensure in over 180 countries. It was an astonishing effort.

Dr Sandy Douglas, an academic clinician at Oxford, describes the relationship with AstraZeneca as very positive, saying they: "... brought in a lot of technical capacity, expertise and experience that we didn't have."[39] This expertise included the capacity to transfer technology to dozens of contract manufacturers. There are reports of positive experiences in those contract manufacturers. The Chief Scientific Officer at Cobra Biologics, Daniel Smith, reports on AstraZeneca teams joining their tech transfer meetings and listening and trying to understand what the company was doing:

> They're a bunch of scientists; everyone wants to talk about how to make it better." Concerns that a large pharmaceutical company would not match the entrepreneurial speed of a small firm were alleviated, as Smith explained: "Everything has to go through a lot of control points… They still do that, but they keep it away from us. And they move phenomenally fast".[40]

Cath Green describes an "interesting dynamic" between Oxford and AstraZeneca, saying that she initially felt the company was a new boss. Whereas resources and activities in Oxford were concentrated, the large organisation had specialised roles spread widely amongst the firm. She says there was a steep learning curve for both sides in the first month of the partnership, and she came to be impressed and inspired by the company, especially regarding the scale of its ambition, the risk it took in investing so substantially prior to receiving clinical trial results, and how it saw the potential for the vaccine to be stored at normal fridge temperature. (Gilbert and Green, 2022)[41]

When asked about the relationship with AstraZeneca, Sarah Gilbert says:

> Well, from where I was sitting, it was just a decision from Pascal Soriot that they were going to do it: right from the top. So he just said yes. He didn't appear to need to be persuaded, he decided that they would do this. And then that was the view of the company, that we're going

[39] *The Pharmaceutical Journal, PJ, April* 2021: 306:7948. DOI:10.1211/PJ.2021.1.77840

[40] *The Pharmaceutical Journal, PJ, April* 2021: 306:7948. DOI:10.1211/PJ.2021.1.77840

[41] In contrast with mRNA vaccines, which required freezing temperatures, OAZ could be stored in a normal fridge: a huge advantage for distribution, especially in poor countries.

> to do what was needed, and they got on with it. It was hard work for us to work with them. It wasn't easy, because they're a very different organisation to us… We just have a very small team. So we had to try and work out how these two things mesh together. And it was hard, but because both sides really, really wanted to make it work, we did make it work.

John Bell says AstraZeneca was genuinely interested in making a contribution to a major global health crisis, for which they deserve a lot of credit.

Manufacturing the vaccine at scale

Scaling the manufacturing of the vaccine involved moving from the initial production of small amounts for testing and development to making billions of doses in large industrial bioprocessing plants or bioreactors for worldwide distribution. Concern for how it was to be manufactured at massive scale had to be brought into consideration of how it was designed. Sandy Douglas became involved in the discussions about the design and production of the drug at an early stage. With a PhD student, Carina Joe, he'd had some success in improving the yield of an adenovirus-vectored rabies vaccine, and although the quantities his team worked with were small he knew the manufacturing process they had used was scalable in theory.[42] Proving that the process worked and could produce the vaccine safely and effectively was essential to attracting a large commercial partner essential for scale manufacturing. The development and testing of the manufacturing process would be undertaken alongside the testing of the vaccine itself.

Adrian Hill says the unsung story of the OAZ vaccine is how in two months, January and February 2020, Sandy Douglas and his team increased the yield of the vaccine by about tenfold:

> And if you think about what that means - there was tenfold more vaccine, 3 billion doses, not a third of a billion doses, to distribute. And, you know, the thing we're most proud of what we did was that number of just over 6 million lives saved, which is an awful lot more important than 600,000. And that's simply a manufacturing process.

Working with Sandy Douglas and Cath Green, and drawing on connections at the BIA, a group of firms joined in the early development of the manufacturing process. Cath Green describes how important the personal connections she'd built in the BIA over many years were, such that: "When I came to these people with urgent and unprecedented requests....there was great trust between us", and when:

> [We] put a call out explaining the work we already had in train, our confidence in our technology, and our need for assistance from industry, the response was heart-warming and incredible. We immediately received offers of support, equipment loans and expertise-sharing from across the UK." (Gilbert and Green, 2022: 140).

Work began in the last week of March to test run the manufacture of 50 litres of the test vaccine in the Portsmouth laboratories of Pall Biotech, a US firm providing services in filtration, separation and purification, and this latterly increased to 200 litres. As this process

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[42] *The Pharmaceutical Journal, PJ, April* 2021: 306:7948. DOI:10.1211/PJ.2021.1.77840

became proven it was transferred to contract manufacturers, Cobra Biologics and Oxford Biomedica in the UK, and Halix BV in the Netherlands. Douglas describes this group of firms as an unusual, unfunded consortium:

> We had a … multilateral confidentiality agreement, which basically said everyone can share everyone's information and work in a very, very cooperative way, which was essential.[43]

But these were commercial companies and contracts were needed to pay for materials and labour, and the situation became tense until funding arrived from the newly formed VTF. After receiving a £400,000 grant from UKRI, the VTF awarded £65 million to build a manufacturing consortium that could not only scale vaccine manufacture but also test, store, transport, and put it into vials.[44] Based on Douglas's initial work on 30 millilitres of rabies vaccine in his laboratory, ambitions expanded from hundreds to millions to billions of doses produced in factories around the world. To impact global health, vaccine production in billions of doses was required, and AstraZeneca undertook to produce 3 billion doses in 2021.

Factories producing vaccines have to operate to the demanding standards known as 'Good Manufacturing Practice' (GMP). The processes used and mediums in which the vaccines are grown are notoriously difficult; essentially they are very hard to
make. Pascal Soriot refers to continual glitches in production, saying the best site the company had produces three times more vaccine out of a batch than the lowest-producing site.[45]

With AstraZeneca's relationships with major manufacturing sites and the financing power to be able to commit to contracts, AstraZeneca activated a programme of global production, and by February, 2021 it was working with 25 manufacturing organisations in 15 countries. The methods and timescales involved in the manufacturing process are shown in Appendix 1.[46] The successful technology transfer from AstraZeneca to these manufacturing plants around the world is one of the extraordinary achievements of the pandemic.

Serum Institute of India (SII)

Building on a long-term relationship with Adrian Hill, the Serum Institute of India (SII) became a crucial contributor to the OAZ vaccine. SII, alongside the COVAX programme, supported equitable global access to the vaccine for low- and middle-income countries.[47]

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[43] *The Pharmaceutical Journal, PJ, April* 2021: 306:7948. DOI:10.1211/PJ.2021.1.77840.

[44] *The Pharmaceutical Journal, PJ, April* 2021: 306:7948. DOI:10.1211/PJ.2021.1.77840. Putting vaccines into vials is highly specialised, and in August 2020 the UK government employed Wockhardt a global pharma and biotech company to provide fill and finish services in its North Wales factory. It booked its entire capacity for two years.

[45] *How vaccines are made, and why it is hard* (2021) The Economist. Available from: https://www.economist.com/science-and-technology/2021/02/06/how-vaccines-are-made-and-why-it-is-hard. Innovations in bioreactors include the use of plastic bag technology, in which vaccines are produced in batches in bags preventing the need for the deep cleaning of equipment after production runs, and allowing scale up through parallel production of approved batch sizes.

[46] *The Pharmaceutical Journal, PJ, April* 2021: 306:7948. DOI:10.1211/PJ.2021.1.77840

[47] India has a long tradition of vaccine production. Schama (2023) reports how the Parel Plague Research Laboratory delivered half a million doses of plague vaccine by 1899, increasing to approaching 3 million by

Based on a 42-acre site on the Poonawalla Bio-Tech Park in Pune, SII is the world's largest vaccine manufacturer by number of doses produced and sold globally. The family-owned company produces more than 2 billion doses annually, and it is estimated that about two-thirds of the children in the world receive at least one vaccine it manufactures.[48]

SII has a history of working with Oxford. Adrian Hill remembers approaching it to make a tuberculosis vaccine in 2007, which it didn't pursue. In 2017 discussions began about a malaria vaccine, developed by Hill, which the first efficacy data showed was working very well in African children.[49] When Covid-19 arrived, SII was approached by a number of potential vaccine producers at the time and Hill asks the question:

> Why did it agree to really prioritise a vaccine candidate from Oxford University, a bunch of academics who've never licensed anything for that stage? I believe it was in large part because malaria is a very difficult disease to make a vaccine against, and it had worked in the previous two months... The Poonawalla family thought, well, maybe we should have a look at their vaccine. And they did and what they looked at particularly was manufacturability.

SII had been looking to expand internationally for some time, selling in high- as well as low-income markets. It made its first international acquisition, Bilthoven Biologicals, a bioengineering and pharmaceutical company, from The Netherlands Government on 29th June 2012. This provided an important manufacturing base in Europe, with access to strategic European markets. At the onset of Covid-19, the company also established an office in London, Serum Institute Life Sciences, to operate as global sales office for the Covid-19 vaccines manufactured in India, and to serve as the sales office for future vaccine launches. It also improved opportunities for UK and European regulatory approvals for its products. While a malaria vaccine wasn't an opportunity for international expansion, Covid-19 was.

In an interview on July 8th 2020, Adar Poonawalla, SII's CEO, said he decided to invest tens of millions of dollars in glass vials alone and produce four different coronavirus vaccines, including OAZ's. This was before clinical trials proved any of them would work. If the vaccines did prove effective, SII would already have hundreds of millions of doses stockpiled to start shipping. If they didn't, SII would end up with useless vaccines, and what he claimed were hundreds of millions of dollars in losses. Poonawalla said it was an easy decision – made with his father, Cyrus, the company founder and Chairman:

> Because we're privately listed and not accountable to investors and bankers and shareholders, it was just a quick five-minute chat between myself and my father.[50]

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mid-1902. He reports that by early 1903 it was producing nearly 1.5 million doses a month, noting that from the beginning of its production it exported hundreds of thousands of doses to African and other poor countries.

[48] See: https://www.bioindustry.org/member/serum-life-sciences-ltd.html. Its portfolio spans Polio, Diphtheria, Tetanus, Pertussis, Hib, BCG, r-Hepatitis B, Measles, Mumps, Rubella, Pneumococcal as well as Covid-19 vaccines.

[49] Phase III trials of the malaria vaccine were undertaken in 2020, and the data are being reviewed by WHO for licensure and approval. It is currently approved for use in Ghana.

[50] *Indian Company Starts Mass-Producing Coronavirus Vaccines Before Trials* (2020) NPR. Available from:

Oxford provided SII with the viral vector vaccine in May 2020 along with a cell substrate – human embryonic kidney cells – in which to grow the new vaccine. The technology of how to manufacture the vaccine was transferred from AstraZeneca. The speed and scale of production was remarkable. By March 2021, 5000 vials were coming off a conveyor belt every minute. By November 2021, SII had made 1.25 billion doses. To produce at this scale SII employed more than 500 new staff to work on Covid-19, and many of its existing scientists worked overtime. Half of production was promised to be delivered to India. Of the 3 billion doses of the OAZ vaccine produced, SII made around one-half.

Cyrus Poonawalla was awarded an honorary degree from Oxford in 2019. In September 2021, SII purchased a 3.9 per cent stake in Oxford Biomedica for $68 million, allowing Oxford Biomedica to expand its GMP manufacturing facilities. In December 2021 SII announced it would donate £50 million to Oxford to fund the creation of the Poonawalla Vaccines Research Building, the largest donation Oxford has received for vaccine research.[51]

Based on its Covid-19 experience SII claims to be expanding its manufacturing facilities, preparing extra laboratories and equipment ready to make billions of doses for future vaccines against viruses.

Key Policy Actors

The Vaccine Task Force (VTF)

While UK governments of recent decades can easily stand accused of a series of significant errors in foreign and domestic policy, there has been a level of consistent support for science. The capacity for policy-making, however, is limited by the high levels of ministerial turnover and capacity within the public service. There were at least 11 UK science ministers between 2010-2022. Sir Charles Godfray, an eminent and highly active advisor to government says:

> As someone who is an enormous admirer of the British civil service, it has some real problems. It is poorly equipped to take difficult decisions on scientific issues.[52]

As shown in Figure 1, the political and policy structures surrounding the pandemic were complicated, and at the initiative of the Chief Scientist, Patrick Vallance, the VTF was created

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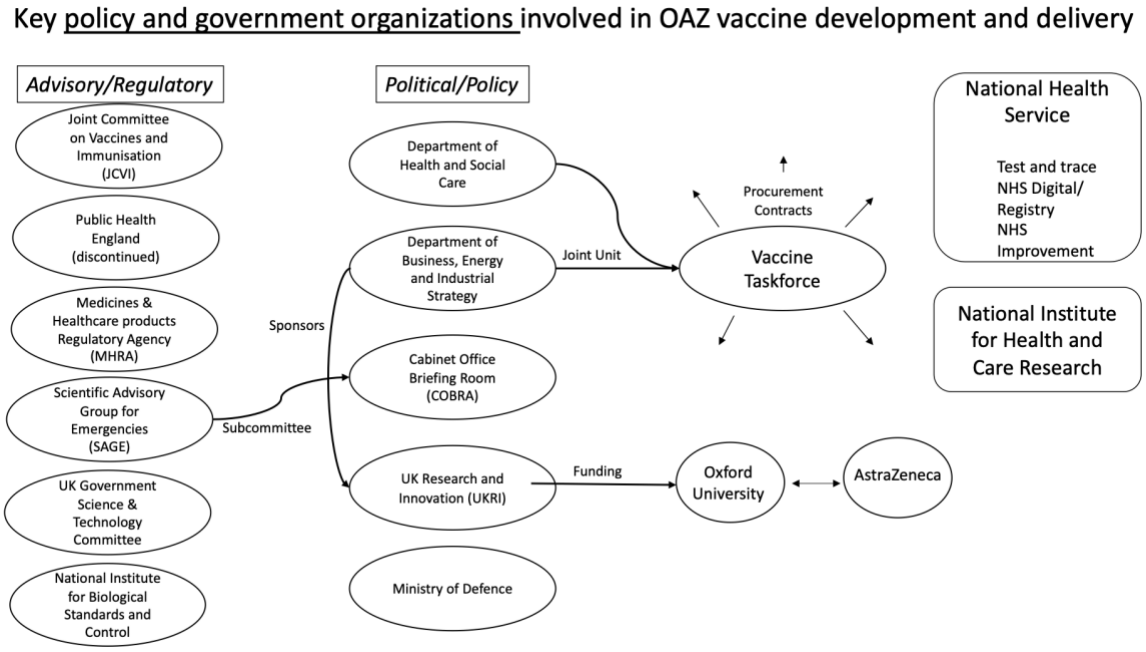
https://www.npr.org/2020/07/08/889112811/indian-company-starts-mass-producing-coronavirus-vaccines-before-trials

[51] *£50m funding for Poonawalla Vaccines Research Building at Oxford University* (2021), Oxford University News. Available from: https://www.ox.ac.uk/news/2021-12-15-50m-funding-poonawalla-vaccines-research-building-oxford-university

[52] In an article in the Guardian in March, 2023 Patrick Vallance is quoted as saying that while government departments had "very good" science advisers, the civil service has lagged behind. He said that when he took up the post in 2018, only 10% of entrants to the civil service 'fast stream' of high achievers held a science, technology, engineering or maths degree, and a target has since been set to achieve 50%. https://www.theguardian.com/uk-news/2023/mar/24/sage-warned-independent-sage-name-would-cause-confusion-patrick-vallance-david-king

to act quickly and avoid and circumvent any bureaucratic obstacles within and between these structures to rapidly vaccinate the population. His suggested Taskforce was designed to rapidly bring those skills into government, and Prime Minister Boris Johnson agreed to set up this specialist unit, led by and working with people outside of government.

Figure 1. Key policy and government organisations involved.



The challenge facing the VTF was immense. It had three objectives:

1. Secure access to promising Covid-19 vaccines to the UK population as quickly as possible.
2. Make provision for international distribution of vaccines.
3. Strengthen the UK's capacity in the development, manufacture and supply chain of vaccines.

On being asked to Chair the VTF Kate Bingham says:

> I felt like I was being asked to take responsibility for a huge amount of government expenditure that would, most likely, prove completely wasted. The longest of all shots.[53]

And her reflections on the circumstances in which it operated were highly divergent:

> I saw how some people and some institutions rose to extraordinary heights in that battle. I saw extraordinary scientists, extraordinary dedication and, in some cases, rapid and imaginative responses to new challenges. But I also saw how some institutions failed the test,

[53] Her book on her experiences, with Tim Hames, is entitled *The Long Shot.*

> did not reform, carried on a blinkered 'business as usual' approach, as the world around them was stricken by disaster. (Bingham and Hames, 2022:3-4).

Novel institutional arrangements introduced quickly to address crises rarely sit easily with existing government structures. The successful AIDS awareness campaign conducted in the UK in the 1980s worked only because it circumvented normal decision processes (Dodgson and Gann, 2021). The pressures on the VTF are seen in the way it felt the need early in its existence to ask the respected scientist and businessman Sir Richard Sykes - former Chairman of GSK, and Rector of Imperial College - to do an audit of its performance to allay concerns and criticisms.

From an initial 190 vaccine candidates, the VTF selected 10 for deeper examination. Andy Pollard was not initially convinced this was the right approach:

> I spoke to her [Kate Bingham] very early on and she was going after 10 different vaccines. I asked her if she was sure you really want 10, because we know that our vaccines will work, we've got lots of data. So do you need to go 10? And she said, yes, of course we do. Because in this industry, it's often not the science that makes the failure. It's lots of other stuff. And of course, she was absolutely right. I mean, I know she's right there.

Because of her background, Andy Pollard says the appointment of Kate Bingham as Chair was centrally important:

> I think that was an absolutely critical decision. It was a task force with a focus. It had a certain simple remit that it had to deliver. And Kate was an extraordinary choice. I mean, she's not a vaccine person. But she does understand both the money side of investment and from her background she also knows what fails in pharma.

Sarah Gilbert shares this view:

> I think they were exactly what was needed. And Kate was exactly the right person to lead it… Within civil service procedures, you have to have a business case and various other things. But there was no science case. So they had to invent how they're going to review the science case: what are these people doing? What's the technical background? What's the likelihood, you may actually be able to supply the vaccine and that it will not only actually be effective, but affordable, and deployable and all the rest of it. So that's what they did to review all of the different technologies and decide which to fund and deliberately chose to support multiple different technologies, which was absolutely the right thing to do.

The Pro-Vice Chancellor (Innovation) at Oxford, Professor Chas Bountra, shares this view:

> Picking Kate was a genius move. She'd been running an investment fund. She thinks like a venture capitalist, clear outputs, milestones, timelines, urgency, getting from A to B quickly, correctly, etc, etc. Secondly, you know, she has a network in this space, she knows who the big entrepreneurs are. She had that sort of convening power.

He also lauds the Deputy Chair, and latterly Chair, of the VTF, Clive Dix, the CEO of a biotechnology company. Chas Bountra says of Dix: "He's a great strategic thinker….He's a great people-person… He creates opportunities".

The diversity of experience within the staff of the VTF was also crucial for its capacity to traverse and coordinate all contributors to vaccine delivery. Resonant with the diverse skills and expertise that resided in the UK's wartime code-breaking facility at Bletchley Park (Dodgson and Gann, 2021), it was the diversity of staff backgrounds and unity of purpose that underpinned its success.

Other roles undertaken in the VTF include those by a Director General within the Department of Business, Energy and Industrial Strategy (BEIS) who was a former bomb disposal engineer; a Manufacturing Advisor with extensive experience at GSK; and a Programme Manager who had been a submarine delivery agent. Logistics support was provided by someone who had worked with RAF air traffic control. There was an Industrial Vaccine Clinician and a Commercial and Legal Negotiator. Staff members were responsible for risk analysis and liaising with foreign governments and NGOs.

Bingham claims that within six weeks of its creation, the VTF had developed a vaccine procurement strategy, built a team of industry and technical experts alongside a small team of Whitehall officials who were experts in commercial negotiation and diplomacy, and says the VTF worked as a single empowered team. She refers to a: "High degree of mutual knowledge and trust within the team and with many external commercial and academic players."[54]

> We were relying on the likes of a bomb disposal expert, an Indian rowing star, an Italian consultant, a submarine delivery agent, a former ambassador, a football pundit and a venture capitalist to get the UK out of the pandemic. (Bingham and Hames, 2022:51)

The VTF also had an external advisory board comprising a combination of people of deep expertise and experience from industry, academia, regulators and funders of medical research, including:

- Sarah Gilbert, Andy Pollard, and John Bell from Oxford
- Professor Robin Shattock - Head of Mucosal Infection and Immunity at the Department of Medicine, Imperial College
- Sir Jeremy Farrer - Director, Wellcome Trust
- Richard Hatchett - Chief Executive of CEPI
- June Raine - Chief Executive of Medicines and Healthcare products Regulatory Agency (MHRA)
- Sir Mene Pangalos - Executive Vice President of BioPharmaceuticals R&D at AstraZeneca
- Ian McCubbin - acting representative of the BioIndustry Association
- Jeff Almond - eminent microbiologist and former VP of Global Research and External R&D for Sanofi Pasteur

The VTF's assessment of the OAZ vaccine, and all 10 vaccines it selected for deep assessment, involved answering 3 high-level questions:

[54] *Romanes lecture - Kate Bingham 'Lessons from the Vaccine Taskforce'* (2021). Available at: https://www.ox.ac.uk/news/2021-11-24-another-war-coming-kate-bingham-dbe-delivers-romanes-lecture

1. Is it safe?
2. How likely is it that it will work?
3. Can it be made swiftly at high quality and at scale?

In practice, it:

> Reviewed the robustness and credibility of manufacturing scale-up plans and capabilities, the likelihood of early delivery doses to the UK, the track record of the vaccine format and of the senior management teams, the preclinical and clinical safety and efficacy data, and the level of understanding of the MHRA approval process. (Bingham and Hames, 2022)

A critical question was would the vaccine be ready for clinical trials in 2020?

Its due diligence was undertaken using a range of experts from industry and academia, reviewing all preclinical and clinical data and conducting a manufacturing analysis of AstraZeneca and other relevant companies such as Cobra Biologics and Oxford Biomedica to review their data and plans for scale up. VTF concluded AstraZeneca had well understood and planned their manufacturing process. This due diligence process found OAZ was a "strong contender" (Bingham and Hames, 2022:131).

Another possible contender for the VTF at the time was the work of Professor Robin Shattock of Imperial College, who was working on self-amplifying RNA vaccinations which could use 1/100th of the dose of mRNA, aiding scale up and manufacturing. VTF reached the conclusion that, despite its promise, as Imperial didn't have the years of testing that Oxford had on its platform, and couldn't secure a partnership with a big pharmaceutical firm,[55] it did not believe the mRNA vaccine would be possible to launch as rapidly as the viral vector vaccine.

Problems with the OAZ vaccine emerged for the VTF in the second half of 2020. Scale-up plans for the vaccine proved too optimistic and it appeared that a target date of 30 million doses by September would be missed. There was also the problem that phase III trials of the vaccine coincided with the drop in the number of infections due to lockdown and social distancing, which delayed clinical trials at a time when other vaccines were progressing. Amongst the 'noise' in the system Kate Bingham also reports disquiet on the part of some at the top of government about a deal signed with a Russian drugmaker, R-Pharm, while at the same time Russia tried to hack Oxford's vaccine research and VTF was made aware that Russia and other states had planned propaganda against the vaccine (Bingham and Hames, 2022:139).

The decision to back the OAZ vaccine, however, paid off, and Bingham acknowledges the crucial contribution of AstraZeneca:

> Selling this vaccine without a profit was an extraordinary act of altruism, considering the sums involved and the rewards from which some of its rivals benefited. AZ has still not received the credit for this that it deserves. Pascal, Mene and their team have been selfless heroes.... All in

[55]Kate Bingham reports that the VTF tried to encourage GSK to work with Imperial, but after a review GSK said no as they would have to build a supply chain from scratch.

> all… It was Oxford's triumph. It was AstraZeneca's triumph as well. (Bingham and Hames, 2022: 254)[56]

SAGE

A committee of experts, the government's Scientific Advisory Group for Emergencies (SAGE) is a subcommittee of COBRA, the UK's civil contingencies committee for handling large disasters such as natural disasters or pandemics. It was chaired throughout the pandemic by Sir Patrick Vallance, the Government Chief Scientist. SAGE's role was to undertake assessments on various aspects of the pandemic to provide advice to the government. It is not a standing body and makes no decisions. It first met in response to Covid on 27th January 2020, and involved experts in epidemiology, virology, public health, and ethicists. It established sub groups in behavioural science, mathematical modelling, and in the transmission of the virus. Its challenge was to provide clear and consistent advice to the government based on the expertise of hundreds of scientists. A member of SAGE, Professor Wendy Barclay, a virologist from Imperial College, talks of being grateful for the opportunity to use her experience and knowledge to address the crisis. She says how enlightening it was to see teamwork at its best between experts in virology, immunology, mathematical modelling, and behavioural science, and seeing how all these voices came together to produce a balanced argument around very specific questions.[57]

At the start of the pandemic, SAGE received significant criticism for the secrecy surrounding it: its membership, research and data, and minutes of meetings, were secret. Following this concern over lack of transparency, SAGE became more open with the names of some members, happy to be identified, and it released some documents, albeit sometimes delayed. As a reaction to the secrecy surrounding SAGE an alternative voice, Independent Sage, was created by a previous Chief Scientist, designed to make information more readily available to the public.[58]

Jeremy Farrar reports that at the meeting on the 27th January, that involved Patrick Vallance, Chris Whitty (Chief Medical Officer for England), Mark Walport (Chief Executive, UKRI) Jonathan Van-Tam (Deputy Chief Medical Officer) and Jenny Harries (Deputy Chief Medical Officer) there was the first discussion about what UK should do, and led to the issuing of a call to UK university vaccine research groups, expecting Imperial and Oxford to apply. It also asked MHRA to streamline its approval process, and suggested Porton Down, the government's top biohazards laboratory, work on developing a diagnostic test.

Kate Bingham relates how the UK government was lucky to have Sir Patrick Vallance, with his background in vaccine and pharmaceutical R&D, as its Chief Scientific Advisor during the pandemic. In her Romanes Lecture at Oxford University she says Vallance saw the potential for vaccines early - and in her book she relates how he pushed for a vaccine strategy at a

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[56] A point echoed by John Bell, who says he has a lot of respect for the company which has not received the credit it deserves, and has been treated badly by some people. https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

[57] https://podcasts.ox.ac.uk/pandemic-people-professor-wendy-barclay

[58] Amongst the criticisms of Prime Minister, Boris Johnson's, performance during the pandemic was the fact he did not attend the first five COBRA meetings in January and February 2020.

brainstorming meeting 27 January 2020 - and how he recognised Whitehall did not have skill to drive forward the development and procurement of unknown vaccines. He suggested the creation of the Vaccine Taskforce to rapidly bring those skills into government. He also, according to Bingham, pushed Whitehall to explore more modern vaccine manufacturing options, wanted to explore all types of vaccine, encouraged the regulator (MHRA) to streamline the approval process, wanted to ensure there were no funding gaps in the development and delivery process, and his experience:

> … had taught him that discovery of a new drug or vaccine was only the very first step in an enormously challenging process that ultimately demanded large-scale clinical trials, complex scale-up and bulk manufacture, plus a robust distribution network to ensure prompt delivery. (Bingham and Hames, 2022:15).

She writes of Vallance that:

> Patrick understood how the best results often came when university research, biotech and pharmaceutical corporations worked cooperatively. (Bingham and Hames, 2022: 11).

John Bell

John Bell epitomises that cooperation. He is Regius Professor of Medicine at Oxford, and the UK's Life Sciences Champion, appointed by the Prime Minister, and he played a key role in determining Oxford's, and indeed the nation's, response to the pandemic. He recalls first becoming aware of the impending crisis in a phone call from Jeremy Farrar at Christmas 2000, when Farrar told him of circumstances in China, saying that "this is probably the start of the big one".[59] As someone who had been warning about the potential of a pandemic for the past 25 years he was alarmed by the speed of transmission of the virus. From there on, Bell was to play a central role in the emerging innovation ecosystem as someone deeply connected to all its elements and with the skills to further foster its connections.

John Bell's connections are summarised by Professor Chas Bountra:

> He's got an amazing network in academia. He's got an amazing network in industry, he's got an amazing network in government. He knows the regulators, he knows many of the funders, etc. etc. He is so charismatic as well. My sense is that he was the guy who managed to bring to the table colleagues from government, colleagues from funders, from Gates, obviously, colleagues across the medical school, but importantly, Mene Pangalos and Pascal Soriot from AstraZeneca. And there's not many people who have got those networks, and who have got that big vision. And who can bring people together like that who can convene.

Andy Pollard says of John Bell:

> John Bell is always good value. Particularly because of his role with the Office for Life Sciences, his understanding of government, and what was going on that side is second to none. And he was also critically involved in brokering the deal with AstraZeneca.

[59] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

Regulating, approving, and distributing the vaccine

All Covid-19 vaccines, indeed all vaccines, are subject to the energetic propagation of disinformation. Whether it is malicious social media, such as in the case of the first vaccinated volunteer, Elisa Granato, being reported as dying, or politicians who for whatever reason questioned the efficacy of particular vaccines, scepticism about vaccines is easily fueled. Add to this the reckless behaviour of President Trump, disinformation campaigns out of Russia,[60] and wilful sensationalising by the popular media, the regulators faced extraordinary pressures. Their rigorous processes essential for vaccine approval needed to be conducted in circumstances where speed was of the essence and errors or miscommunications would be pounced upon as evidence of malfeasance.[61]

UK Approval: MHRA

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for vaccine approval in the UK. It has been widely lauded for its role during the pandemic. Cath Green says: "The MHRA's proactive approach is a critical part of this story." (Gilbert and Green, 2022:107). Kate Bingham says that June Raine, the CEO of MHRA, arranged a "close partnership" model between vaccine companies and MHRA whereby MHRA played more of an air traffic control role than policeman, and that she was absolutely critical to the vaccine rollout: a "gamechanger." (Bingham and Hames, 2022: 235). Andy Pollard says:

> I think they were astonishing. I mean, they managed this fine line between being collaborative and expediting things. But being tough enough that it kept us on our toes and made sure that we were doing, obviously making sure the quality was there, and that the safety of the volunteers was paramount. So I think they're good. And they were flexible, recognising the importance of keeping moving… They were exceptional.

Other regulators were not so flexible and responsive.

USA approval: FDA

The connections between the OAZ vaccine and the USA's Food and Drug Administration (FDA) requires a great deal of unpicking, and is inseparable from the politics of significant and obvious 'vaccine nationalism'. As Andy Pollard says in an understated way: "the whole American bit is very difficult to understand."

There was initial support for the vaccine, with the *Financial Times* reporting on the 25th August 2020 that President Trump was considering 'by-passing' normal standards and fast

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[60] *Russian Disinformation Campaign Aims to Undermine Confidence in Pfizer, Other Covid-19 Vaccines, U.S. Officials Say* (2021) The Wall Street Journal. Available from: https://www.wsj.com/articles/russian-disinformation-campaign-aims-to-undermine-confidence-in-pfizer-other-covid-19-vaccines-u-s-officials-say-11615129200

[61] In the case of some Russian propaganda it was claimed the vaccine would turn recipients into monkeys. An alarmingly popular alternative view was that vaccines were a plot by Bill Gates to insert microchips to control behaviour.

tracking OAZ approval in time for the US election in November.[62] By the 31st August 2020, phase III clinical trials began in the US run by AstraZeneca, although the decision was made that its results would not be pooled with other trials in the UK, Brazil, and South Africa as the US trial had a slightly different protocol. Despite the OAZ vaccine being awarded $1.2 billion from Operation Warp Speed,[63] the clinical trial was slow to start and then had a 7-week pause due to the SUSAR (Serious Adverse Reaction) reported in the UK clinical trial.[64] As Kate Bingham wryly notes: "When American company Johnson and Johnson had a SUSAR in its clinical trial, the trial was only paused for a week." (Bingham and Hames, 2022:139).

On 6th October 2020, the FDA introduced new guidelines for getting emergency approval (Emergency Use Authorisation – EUA), including a requirement for follow-up data for a median of at least two months after final vaccinations in phase III trials. The UK had produced this already, but there was no way a US clinical trial could produce this before the November election. It was possible that the FDA would consider UK data, but it is not clear whether this was explored or pursued. (Gilbert and Green, 2022: 242).

The politicisation of the approvals process and further evidence of vaccine nationalism is seen in the quote on the 9th October 2020 from House Speaker Nancy Pelosi:

> We need to be very careful about what happens in the UK. We have very stringent rules in terms of the Food and Drug Administration here, about the number of clinical trials, the timing, the number of people and all the rest... My concern is that the UK's system for that kind of judgement is not on a par with ours in the United States. So if [prime minister] Boris Johnson decides he is going to approve a drug and this president embraces that, that is a concern that I have.[65]

Some of the practical difficulties that arose are described by Andy Pollard:

> There was one point where they said we just got our (Oxford's) phase I results. And we don't believe any of your data, you have to send us all the blood samples, so that we can test them in our laboratories and check that what your laboratories are doing is correct. Well, I said, it's not my laboratories, we've sent these to the UK public health agency to do all the testing to ensure that it's independent. And they are the only place that actually has a properly validated assay. And I'm talking to your people at Operation Warp Speed, and they do not have an assay yet. So how could you possibly take our blood samples?

Confusion and contradiction continued. On the 22nd March, 2021, the US's National Institute of Allergy and Infectious Diseases (NIAID) announced the successful results of the AstraZeneca US clinical trial, reporting the same efficacy results as the company. It said the

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[62] *Trump considers fast-tracking UK Covid-19 vaccine before the US election* (2020) Financial Times. In a sense this may have led to the FDA feeling under pressure and needing to prove they wouldn't rush anything.

[63] Operation Warp Speed was created by The Trump administration with $10 billion allocated to seven companies to try to turn basic research—often funded by the government—into effective, widely distributed vaccines—but with no guarantee they would be widely affordable or available.

[64] Note that the UK clinical trial was restarted 6 days after the SUSAR. The Brazil trial was restarted 2 days after that, and the South African 3 days after that.

[65] *US should not approve vaccine based on UK trials, says Pelosi* (2020) Financial Times. Available from: https://www.ft.com/content/413970f7-3f81-40f5-97ba-d34a6d4d0d64

Data and Safety Monitoring Board (DSMB) had found no safety concerns and there were no incidents of blood clots, which had become a source of public concern.[66] The next day, however, NIAID reported concern that AstraZeneca may have included outdated information from that trial, which may have provided an incomplete view of the efficacy data. It "urge(d) the company to work with the DSMB to review the efficacy data and ensure the most accurate, up-to-date efficacy data be made public as quickly as possible".[67] This public intervention was described by Stephen Evans, professor of pharmacoepidemiology at the London School of Hygiene & Tropical Medicine, as 'unprecedented', and AstraZeneca released a statement saying it had published the results up to 17th February. It said as the trial was continuing, there would be more data available, which could alter the results at least slightly, although it did not expect that to be the case.[68]

At this point, OAZ already had emergency approval in more than 70 countries. Rather than seeking emergency approval in the US, AstraZeneca announced in July 2021 that it was aiming for full FDA approval ('Biologics License Application'). By March 2022, however, Mene Pangalos, said the UK drugmaker would consider not submitting its Covid-19 vaccine for approval in the US if it finds it is "banging its head against a brick wall indefinitely" with regulators.[69] On 10th November 2022, Pascal Soriot announced AstraZeneca would not pursue FDA approval, citing declining need and plentiful access to mRNA vaccines.[70] According to Kate Bingham, AstraZeneca was never likely to sell in the US anyway, it simply wanted FDA authority to add credence to delivering to low and middle income countries. She also notes that OAZ was not allowed to apply for emergency use, instead requiring a full licence and a ten-fold demand of paperwork (Bingham and Hames, 2022:139).

The OAZ vaccine was never used in the USA. John Bell's view in a podcast with Andy Pollard is typically forthright:

> The Americans hated this vaccine, largely because it was a not-for-profit product…and they were also a bit grumpy that none of their universities have been able to produce anything as far as I can see… There were lots of reasons why they weren't going to like it and they behaved very, very badly in my experience and AstraZeneca bore the brunt of that and we got a bit of the brunt… I don't think you (Andy Pollard), Adrian and Sarah set out to develop a vaccine for the USA, frankly. I don't think that was your ambition. If they wanted to use it that's fine, if they didn't want to use it that's fine too.[71]

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[66] *Statement—Investigational AstraZeneca Vaccine Prevents COVID-19* (2021) NIAID. Available from: https://www.niaid.nih.gov/news-events/statement-investigational-astrazeneca-vaccine-prevents-covid-19

[67] *NIAID Statement on AstraZeneca Vaccine* (2021) NIAID. Available from: https://www.niaid.nih.gov/news-events/niaid-statement-astrazeneca-vaccine

[68] *US agency questions AstraZeneca's Covid vaccine trial data* (2021) The Guardian. Available from: https://www.theguardian.com/business/2021/mar/23/us-health-agency-astrazeneca-covid-vaccine-trial-data

[69] *AstraZeneca prepared to ditch effort to secure US approval for Covid vaccine* (2022) Financial Times. Available from: https://www.ft.com/content/e1edb2b2-0e12-4c83-9257-eeeb2ba29267

[70] *AstraZeneca no longer pursuing U.S. approval for COVID vaccine* (2022) Reuters. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/astrazeneca-withdraws-us-application-covid-vaccine-2022-11-10/

[71] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

European process

The relationship between the European Union (EU) and the OAZ vaccine was difficult and contentious. Essentially the EU claimed at various times that AstraZeneca breached a contract for vaccine delivery and that OAZ was less effective than other vaccines for older age groups, with concerns about side effects. As a result, and with an accompanying bad press, there was comparatively poor uptake of OAZ when it was made available. From a regulatory point of view, the European Medicines Agency (EMA), the EU regulator, granted a conditional marketing authorisation for the OAZ vaccine on 29th January 2021.[72]

Any connections between AstraZeneca and the EU have to be assessed in the context of the extreme contention during the negotiation and aftermath of the British government's decisions to leave the EU's Single Market and Single Customs Union (so-called 'hard' Brexit). Conditions were ideal for polarised positions, aided by elements of political posturing and popular presses thriving on hostile nationalism resulting ultimately in vaccine nationalism.[73]

A problem arose when AstraZeneca stated that, because of a glitch in production at a hub in Belgium, deliveries to the EU would fall short of their agreement on deliveries for the first three months of 2021.[74] The EU were expecting 80 million, AstraZeneca said it could deliver 31 million. The EU suggested that vaccines being produced in the EU might be being sent elsewhere, and demanded more transparency and explanations from AstraZeneca. In its defence, AstraZeneca said the contract only committed to meet the EU's demands to its "best effort". Furthermore, in an interview with Italy's *la Repubblica* newspaper, Pascal Soriot said the EU's deliveries were delayed in part because the bloc signed its contract three months later than the UK, and therefore EU manufacturing facilities were still catching up. A deal with the UK Government for 100 million doses was signed three months before a EU deal for 400 million doses was agreed.[75]

The politics surrounding the vaccine became more heated.[76] The European Commission claimed AstraZeneca was contractually obliged to use vaccines produced at UK plants to fulfil

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[72] *EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU* (2021) European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-astrazeneca-authorisation-eu#:~:text=Update%3A%20COVID%2D19%20Vaccine%20AstraZeneca,Commission%20on%2029%20January%202021.

[73] With much of the discussion, especially in the press, displaying various degrees of nationalism if not xenophobia, much of the record of this time depends on the more sober and reliable *Financial Times*.

[74] AstraZeneca official statement says: "This is mainly due to lower than anticipated production yield impacting the number of doses produced per batch." *AstraZeneca's COVID-19 vaccine: European Union supply commitment* (2021) AstraZeneca press release. Available from: https://www.astrazeneca.com/content/astraz/media-centre/articles/2021/astrazenecas-covid-19-vaccine-european-union-supply-commitment.html#

[75] *The UK's row with the EU over supply of the AstraZeneca vaccine explained* (2021), ITVx News. Available from: https://www.itv.com/news/2021-01-29/euuk-covid-vaccine-row-explained

[76] UK government ministers have regularly used the OAZ vaccine as evidence of 'Brexit Benefits', that is of the ability to act independently of the EU's regulations. In actuality there was nothing preventing the UK acting as it did within the EU (and it was still party to its rules at the time). Although this view is discredited, that it continues to be used by ministers is further evidence of the inseparability of politics and vaccines.

its delivery obligations to EU states.[77] Boris Johnson contended that the UK's contract with AstraZeneca was watertight and signed 3 months earlier than Europe. The EU's Health Commissioner, Stella Kyriakides said the EU rejected "the logic of first come, first served." "That may work at the neighbourhood butcher's but not in contracts — and not in our advanced [vaccine] purchase agreements."[78]

It is difficult to assess the rights and wrongs of the situation as key details of the publicly available EU/AstraZeneca contract are redacted. Kate Bingham assesses that comparing the legal contracts between AstraZeneca and the UK and AstraZeneca and the EU, the UK's was much more commercially sensible (Bingham and Hames, 2022).

Uptake of the OAZ vaccine was slow initially in the EU because EU countries restricted its use for older ages until efficacy had been proved. There were also a substantial number of negative headlines suggesting it was not as effective as other vaccines. In France, the vaccine was initially only offered to people aged between 50 and 64 with co-morbidities and healthcare workers. Spain advised it not be used on those older than 55 years old. Germany and Italy offered the jab to everyone younger than 65,[79] and Germany later suspended its use for those under 60.[80]

In late February 2021 the EU changed tack and began encouraging the uptake of OAZ.
At this point in time, according to Our World in Data, the EU had inoculated 6.82 per 100 people, compared with 28.6 in the UK, 20.4 in the US, and 91 in Israel.[81]

France's top vaccine adviser, Dr Alain Fischer, claimed to be perplexed:

> For reasons that I find profoundly unfair, this vaccine has gotten relatively bad press in France. It is effective. It is safe. It should be used without a second thought and without delay.[82]

At one stage a French health ministry official called for a "collective rehabilitation campaign" to improve its reputation."[83]

Previously sceptical politicians changed their views. German Chancellor Angela Merkel acknowledged that there was "an acceptance problem with the AstraZeneca vaccine at the moment" that was slowing the vaccine's rollout.[84] In an interview with the *Frankfurter*

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[77] *EU demands UK covid vaccines from AstraZeneca to make up shortfall* (2021), Financial Times. Available from: https://www.ft.com/content/d814b2dc-a803-4680-b8c4-ffa2a4c370ad.

[78] Ibid.

[79] *Europe's AstraZeneca stockpile mounts as citizens snub jab* (2021), Financial Times. Available from: https://www.ft.com/content/767fdd85-5329-479d-b565-4ec85d28b492

[80] In January 2021, a German newspaper (followed by Reuters) published that the vaccine was only 8% effective in older persons. By the time data came out to show this was false, German policy was already to not give OAZ to the over 65s.

[81] *Europe's AstraZeneca stockpile mounts as citizens snub jab* (2021), Financial Times. Available from: https://www.ft.com/content/767fdd85-5329-479d-b565-4ec85d28b492

[82] ibid

[83] Ibid

[84] Ibid.

Allgemeine newspaper in late February 2021 she urged people to keep an open mind about it: "All the authorities tell us that we can trust this vaccine."[85] At the same time, French President Emmanuel Macron, who had called the vaccine 'quasi-ineffective' on people over 65 and that the results were 'not encouraging' for 60-65 year olds, stated that: "In view of the latest scientific studies, the efficacy of the AstraZeneca vaccine has been proven" - "If that's the vaccine that's offered to me, I will take it, of course."[86] By March, 2023, Germany had administered 12.8 million doses of the OAZ vaccine and France, 7.8 million. The EU as a whole had used 67 million doses.[87]

The row between the EU and AstraZeneca was set to reach the Belgian courts in late September of 2021, but was settled out of court earlier that month. The settlement included set monthly figures for AstraZeneca vaccine delivery, and a rebate for late delivery, increasing per month.[88]

Distribution in the UK

The author received his first AZ vaccine on 10th February, 2021 in a local vaccination service in Wembley, London, and his second AZ vaccine on the 3rd May, 2021 in the Francis Crick Institute in Kings Cross, London. Both vaccinations were remarkably well organised, with throughputs of thousands of patients a day. He remembers it as a happy experience, and after being inoculated in a cathedral of science, the Crick Institute, felt a profound sense of gratitude to the community of researchers whose work over decades had led to this point. The following photographs illustrate some of the experiences of vaccinations in the UK.

[85] Ibid

[86] Ibid.

[87] *Covid-19 vaccines doses administered by manufacturer* (2023) Our World in Data. Available from: www.ourworld in data.org/grapher/covid-vaccine-by-manufacturer?tab=table

[88] *EU and AstraZeneca reach deal to end vaccine row* (2021), BBC. Available from: https://www.bbc.co.uk/news/world-europe-58426880

It is widely accepted that the UK government made a number of significant mistakes during the pandemic, such as its £37 billion 'Track and Trace' system which failed to achieve its main

objective.[89] Its Covid-19 vaccination programme, however, can be described as an almost unqualified success.[90] The study by the King's Fund that makes this claim, makes the following observations:

> System-working, joining up the NHS, local government and the voluntary sector was a hallmark of the vaccine roll-out. Local knowledge and delivery were crucial. Volunteers also played a vital role, not just in acting as stewards at vaccination sites, but also in terms of community outreach, for example with faith communities and others offering sites for vaccination which in turn built trust in the vaccine and in the NHS.
>
> The NHS has never used so much data so quickly and so powerfully, supporting the delivery of vaccine doses, recording any adverse reactions and, most importantly, allowing NHS staff to map who had the vaccine.[91]

One year to the day after Brian Pinker received the first OAZ vaccine, around 50 million AstraZeneca vaccines had been administered in the UK.[92]

Viral diseases do not respect national borders, and the need for vaccines was global. As Sarah Gilbert put it: "When it's a pandemic, we have to vaccinate everywhere for the benefit of all of us."

COVAX

Covid-19 Vaccines Global Access (COVAX) is a global initiative, created early in the pandemic to enable equitable access to Covid-19 vaccines. It is part of the Access to Covid-19 Tools (ACT) Accelerator which brings together governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy, with the aim of providing innovative and equitable access to Covid-19 diagnostics, treatments and vaccines.[93] [94] As of November 2022, COVAX had delivered 1.8 billion Covid-19 vaccine doses to 146 countries, with 191

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[89] *Covid-19: NHS Test and Trace failed despite "eye watering" budget, MPs conclude* (2021). The BMJ. BMJ 2021;375:n2606. Available from: https://www.bmj.com/content/375/bmj.n2606

[90] *The Covid-19 vaccination programme: trials, tribulations and successes* (2022), The King's Fund. Available from: https://www.kingsfund.org.uk/publications/covid-19-vaccination-programme?gclid=Cj0KCQjwiZqhBhCJARIsACHHEH9-v1unGa3tF3AVpKU8X9cVS9eD_nGUX8HX5s6QTd-C04UUKSvRLiQaAuGIEALw_wcB#introduction

[91] ibid

[92] *One year anniversary of UK deploying Oxford-AstraZeneca vaccine* (2022) Department of Health and Social Care. Available from: https://www.gov.uk/government/news/one-year-anniversary-of-uk-deploying-oxford-astrazeneca-vaccine

[93] *COVAX explained* (2020), Gavi, Available from; https://www.gavi.org/vaccineswork/covax-explained.

[94] For an interesting representation of the complexity of COVAX's set up and implementation, this learning paper describes the 50+ workstreams and innovations required to be developed in order for COVAX to work.

countries participating in the initiative.[95] It is coordinated by Gavi, CEPI, and the WHO, and the key delivery partner is UNICEF.[96]

AstraZeneca was the first global pharmaceutical company to join COVAX in June 2020.[97] Not only was it timely, but it also offered significant supply. In February 2021, COVAX published its first projections of vaccine availability (for Q1 and 2 of that year) which included 336 million doses of OAZ, and 1.2 million of Pfizer-BioNTech for Q1 with up to 40 million to be supplied later that year.[98] AstraZeneca claimed that their Advanced Purchase Agreement with Gavi to provide 170 million doses to COVAX, as well as the committed supply of OAZ from the Serum Institute of India, was part of its "equitable access strategy", which resulted in 247 million OAZ doses being supplied in 2021.[99] AstraZeneca now state that together with their partners, it is the largest contributor to COVAX, providing two thirds of all COVAX vaccines supplied.[100]

Beyond AstraZeneca's proactiveness in joining and supplying COVAX, the suitability of OAZ vaccines can also be attributed to the fact they do not require an ultra-cold chain like mRNA vaccines, making logistics for transporting to and storing in lower income countries much easier. And they remain cheaper and more competitive on price.[101]

Vaccine supply through COVAX faced many difficulties, including vaccine hoarding, export restrictions and nationalism (for example, when India halted COVAX exports from SII to address urgent domestic needs).[102] A WHO Learning Paper on COVAX states that these difficulties are to be expected in future pandemics, but can be mitigated by, for example, increasing and geographically diversifying vaccine manufacturing.[103]

CEPI

The Coalition for Epidemic Preparedness Innovations (CEPI) was launched at the World Economic Forum Annual Meeting (Davos) in 2017. It is an innovative global partnership

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[95] *COVAX: Ensuring global equitable access to COVID-19 vaccines* (2022), UNICEF. Available from: https://www.unicef.org/supply/covax-ensuring-global-equitable-access-covid-19-vaccines.

[96] *COVAX explained* (2020), Gavi, Available from; https://www.gavi.org/vaccineswork/covax-explained.

[97] *AstraZeneca R&D: Turning Science into Medicine* (2022), AstraZeneca. Available from: https://www.astrazeneca.com/content/dam/az/r-and-d/pdf/turning-science-into-medicine.pdf.

[98] *The COVAX Facility: Interim Distribution Forecast - latest as of 3 February 2021* (2021), Gavi. Available from: https://www.gavi.org/sites/default/files/covid/covax/COVAX-Interim-Distribution-Forecast.pdf

[99] *AstraZeneca 2021 Annual Report* (2021), AstraZeneca. Available from: https://www.astrazeneca.com/content/dam/az/Investor_Relations/annual-report-2021/pdf/AstraZeneca_AR_2021.pdf

[100] *AstraZeneca R&D: Turning Science into Medicine* (2022), AstraZeneca. Available from: https://www.astrazeneca.com/content/dam/az/r-and-d/pdf/turning-science-into-medicine.pdf.

[101] *Covid-19 Market Dashboard* (2023), UNICEF. Available from: https://www.unicef.org/supply/covid-19-market-dashboard

[102] *Covax scrambles to make up vaccine shortfall due to Indian export halt* (2021), Financial Times. Available from: https://www.ft.com/content/5f38b956-9eaf-4026-99ee-b7887e38dd16.

[103] *COVAX: Key learnings for future pandemic preparedness and response* (2022), World Health Organisation, Available from: https://www.who.int/publications/m/item/covax--key-learnings-for-future-pandemic-preparedness-and-response

between public, private, philanthropic, and civil society organisations working to accelerate the development of vaccines against epidemic and pandemic threats. It was founded by the governments of Norway and India, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum[104] and is one of the coordinators of COVAX.

CEPI's aim is to take an "end-to-end approach, operating as both a funder and a facilitator". It endeavours to "fill the gaps that exist in vaccine funding and R&D implementation."[105] The urgent need for such a coordinating body was evidenced through the Ebola epidemic, where the global response fell tragically short. A vaccine which had been under development for over a decade and proved to be 100 percent effective took over a year to be deployed - costing many lives and suggesting that much of the epidemic could have been prevented.[106]

Oxford University has been involved with CEPI from its inception. In 2017, Sarah Gilbert responded to a CEPI call for proposals, seeking funding for the platform technology she was working on. While ultimately successful,[107] it took 18 months from the deadline of the application until contracts were signed. While this can be attributed to the newness of CEPI and the difficulty they faced in dealing with granting funds to a partnership application (Oxford submitted this application in partnership with Janssen Vaccines), it is a long time to wait to move funds - especially for an organisation that was set up to help speed up the vaccine process (Gilbert and Green, 2022).

When in February 2018, WHO added 'Disease X' to their list of priority diseases, CEPI followed by putting out a call for platform technologies to combat it. Sarah Gilbert applied for funding, but was unsuccessful. CEPI believed that the type of vaccine she was working on couldn't be produced rapidly enough (Gilbert and Green, 2022).

Sarah Gilbert began negotiating with CEPI on 13 January, and managed to secure seed funding to support Oxford to manufacture clinical trial materials. On 4 June 2020, CEPI announced it would invest $384 million in an AstraZeneca partnership which would support the manufacture of 300 million OAZ doses.[108]

According to CEPI's portfolio, it has run 19 proposal calls for Covid-19. These calls range from vaccine platform technologies for Disease X and Covid-19, to calls for database support and supply of aluminium overseals for the vaccines.[109] OAZ's grant of $384 million is the third

[104] To date, CEPI has secured financial support from Australia, Austria, Belgium, the Bill & Melinda Gates Foundation, Canada, Denmark, the European Commission, Ethiopia, Finland, Germany, Hungary, Iceland, Indonesia, Italy, Japan, Kuwait, Lithuania, Luxembourg, Malaysia, Mexico, Netherlands, New Zealand, Norway, Panama, Romania, Saudi Arabia, Serbia, Singapore, Switzerland, The Republic of Korea, United Kingdom, USAID, and Wellcome. See https://cepi.net/about/whoweare/

[105] CEPI website. Available from: https://cepi.net/

[106] CEPI website. Available from: https://cepi.net/

[107] Oxford and Janssen Vaccines were granted up to $19 million for Lassa, MERS and Nipah Vaccines - see https://cepi.net/research_dev/our-portfolio/

[108] *CEPI partners with AstraZeneca to manufacture 300 million globally accessible doses of COVID-19 vaccine* (2020) CEPI. Available from: https://cepi.net/news_cepi/cepi-partners-with-astrazeneca-to-manufacture-300-million-globally-accessible-doses-of-covid-19-vaccine/

[109] See CEPI Call for Proposals: https://cepi.net/get_involved/cfps/

largest grant - only behind S-Trimer by Clover Biopharmaceuticals (China) and Novavax (USA).[110]

Despite the difficulties they faced early on with grants and contracts, CEPI appear to have hastened the development process with its newly articulated aspirational goal that vaccines should be ready for initial authorisation and manufacturing at scale within 100 days of recognition of a pandemic pathogen, when appropriate. Together with McKinsey, CEPI undertook research to identify innovations that could accelerate the development process and challenges that would need to be overcome to meet the 100-day aspiration, and have published it in a report: Delivering Pandemic Vaccines in 100 Days.[111] The range of CEPI's activities and its partners are included in Appendix 2, illustrating the extent of the connections available in its network.

Oxford's wider contributions and lessons

If it is not crass to say, given the magnitude of its devastation, Oxford had a 'good' pandemic in the sense that it made a huge contribution to managing it. John Bell says he can think of no other example where a university had such a benefit to human health in such a short period of time.[112] The major contribution alongside the development of the vaccine was the Recovery Trial. Through a randomised evaluation of Covid-19 treatments in 47,000 participants in nearly 200 hospitals in six countries, the Recovery Trial identified four effective treatments, including the first to be discovered - dexamethasone - which is inexpensive, easily administered and available in most hospitals. The Recovery Trial saved hundreds of thousands, if not millions, of lives.[113] Another major contribution, actively promoted by John Bell, lies in efforts to help build the nation's testing capacity, which in a matter of months moved from a limited number of testing machines in universities to a system capable of one million tests a day, with results integrated with national data collection.[114]

In her Vice Chancellor's Oration in October, 2022, Professor Louise Richardson, emphasised the range of Oxford's contribution:

> Oxford rose superbly to the emergency of the pandemic and contributed our expertise in ways too numerous to recount, but included developing tests and treatments, the contact tracing behind the COVID app, detecting hotspots and patterns of infection, and analysing everything from the effectiveness of government responses to the needs of children affected by lockdown.

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[110] See CEPI Portfolio: https://cepi.net/research_dev/our-portfolio/

[111] *Delivering Pandemic Vaccines in 100 Days* (2022) CEPI. Available from: https://100days.cepi.net/wp-content/uploads/2022/12/CEPI-100-Days-Report-Digital-Version_29-11-22.pdf

[112] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

[113] *The RECOVERY Trial - two years on* (2022) Oxford University. Available from: https://www.ox.ac.uk/news/features/recovery-trial-two-years

[114] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

Richard Cornell convened meetings of all the university's Covid researchers to share knowledge throughout the pandemic. It included teams looking at:

- Covid testing
- Track and trace app
- Recovery Trial
- Immunology
- Virus protein structure
- Antibodies
- Genome sequencing
- Challenge studies in animals

Researchers in universities are commonly driven in their work by priority, that is making discoveries first. This can lead to elements of competition, and indeed Oxford University had two major groups working on vaccines: the Jenner Institute and the Oxford Vaccine Group (although they often research vaccines for different diseases). The Jenner Institute sits within the Nuffield Department of Medicine, the Oxford Vaccine Group sits within the Department of Pediatrics. Both sit within the Medical Sciences Division and both have independent Principal Investigators. Any competition between these groups, such as it was, was replaced by high levels of collaboration during the pandemic, and indeed collaboration across the university was a feature of the development of the vaccine.

Oxford's Pro Vice-Chancellor (Innovation) Professor Chas Bountra says:

> People trust academics on the whole. Academics tend to think not in terms of three, four years, they're thinking next 20-30 years essentially. They're not thinking national, they're thinking international. But also in a place like this you know, we've got all the expertise. We've got brilliant people in all areas of medicine, we've got amazing engineers, computational scientists, material scientists, physicists, data scientists, etc. We've got social scientists, we've got the business school, we've got people in humanities, thinking about ethics and philosophy. And we've got all the technical skill sets.

Charles Godfray, Director of the Oxford Martin School - a research and policy unit based in the Social Sciences Division of the University - argues the pandemic changed the way Oxford is seen:

> Oxford has suffered in the past from being seen as the Humanities University. That was never really true, but is in contrast to Cambridge, largely because of the Laboratory of Molecular Biology, and some of the other things that they have really done well with their innovation ecosystem. I think (the pandemic) has given Oxford more confidence in how we see ourselves.[115]

The challenge of contemporary universities is balancing the logic of discovery with the logic of the market. The university's approach to the commercialisation of its research has changed

[115] The LMB is a Medical Research Council facility in Cambridge. Its researchers have won a dozen Nobel Prizes.

dramatically. Adrian Hill refers amusingly to his first encounter with Oxford's technology transfer office as literally being one man in his slippers and a dog. Charles Godfray says:

> I've been back in Oxford for 15 years, and even in that period, the culture of doing research here has changed. People who do really good applied research, who start spinouts, get almost as much esteem, which would have been different even 20 years ago.

A point supported by Tess Lambe:

> Working with pharma a number of decades ago was seen as going over to the dark side. We need to get rid of that mindset. We need to applaud those types of interactions. We also need to work on spin outs and spin offs and ensure innovation is applauded and lauded within Universities. In this way, we can ensure we have an interaction between different mindsets, an entrepreneurial mindset, and a basic science mindset because there's so much that we could be pushing forward.

Although Oxford was to receive no royalties during the pandemic, Cath Green reports being hopeful that if the vaccine made money for someone, Oxford would at least get some returns on its investment. According to one analysis, it "could make millions after it ends through a web of patents including those held by Vaccitech, a for-profit spinoff."[116] Sarah Gilbert reflects:

> I think what we could have done is built in some more revenue coming back into Oxford, but not in a very large way. Because most importantly, the vaccine was available for use in low income countries at a low price.

Post-pandemic, Oxford University has received a significant dividend for central coffers from its license, although not in the same order of magnitude as the profits made by a number of Covid-19 vaccine companies. The success of the vaccine has also been instrumental in attracting additional philanthropic donations to the university. Whatever financial returns accrue, however, the dominant logic remains that of discovery. As Charles Godray says:

> We mustn't forget the fundamental research.. people really want the wonderful fundamental research that gets into *Nature* and things like that.

And the scientific rewards can be gratifying. The Copley Medal is the Royal Society's most prestigious award, with previous winners including Pasteur, Darwin, and Einstein. In 2022 the Medal was awarded to the "researchers, technicians, students and support staff responsible for the development of the Oxford-AstraZeneca vaccine for their rapid development and deployment of a vaccine against Covid-19". It was the first time in the nearly 300-year history of the Copley Medal that it was awarded to a team.

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[116] *They Pledged to Donate Rights to Their COVID Vaccine, Then Sold Them to Pharma* (2020) KFF Health News. Available from: https://khn.org/news/rather-than-give-away-its-covid-vaccine-oxford-makes-a-deal-with-drugmaker/
The article reports Vaccitech's ownership includes a 50 per cent stake held directly or indirectly by Oxford University.

The public's appreciation of the scientists behind the development of the vaccine was movingly revealed on 29th June, 2021 at the Centre Court at Wimbledon. An announcer said to the crowd that people responsible for the development of the vaccine were being honoured in the Royal Box. A camera shot focussed on Sarah Gilbert; the crowd began to clap. A young man stood and applauded and soon the whole stadium was standing and clapping. An "emotional moment" said one TV commentator, while another said it was "one of the biggest cheers you'll ever hear in a sporting stadium".

The gratitude shown towards the researchers, and to the companies involved in developing the OAZ vaccine (although this is perhaps less evident than it should be), is compounded by their motivation to address a public health crisis. Their desire was not, as could be argued to be the case in some other Covid vaccines, to profit, or to demonstrate or develop a particular science and technology, but to improve public health globally.

Innovation and innovation ecosystems

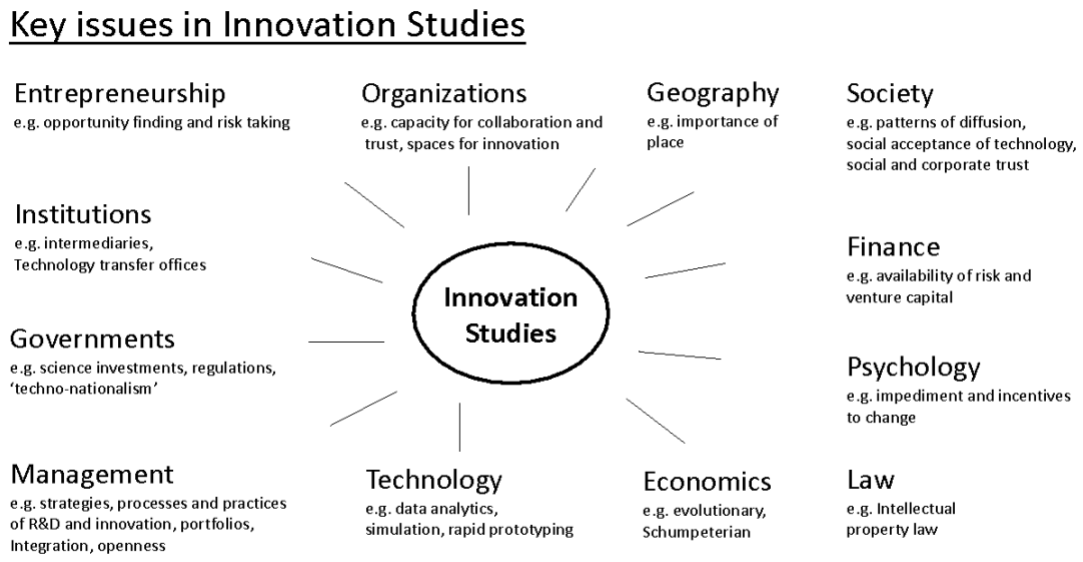
The value of using innovation as the lens to analyse the OAZ vaccine is that it can bring multiple perspectives to bear.

Innovation Studies

Innovation Studies is now a well-developed field (Fagerberg et al, 2013; Dodgson et al, 2015), encompassing a wide range of issues (see Figure 2). As a highly interdisciplinary field of knowledge it can draw on many perspectives to explain complex phenomena, and it is a useful lens, for example, on the connections between science and business. If, simply, science is motivated by issues such as curiosity and prestige, and business by profit, growth and increasing concern for corporate social responsibility, including sustainability. Innovation – the successful application of new ideas that add value – and entrepreneurship – the seeing of opportunities and taking of risks - link research and business. They are characterised by the creation of options and connections and search for opportunities and efficiencies.

As an emerging field in the 1970s and 1980s, much of the debate on the subject addressed whether innovation resulted from 'science push' or 'market pull', with the consensus being that their relative influence was determined sectorally and temporally. In recent times the focus of Innovation Studies has arguably moved towards 'market pull' research and concern for organising practices in firms, with substantial attention placed, for example, on notions of 'open innovation' (Chesbrough, 2003), 'democratic innovation' (von Hippel, 2005), and 'lean thinking' (Womack and Jones, 2003). This is to be welcomed, but it has directed much of the research agenda in the field over the past two decades and meant that less attention has been placed on the driving force of basic research for innovation. Basic research is often portrayed, and indeed defined, as 'far from market', or 'pre-competitive', but given the pressing challenges confronting the world, there is much value in quickly and effectively connecting it with business. The connections that move research into action often take place in innovation ecosystems.

Figure 2. Key issues in innovation studies



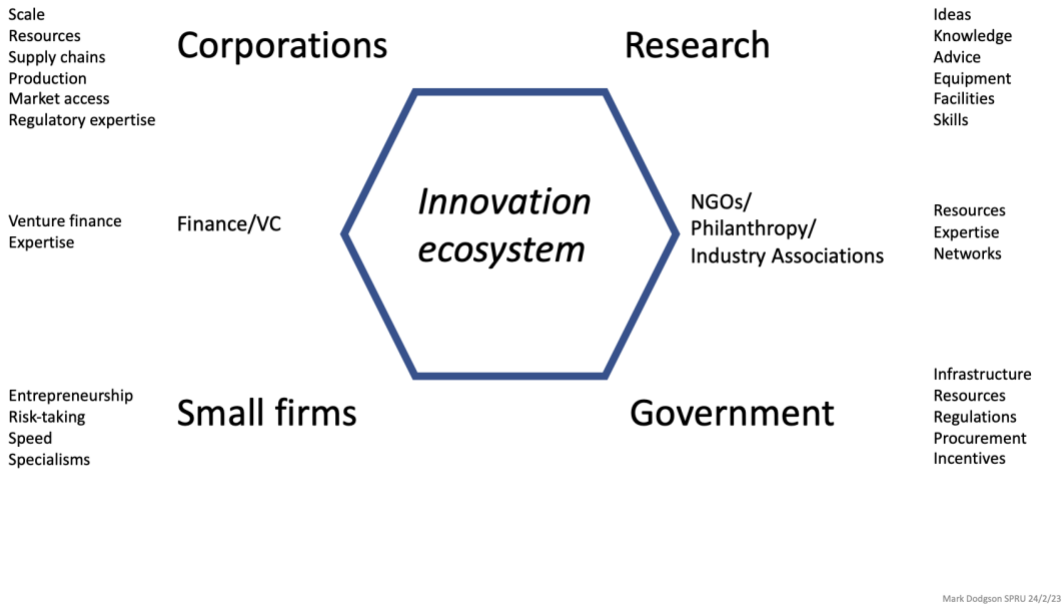
Sources: Fagerberg, J., Mowery, D., and Nelson, R. (2006) *The Oxford Handbook of Innovation*, (eds), Oxford, Oxford University Press.
Dodgson, M., Gann, D. and Phillips, N. (2014) *The Oxford Handbook of Innovation Management*, (eds), Oxford, Oxford University Press.
Dodgson, M. (2016) *Innovation Management: Critical Perspectives on Business and Management*. (ed.) Volume 1: *Foundations*; Volume 2: *Concepts and Frameworks*; Volume 3: *Important Empirical Studies*; Volume 4: *Current and Emerging Themes*. London, Routledge

Innovation Ecosystems

Innovation ecosystems are commonly defined as interconnected organisations that create and appropriate value through innovation, usually connected to a focal firm or platform (Autio and Thomas, 2014). For our purposes, the interconnections occur to deal with a crisis: the need to respond to a pandemic. In our framework, the contributing organisations include large and small firms, researchers, and governments; and these can be complemented by actors from finance and venture capital and from organisations such as NGOs, philanthropists, and industry associations. The various contributions made to innovation ecosystems is shown in Figure 3. No one actor in the ecosystem possesses all the required capabilities and resources for its effective operation: collaboration is *sine qua non*, especially in crises and when the challenges are complex.

The antecedents of innovation ecosystems can lie with large firms, such as that around telecoms company BT in Martlesham and pharmaceutical company GSK in Stevenage, in small, entrepreneurial start-ups, such as that based around 'Silicon Roundabout' in the East End of London, or around a research base, as in this case of Oxford University (ter Wal et al, 2015). A feature of innovation ecosystems is that they connect 'suppliers' and 'users', and in the public health context of the OAZ vaccine, the users are the public reached through the medium of the NHS. The innovation ecosystem that evolved to create the OAZ vaccine includes all the actors in Figure 3. Key actors included the researchers at Oxford and their international scientific, business, and government connections; AstraZeneca and its international manufacturing network, especially SII; the cluster of small specialist science-based firms around Oxford and more broadly in the UK and in Italy; governments as funders, regulators and 'users'; the BIA as an industry association; NGOs, such as Gavi, CEPI, and COVAX; and philanthropists such as Wellcome and Gates'.

Figure 3. Contributors to innovation ecosystems



As the evidence of the rapid and successful development of the vaccine showed, its supportive innovation ecosystem coalesced and operated very effectively.[117] A number of interviewees referred to the circumstances in which the vaccine was developed as 'war-like' conditions. A germane policy question is how these conditions could be developed in 'peace time'; that is what can be learnt from the OAZ case about the conditions in which innovation ecosystems can respond quickly and effectively to future crises, and even perhaps avert them?

Lessons for innovation ecosystems

A simple, idealised three-stage conceptualisation is suggested to answer this question. Stages are not mutually exclusive and are suggested for analytical purposes rather than prescription.

LATENCY > ANIMATION > INTENSIFICATION

Latency

Included here are the pre-existing capabilities and resources that underpin innovation ecosystems, which may already exist and be drawn upon, or be in embryonic or under-developed forms that can rapidly be bolstered and redirected. Latent capabilities are insurance policies against crises.

[117] It is possible to reflect with hindsight how the vaccine could have been developed even faster, but considering the novelty surrounding it, and the extent of the contextual difficulties caused by the pandemic, political rigidities and media mischief and incompetence, the effectiveness of the innovation ecosystem cannot be considered anything but remarkable.

Deep and wide scientific expertise

Oxford university researchers had the depth and breadth of expertise and experience to develop the OAZ vaccine built over many years, working, for example, on vaccines for MERS and Rabies. The Oxford Research Group is nearly 30 years old and the Jenner Institute is nearly 20 years old. Sarah Gilbert says:

> I think you need to emphasise the kind of breadth and depth of experience at Oxford in vaccine development, going back many, many years. And the fact that because of the number of researchers working in that area, we had joined forces, for example, to have our own vaccine manufacturing facility, and to have a clinical trial centre, and to have a group that makes vaccines for people to use in their preclinical testing.

The type of research undertaken to develop vaccines is discussed below, but here three points can be made. First, although vaccine development occurs in response to a demand or need, basic science underpins much of the knowledge that is put to use. When asked about the lessons from the OAZ vaccine, Professor Chas Bountra responded that:

> The lesson is having the sort of long-term research investment that allows you to seize opportunities when they arise.

Tess Lambe refers to the research behind the platform used for developing the vaccines, saying:

> On making these platforms, I can tell you now that fundamental basic science is hugely important.

The second point is the importance of diversity of approaches. This is captured in Sarah Gilbert's views on the role of mRNA alongside viral vector vaccines:

> We've already got lots of (viral vector) vaccines against lots of diseases and they will carry on, that's not going to change. So we're really just thinking about outbreak pathogens and pandemic preparedness or novel approaches and uses for vaccines, of which there are some, such as cancer therapeutics, particularly personalised cancer vaccines, where I'm sure mRNA vaccines will have a big role to play. Because they can be made so fast, it doesn't really matter if they're expensive, because they become one of the cheapest parts of the whole pathway of treating that patient anyway. So I think RNA vaccines will really be used a lot in that kind of area. If we're thinking about other outbreak pathogens, and being prepared for that, RNA vaccines certainly have a role to play, it's going to be a question of where they can be manufactured? And is the technology going to be made available widely?

The third point is the purpose of the research. In her Oxford University Vice Chancellor's Oration in October, 2022, Professor Louise Richardson, refers to this aspect of this research:

> The ability to choose to treat the products of our research as an infinite social good, rather than merely goods to market, distinguishes university collaborations from purely commercial ones, underlining the powerfully humane nature of our mission.

Building and maintaining such a resource is predicated on appropriate funding. It is salutary to learn of the continuing difficulties experienced in finding funding for vaccine research.[118]

Adrian Hill puts it this way:

> There's a lot to learn about what accounts for the delay (in vaccine development) in normal times compared to the pandemic. And the short answer I'm afraid is gaps in funding and time to get funding in a university setting. So if we see a promising result, to go into the clinic is not just the cost of the clinical trial, it's another bigger cost, which is manufacturing the vaccine to GMP. Used to be a million pounds, it's well over a million now. Add on to that the cost of a trial is the best part of a million and funding agencies are looking at probably £3 million, they don't tend to give out money in that scale to most academics, you know, £1.5 million is still a pretty good academic grant. So the capacity for translational research needs to be there in a country. We're better off than most in the UK, but it's still an expensive game.

The costs of such funding has to be judged in comparison to the costs of the pandemic. It is estimated that the UK's GDP declined by 11 per cent in 2020; estimates of the total amount of money spent on the pandemic range from £311 billion to £407 billion, and led to a budget deficit of 15 percent of GDP, a higher proportion than during the global financial crisis of 2008-9.[119] Properly funding vaccine research is a very inexpensive insurance policy against future pandemics, a point made by Adrian Hill:

> What I'm banging the table on at the moment is for people to take pandemic response into a separate category that does not drain the health budget. It's not a health issue, it's biosecurity. And I would say bio-defence issue. And the amount of money that is spent on defence is the sort of amount of money you need to secure this country against bio threats. And rather than challenge the limited resources of our colleagues in the NHS, I think this needs to be in a defence budget. Because it is bio-defence, and it's not as expensive as a nuclear submarine.

A key element of latency lies within the community of science. The Oxford team was a part of, and drew upon, an international community of scientists and researchers - from surveillance systems that publish data on emerging threats, to research collaborators and international partners conducting tests and trials, to groups such as the WHO and CEPI. Institutional and personal connections in these communities add to the strength and breadth of latency. As innovation ecosystems become animated, they connect more cohesively with the related ecosystems to which their partners belong, adding to its strength and depth.

The community of science furthermore also provides an early warning system, attuned to remote signals and signs of potential dangers, capable of absorbing, processing, and communicating information about emerging threats.

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[118] At the time of writing, there was uncertainty around Research Council budgets, and the UK was still prevaricating over rejoining the EU's Horizon Programme of scientific research.

[119] *The economic impact of Covid-19 lockdowns* (2022) The House of Commons. Available from: https://researchbriefings.files.parliament.uk/documents/CDP-2022-0215/CDP-2022-0215.pdf

Manufacturing capability and agility

The development of the vaccine relied on the ability of the CBF at a very early stage to manufacture it in small quantities. Such a facility is rare in universities and proved invaluable. Latterly, the capacity of small specialist contract manufacturers and suppliers, and AstraZeneca's global manufacturing network, especially including SII, was critical to the success of the vaccine: to its small scale manufacture for development and testing, and to massive scale production for distribution. A lack of manufacturing capacity was seen as an impediment to the rapid development of the vaccine. This had been recognised for some time, and a UK policy designed to address it took the form of the Vaccines Manufacturing and Innovation Centre (VMIC), established as a not-for-profit in Harwell near Oxford in 2018 to provide the UK with a bespoke vaccine development and manufacturing capability. Sarah Gilbert explains the thinking behind the Centre:

> The vaccine manufacturing innovation centre that was starting to be built at Harwell was supposed to be the next step in the chain. So that once a vaccine had been manufactured for the first time in the university, seed stocks and methods could be transferred over to be made, to be manufactured at a larger scale to continue the clinical development through phase two and phase three trials, potentially also to manufacture for outbreaks. So VMIC was supposed to be the next stage, to be flexible to have the capability to rapidly respond to take over from manufacturing here at the University, and support clinical trials with vaccine supply. So we're really lacking that next phase of manufacture.

VMIC's funding accelerated during the pandemic and in total it received £245 million in government investment. In late 2022, VMIC was sold to an American contract pharmaceutical company promising investment to complete the facility. Due to a decline in the company's stock price, that investment was reported to have slowed,[120] and latterly appears to have been mothballed.

Kate Bingham told a hearing of the Commons Science and Health Committees in November, 2022 that the UK's pandemic preparedness had declined since the emergency ended, indeed she said it had gone backwards.[121] This is a view shared by Lord Bethell, a Health Minister in 2020 and 2021, and is quoted as saying:

> For me it's totally heartbreaking. What you should do after a big pandemic is find other uses for that infrastructure. You turn the machines and the infrastructure to doing other public health screening. And then when the next pandemic turns up you have a platform to scale up from. But it has all been closed, the mega labs have been shut or sold. I think we will live to regret that.[122]

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[120] *Progress at Harwell's Vaccine Manufacturing and Innovation Centre slows after purchaser profit warning* (2022) The Business Magazine. Available from: https://www.businessinnovationmag.co.uk/progress-at-harwells-vaccine-manufacturing-and-innovation-centre-slows-after-purchaser-profit-warning/

[121] *Disease X is coming. Are we ready for the next pandemic?* (2023) The Times. Available from: https://www.thetimes.co.uk/article/disease-x-is-coming-are-we-ready-for-the-next-pandemic-ck29hmxx7

[122] Ibid.

Clive Dix, who was Deputy Chair and latterly Chair of the VTF, is even more excoriating, saying the government has systematically dismantled schemes developed during the pandemic, leaving the nation 'recklessly exposed'.[123]

On 12th April 2023 the Engineering and Physical Sciences Research Council (EPSRC), part of UK Research and Innovation (UKRI), announced a £12 million investment to fund a Future Vaccines Manufacturing Hub for seven years, up to 2030. Led by Sarah Gilbert and a colleague at University College London, the hub aims to deliver new platform technologies that can manufacture many different types of vaccine, develop improved, streamlined manufacturing processes focussing on product quality and stability, and make mass programmes of non-invasive vaccines, such as oral vaccines a reality. Sarah Gilbert is quoted as saying:

> Although vaccine developers worked rapidly in 2020 to achieve licensure of Covid-19 vaccines using multiple different technologies, there are still many improvements that can be made in vaccine manufacturing.
>
> In the next iteration of VaxHub we will work to increase sustainability of vaccine manufacturing by improving manufacturing yields, improving thermostability so that vaccines do not need to be refrigerated or frozen for storage and distribution, and assess alternative ways of making vaccines available for mass immunisation when needed.[124]

While this investment is certainly important and to be welcomed, given the significance of the vaccine manufacturing challenge faced during the pandemic, the question remains over whether a commitment of less than £2 million a year is of itself sufficient.

The UK's Covid-19 Inquiry aims to examine, consider and report on preparations and the response to the pandemic, and has in its terms of reference to: "highlight where lessons identified from preparedness and the response to the pandemic may be applicable to other civil emergencies". The OAZ case clearly shows that a key element of the Inquiry has to lie with assessing the true value and status of the UK's scientific and manufacturing capabilities.

Animation

Research collaboration and coordination

Researchers in Oxford University responded to the crisis of the pandemic in a collaborative and coordinated way, and that collective effort extended to their wider scientific communities in other universities, and included working effectively with businesses, regulators, funders, and the hospitals involved in clinical trials. Reference was continually made by respondents to 'the team'. Indeed, as we have seen, the Royal Society's Copley Medal was awarded to the team.

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[123] Michael Savage and Toby Helm, "Britain in 'recklessly exposed' to new pandemics, expert warns', The Observer, 10/6/2023.

[124] *£12 million investment for Future Vaccines Manufacturing Hub* (2023) Oxford University. Available from: *https://www.ox.ac.uk/news/2023-04-12-12-million-investment-future-vaccines-manufacturing-hub*

Andy Pollard describes the collaboration within Oxford:

> I think the critical innovation from Oxford's point of view was that the senior group of us got in the room together and said, okay, Andy will lead the clinical trials and tests, Tess Lambe will lead the laboratory side of things, Sarah was project managing and doing the funding. And then Catherine and Sandy were doing the manufacturing optimisation. And that's what we then did, because normally, when you know as scientists, we were working on things we're interested in, driving our own programmes.

He says this has to be considered in the context of Oxford's organisational structure (a point supported by John Bell):

> The important thing about Oxford is that it has a very unusually devolved structure, that the power and the funding is essentially in the periphery with the people like me: the academics and the heads of departments. So it's a really devolved structure.

A number of attendees at the meeting of Oxford researchers convened on 20th January, 2020 related in informal discussions just how powerful was the concern firstly, to direct their efforts towards responding to the pandemic, and second, to coordinate their activities to maximum effect. To collaborate effectively in innovation ecosystems, universities first have to collaborate with themselves.

It is notable that when talking about their counterparts in AstraZeneca, and despite the cultural differences between a university and a large pharmaceutical firm, Oxford researchers refer warmly about their competence and dedication and how the collaboration led to enduring friendships. Such dedication to a shared cause is crucial for animating innovation ecosystems.

Tess Lambe's outlines her views on building connections within innovation ecosystems:

> You have to have the same mentality across those different types of stakeholders. They all have to want the same end game. How you get that mentality across the board is difficult when you're not facing an outright pandemic threat. I think a good example is perhaps global warming and the climate crisis. People are not as concerned because they see it as something that will happen in the future. And they think it's somebody else's problem.
> So I think you need to present a coherent, cohesive pathway, where all the players know their worth and feel they are valued, that they have a say and that they have a unique, bespoke role to play. Actually identifying their role and having a roadmap that they all can buy into is one way that we may be able to surmount the problems we are facing. So you almost need to play to the strengths of each of these stakeholders and structure the roadmap to demonstrate it will benefit them and that they have a unique perspective, a unique way of delivering and are instrumental in the successful solution.

Collaborative international agencies and organisations, such as the WHO, Gavi, COVAX, and CEPI, and philanthropic organisations, such as Gates', played central roles in the animation of the innovation ecosystem, bringing with them their networks of connections and collaborations. The OAZ vaccine was developed within a network of networks.

Risk tolerance

Risks were assumed by the Oxford researchers, for example, in pursuing a vaccine that may not be required, in reallocating CBF capacity ahead of contracted work, in spending money that had yet to be received, and in organising trials without guaranteed supply of vaccines. Risks were assumed by the network of small specialist manufacture and supply firms, working to assist the University in the absence of contracts. Risk was a feature of AstraZeneca deciding to back the production of a vaccine, a field in which it had little experience, and gear up for large-scale manufacturing of an unproven product. It was a huge risk to commit to produce a vaccine at cost and ensure equitable access. Also, as John Bell reminds us:

> Remember, they were the first pharma company to do a deal around a COVID product. So there was no history of this where people were doing this deal or that deal. So they were kind of out there and they had to bite or not bite and they agreed that they would bite.

Such risks reportedly proved too much for GSK which decided not pursue an Imperial College vaccine because of the cost of setting up manufacturing. SII assumed the risk of scaling up a bottling facility in the hope a vaccine would be available. The management of risk was a key feature of the VTF.

Risk avoidance is an accusation often directed at business, government and research funders. Risk was understandably embraced during the pandemic, and if it could be assumed during a crisis it is worth considering its value in preparing for or avoiding future crises. There is much to be learned from the approach to risk adopted by the VTF, reflecting the venture capital-like methodology of developing a portfolio of potential investments and increasing commitment to a smaller number as more information becomes available. A sensible approach to risk ensured that there was no lock into one vaccine or means of producing vaccines, and emphasised the value of diversity in future options with rapid investment once efficacy is proven.

Astute regulation

Regulations can animate and focus innovation ecosystems, or they can provide obstacles. Balancing the need for stringent protocols for approval in the face of an overwhelming public health crisis involved a judicious balance. While the experience of Oxford researchers with the UK regulator during the pandemic was highly positive, and they offer testimony that this balance was successfully achieved, hurdles, which at their worst reflected vaccine nationalism, impinged on relationships with European and US regulators. The delays and obstacles put in the path of the OAZ vaccine's approval by some regulators belies the severity of the public health crisis being faced, and serious questions remain to be asked about the relative weighting of financial and political versus public health considerations in the future. The lack of transparency and changing demands shown by some regulators were hindrances limiting the activation of the innovation ecosystem. Positives have emerged, though, and as will be seen below the vaccine left a legacy for rethinking and quickening the whole approvals process by the UK regulator.

Leaders and boundary spanners

Leadership is a crucial factor in animating innovation ecosystems, and was clearly demonstrated in the OAZ case. Andy Pollard says:

> I think our Vice Chancellor was, during the pandemic, great at being an enabler for the vaccine programme. And she was very supportive. We knew that she had our backs. And she was obviously able to reach into government, to reach into AstraZeneca, and talk with them. That was important. John Bell clearly was critical. We worked closely with him throughout the whole of the pandemic. I met every week with him for 18 months.

Leadership, in the sense of determining actions in uncertain and difficult circumstances, was certainly a feature of Mene Pangalos and Pascal Soriot during the pandemic, a plaudit also applicable to Adar and Cyrus Poonawalla. Kate Bingham took on and won a long shot.

Individuals who communicate and convene across disciplinary and organisational boundaries - 'boundary spanners' - were a feature of the development of the vaccine. Examples include Andy Pollard, with his connections with the policy, regulation, and clinical testing communities; Cath Green, with her links with the BIA; Adrian Hill with his scientific and policy connections and relationship with SII, and John Bell with his connections with government and business. Such *animateurs*, individuals who span boundaries and build connections, are a precious resource.

To illustrate the point, Andy Pollard describes the extent of his pre-existing connections with policy-makers:

> I knew the key players already, largely because of my role as chair of JCVI over the last 10 years. In the early discussions talking to Patrick Vallance, or to Jonathan Van Tam or Chris Whitty, I regularly spoke to them and told them what we were up to, what was happening with the trials, and made sure they stayed briefed. So I think that was quite important as a link into government because they were then on SAGE and talking to the ministers. Jonathan Van-Tam has been a colleague for a long time, before he was Deputy Chief Medical Officer, and I worked with him on other committees. So it was very easy to reach them for discussion and advice.

Trust

One of the characteristics of effective innovation ecosystems (and of so-called national systems of innovation: Lundvall, 1992), is the extent of social cohesion and trust.[125] Convention has it that researchers, whose priority is generally discovery, and business, whose priority is generally profit, face significant communications difficulties resulting from their different purposes, cultures, and time horizons. The relationship between Oxford University and AstraZeneca could potentially have been tension filled, as is the case in many collaborations (Dodgson, 2018), but was mitigated by unified and pressing ambition, by the commercial experience of Oxford's academics, and the scientific basis of AstraZeneca's

[125] The extent of the social trust surrounding the innovation ecosystem is the extraordinary numbers of people volunteering to test the unproven vaccine. Volunteers trusted the scientists, and as shown in the BBC Panorama documentary, many wanted to 'do their bit' to address the social trauma the pandemic created.

business.[126] Oxford respondents universally reported good working relationships with AstraZeneca, with its scientists and leaders: both Andy Pollard and John Bell report regular conversations with Pascal Soriot. John Bell refers to the unifying effect of the substantial pressure on two organisations trying to deliver in the face of a crisis, and how important it was to maintain trust in the product.[127]

Trust within the innovation ecosystem is also seen in the preparedness of the early manufacturing companies to work without a contract, and in the university researcher's relationship with SII and MHRA. There was trust between the Oxford researchers and the VTF: Kate Bingham says of working with Andy Pollard:

> The bonds of trust that were forged early on would be invaluable as we faced the inevitable bumps in the road later (Bingham and Hames, 2022:131).

While there is evidence of collaboration and trust between UK, European and US scientists, this did not extend to politicians and lack of trust is seen in the ill-judged comments made by political leaders and the obstacles placed by the latter two's regulators.

Intensification

Communications in times of crisis

The Covid-19 pandemic was a health, social, and political crisis, in which a positive outcome was not a foregone conclusion. The crisis animated the innovation ecosystem, but for it to respond effectively, action within it needed to intensify: to strengthen and sharpen. A crucial factor in the development of the vaccine, and for sustaining high intensity connectivity, was the attempt to communicate effectively in circumstances where the crisis induced misinformation, disinformation, and panic.[128] Poor information, potentially malicious, could derail elements of the ecosystem and its entire operation. Citizens around the world, exposed to daily reports on a matter of immediate and pressing concern, had to be able to trust particular sources of information. Politicians facing unenviable choices needed quality insights and guidance. A crisis remains a crisis if it is obfuscated or ignored; it can only be addressed once it is accepted as such, and this requires outstandingly effective communications.

Andy Pollard reveals the extent of the communications challenge:

> At the peak of activity, we'd got 18 people in the university dealing with phone calls from journalists, and we were getting up to 1000 contacts per hour. Initially it was just all coming to us as PI's (Principal Investigators) individually, but then we got the university to be the buffer, which really helped. Then we only engaged with major news outlets. But it was the

[126] AstraZeneca's global R&D expenditure in 2020 was $6 billion.

[127] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

[128] The extent of the anti-scientific, deeply personalised, massively misinformed, but influential campaigns against Covid vaccines are described in Schama (2023). It was not only politicians, the media, and competing companies that misinformed. The Chief Medical Officer of Queensland, Australia, opposed the use of OAZ for people under 40. She subsequently became Governor of Queensland.

> stories like when I put a pause on the trial, and a potential adverse reaction in the UK, that caused huge global interest. That was a routine pause which is part of our protocols regulatory process…We go through a process independently looking at it. And the MHRA looked at it, and then they got their independent committees to look at it all within one week. And everyone says it's fine, restart the trial. But the impact of that pause was it was global news. It was everywhere. And what was being said about it, and about our handling of it, was just awful… We just have to put out our next clear statements and try and remain measured, and not engage with it because it was absolute madness and chaos.

Sarah Gilbert outlines her experiences:

> Sundays were often preparing for press conferences, but it was important that we…did prepare for communication with the public. Because it's very easy as an academic to just say something off the cuff, which is well meant, but actually your exact choice of words leads people to get the wrong end of the stick, and turns out to be unhelpful. So we would scrutinise press releases, and they'd be circulated amongst a number of us and we'd all got the chance to tweak and optimise and explain why that wouldn't work there and we needed to say it a different way. The Science Media Centre in London[129] were absolutely fantastic, and really, really helpful to us in press conferences. The first one I went to related to Covid-19 was in person in London, but then they all went online. And all the journalists were joining online. So we give a presentation and journalists get to ask questions, we try to make sure that we're doing that in a way where we're using accessible language that they can just directly report. And I did actually log in, just as an observer to another, to somebody else's science media press conference, and realised that what the scientists on the call were talking about was completely incomprehensible. They should put it into lay language. And the journalists were really clutching at straws to understand what was going on. And it didn't get very widely reported, because the journalists couldn't understand it. Whereas we were always trying to make sure that we had explained it so they could understand it. And it's also important to explain when we don't have that answer yet. We can't answer that question. Because we need to wait for data to come out of the trials, or we can't tell you about an adverse event because it's being investigated.

John Bell refers to the difficulties caused by the sheer amount of misinformation surrounding the vaccine, and the University's response:

> The amount of informed good press the university got out was remarkable, and the university communications team deserves a big tick. And we were lucky because we have a couple of very good communicators on the team. Andy Pollard is very impressive as a communicator, and the press likes to talk to people who are good communicators because it just makes it easier for them and it's a good story. So he was a real asset for us as we got into it. And I'm very close to the government, particularly the Department of Health, and was advising them on a daily basis. And so I had reach into the government and could make sure they didn't go off on a tangent.

In an age of mistrust in institutions and experts, of suspicion of the motives of government and 'big pharma', effective communications in a crisis is absolutely crucial to keep decision-makers and the public properly informed. Social media provides opportunities for the dissemination of harmful and dangerous misinformation and generative AI can readily offer

[129] See: https://www.sciencemediacentre.org/

plausible depictions of a false reality. In such circumstances crises are not ameliorated but accentuated. University researchers can be considered the least partial of those communicating the realities of situations that can be complex and may have conflicting messages. The onus is on scientists, as demanding as this can be, to be the frontline of providing important and necessary information in widely comprehensible forms. As seen in the continuing controversy over the source of SARS-CoV-2, whether it was, for example, Wuhan's wet market or Institute of Virology, with its enormous geopolitical as well as health policy implications, transparency and openness is key. As Sarah Gilbert explains it is better to endure the scepticism of the response to "we don't know, and are finding out", than the ignominy of being proven wrong and the deleterious consequences for informed voices. With the severe pressures put on scientists in the media to demonstrate their expertise by providing 'the answer', it takes confidence to refer to uncertainties and probabilities.

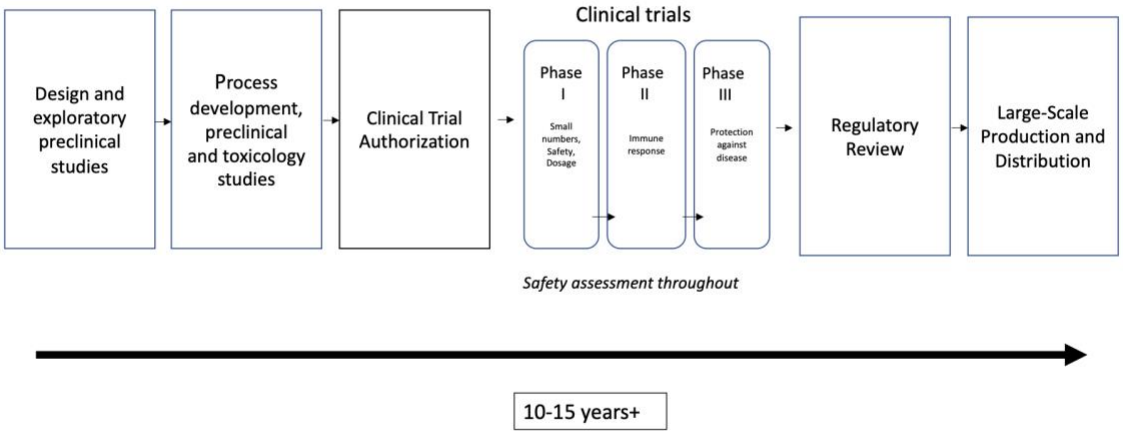
Concurrency

Long recognized in the engineering and product innovation literature, concurrency is well understood as an aid to speed. The development of the Boeing 777 offered a classic case where manufacturing of the aircraft had begun as important components were still being designed. We have seen the value of time compression in the early manufacture of the vaccine in CBF and in conducting phase II and III trials concurrently. An issue in structuring this report has been that the development of the vaccine was not always sequential: attention was paid to manufacture, regulation, and distribution during the early stages of its development. The close professional and personal connections between those involved in designing, developing, testing, and preparing for manufacturing, with extensive knowledge sharing, greatly assisted concurrency and facilitated the speed of development of the vaccine.

The speed with which the UK regulator approved the vaccine accelerated the rethinking of the approvals process from more sequential stages (Figure 4) to concurrent stages (Figure 5).[130]

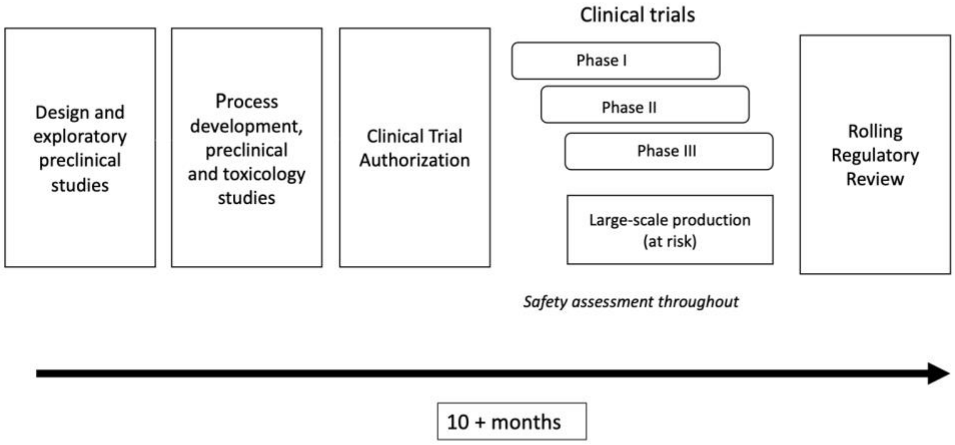
[130] https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan

Figure 4. Sequential approval process



https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan/uk-covid-19-vaccines-delivery-plan

Figure 5. Compressed approval process



https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan/uk-covid-19-vaccines-delivery-plan

A common development path for a vaccine involves movement from university research to specialist biotechnology and scientific service companies and on to large pharmaceutical companies to licence. Adrian Hill suggest the process could be compressed, with universities taking control of more of the development of the vaccine before passing it over to large manufacturers, and thereby speeding the process:

> I think, high-level, that the traditional route of academia to biotech to Big Pharma to product and licensure doesn't actually need to be followed. And in fact, I would now say that that is very much the less desirable route for vaccines for most of the world, particularly low income

> countries. I think what we have illustrated in malaria first, and then immediately afterwards in Covid-19, is that there is a new route for academics, which is to develop your own vaccine, ideally going into a phase one trial which academics can do. And then, if those results look promising, partner not with a biotech, nor found a biotech, nor knock on the door of Big Pharma who generally are half hearted at best for products that are of low value. The new route is to go directly from the university to manufacture. And as the world learned to its cost during the pandemic, most of the large vaccine manufacturers in the world are in Asia. They're in India, they're in South Korea, they are in China.

The OAZ vaccine reveals the extent of the opportunity available for universities prepared to invest and take the risk of extending their range of capabilities in broadly defined 'commercialisation' activities as a means, not only of making money, but of increasing concurrency and speed in times of pressing need.

Extraordinary decision making bodies

The vaccine experts interviewed for this report universally lauded the performance of the Vaccine Task Force during the pandemic. Key factors behind its success include its leadership, the diversity of skills and coherence of organisation of its team, its approach to risk, and its capacity to make decisions backed by the authority of the Prime Minister.[131] It brought innovation into the realm of government which rarely offers a welcome for change and risk.

Kate Bingham outlines the importance of an innovative mindset in government:

> My job as an entrepreneurial investor: Interpet incomplete and fluid scientific pre-clinical and clinical data to build plans and teams, mitigate risks, and invest to develop new drugs to save lives, protect people and meet needs of investors. This innovator mindset was critical to the success of VTF. But this mindset is not present today in the government machine.[132]

She argues the need to embed scientific thinking and specific scientific knowledge in policy making, increasing STEM skills in the civil service. She advocates that government should appoint a permanent pandemic security expert from the private sector - perhaps as minister - who convenes a team of experts to stay close to scientific developments and help predict future pandemics, works with companies and governments globally, and has a budget.

The success of the VTF offers a template for the intensification of action in response to other crises, perhaps most pressingly in the case of climate change.

Pasteur's Space

Donald Stokes' 1997 book *Basic Science and Technological Innovation*, offers the insight that research which can be distinguished as a quest for fundamental understanding or consideration for use is also combined in what he calls use-inspired basic research in 'Pasteur's Quadrant' (See Figure 6). He uses the example of Pasteur because:

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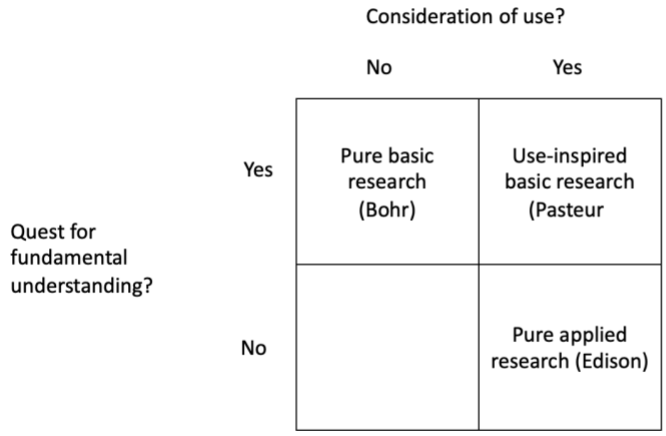
[131] It was helpful that Kate Bingham is married to a Conservative MP in a position to advise on the intricacies of UK politics and policy-making.

[132] *Romanes lecture - Kate Bingham 'Lessons from the Vaccine Taskforce'* (2021). Available at: https://www.ox.ac.uk/news/2021-11-24-another-war-coming-kate-bingham-dbe-delivers-romanes-lecture

> No one can doubt that Pasteur sought a fundamental understanding of the process of disease, and of the other microbiological processes he discovered… But there is also no doubt that he sought this understanding to reach the applied goals of preventing spoilage in vinegar, beer, wine, and milk and of conquering *flacherie* in silkworms, anthrax in sheep and cattle, cholera in chickens, and rabies in animals and humans. (Stokes, 1997:12).

Figure 6

Pasteur's Quadrant



Donald Stokes: *Basic Science and Technological Innovation*

Sarah Gilbert describes the kind of research she does and her approach to vaccine development, which resonates completely with the idea that it combines fundamental understanding and concern for use:

> We talk about translational research. So this is taking developments from early stage research through into implementation. And when we work at building a vaccine that means taking into account a lot of regulatory requirements, and also a lot of technical issues that we have to comply with. So it really requires developing a very broad overview of the field. We need to understand why we need the vaccine, who's going to use it, who's going to pay for it? How do we achieve what we want to achieve in terms of immunology and protection against disease? And then how do we comply with all the regulations around manufacturing? How do we make a vaccine that can be distributed and stored and delivered to people? And how can we do that for a price that doesn't stop it, actually, from being used?
>
> we need people trained in lots of different scientific areas, we need people who understand biochemistry and cell biology and biology and molecular biology and all of those things. So training in those disciplines is required. (But) we start from do we need a vaccine, how are we going to make a vaccine, and then start to look at what's available to do it?

Tess Lambe's research fits centrally at the interface Stokes describes:

> I seem to sit at the interface of both basic and applied science... It's unusual to get this kind of hybrid scientist, who tend to either be either very clinically focused, or basic research focused.

> And actually I think there's strengths in both and we need to ensure that they complement each other; that they speak to each other and it's not a foreign language. And that is one thing that I found when I speak to individuals who are very interested in looking at a bespoke T cell or B cell in a vaccine trial. They won't understand how to go about running a trial or how important the regulations are around that. Equally, individuals who are running trials just looking to get products to market don't understand that they have a wealth of samples that could be shared that would advance basic understanding and translational research. So I think people being at the interface, and policy encouraging those types of interactions, including interactions with industry, are hugely important.

The case of the OAZ vaccine provides the opportunity to develop the idea of Pasteur's quadrant, particularly as the context in which science is undertaken now has changed since Stokes' book 25 years ago. Stokes himself completely understood the multiple, complex and unequally paced pathways between basic and applied research and explored a more evolutionary metaphor for the relationship.

> ...it would be playful to see a double helix in the intertwined upward course of scientific understanding and technological capacity, the one-dimensional, one-way model of the link between basic research and technological innovation clearly needs to be displaced by an image that conceives of their dual, upward trajectories as interactive but semiautonomous. These trajectories are loosely coupled. Science often moves from an existing to a higher level of understanding by pure research in which technological advances play little role. Similarly, technology often moves from an existing to an improved capacity by narrowly targeted research, or by engineering or design changes, or by simply tinkering at the bench, in which fresh advances in science play little role. But each of these trajectories is at times strongly influenced by the other, and this influence can move in either direction. (Stokes, 1997:87).

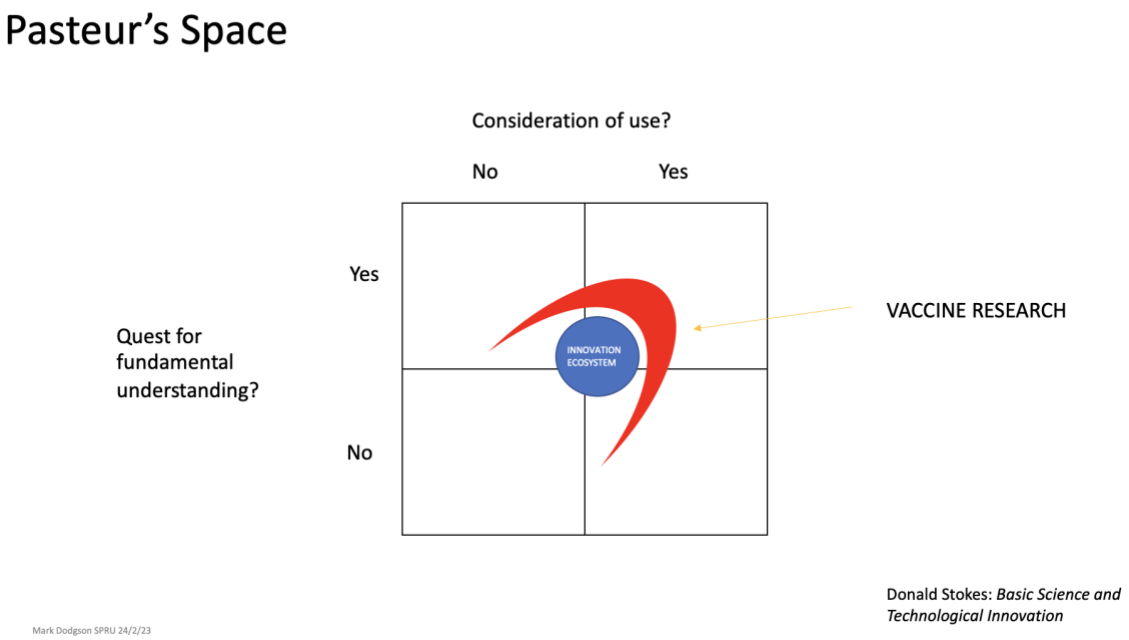
Other influential factors have added to the complexity of the connections along the research continuum of basic science to technological innovation. These now include the demand for speed in the face of existential crises, the increasing importance of eScience and AI, extensive and increasingly international collaboration in the production and use of science, including connectivity between science, technology and engineers, and greater knowledge of data processing and project management. It could also be argued that trends in policy, such as 'missions', and in management thinking, such as agility and openness, have influenced the conduct of science. Furthermore, it could be argued that public voices have become more vocal about the need for ethical research with particular concerns for sustainability.

In a sense, Pasteur's Quadrant has become a category of research, recognized by research funding bodies as 'translational research' and 'third stream', alongside traditional funding for science and higher education and business R&D and innovation. What this does not do is capture the organic and fluid connections between more fundamental and applied research, and the iterations that may occur sequentially or concurrently and can vary over time. It can imply that research is undertaken in distinctive 'quadrants' of divided parts. More useful in capturing recent changes in the context and conduct of science, and reflecting Stokes' rich appreciation of the realities of research, is the notion of Pasteur's Space. That is, it is not a category of research, in a quadrant distinct from others, but an evolutionary place where research is conducted that draws on both the 'push' of scientific advance and the 'pull' of demand in ways that may be hard to predetermine and sequence, but are necessary for it to

be successfully undertaken. It is a particularly appropriate frame of analysis for medical research.

The question arises that if the research in Pasteur's Space evolves and changes, what lies behind these dynamics? To an extent an answer lies in the innovation ecosystem to which it connects (see Figure 7). Accepting for a moment that an innovation ecosystem moves from latency to animation to intensification the interactions and iterations increasingly take place in Pasteur's Space, and while the momentum might move from the top left - pure basic - to bottom right - pure applied - quadrant, or *vice versa*, the connections to both remain important. In a sense, by linking the conduct of research with the evolution of innovation ecosystems, the connection is made between suppliers and users, science push and market pull. Concerns that more basic research is inconsequential and impractical are alleviated as business and government are partners in determining the trajectory of research. Similarly, concerns that support for business innovation is 'industrial welfare' is diminished if it is connected to public good research. The concerns of citizens about the nature and purpose of research can be reflected by engagement by NGOs and philanthropic endeavours, and those of industry through particular businesses and industry associations. The broader the coalition in the innovation ecosystem, and more active its various constituents, the greater social and political legitimacy in the research.

Figure 7. Pasteur's Space



Lessons for policy

The success of the OAZ vaccine holds many lessons for public policy for science and research, industry and innovation, and health. Key lessons can be learned about the importance of speed and risk, neither of which commonly sit comfortably with governments. Public policies tend to focus on the known and proven, with decisions made sequentially dependent on proven performance and review on previous stages before progress is permitted. In contrast the vaccine involved rapid decision making and an unusual level of risk tolerance, and we have

seen some of the factors, such as the VTF, which accelerated decision-making and assumed risk. To prepare for and deal with forthcoming crises, be they climate- or health-related, there is value in policy focusing on emergent, concurrent processes around latent capabilities. The antipathy towards 'picking winners' will need to be replaced by a policy approach of creating options and placing bets on expert partners prepared to collaborate and skilled at connecting in innovation ecosystems as a form of insurance policy. Policy targets need to extend beyond the remit of individual government departments towards the whole ecosystem, challenging and reformulating existing institutional arrangements.

Such a seachange requires more than political will, although much will depend on this, and involves a stepchange in policy making competence. As well as changes in the public service itself, involving more 'experts', especially in science and technology, in comparison to 'generalists', universities and academics have a crucial role to play. This includes encouraging more policy involvement by academics, as seen in the exemplar 'animateurs' in this study, and include the encouragement of job rotation and secondments, and, importantly, better educational programmes across the disciplines that address issues such as systems thinking, risk management, and complex project governance. The challenge for researchers is to both be highly competent in one part of the continuum from basic research to technological innovation, and also highly cognizant of and responsive to connections in that continuum. There is also a pressing need for policy makers and academics to better appreciate the challenges of private sector management, its pressures and demands, and the turbulence caused by global disruption to trading regimes and supply chains, along with the impact of new technologies.

Adding to the increasing demands on researchers is the essential requirement, in this age of misinformation and incapacity to address complexity, to become expert communicators. Amongst all the contributors to innovation ecosystems, researchers are among the most trusted. The social good objectives of Oxford's research described by its then Vice-Chancellor, Professor Louise Richardson, and the concern of the university's community not to profit from the pandemic, reveal different motives than those that can be too easily ascribed to some politicians and business people. The role some politicians played during the pandemic is questionable to say the least. The period saw reprehensible behaviour by numbers of people seeking to profit from suffering. And while the preparedness of AstraZeneca in agreeing not to profit from sales in low income nations is entirely laudable, and provides a fine example of businesses behaving responsibly and decently and delivering important social value, the high profits enjoyed by other Covid-19 vaccine producers does question their motives when it comes to addressing public health concerns.[133] In such circumstances it becomes incumbent on universities and researchers to redouble their efforts to improve their communications

[133] *How Pfizer Won the Pandemic, Reaping Outsize Profit and Influence* (2022), KFF Health News. Available from: https://kffhealthnews.org/news/article/pfizer-pandemic-vaccine-market-paxlovid-outsize-profit-influence/ and Moderna meets forecast with $18.4 billion in COVID vaccine sales in 2022 (2023) Reuters. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/moderna-generates-184-billion-covid-vaccine-sales-2022-2023-01-09/

skills, and for their funders to support them to do so. Higher education policy needs to significantly extend efforts to train future and current researchers in communications skills.[134]

The innovation ecosystems approach raises questions about the efficacy of funding that concentrates *entirely* on basic research in universities, usually in the science and higher education portfolios, and that directed *entirely* towards industrial research and innovation, usually in the industry and business portfolios: that is, in distinctive quadrants in Stokes' formulation. Such funding is essential, but so is recognition of the infusion of research problems in Pasteur's Space that cut across portfolios and departments in occasionally unpredictable iterations and timings. This requires flexibility in research funding objectives and assessments and in inter-departmental coordination. As well as funding for the 'Third Stream' or 'knowledge transfer/commercialization' or 'translational research', that is, research in Pasteur's Space, there needs to be support for the whole continuum of research, from the most basic to the most applied, that allows the mobility of objectives in Pasteur's Space as an innovation ecosystem develops and in response to a crisis. Essentially, grant-based research funding should allow the possibility for movement of objectives into Pasteur's Space in line with emerging needs and possibilities. Researcher-based funding should weight support for those comfortable traversing Pasteur's Space and engaging with the innovation ecosystem that influences its development.

A final reflection

The development of the OAZ vaccine is a story of science, government, business, and other organisations, but it is also a story of people and their individual experiences. It was a personal journey involving massive amounts of hardwork and sacrifice. John Bell says although it was:

> Tiring, exhausting and stressful, I do look back and think boy it was really remarkable to be part of that.[135]

Asked about how she coped with the pressure, the indomitable Sarah Gilbert says:

> Well, working out what the next thing to do and getting on with it. But as the team, you know, we did have a big team of people working on this, it was seven days a week for quite a long time.

Andy Pollard says:

> There wasn't an opportunity to sit back and reflect on the positive because every waking moment was so focused. So if you're going through that intense period, it's very difficult to say there was a good moment. Even when we finally got the results in November of 2020, I was up for most of the weekend, and not sleeping because we were trying to get the data, all claims that could go to the unblinded statisticians to do the analysis. This was then presented

[134] While many researchers' skill sets might not include the ability to communicate effectively and broadly, all researchers should be aware of its importance and of where best to seek advice and training on how to do it.
[135] https://podcasts.ox.ac.uk/pandemic-people-sir-john-irving-bell

> to the data safety monitoring committee, and then I went to that meeting and they told me the results. It was only if we met the criteria that I could know what the results were, otherwise we had to keep going. So then we had the results. But the next step having positive results was it had to be verified by AstraZeneca statisticians and then it was a whole series of meetings on the Sunday. And so we finally got everything sorted by Sunday night, Monday morning, and then there were radio interviews, and down to Number 10, to do the Number 10 presentation. And I said to my wife, when I got home that evening, was I coherent in what I said on the platform next to Boris (Johnson). And she said, yes, it sounded fine, because I have no idea what I said. I was so tired.

With the best of intentions, those developing the vaccine were exposed to horrendous abuse and even death threats. Scientists, most comfortable in laboratories, quickly had to adjust to being expert communicators in the world's media; media that could be hostile and misinformed, and in all cases struggled with issues of any complexity. In interviews, key respondents were asked about their highlights and lowlights during the pandemic. Dealing with the media was universally the lowlight. Even the vastly experienced and media-savvy John Bell says the negativity and hostility to the vaccine was a huge surprise. Andy Pollard, with his passionate dedication to public health, says his highlight was cycling to work in empty streets: the information about the need for isolation had worked and he knew that this would save lives. Sarah Gilbert's highlight was receipt of the vaccine effectiveness data on the 1st March 2021, which showed that the first dose of the vaccine was keeping 80 year olds out of hospital and stopping 70 year olds from becoming infected:

> We've made a vaccine that was being used and it was actually making a difference.

For Tess Lambe it was walking home after the first dose of the vaccine was injected into the first volunteer. She says she was weeping, knowing that:

> What the team had achieved might mean we were one step closer to helping keep people safe.

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Appendix 1: The manufacturing process

Oxford/AstraZeneca vaccine manufacturing process

AstraZeneca is supported by manufacturing capacity in 15 countries, across 25 different manufacturing sites and more than 20 analytical testing sites. Mass supply is achieved by developing an optimised, repeatable and scalable manufacturing process – which can be transferred to contract manufacturers – and building an extensive analytical network.

Stages 1-4 take about 60 days

1. Cell infection
Adenovirus vector is engineered from adenovirus DNA by removing essential genes to stop it being able to replicate. The coronavirus spike protein DNA is added to create the full genetic sequence for the adenoviral vector vaccine.

The genetic code is introduced into living 'producer cells' derived from a human cell line, created more than 50 years ago. It is transcribed and translated using the cells' machinery to form identical copies of the COVID-19 adenoviral vector vaccine.

2. Cell growth
As the cells grow and multiply, they are moved to bioreactors of increasing size. Conditions, including pH and temperature, are tightly controlled to ensure growth occurs at an optimal rate.

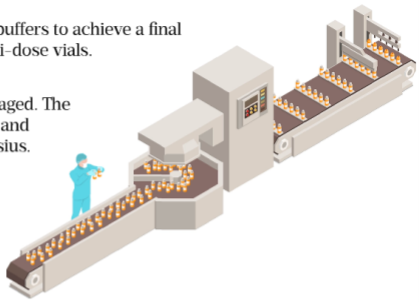
3. Harvesting
A chemical is added to lyse the cells, bursting them open, and the vector vaccine is harvested.

4. Purification
The vector vaccine is then further tested, filtered and purified (at this stage, some of the sample can also be removed to create another batch of vector vaccine working stock).

Stages 5–6 take 30–60 days

5. Fill and finish
The vaccine is combined with buffers to achieve a final formulation and filled into multi-dose vials.

6. Labelling and packaging
The vials are labelled and packaged. The finished drug product is stored and transported at 2–8 degrees Celsius.



Stages 7–9 take 7–14 days

7. Testing and quality control
Testing is completed (over the whole manufacturing process, more than 60 tests per batch are conducted to ensure safety, purity and efficacy).

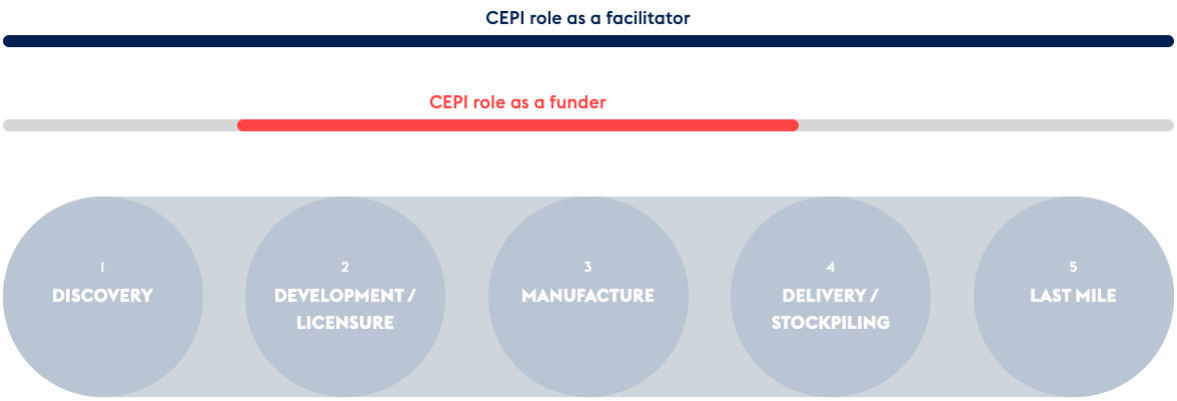
8. Regulatory release
Documentation and batch records are submitted and reviewed by regulators, and release is authorised.

9. Distribution
Vaccine is shipped to distribution hubs across the globe, where governments and multinational organisations take ownership and organise further distribution.

Total time: 97 to 134 days

Source: AstraZeneca

Appendix 2: CEPI



Academia	Industry	Industry	GAVI	Countries
Governments	Governments	BARDA	UNICEF	WHO
Wellcome Trust	Regulators	CMOs	PAHO	UNICEF
NIH	Wellcome Trust	Regulators	Governments	Responding
IMI	NIH	Governments	WHO	Organisations (eg,
GLOPID-R	EC	WHO	Industry	MSF)
Industry	IMI	GHIF	Pandemic Emergency	
Regulators	BMGF		Facility (World Bank)	
Biotech	BARDA/DTRA etc.		WHO Contingency	
	WHO		Fund	
	Biotech			
	PDPs			

BARDA:	Biomedical Advanced Research and Development Authority	GLOPID-R:	Global Research Collaboration for Infectious Disease Preparedness
CMOs:	Contract Manufacturing Organisations	IMI:	Innovative Medicines Initiative
DTRA:	Defense Threat Reduction Agency	MSF:	Médecins Sans Frontières
EC:	European Commission	NIH:	National Institutes of Health
GAVI:	Global Alliance for Vaccines and Immunisation	PAHO:	Pan American Health Organization
GHIF:	Global Health Investment Fund	PDPs:	Product Development Partnerships
		UNICEF:	United Nations Children's Fund
		WHO:	World Health Organisation

List of Figures:

Glossary

BIA - BioIndustry Association
CBF - Clinical Manufacturing Facility
CEPI - Coalition for Epidemic Preparedness Innovations
COVAX - COVID-19 Vaccines Global Access
EMA - European Medicines Agency
FDA - Food and Drugs Administration
Gavi - Vaccines Alliance
GMP - Good Manufacturing Practice
JCVI - Joint Committee on Vaccination and Immunisation
MHRA - Medicines and Healthcare products Regulatory Agency
mRNA - messenger RNA
NIAID - National Institute of Allergy and Infectious Diseases
SAGE - Scientific Advisory Group for Emergencies
SII - Serum Institute of India
VTF - Vaccine Task Force
UKRI - UK Research and Innovation
VMIC - Vaccine Manufacturing and Innovation Centre
WHO - World Health Organization