Witness Name: Sir Andrew Pollard
Statement No.:
Exhibits:
Dated: 5/10/2024

UK COVID-19 INQUIRY

WITNESS STATEMENT OF Professor Sir Andrew Pollard

I, Andrew Pollard, will say as follows: -

Overview of my role at Oxford University, including in relation to the Oxford Vaccine

1. I am the Ashall Professor of Infection and Immunity in the Department of Paediatrics and the Pandemic Sciences Institute and Director of the Oxford Vaccine Group in the Department of Paediatrics at the University of Oxford, and a Consultant Paediatrician at Oxford Children's Hospital. I have been in a senior academic and clinical position in Oxford since 2001. The Oxford Vaccine Group is a research group in the University Department of Paediatrics with ~200 staff and students investigating immunity and the vaccine design, development, testing and evaluation. Over the past 23 years I have led studies on immunity, and development and/or evaluation of vaccines against meningitis, pneumonia, typhoid, paratyphoid, influenza, hepatitis B, (pandemic) influenza, Ebola, RSV, rabies, plague, Q fever and COVID19.

2. In these programmes my research has included understanding immunity in children and various stages of vaccine development from design in the laboratory and preclinical testing, through manufacturing to clinical trials in humans and testing of immunity in the laboratory, and epidemiology of infectious disease. My main area of research has been in bacterial vaccines and particularly vaccines

that protect children against life-threatening and serious bacterial infections such as various types of meningitis, pneumonia and typhoid/paratyphoid, with a particular interest in the immunology of B cells (which make antibodies). I have also led programmes on germs that cause outbreak diseases including plague (the cause of the black death), Coxiella (the cause of Q fever), and the viruses Ebola and pandemic influenza. I led the clinical development of the Oxford AstraZeneca COVID19 vaccine in the pandemic. I have worked on new vaccines which we have developed in my laboratory as well as collaborations with academics, biotechnology companies and industrial vaccine developers to enhance understanding of how vaccines work and to accelerate development of life-saving vaccines. In addition to research in the UK, I have also conducted disease surveillance in South Asia and vaccine testing in Asia, Africa and Latin America.

3. I have been chair of the Department of Health and Social Care's (DHSC) Joint Committee on Vaccination and Immunisation (JCVI) since 2013 and my current extended term in office ends in Q4 2026. I held roles at the World Health Organizations SAGE (vaccine policy committee) for 6 years (2 terms) until 2022 and was chair of the European Medicines Agency Scientific Advisory Group on vaccines 2012-2020 (the role was terminated on the eve of Brexit). I did not chair or participate in the COVID19 JCVI committee during the pandemic as I led the clinical development of the Oxford-AstraZeneca vaccine, but have continued to chair JCVI with regard to all other vaccines. The work of JCVI on COVID19 has been incorporated into the main work of JCVI during 2024. At WHO I was a member of working groups on HPV (cervical cancer) vaccines, and chair of the influenza and pneumonia vaccines working groups.

4. I first became involved in discussions about the novel coronavirus that had been detected in Wuhan when I was contacted by Sir Jeremy Farrar on 25th January 2020, who asked for advice about clinical trials of a potential new vaccine being developed in the USA. The following day these discussions looped in Dame Sarah Gilbert who was already working on a coronavirus vaccine using the Oxford vaccine platform, Chadox1, and I worked with Sarah from that point, initially on a funding proposal with Oxford colleagues and plans for clinical trials

over the next month, while the preclinical vaccine development work was continuing.

The Ministers, Special Advisors, Senior Civil Servants and other key UK Government and non-Government bodies and individuals.

5. My main *initial* interaction with the UK Government was with Sir Patrick Vallance starting in early March 2020 and then I provided regular ad hoc updates to him, and also interacted with him in meetings in his role as Chief Scientist and during the foundation of the Vaccine Taskforce until Dame Kate Bingham took over. As the clinical development of the Oxford Vaccine progressed, these update meetings also included the CMO and DCMO, Sir Chris Whitty and Sir Jonathan Van Tam as we (Oxford) progressed closer to having a product that could be potentially deployed by the NHS. These meetings were for information sharing of trial progress and the latest trial results and were not formally minuted. The CSA, CMO and DCMO were readily available for discussion and updates throughout 2020 and 2021 providing a conduit into Government of information on our vaccine development progress so that they had real time information. In my view, the immediacy of availability of the chief scientist and chief medical officer in Government was exceptional and provided a remarkable and critical connection to provide information on the latest developments from Oxford and the UK scientific community more widely during the pandemic. The fact that they brought together their own expertise from medicine, epidemiology, basic science and industry meant that the UK had the best possible group of individuals leading our science in Government in the pandemic. This was very good luck for the UK in a pandemic and it could have been very different. It will not be possible to have the perfect range of skills and knowledge among science advisers for every crisis and so the network of the chief scientists to access the necessary expertise outside of Government is a key part of resilience and a system to appoint relevant external experts may be needed if that expertise is not present in Government.

6. There were regular interactions with Dame Kate Bingham and later Dr Clive Dix during 2020/21. Dame Kate was always available for a discussion about UK and international clinical trial logistics, funding, and advice on interactions with other countries and organisations. I met with her frequently, to share the latest information on our vaccine development programme. These were informal meetings and not minuted by me. Her vision for VTF was critical for the UK and the systems she put in place to ensure delivery of the programme must be carefully analysed as a blueprint on how to defend against such a threat in the future. Key aspects that made the VTF a success are independence from the political and bureaucratic processes of Government, which was critical for important decision-making and the non-political appointment of an exceptional technical team which made it possible to gather intelligence about products in development and make critical and timely technical decisions (i.e. was the science right, could the product be manufactured, was it scalable?) and then contract with enough developers that there would be access to doses even if multiple products failed (as would normally be expected).

7. There were no regular interactions with Ministers. Dame Sarah Gilbert and I met with Matt Hancock MP in a zoom call on 19th April 2020 to briefly discuss upcoming plans for the trials (which started that week) and he offered to assist with provision of PPE, which we were not able to source for the clinical trial facility in Oxford (required to protect staff and the public during delivery of the trials). He asked the CEO of our local hospital trust, Dr Bruno Holthoff, to help. With Bruno's assistance we partnered with the Oxford University Hospitals (OUH) throughout 2020 on various logistical aspects, sharing of research staff and OUH was instrumental in supporting our efforts.

8. The vaccine team had a short briefing with the Prime Minister, Mr Boris Johnson when he came to Oxford on 18th September 2020, and I spoke with Mr Hancock when he visited the Oxford Vaccine Centre on 2nd June 2021. To my recollection, Mr Sharma MP attended some discussions with BEIS where I was updating officials on the clinical trials of the Oxford Vaccine, although I don't have a record of those interactions. Sir Keir Starmer visited the Oxford Vaccine Centre on 16th November 2020 and I spoke with Sir Keir on 19th March 2021 on zoom about the

vaccine roll out. I attended and presented at a Downing Street briefing on 23rd November 2020 when the interim results about the vaccine were available, which included Sir Chris Whitty and the Prime Minister (who joined on screen from another room as he had COVID at the time).

9. Interactions with Government officials included BEIS (finance for clinical trials as host of VTF and latterly regular briefings about vaccine deployment), OLS (assistance with making packs for home-swabbing of trial volunteers and PCR testing of trial volunteers using the lighthouse laboratories), DHSC (some funding discussions and various requests for information from DSHC Comms).

10. I gave evidence to parliamentary committees during the pandemic including:

Science and Technology Committee 26th October 2021
Science and Technology Committee 16th June 2021
Science and Technology Committee 4th November 2020
Science and Technology Committee 25th March 2020

I also gave evidence to various All-Party parliamentary group meetings but I am unable to find published minutes of these meetings. These were often reported in the media.

11. I had very frequent meetings with colleagues in AstraZeneca (AZ) from May 2020 with calls several times every week and often on most days of the week. These were both with the vaccine researchers at AZ as well as the senior management including the CEO, Sir Pascal Soriot. Dr Tonya Villafana (based in the USA) was the scientific lead with whom I had the most interactions in 2020/21 but Dr Justin Green (based in the UK) later became the main contact for the vaccine. Some reflections on those interactions are in a podcast with Sir Pascal which is available on Oxford University podcasts website "The Oxford Colloquy, Pandemic People". In that discussion, Sir Pascal reflects on the decision at AZ to team up with Oxford and the success of the partnership in having substantial impact in the pandemic and saving many lives.

12. There was also a joint oversight group which included representatives from AZ, Oxford and DHSC represented by the DCMO which met regularly to monitor the Oxford-AstraZeneca partnership through vaccine development, upscaling of manufacturing and then continued for briefing on progress with the global roll out and various booster studies.

13. Although I recused myself from the JCVI COVID19 committee and did not attend the committee as a member, I was asked to present data from the Oxford-AstraZeneca COVID19 clinical trials to the committee in 2020 and 2021 as a vaccine developer. Those should be represented in the JCVI COVID19 committee meetings and may form JCVI evidence to the Inquiry.

14. The MHRA, as the UK regulator, reviewed applications for each of the clinical trials undertaken in the UK and approved both the trial protocol and manufacturing plans at each step. They provided a very rapid review service with the review for the phase I study completed in just 7 days. There were subsequently multiple amendments to protocols and manufacturing changes as the trials progressed and MHRA were highly responsive to ensure that they provided rapid but high-quality input and revisions to the vaccine development programme. There were also points of contact for the vaccine development programme covering preclinical studies, manufacturing and the clinical aspects who made themselves available for discussions at short notice as the trial progressed and ensured that when decision points were reached the MHRA was already fully briefed for rapid reaction. At the end of 2020, the MHRA initiated a rolling review of the vaccine manufacturing and trial data which meant that the usual long delay from submission to approval was circumvented as much of the information had already been reviewed prior to the final submission of documents. The process for reviewing the vaccine development programme and finally approving use of the vaccine at the end of 2020 was exceptional and difficult to see how it could have been more responsive, high quality and capable.

15. Regulatory criteria for measurement of efficacy for the pandemic vaccines was stringent. By this I mean the statistical certainty on the efficacy measurement which vaccines have to meet for approval. “Confidence intervals” are used to

provide more confidence in the efficacy estimate. So, for example, a vaccine with a measured vaccine efficacy of 50% with a lower bound of the confidence interval of 30% is considered very likely to have a true vaccine efficacy of over 30%, giving some confidence that the measured VE is likely to be beneficial. To provide this level of confidence the number of cases accumulating in a clinical trial has to be higher than if the lower bound of the confidence interval was, say 10%. This might be considered important where a vaccine is to be given to millions of people and the risk to any one individual is low, but it also means that more cases have to accumulate and there is therefore a delay before the vaccine can be approved. In 2020, ~10,000 people were dying globally every day and so any delay meant a delay in availability of life saving vaccines. Given the pandemic experience it will be important for regulators to debate these issues prior to the next pandemic. What if the pandemic had killed 10% or 20% of people instead of <1%, how certain would we need to be on the point estimate of the vaccine efficacy for regulatory approval? Would we be content with any vaccine that provided some protection (say only 30%) even if that protection was less than ideal but the alternative was very high mortality, where a vaccine might save 1 in 3 lives? Or if the point estimate of efficacy was 50% (half of lives saved) could we live with some uncertainty about the efficacy and accept a lower bound of the confidence interval above 0-10%, which would mean that we would have less confidence that the true efficacy was 50% but that it would likely by of some benefit. We do have malaria vaccines licensed with low efficacy because the benefits of low efficacy where many children become seriously ill remains positive in terms of cases prevented and lives saved. Furthermore, we need to have standing views from regulators about how best to manage a high mortality pandemic, for example one in which mortality is 30%. In this situation where up to 1 in 3 people are dying, should we wait for clinical trials before licensing, or would it be better just to roll out a promising vaccine technology and have rigorous plans in place to observe whether it works in an observational study rather than spend time on prelicensure trials – what would be the regulatory framework for such an approach? It is essential that regulators consider a wide-range of the potential scenarios so that these decisions are not being made in the face of a serious threat but the rules are already known by developers in advance. To my knowledge no such plans are in place today.

This is especially important since the major vaccine developers consider pandemic vaccines too high risk, and did not develop vaccines for the pandemic.

16. The MHRA undertook routine inspections of the conduct and quality of clinical trials of the Oxford-AZ vaccine on two occasions during 2020 to ensure that the studies were being conducted appropriately and compliant with regulation and advice. Other regulators also undertook compliance reviews of our work. This is an important regulatory function to check that the data being produced in clinical trials are reliable, but in a pandemic this is a very time-consuming for developers. If regulators worked together and had agreements in place, then this function could perhaps be done only by one regulator rather than the burden of multiple inspections by different regulators being placed on developers in a pandemic.

17. All stages of the vaccine development process required ethical approval and this was coordinated in the UK by the National Research Ethics Service at the Health Research Authority. The ethics application for our phase I trial was submitted on 13 March 2020 and the Berkshire research ethics committee met on 17th March and reviewed the application and asked me and my team to attend and respond to questions – this expedited review took only 4 days from submission to approval. This was the pattern for the whole programme with a very responsive team at HRA and an engaged independent ethics committee with insightful comments and rapid turnaround that allowed development to continue with high quality ethical review and without bureaucratic delays. Ethical review can cause delays in vaccine development because a new application may take a month or two from submission to a final decision being made at routine meetings. The rapid turnaround in the pandemic shows how the system can be geared up to respond in a crisis. We experienced similar expedited review in the trials undertaken in Oxford of Ebola vaccines (responding to the West African Ebola outbreak) and also in 2009 in the swine influenza pandemic, indicating that a system is already baked-in for rapid review in an emergency. It is important to note that the reviews did not cut corners and the panel was as a stringent as we experience in peacetime, the main difference being that the panel was immediately available rather than working to a fixed timetable.

The individuals within Oxford University who were the key decision makers in respect of the development of the Oxford-AstraZeneca vaccine.

18. The leads on preclinical development, manufacturing and initial funding for the Oxford-AstraZeneca vaccine was Dame Sarah Gilbert from January 2020. Sir John Bell represented the University in developing the agreement with AZ at record speed in April/May 2020. Subsequently, From March 2020, I was the lead for the clinical trials and Oxford lead for licensure (with AZ) of the vaccine. A very large number of individuals played pivotal roles across the University in the vaccine development including many senior, academic and administrative staff. It is noteworthy that the many support staff in the University who were essential to the operation of the research including Academic Department Administrative staff, the research governance team, research contracts team, legal team and the buildings staff & cleaners who ensured that the facilities kept operating during the pandemic and the staff working in the clinical and laboratory facilities were kept safe.

Structures and processes (e.g. sub-committees, working groups, specialist bodies and other decision making bodies, whether formal or informal) in which the individuals referred to in subparagraphs (b)-(c) operated insofar as they are relevant to the development of the Oxford-AstraZeneca vaccine.

19. This is covered in the description above.

How the relationships referred to above operated in practice, including any challenges presented by such relationships.

20. There was a very good working relationship with the vaccine scientists, data managers and statisticians in AstraZeneca who formed a very strong collaboration with the Oxford team to achieve the common goal. There were

inevitably some differences in approach between academia and industry but the regular opportunities for dialogue described above and shared mission meant that this could be overcome and the joint mission of the two organisations was clear and allowed critical alignment throughout the development programme.

21. There was a very good working relationship with the VTF and with the CMO/CSA which meant that there was good engagement with flow of information necessary for decision-making. The DCMO represented DHSC on the oversight group for the AZ-Oxford partnership which further ensured a close understanding of the vaccine development progress, recruitment and challenges.

22. As described above the MHRA and HRA/ethics committee were very responsive and supportive of the vaccine development programme.

Preparedness to develop vaccines

The preparedness of the UK for the rapid development of a 'Disease X' vaccine in early 2020.

23. By Disease X, we mean a new virus or bacterial infection which has not been anticipated and for which we have no current vaccine development programme. To be prepared for disease X it is important to have available platform technologies (such as mRNA, viral vector vaccines and inactivated vaccine capability). But we also need to build understanding of how to make vaccines against a range of viruses so that the rules for how to approach a disease X are better understood. So this question should also be extended to diseases which we do know but don't have a licensed vaccine. In early 2020, we were not well-prepared to make vaccines for disease X or even a coronavirus (as is obvious because only Oxford made a vaccine in the UK, and if this hadn't worked, which was entirely possible, billions of fewer doses would have been available globally). Nevertheless, we were better prepared than we would have been if the pandemic had happened 5 years earlier. I discuss below the key elements that made it possible to make the Oxford vaccine and how these to a large extent are good fortune.

24. Although we have a much clearer understanding and knowledge in individuals and institutions about what is needed, which means that we are to some extent in a better position today, there is no clear plan about how to maintain this expertise and institutional focus on preparedness. I do not think the UK is yet "well prepared" for rapid development of a Disease X vaccine or many other known potential threats, but we do have more knowledge about how we could do better.

25. Preparedness would mean that we were investing, in response to the recent pandemic, extensively in the infrastructure and people who we would need in post to respond to a future pandemic. The main vaccine development Government funding pot for outbreak vaccine development from the UK vaccines network, chaired by Sir Chris Whitty, had funding in 2015 for a 5 year period and this pot has been recently renewed. This research is critical to ensure that disease X preparedness is in place. Funding is needed so that scientists have done the necessary and laborious homework to examine the genetic code of a wide variety of viruses, to test vaccines made from components of the virus and to then have a good idea which bits of the virus or bacterium to include if any one of them emerges or in a disease X vaccine. At this stage we do have this information for some viruses – for example, we would be in a strong position to make a vaccine for a completely new coronavirus or influenza virus but there are other families of viruses for which we do not yet know what rules to apply in designing the vaccine. It is also important to note that it is not certain that we will ever be in a position to make a vaccine for some Disease Xs that appear - there are viruses, like HIV, which has been extensively studied for the past 40 years with huge investment and yet we still do not have a vaccine because the virus continues to be very tricky. As history has shown, infectious diseases are capable of wiping out large numbers of people and yet we spend a trivial annual budget on research and development to defend our community against these microbial threats. We also do not have sufficient investment in routine immunisation services to maintain high vaccine coverage and access to and confidence in vaccines in peacetime, that would make uptake better in a pandemic. We need to understand how to reach the unreached communities when there is no pandemic, so that we know they can be protected in a

pandemic. We spend up to 54 billion each year on defence against future military threats (according to the Government website) as military conflict is seen as more likely than the existential threat of infection. A very small fraction of this is spent on microbial threats. The US approach may have some merit in considering the microbial world as a (bio)defence issue. There is considerable funding in the USA for vaccines stockpiles, for vaccine research centres and a vaccine clinical trial networks.

26. While we do have some ideas for many known families of viruses, we know less about most bacteria and almost nothing about fungi. This raises a significant issue about the investment and scientific capacity and capability in these fields.

27. Investment in a manufacturing facility is needed to ensure that rapid development can proceed in a future pandemic (the plans for the Vaccine Manufacturing Innovation Centre, VMIC, were shelved) which would mitigate some of the difficulties in 2020 in vaccine development. Small facilities like the clinical manufacturing facility in Oxford are ideal to get vaccines made and into the first clinical trial but are not sufficient for larger scale trials or commercial production. Today (as I write in October 2024, our manufacturing facility is overstretched with projects on vaccines against viruses and cancer and we have long waiting lists – in my view VMIC could have filled some of this gap in capability for small to medium scale production and allowed more rapid innovation in vaccines in the UK post-pandemic. However, I was not involved in the decision to shelve VMIC and cannot comment on the rationale.

28. Once developed, limited on-shore capacity for vaccine production and the fill-finish capability (putting doses in the glass vials) remains a risk. It is also important to note that the expertise in manufacturing with different vaccine platforms is very limited in the UK as a result of the limited commercial manufacturing onshore. There is some contract manufacturing available in the UK.

29. On a more positive note, the strategic partnership between CEPI (the coalition for epidemic preparedness and innovation) and Oxford University, and CEPI's

funding of other research activities in the UK and elsewhere provides some of the funding to begin to tackle the many outstanding questions about how to make vaccines for different virus families and how different platform technologies might perform with each of them. However, there is so much to do and very few programmes initiated, that we are really not prepared for the majority of possible scenarios. CEPI does receive some funding from the UK Government and from the Wellcome Trust.

30. Another important positive is the partnership between the UK Government and Moderna which means that there will be a research and development laboratory in Harwell in Oxfordshire and also a large-scale mRNA manufacturing facility. This is an important development from the perspective of preparedness as it means that there will be onshore manufacturing at scale using a platform technology that can be produced very quickly for clinical trials and is also more straightforward to scale up than traditional vaccine platforms. This is a major boost to preparedness in the manufacturing capability, assuming the research is in place to make a vaccine against Disease X in the first place. Moderna also has put in place an mRNA access programme with Oxford University which means that researchers can develop vaccines in Oxford using Moderna's technology. However, there is no big pharma manufacturing available in the UK using other vaccine platforms (except for the live attenuated influenza vaccines) and so we do not have capability if mRNA turns out to be the wrong platform for a particular disease.

31. There has been a temptation to say "the Americans are already working on vaccines for "x" and so we should invest elsewhere. One lesson from the pandemic is that we can't rely on others to share and that multiple attempts to hit the target are needed to increase the chance of success of at least one of them.

32. Internationally similar conversations are happening about preparedness and how we might try to research solutions for the huge number of known (and unknown) microbial threats out there. There is a need for these efforts to be better coordinated so that we learn in real time from the experience of other vaccine developers around the world, especially the work in industry. On the other hand,

many vaccines in development don't make it and one potential risk is if the UK decides to leave some diseases to others, we may end up with no hits on target. In the pandemic there were around 350 vaccines that were being developed but only ~8 were eventually approved for global use by the WHO. Here in the UK, there were only 3 vaccines available in time for the 2021 roll out, with most doses being the Oxford-AZ and Pfizer-BionTech vaccines, this is a stark reminder that multiple efforts are needed to be sure of having a product and a strong endorsement of the approach taken in the pandemic by the VTF and especially Dame Kate Bingham. Here it is important to note that the timeliness of vaccines is critical (see the 100 day mission form the G7) – there is little impact from a vaccine being available late when all those who are susceptible to the disease have already died. Globally the Oxford-AZ and Pfizer vaccines were the most widely used in 2021 and prevented the most deaths because they were available early and were produced at huge scale.

Lessons learned from vaccine development during the MERS, SARS-CoV-1, Ebola, Nipah and other epidemics, and previous pandemics of influenza and HIV.

33. Prior global efforts to develop vaccines against serious infections caused by coronaviruses (SARS-COV-1 and MERS) had resulted in extensive testing of coronavirus vaccines in animals in the 20 years before the pandemic and this had produced a lot of information about the potential component of the virus which could be made into a protective vaccine – the spike protein. This work in Oxford was led by Dame Sarah Gilbert. The global work had provided a strong basis for the selection of vaccines which induced both T cells and antibodies and for this reason favoured use of viral vector vaccines as a platform technology, which was the technology most tested in Oxford prior to 2020. In some of the animal studies with coronaviruses in the 2 decades prior to the pandemic, vaccines which were developed by scientists around the world (and tested in animals) that did not produce a balanced antibody and T cell response appeared to put some animals at risk of enhanced disease (i.e. the animals had more abnormal pathology once exposed to the virus if they had been vaccinated). As it

turned out this was not the case for SARS-CoV-2 vaccines but this potential concern was very carefully monitored when the first vaccines were rolled out, and scientists were especially concerned about the inactivated vaccines, and potentially protein vaccines, which were considered more likely to stimulate such aberrant immunes responses…..but didn't. This potential issue was discussed extensively in early 2020 and a report of these considerations which I helped prepare are published (AP1 - INQ000485225). This issue highlights the importance of research to examine both safety and protective efficacy of vaccines so that potential risks and the components needed for protection are known and managed long before the new pandemic virus arrives. Of course, small scale animal or human studies are insufficient to identify very rare side effects.

34. Extensive work has been undertaken in Oxford in response to Ebola and influenza outbreaks and this is discussed later in this report. In these cases, the vaccines had been designed and tested in animals initially by commercial partners and in Oxford, our role across several different scientific teams had been clinical development and studying the immune response. The capabilities in the laboratory evaluation of vaccines in Oxford has been built over the past 3 decades because of ongoing work investigating non-pandemic vaccines so that all the skills to study immunity were in place in 2020. One important part of the work on these outbreaks in the 15 years prior to 2020 was building of knowledge about how to rapidly scale up operations to deliver the logistics of rapid clinical trials, which was then applied in 2020. It also tested the system for rapid regulatory review (MHRA), and ethical review to ensure that development continued at pace, all good preparation for the pandemic. As a side note, there was a pause in one of the Ebola studies (a vaccine from Johnson and Johnson) during the West African outbreak, which was undertaken while a potential safety signal was evaluated by the company, independent experts and the regulators. This is mentioned here as it is a reminder that this is a standard procedure that occurs in clinical trials, and is discussed further below. The Ebola study did restart here in the UK after this evaluation and the vaccine is now licensed.

35. Today, there are vaccines in development in Oxford against different strains of Ebola and one of these was rapidly developed in the recent Sudan strain Ebola outbreak (2022) and manufactured in partnership with Serum Institute of India for delivery to Uganda in record time (programme led by Professor Teresa Lambe). This work builds on the experience of investigators in Oxford working on Ebola outbreaks and on the COVID 19 response.

36. There are a wide range of vaccine development programmes in Oxford which target most of the viruses and bacteria on the Governments list (AP2 - INQ000484809) of outbreak threats – the Government list is shown below and those with active programmes in Oxford are highlighted in red. The work on these vaccines expands our knowledge on both the design of vaccines for protection of humans and also the way in which our immune systems work to protect us from these infections, laying important scientific knowledge to frame how best to tackle disease X in the future.

Priority pathogen list: viruses

Priority families : Exemplar pathogens

Arenaviridae: Lassa fever virus
Coronaviridae: Middle East respiratory syndrome (MERS)
Filoviridae: Marburg virus, Sudan ebolavirus
Flaviridae: Zika virus
Hantaviridae: Hantaan virus
Nairoviridae: Crimean Congo Hemorrhagic Fever (CCHF) virus
Paramyxoviridae: Nipah virus
Phenuiviridae: Rift Valley Fever (RVF) virus; Dabie bandavirus (formerly severe fever with thombocytopenia syndrome virus)
Picornaviridae: Enterovirus 68
Togaviridae: Chikungunya virus

Priority pathogen list: bacteria

Priority families: Exemplar pathogens

Coxiellaceae: Q fever (Coxiella burnetii)

Yersiniaceae: Plague (Yersinia pestis)

Explanation of the role of 'platform technology' in the development of new vaccines. The Oxford-AstraZeneca vaccine

37. In retrospect it is quite extraordinary that Oxford University was able to develop a coronavirus vaccine (with AstraZeneca) that was deployed at scale with more than 3 billion doses distributed. No other University in the world was able to do this and it is not clear that it would have been possible anywhere in the UK in previous decades (including Oxford), which of course also means that it is unclear whether this will be possible in the future without careful planning to sustain the vaccine ecosystem in academia and industry in the UK. The answer is that the pandemic happened at the right moment in history when a series of critical building blocks were in place that meant that the personalities, capacity, skills, know-how and infrastructure, and an enabling environment in the University were all in place at the same time.

38. Academics in the University system are driven by their interest in science varying from chemical processes in biology to the structure of molecules or cells to the interactions of the immune system with bacteria and viruses. Others work more in the translational space, taking new vaccines or treatments from the laboratory into human testing, which requires a group of experts in manufacturing (as rightly putting vaccines or drugs into people is tightly regulated) to make the product that is going to be tested. The academics who lead vaccine programmes will often have skills that span all of these fields or may work together in small teams to ensure that they can get from the discovery of a new vaccine to its testing in people. However, this all depends on funding and this has to be obtained from Government (such as MRC, Innovate UK or NIHR) or non-Governmental funders such as Wellcome Trust, Bill & Melinda Gates Foundation or the Coalition for Epidemic Preparedness and Innovation; or from industrial partners. Because the grant applications to get the money for research from these funders are laborious and are often unsuccessful, academics have to be highly motivated or

passionate about the disease area or question that they wish to work on. And very persistent. So, for example, I have focussed for much of my career on vaccines for bacteria which cause serious infections or death in young children because I have seen so many awful cases in my clinical practice that I am driven to fight against these germs, particularly various types of meningitis, pneumonia and typhoid/paratyphoid. In Oxford across several Departments in the medical school we have a large number of vaccine scientists working in this way on their areas of interest, eg coronavirus, lassa and influenza (Gilbert), malaria (Hill, Draper), typhoid/meningitis/pneumonia (Pollard), Barnes (Hepatitis C), Lambe (Junin, Ebola, Marburg, Congo Crimean Haemorrhagic Fever), melioidosis (Dunachie), rabies (Douglas), HIV (Hanke), Green (Manufacturing). While around 400 scientists were working on vaccine programmes separately in Oxford at the beginning of 2020, there were nevertheless a number of interdependencies which have allowed this to happen with shared space, equipment and access to some core facilities, but these programmes largely operated separately. Note that all of this depends entirely on the ability of the academics in post to competitively obtain funding from Governmental, NGO or from industrial funders. Funders therefore determine whether or not investment in vaccines is a priority and then academics have to fight for this funding, often competing against funding for other health priorities (diabetes, cancer etc).

39. Because there are so many vaccine programmes in Oxford driven by investigators working with their own teams on their own diseases of interest across several departments, there was huge capacity and a skilled and experienced workforce who could be brought together in the face of a pandemic. A key decision in February 2020 was to break down the normal silos of the disease-specific teams among many Oxford research groups and departments and form into new teams with clear leadership covering different aspects of the development pathway, e.g. I was the lead investigator for the global clinical trials with my clinical team made up from clinical trial staff from across the different vaccine research groups in Oxford, and also incorporated research staff redeployed from our local NHS hospitals into the effort. Within teams that were formed, there was expertise in the animal studies (which could be run rapidly to provide evidence to support the clinical trials in April 2020)l; the clinical staff

could organise the logistics for a socially-distanced safe clinical trial environment in lock-down and run a trial with up to 250 people vaccinated in Oxford per day; there was a manufacturing team who could provide the doses for use in human studies; and there were staff who could run laboratory assays at large scale to evaluate the vaccine immune responses.

40. One example on the clinical side which shows the importance of pre-pandemic activity: we had been running very large scale international trials on typhoid vaccines (~100,000 children were recruited in 207/18 into a trial in South Asia) which meant that as 2020 dawned we had staff in place with expertise to deliver clinical trials with collaborators in other countries, including a good understanding of the complex logistics and various practical and international regulatory barriers to doing so, which was critical in the pandemic. Without this human capital, critical mass and know-how, it would not have been possible for a group of academics to develop the Oxford-AZ vaccine, even if the science was there.

41. Of course, not all of the vaccine clinical trial activity was in Oxford. Trial sites across the NHS, in universities and hospitals in Brazil and South Africa all contributed to the development work, involving several thousand researchers. To have these networks available for use in future pandemics requires that they are active between pandemics to ensure that the skills and quality is in place and ready to get into action when a pandemic strikes. Initiatives at CEPI and the Bill & Melinda Gates Foundation are currently considering how best to support this. Trial sites have to be doing something, "to be kept warm", in peace time to build expertise and experience for a pandemic.

42. Even though various different types of vaccines were developed around the world, the vaccine platform also proved to be critical when it came to scale up and deployment. When billions of doses are needed quickly, the trials have to go fast but the biggest hurdle is often manufacturing scale up. If we examine which vaccines were deployed at very large scale early in the pandemic globally (i.e. in the first half of 2021), it is only viral vectors (eg Oxford-AstraZeneca vaccine, Johnson and Johnsons Vaccine and the Chinese company Cansino), RNA vaccines (Pfizer and Moderna) and inactivated vaccines (Chinese vaccines from

Sinopharm and Sinovac). That is because each of these uses a vaccine platform which is more readily scalable, as it turns out. For viral vector vaccines it takes about 3 months to start producing doses for clinical trials from a standing start, but for RNA vaccines, doses can be ready for trials in about 6 weeks (at least now that the processes are better established). Systems in place to ensure that manufacturing using these vaccine platforms can be deployed rapidly could make a huge difference in a pandemic. However, it is important to note that these platforms might not always be ideal for a particular pandemic threat and it is critical not to disinvest in older technologies. For example, the Chinese inactivated vaccines were some of the most widely used and accessible for low and middle income countries (LMICs) early in the pandemic and saved many lives. They are very simple to make as they only require growing the pandemic virus in a facility and then inactivating it chemically so that it can't cause disease, using the same technology as is used for inactivated polio vaccines, (polio vaccines were developed in the 1950s). This process has the advantage that it isn't necessary to know anything about the virus or which parts of it are needed for protection in a vaccine, as long as it will grow in the laboratory to make the doses. We did have such a facility in the UK, run by the company Valneva, initially contracted to make doses for the UK in the pandemic, but this contract was cancelled and it may now be less likely that the UK will have this capability in the future. By contrast, for both RNA vaccines and viral vectors, it is necessary to have knowledge about which component of the virus is targeted by protective immunity so that the corresponding gene or part of a gene can be included in the vaccine.

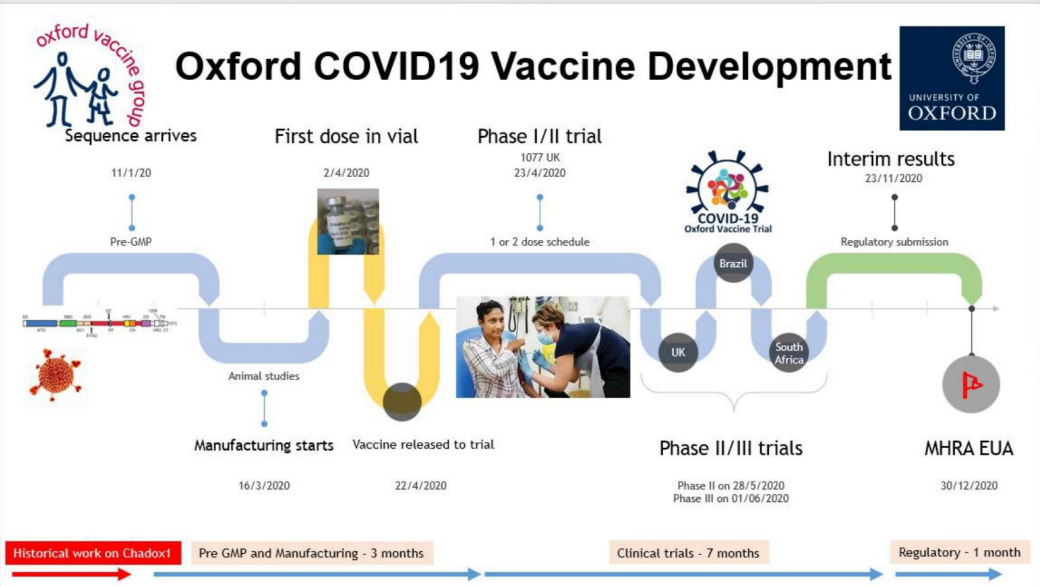
43. Today there remains very limited industrial scale vaccine manufacturing in the UK that can work across multiple vaccine platforms to allow multiple hits on target. We are somewhat limited, to my knowledge, to the Medimmune manufacturing of the live attenuated influenza vaccine and the anticipated Moderna plant at Harwell which is not yet built at the time of writing.

44. In Oxford we used a viral vector platform using a chimpanzee adenovirus, ChadOx1, which had been used as the vaccine platform over the previous decade for various products – for example Sarah Gilbert had been working on

vaccines for MERS coronavirus amongst others and I have made ChadOx1 vaccines for meningitis and plague. Having exquisite knowledge about the platform and its manufacture proved critical – the Oxford team knew how to make it in the manufacturing facility from years of experience and also what dose was likely to be well-tolerated and produce strong immune responses, saving time that would otherwise be spent on checking different doses in early human trials which could take months longer.

Chronological overview of the key stages in the development, manufacture, procurement and approval of the Oxford-AstraZeneca vaccine.

45. The timeline for the development of the Oxford-AstraZeneca vaccine is outlined below. The red arrow in the bottom left corner refers to the work done prior to 2020 which established the performance of the viral vector platform, ChadOx1 in various clinical studies of vaccines which were done using Oxford's technology. Of importance were the studies led by Dame Sarah Gilbert of the MERS coronavirus vaccine which established before the pandemic a) that a coronavirus vaccine for MERS was protective in animal models (vaccinated animals were protected from the disease when deliberately exposed to the virus) and b) phase I human studies had shown that humans made similar immune responses to those that protected animals.



46. On 11th January 2020 the sequence was available in Oxford and Sarah Gilbert and her colleagues used it to switch the MERS coronavirus spike protein gene in the vaccine for the SARS-CoV2 gene to make the prototype COVID19 vaccine which was then tested in animals during the first few months of 2020. The work on manufacturing was also underway and work started in the Oxford manufacturing facility in March 2020 to make the first doses that were used in the phase I study. The phase I study was initiated on 23rd April 2020 in healthy adults under 55 years of age (1077 individuals recruited) paving the way for initiation of the phase II studies in older adults on 28th May 2020. In parallel work was ongoing to set up the phase III studies and these started in the UK on 1st June 2020, initiated shortly afterwards in South Africa and Brazil. These studies were included in the interim results which were first discussed with the trial independent safety monitoring committee on the evening of Saturday 21st November 2020 and made publicly available on 23rd November 2020. This had been preceded by an intense period of data checking which continued at pace alongside further analyses for regulatory submission which was undertaken in a rolling manner with the approval on 30th December 2020.

My role and responsibilities in the development and manufacture of the Oxford Covid-19 vaccine.

47. My role was as Chief Investigator for the clinical trials of the Oxford-AstraZeneca COVID19 vaccine in the UK, Brazil and South Africa. In this role I was acting for the legally responsible institution (the sponsor), Oxford University, in which I had responsibility and oversight for the clinical development work led by Oxford across more than 30 national/international clinical trial sites, including study design, the research protocol, logistics, clinical operations, interactions with AZ, safety etc.

Phase I clinical trials

48. The phase I clinical trials were initiated on 23 April 2020 with the first volunteer vaccinated on that day. The aim of the phase I study was to evaluate whether the

vaccine was safe and induced immune responses in a relatively small group of individuals. In addition, following discussion with the UKs leading mathematical modellers while the protocol was being developed in March 2020, the sample size was increased to ~1000 as they predicted (without a lockdown) that there could be so many cases of COVID19 in the study that we might be able to measure vaccine efficacy in our first study by the Summer of 2020 – the lockdown did reduce transmission and so it was not possible to obtain a measure of efficacy in the initial study. Across 5 clinical trial sites (Oxford, Southampton, Imperial College and St George's Hospital in London, & Bristol) 1077 individuals were enrolled by 21st May 2020 to receive either the Oxford-AZ vaccine or a control vaccine. This study showed that the vaccine did not have any unexpected side effects in this population of healthy young adults. The vaccine also induced good antibody and T cell immune responses, which were improved by giving a second dose. Because of the improved immune response with 2 doses, the programme was switched to evaluation of a 2 dose regimen. The immune responses included production of high levels of neutralising antibodies which are thought to be protective against SARS-COV2 infection providing a strong rationale for continuing development, consistent with observations in earlier animal studies (see AP3 - INQ000231521).

Phase II clinical trials

49. Following the success of the phase I clinical trial, a phase II study was launched to evaluate the immune response and safety of the vaccine in older adults and compare this with a younger adult age group. Again this was planned as a typical modest-sized phase II study to provide sufficient data across all target age groups on immune responses and safety. This study was run in Oxford and Southampton. From May 30th-August 8th 2020, 160 individuals were enrolled aged 18-55, 160 at 56-69 years of age and 240 who were over 70 years of age. In each of these groups the individuals were randomised to receive either the Oxford-AZ vaccine or a control vaccine. The study showed similar and strong immune responses across all ages, including the most elderly and again clear evidence that 2 doses provided stronger immune responses than did one dose (see AP4 - INQ000485231).

Phase III clinical trials

50. Phase III clinical trials were planned to measure the efficacy of the vaccine across all ages and were launched on 1st June 2020 across sites in the UK and subsequently in Brazil and in South Africa. The aim of these studies was to measure the efficacy of the vaccine by comparing protection against COVID19 following vaccination with the Oxford-AZ vaccine with a control group who received a vaccine which did not protect against COVID19. The volunteers and staff were blinded to the treatment allocation so that they did not change their behaviour as a result of knowing their vaccination status. The study planning had begun in April when the first lockdown was successfully reducing transmission of the virus and therefore it was realised that it would be difficult to measure efficacy unless the phase III study was quite large so that enough cases would occur in the study population. Furthermore, because of uncertainty about future social-distancing/lockdown policy, it was very unclear whether the return of cases would be patchy geographically, so 19 trial sites were set up across the UK, including two in Scotland, one in Wales and the rest in England (mainly in NHS Trusts) to increase the diversity of the population enrolled and increase the chance of capturing cases occurring when the next wave arrived. For these reasons, and also to provide data from LMICs with diversity in ethnicity and social circumstances, parallel trials were also initiated in Brazil (6 sites) and South Africa (7 sites). Because the funding that was available from HMG was only for recruitment in the UK, separate protocols were developed while funding was being obtained in Brazil and South Africa and to adapt to local requirements.

51. The study in South Africa provided data in a healthy young African population and also in individuals living with HIV. A small study was also run in Kenya to provide additional data in an East African population.

52. An interim analysis of the Oxford-AZ vaccine efficacy was undertaken and presented in public on 23rd November 2020. This analysis and subsequent efficacy analyses used pooled data from the UK (Phase I/II and III studies), South Africa and Brazil to maximise the power available for safety and efficacy and included a total of 24,422 volunteers over 18 years if age. The timing of

interim and final analysis of efficacy is determined by the number of cases accumulating in the trial (i.e. the number of people who develop COVID19 and therefore can contribute to the analysis to assess whether there is a smaller number in the vaccinated than the unvaccinated group) rather than the size of the of the trial per se. So the timing of an analysis is affected by a) number of volunteers recruited in the trial such that more volunteers would shorten the time to accumulate sufficient cases, b) the attack rate of the virus (which is in turn affected by lockdown and social distancing) such that a higher attack rate means that the analysis can be done sooner and c) the regulatory requirements for the number of cases in the study which were necessary to meet the pre-determined statistical endpoint (vaccine efficacy of say least 50% with a lower bound of the confidence interval above 30%). The only factor the trial investigators could have modified in mid-2020 was the number of participants recruited into the clinical trial (which would likely have allowed an earlier accumulation of cases and thus measured efficacy), but this was not possible because of the limited manufacturing capacity.

53. So it could have been possible to get a vaccine available more quickly for the population in 2020, if either there had been more manufacturing capacity and therefore more doses and more volunteers or the regulatory criteria were less stringent so that fewer cases had to accumulate in the trial before a license was awarded (see AP5 - INQ000485232 and AP6 - INQ000485233).

54. The interim and final analyses of the clinical efficacy and safety of the vaccines showed high levels of protection against severe disease and death (essentially 100% but as with the other vaccine developers, there were insufficient severe cases to have certainty on the actual protection against severe outcomes) and very high levels of protection against milder infection - vaccine efficacy was 81·3% [95% CI 60·3–91·2] for those with a longer dose interval (≥12 weeks) and 55·1% [33·0–69·9] in those with a short dose interval (≤6 weeks). The variation in dosing intervals arose because of a delay in manufacturing during the conduct of the trial, which meant that some individuals had to wait for a new manufacturing run before they could receive their second dose, resulting in the creation of long and short interval groups. This also meant that it was possible to measure the

vaccine efficacy of the first dose, which proved to be very highly efficacious giving over 76% protection.

55. There were no significant safety concerns raised in these large clinical trials, other than the well documented minor side effects which are mentioned below. During the phase III clinical trial the study was paused on two occasions where potential safety signals were evaluated by the independent safety monitoring committee and regulators in the 3 countries. This is routine practice in clinical trials to ensure that there is an independent assessment of any potential serious side effect and trials can be terminated if there is considered to be a risk to safety. In both cases, the national regulators and independent assessors agreed that the trial should continue. The monitoring of possible side effects in a large trial is difficult as there are many conditions that can happen by chance, meaning that there will be many diagnoses of new conditions affecting trial volunteers during the course of a trial which are not caused by participation in the trial but each must be carefully considered by experts. The trial independent safety monitoring committee and MHRA reviewed each event very carefully without the review causing any unnecessary delay in progress of the clinical trial. The capability of regulators to provide real time review in this way was exceptional during the pandemic and the avoidance of the long delays that are caused by this process in normal times likely resulted in many lives being saved by the earlier availability of the vaccine.

56. Following the final analysis of the phase III clinical trial in the UK, it was agreed with regulators that the Oxford Research team would continue to follow safety in the volunteers who had been in the study, most of whom were "unblinded" from group allocation (Oxford-AZ vaccine vs control) by early 2021. This follow up was undertaken to provide further information on longer term safety. Many of the individuals in the trial were health care workers or in other eligible groups and have subsequently received booster doses of various different COVID19 vaccines. There were no concerning safety signals identified by the safety monitoring committee. Safety has also been monitored in various studies of 3rd and 4th dose booters of the vaccine. These studies have shown that common

minor side effects become less common with subsequent doses of the vaccine and that there are clinically useful booster responses obtained by using additional vaccine doses.

57. The booster studies showed that a 3rd dose boost induced good immune responses after previous doses of the Oxford-AZ vaccine and after doses of various other vaccines, including the Chinese inactivated vaccines used in LMICs. Various other mix and match studies were also undertaken by a consortium of UK researchers (see AP7 - INQ000485234, AP8 - INQ000485235 and AP9 - INQ000485236).

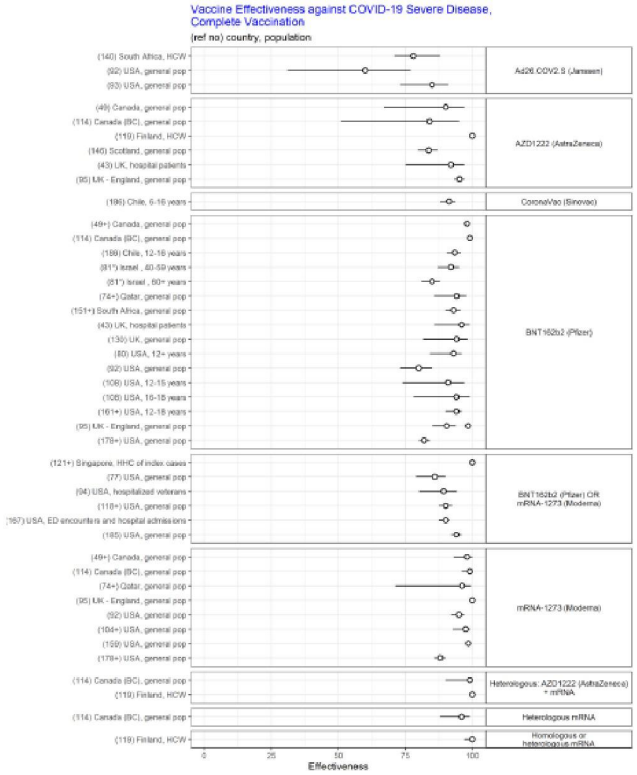
Licensure

58. The vaccine was first licensed by the MHRA on 30/12/2020 following a rolling review of manufacturing and clinical trial data. The reporting of the clinical trial data was complicated by the need to provide a pooled analysis of the UK and international trials and because of the limited capacity in a University to prepare the mass of supporting data required for a regulatory submission. The reason for the separation of the trials was related to funding which was only available for trial activity in the UK from the Government, which meant that a separate process had to be followed to fund an initiate the trials in Brazil and South Africa. Fortunately, AstraZeneca were able to provide exceptional support for the licensure process which allowed the data to be pulled together in the month from the first look at the high-level interim analysis through to the pre-Christmas submission of the data.

Post-licensure studies (including phase IV)

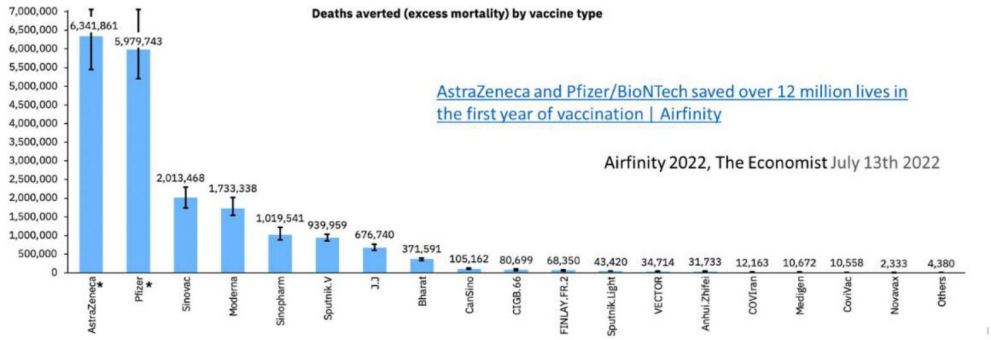
59. There were multiple post-licensure studies of COVID19 vaccines to document their effectiveness either by using linked databases (to determine whether those vaccinated were less likely to get infection, be hospitalised or die) or clinical observational studies of various designs which directly compared vaccinated individuals with unvaccinated controls to evaluate vaccine effectiveness. These studies have been extensively reported and were summarised in real time by Johns Hospkins University. Perhaps the most important analysis is the one which shows that the risk of severe disease and death is massively reduced by

whichever vaccine was used around the world, which should have been the focus of global policy and would have led to earlier sharing of doses for those most likely to succumb showing high effectiveness of all products (from Viewhub, Johns Hopkins):



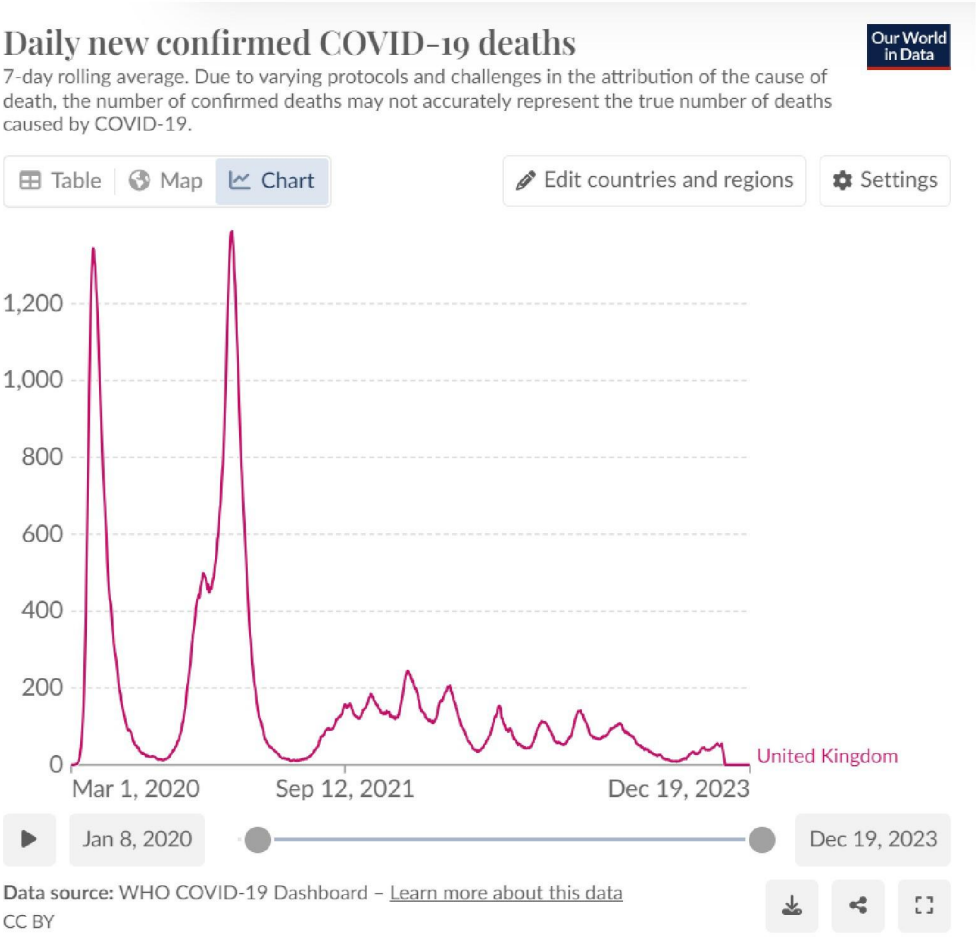
Vaccine Impact

60. The Oxford-AZ vaccine was rolled out in the UK starting from 4th January 2021, with the first doses being given in Oxford. Subsequently, approximately 3 billion doses were distributed worldwide. An analysis by Airfinity in 2022 assessed the likely impact of the COVID19 vaccines during 2021 as shown in the figure below.



61. This analysis, which is extrapolated from a modelling study from Imperial College suggests that the Oxford-AZ vaccine saved more lives globally than any other vaccine in 2021. The first year of vaccine rollout (2021) was the critical time for vaccine roll out as by 2022 a high proportion of the population of the world had either been vaccinated, or infected (and thus died from or survived COVID19). Subsequent vaccine doses provide some extra protection for a modest period of time but it is the first two doses which provide the biggest leap in protection for a population.

62. Examining the UK data (below) it is clear that the pandemic of deaths from COVID19 ceased as soon as the vaccine was rolled out at pace in older adults (see graph below), with no further major spike in deaths since the first half of 2021. The doses in 2021 in the UK were almost entirely from AZ and Pfizer showing the remarkable impact of the UK programme on severe COVID19.



63. The initial roll out of the vaccine changed the UK population from a naïve population with many susceptible to severe disease, especially older adults, to an immune population where the severe consequences of COVID19 have essentially disappeared, protecting individuals and the NHS. Uptake was extraordinarily high in older adults, and was largely from the Oxford-AZ vaccine. Unfortunately, the most frail in society remain at risk from a wide range of respiratory viruses, including COVID19 because of their underlying health condition. Now it isn't the direct effect of a pandemic virus in virus-naïve individuals that is the problem but the consequences even of a mild infection in someone who is very frail. Booster doses have reduced the hospitalisation rate to some extent over the last few years but overall population immunity against the virus is quite good and so a relatively small proportion of the population are at risk of hospitalisation or death today.

How the development of the Oxford-AstraZeneca vaccine built upon prior work already carried out in response to previous epidemics/pandemics.

Human Resources

64. The Jenner Institute moved to Oxford in the mid-2000s as a *virtual* institute across Oxford led my Professor Adrian Hill, with many researchers across the University affiliated to the Institute and working on vaccines against various diseases building critical mass and expertise, notably it hosted the work of Dame Sarah Gilbert on coronavirus vaccines before the pandemic. The development of the Oxford-AstraZeneca vaccine built on a long history of vaccine research in Oxford which I have outlined above. In my department, The Oxford Vaccine Group was founded 30 years ago and currently includes ~200 staff and students who work on vaccine design, development and testing and the science of immunity. The know-how from extensive work from the laboratory to the clinical trial setting over decades means that there is considerable institutional knowledge and a critical mass of people who were in a position to respond to the COVID19 pandemic. Unfortunately, there is no core investment in vaccines in Oxford or any other UK academic institution.

Vaccine platform

65. One key component of prior work at Oxford University was the development of a vaccine platform that could be used as the basis for vaccines against a variety of diseases using the same manufacturing approach. The development of the chimpanzee adenovirus viral vector platform, ChadOx1, was a key achievement prior to the pandemic and is the platform on which the Oxford-AZ vaccine is based. Indeed, the platform had been extensively studied as the backbone of vaccines against a variety of serious infections from viruses to bacteria. The work on the MERS coronavirus vaccine which reached phase I clinical trials prior to the pandemic was critical preparatory work for a coronavirus pandemic as it showed that a conoravirus vaccine against MERS would protect animals and also induced the same type of immune responses in humans, building

confidence that the same approach could work for the pandemic coronavirus COVID19.

66. The wide variety of work in Oxford on the full life cycle of vaccine science and product development meant that the skills were in place to respond to a pandemic but the convergence of this expertise with an established Oxford chimpanzee adenovirus vaccine platform and experience of making a MERS coronavirus vaccines was pivotal.

67. In Oxford scientists had worked on vaccines for many different diseases that *do* cause outbreaks, including influenza, malaria and typhoid and various diseases which *might* cause outbreaks such as MERS coronavirus and those that cause *occasional* outbreaks such as plague. However, there was also experience of rapid response to disease threats as Oxford scientists were also working on vaccines for new outbreaks from partnerships with industry, for example in my team we worked on novel influenza viruses vaccines in responses to H5N1 bird flu cases in 2005 and undertook large Government funded studies on pandemic H1N1 swine flu vaccines in children in 2009. An important component of the experience in Oxford was the response to the Ebola outbreak in West Africa in 2014/15 in which multiple vaccines were first tested in Oxford with funding from Wellcome Trust and European Commission, in collaboration with industry partners. A feature of these studies was the need to work out systems to rapidly respond internally in Oxford by aligning staff, logistics and effort to the outbreak disease and also working expeditiously with agencies like national ethics committees and MHRA – these experiences proved critical to the response to pandemic coronavirus in 2020 as the mechanisms were already established.

68. The manufacturing infrastructure in Oxford with our small facility that can make vaccines (the clinical biomanufacturing facility, CBF) at the quality necessary for human studies was established over the previous decade and a half and meant that there was concentrated expertise on site to make the first doses of the Oxford Vaccine quickly and thus to respond to the pandemic without delay. This is a highly regulated process and it is very important to maintain the expertise of staff who are trained to undertake the work which is regularly inspected by the

MHRA and has to conform to quality standards. Several commercial manufacturing organisations had also worked with Oxford on other projects and were able to engage rapidly when requested by the Oxford team, for example our phase II trial and some of our phase III trials were supported by manufacturing in Italy.

69. Laboratory research and Clinical Trials

There is extensive experience among investigators in Oxford on the laboratory and computer science used to design new vaccines as well as the laboratory studies that are required to evaluate them by measuring immune responses to vaccines (antibodies and T cells) with several hundred trained scientists working in these domains. The expertise resides in the Department of Medicine and the Department of Paediatrics.

70. At the start of the pandemic there was very limited capacity for laboratory assays (antibody and neutralisation assays) to be set up and run in the UK to meet with the stringent requirements for regulatory approval. It is a laborious task to get these tests set up to meet the stringent regulatory criteria. Some capability existed at UKHSA Porton Down but it was insufficient to provide the support needed for our trials, let alone the global need for this expertise. The lead at Porton Down was Dr Bassam Hallis who did not have the necessary funding from UKHSA to expand his operation and so I introduced him to Dame Kate Bingham on 5th July 2020 and the VTF then helped expand capacity in his team. UKHSA subsequently played a vital role in regulated laboratory activity for vaccine developers.

71. At Oxford, there is also considerable capacity in running clinical trials of vaccines in the UK and internationally across all phases of clinical development as a result of the extensive peacetime activity in vaccine development in the University. For example, there were approximately 100,000 children and adults in UK and international clinical trials (phase I-IV) and other types of human studies run by the Oxford Vaccine Group from 2017-2020. The team with the know-how to run these large trials was in place because of this research carried out on vaccine development from a range of funders (eg MRC, European Commission, Bill &

Melinda Gates Foundation, Wellcome Trust, NIHR, Innovate UK, Global Alliance for Vaccines and Immunisation and industry partners). To run large studies requires clinical expertise but also expertise in data management, regulation, project management and logistics, quality assurance, statistics, clinical operations etc.

Funding arrangements for the development of the Oxford-AstraZeneca vaccine.

72. One significant challenge faced by our team for the Oxford vaccine development programme was access to finance and much time was devoted to obtaining funding (further information below and for initial funding should be discussed with Dame Sarah Gilbert). Clearly some due diligence is needed by Government prior to investing in vaccine developers, even in a pandemic, but a system needs to be in place much earlier than it was in 2020 to ensure that lack of money does not result in delay in execution of a development plan. Indeed, around the world many developers found the major hurdle to be funding. It is essential that there is clarity that costs will be covered so that financing doesn't become a distraction. This is especially important for an academic institution which does not have an alternative source of funds to access for the work. In theory industrial partners have deep pockets and might not have such restrictions on making decisions, but I have heard from industry that the lack of success from the major vaccine producers (apart from Pfizer) in developing a vaccine was partly due to the perception of (financial and reputational) risk. It is noteworthy here that the US Government understood this issue and made $1 billion dollars available to each of the vaccine developers and provided substantial support and coordination of clinical trials through existing NIH funded vaccine and HIV centres (who brought generic clinical trials expertise) across the US (I understand that Pfizer declined the funding offer from the US Government). Note that no such core-funded vaccine laboratory research or focussed vaccine trials infrastructure exists in the UK. In the pandemic, the UK approach was eventually coordinated by the Vaccine Task Force but this was complicated by the task force sitting in BEIS providing authorisation but the clinical development funding coming from NIHR,

which is in DHSC, and communication between the two not being well coordinated.

73. Several initial grant applications were made to UKRI in February 2020 for relatively small amounts of funding for various aspects of development (eg £2,174,847.97 awarded on 4th April 2020). There were also extensive discussions with CEPI led by Dame Sarah Gilbert. Initial funding from NIHR was £9,899,585 for the phase I/II studies and the contract was signed on 20th April, 3 days before the trials started, which meant that all of the preparatory work involving hundreds of staff was undertaken at risk. It became clear when the Phase I trials started on 23rd April 2020 that lockdown was already very successful in reducing transmission of the virus and cases of COVID19 were falling rapidly which meant that much larger trials would be needed to capture enough cases to measure vaccine efficacy. Once the VTF was established, further funding for the clinical development programme in Phase III was better coordinated. It is important to note that only ~£30M was spent on the full clinical trials programme in the UK showing extraordinary value for money through the academic development programme (compared with 1 billion committed for each vaccine in the US). After the first wave of COVID19 passed in the UK, it wasn't known where or how future waves of transmission would appear. Our strategy was to have sites across the UK in case the inevitable return of COVID19 was regional, and to expand to international sites to both increase the chance of operating in countries with the next wave of COVID19 to get cases in the study which would allow us to measure vaccine efficacy and also to ensure that as wide a population as possible was represented in terms of ethnicity, sociodemographic factors and geography. The data from all of these trials would be used to apply for a license if successful, so ideally this would all be coordinated through one funder simplifying operational practicalities. NIHR with support from VTF agreed that the budget should be provided for the UK trials. I was not able to obtain funding for expanded clinical trials outside of the UK from the UK Government and did not waste time pursuing this when I received push back from DHSC. We were embarking on a massive national and international programme over the next few weeks and an alternative route to fund non-UK activities was needed. At this stage I established a collaboration in South Africa

and the country chief investigator (Professor Shabir Madhi CBE) approached the Bill & Melinda Gates Foundation who funded the trial in South Africa. At the same time I worked on funding with our chief investigator in Brazil (Professor Sue Ann Clemens CBE)) and we approached a charity, the Lehmann Foundation, who generously funded the trial in Brazil with additional substantial support coming from a Brazilian private hospital network. This piecemeal approach to funding had a significant knock-on effect later when we came to the license application. The lack of funding up front meant that there was considerable uncertainty and so I proceeded at risk with 3 separate trial protocols since there was a chance that any of the trials might not go ahead if funding could not be found or if there was a regulatory obstacle that wasn't initially foreseen – while this made it operationally easier in setting up the studies with bespoke ethical and regulatory requirements in each country, at the end of 2020 this created a technical difficulty for regulators in combining the data from 3 protocols instead of the ideal which would have been to have run the programme using a single protocol across all of the countries.

74. AstraZeneca provided in-kind support for the clinical trials in the UK and Brazil through provision of trial-monitoring support (personnel to check on the quality of work at the trial sites). Later they also provided direct funding to the University for booster studies and to complete the study of the vaccine in Children. Of course AZ also invested in manufacturing and then in the extensive work on licensing.

How funding arrangements for the Oxford-AstraZeneca vaccine were expedited.

75. From our experience, having a clear Government plan for funding vaccine development in a pandemic needs to be in place and ready to go *before the pandemic*. The danger is that academic or industrial developers consider the financial risk of proceeding too high if there are no clear signals at the beginning that would allow the development to proceed without hindrance (obviously with appropriate milestones of success). In the absence of this there is a risk that development teams either don't start or that they are distracted by the efforts to secure and repeatedly reapply for funding. This may be less of an issue for big

pharma, with deep pockets, but it is important to note that, with the exception of Pfizer, no big vaccine companies produced a vaccine that had a major impact in the pandemic. The two largest vaccine producers in Europe, GSK and Sanofi (in partnership) were not successful in their initial vaccine development efforts and did not produce a product in 2021. The large American vaccine company, Merck made 2 different vaccines, both of which were not taken forwards. There are several explanations given for the limited contribution from "big pharma" but it is clear that there were scientific difficulties with the initial products as mentioned above but, given that making a spike protein vaccine is not rocket science, the lack of progress in reassessing and retooling when challenges were faced suggests that there were additional issues at play which are not clear – on the grapevine some have blamed bureaucratic challenges and difficulties making decisions at speed in a large organisation, and others that it was the pharma attitude to risk. This means that the pandemic response depended on small biotechs (eg Moderna, and Novavax) or a University (Oxford) for whom financing is a critical issue. There should be a dialogue with big pharma to ensure that the obstacles experienced in 2020 are understood and don't limit development in future pandemics.

76. An immediate vaccine fund is needed to initiate credible projects in future pandemics, while the due diligence, by an entity with the skillset exhibited by the VTF, is undertaken to ensure that major investment is focussed on likely products that meet scientific, manufacturing, safety, efficacy and deployment requirements.

The role of different parties in developing the Oxford-AstraZeneca vaccine:

Clinical BioManufacturing Facility ("CBF**");**

77. The clinical biomanufacturing facility made the first batch of the Oxford vaccine which was used in the phase I trials. Subsequent batches were made in Italy at Advent and then by AstraZeneca and contract manufacturing locations in the UK. CBF is part of Oxford University.

Jenner Institute;

78. The Jenner Institute is a virtual institute which encompasses a coalition of research groups across Oxford University and the Pirbright Institute (in Surrey) who work on vaccines. In Oxford the research groups which are incorporated into the Jenner Institute are based in three departments – Paediatrics (.e. the Oxford Vaccine Group), Medicine and Biochemistry. In the pandemic researchers in these different departments were involved in the Oxford-AZ vaccine development. The Jenner Institute Director is Professor Sir Adrian Hill, who also leads the Jenner Institute Laboratories.

Nuffield Department of Medicine;

79. This is a large department in the Medical Sciences Division of Oxford University which incorporates research and teaching in a variety of medical disciplines and also is the home for some of the many Oxford investigators who work on vaccines, and hosts the Jenner Institute. Other Departments in which vaccine research is undertaken include Paediatrics and Biochemistry. The main leadership for clinical development was from Paediatrics (Pollard, Oxford Vaccine Group) and for Preclinical and manufacturing was from Nuffield Department of Medicine (Gilbert and Green).

Oxford Vaccine Group;

80. This is a large research group of ~200 staff and students based in the Department of Paediatrics at Oxford University which is led by me as the Director. In the pandemic, my team at the Oxford Vaccine Group provided the key clinical and logistical leadership for the development of the Oxford-AZ Vaccine in the UK and for the global operations in Kenya, South Africa and Brazil.

Vaccine Knowledge Project;

81. This is a public-facing website which I initiated 15 years ago to provide independent information for the public about licensed vaccines. We try to cover the main vaccines in the UK immunisation programme and information about the diseases that they prevent (see AP10 - INQ000484799).

Centre for Clinical Vaccinology and Tropical Medicine ("CCVTM");

82. This is the building where clinical trials of vaccines are undertaken in Oxford. it has outpatient rooms which can be used for trial volunteers to attend visits for vaccination and blood-taking. CCVTM was the nerve centre for global clinical operations and trial logistics in the pandemic including quality assurance, database managers. It was also the home for the doctors and nurses working with trial volunteers as a local site in Oxford and coordinating the national and international network of UK and global sites. During the pandemic the facility was too small and so we obtained 2 very large mobile clinics from a commercial organisation which increased the capacity and made it possible to deploy the trials on a large scale, but at substantial cost. We did discuss mobile clinics with the British Army but they were unable to provide the necessary equipment for our needs.

AstraZeneca, including the key individuals within AstraZeneca;

83. Discussions with AstraZeneca were initiated in late April 2020 and a licence agreement was made with them in May 2020 to produce the Oxford vaccine. They key decision-makers for this interaction on the agreement were Sir John Bell in Oxford and Sir Pascal Soriot and Sir Mene Pangalos at AZ. During 2020 AZ worked on upscaling of manufacturing and partnership with more than 20 manufacturing partners to enable global production and distribution of the vaccine. They Initiated clinical trials of the vaccine in the US and in Japan and had some interactions in Russia. They also made a partnership with Serum Institute of India (SII) which was critical for production as the world's largest vaccine manufacturer and SII also ran a clinical trial in India. The responsibility for the conduct of the trials in the UK, South Africa or Brazil remained with Oxford but AZ did provide some support – in the UK they provided support for clinical trial monitoring and in Brazil they acted as Oxford University's legal representative with regulators and also provided monitoring support to the trial sites in Brazil. The global clinical trials which were under my team in Oxford provided the key data for the licensing of the vaccine in more than 180 countries following the initial approval in the UK by MHRA. When the first vaccine efficacy

results were available at the end of November 2020, AZ statisticians verified our analysis of the clinical trials and then the AZ regulatory team had a critical role in preparing the file for licensure in the UK and globally and worked around the clock to assemble all of the documentation required by global regulators. AZ then coordinated global manufacturing and distribution of vaccine as the market authorisation holder.

UK Vaccine Taskforce ("VTF");

84. The VTF was initially the brainchild of Sir Patrick Vallance until Dame Kate Bingham was appointed to lead it. VTF were key in assessing the potential vaccine technologies and capabilities of developers to make and test vaccines so that contracts could be put in place for the Government. The main role the VTF had in development of the Oxford-AZ vaccine was around approving financial support for the vaccine development work and in discussions on technical aspects of manufacturing. I had many discussions with the VTF about progress and help with logistics. I also engaged with VTF to expedite laboratory testing (tests to measure antibody levels) at UKHSA which was a key asset for our vaccine development, and many other studies which were conducted, and by facilitating interactions between UKHSA Porton Down and VTF, funding was released to substantial enhance capacity so that we could produce the results that were required by regulators for vaccine licensing.

UK Research and Innovation ("UKRI");

85. UKRI provided some initial rapid-response funding for the development of the Oxford-AstraZeneca vaccine as mentioned above (~ £2M)

UK BioIndustry Association ("BIA");

86. I did not have any significant interaction with the UK Bioindustry association, but they did provide coordination, advice and assistance in facilitating manufacturing and worked closely with VTF.

Vaccines Manufacturing and Innovation Centre ("VMIC");

87. VMIC was not in place in time for the pandemic and has not been subsequently taken forward by HMG.

Coalition for Epidemic Preparedness ("CEPI");

88. I had some interactions with CEPI during the pandemic but Dame Sarah Gilbert was responsible for interactions with them and is in a better position than me to comment.

Wellcome Trust;

89. I had interactions with Sir Jeremy Farrar, Director of the Wellcome Trust, during the pandemic from January 2020 (first when he talked with me about clinical trials with a US biotech company) but mostly discussing progress with our vaccine development and emerging events, but the Wellcome Trust did not play a role as a funder of the Oxford Vaccine.

Vaccitech;

90. I did not have any dealings with Vaccitech and they did not play any role in the clinical development of the vaccine. The relationship with them is best directed to Sir John Bell and Dame Sarah Gilbert as it relates to the licence agreement and not vaccine development per se.

Vax-Hub;

91. I was not involved in the Vax-Hub project and questions on this are best directed to Dame Sarah Gilbert.

Advent Sri;

92. Advent are a contract manufacturer who were a key partner for manufacturing for the clinical trials in the pandemic. They had experience of manufacturing viral vectors and were able to produce doses of the Oxford vaccine for use in the pandemic trials with more capacity than we had in our very small facility in the University. Unfortunately, the facility is based in Italy which added logistical challenges for transport of vaccine to the UK, especially during lockdowns. On one occasion, I had to rent a private jet to fly doses from Italy to the UK to ensure supply for the clinical trials was available at sites when it was needed.

Serum Institute India ("SII");

93. Serum Institute of India (SII) is the largest global manufacturer of vaccines and were a partner in the global production of the Oxford-AZ vaccine. They also conducted clinical trials in India of the vaccine to support licensure with the regulator in India. Indian manufacturing was a critical step for the approval of the vaccine made at that facility by the World Health Organisation in February 2021 for global use via COVAX.

SK Bioscience;

94. SK was a manufacturing partner of AZ and was one of the first 2 manufacturing sites approved by WHO for supply to COVAX, making them a key part of the global effort to protect populations from COVID19.

Oxford Biomedica.

95. Oxford Biomedica acted as a contract manufacturing organisation for AZ in the pandemic and produced doses of the vaccine.

The initiation and development of the relationship between Oxford University and AstraZeneca.

96. Sir John Bell was involved in the agreement with AZ and he would be best placed to discuss the initiation of the formal relationship. I attended one of the first meetings with AZ at which they were interested in a partnership but I did not participate in any of the formal interactions around licensing the vaccine to them. The first meeting was mostly about fact finding and it was clear that they had limited experience of vaccine development (which we did have), mostly through their takeover of Medimmune who make the nasal spray influenza vaccine for children, but AZ had very considerable experience of global manufacturing and distribution (which we did not have). I had very extensive scientific interactions with their team subsequently and continued to do so through to the end of 2023 as we tied up final reports for global regulators.

Innovations introduced and lessons learned

Explanation of innovations introduced to accelerate the development, procurement, manufacturing and approval process for Covid-19 vaccines during the pandemic.

The development of the Oxford-AstraZeneca vaccine followed a standard approach to vaccine development with preclinical work followed by animal studies and then clinical trials. The acceleration in development was not a change in the scientific process or through short-cuts but as a result of a) proceeding through development without pauses to obtain funding, and therefore working at financial risk where funding had not been secured; b) hugely increased timeliness and responsiveness of NHS, ethical and regulatory approval processes that are not sustainable in peacetime; c) focus of large teams in Oxford, at trial sites and at AZ on one product to provide the capacity and capability to move more rapidly; d) simplified organisational decision-making meaning that decisions could be made in real time whether in Oxford or at AZ.

97. AZ would have to comment on innovations in large scale manufacturing processes.

98. The approvals process used by the MHRA using rolling review was an important innovation. The standard process is to wait until all of the data are prepared by the vaccine developer and then start the review…..but in the pandemic the MHRA used rolling review, reviewing data as they emerged. This undoubtedly saved a lot of time as the clock started much earlier than would be possible without this innovation. As a result the vaccines were approved and deployed earlier than they would have been following standard procedures, but without any difference in the quality or scrutiny given. The MHRA would be best placed to advise whether such an innovation could be put in place routinely but certainly this should be used in emergency situations.

99. The vaccine task force was a brilliant innovation which allowed sensible, accessible and rapid decision-making.

Lessons learned in relation to public/private sector collaboration.

100. The relationship built between Oxford and Astrazeneca was key to the success of the partnership. However, these relationships were not in place prior to the pandemic and it is important to consider whether stronger relationships between academia and industry could help with improving vaccine development in a pandemic and enable partnerships better in peacetime. Could relationships be supported in peacetime by incentives from Governments so that close working and understanding of the differences in culture and execution of research is in place prior to an emergency situation. This is done by the European Commission IMI programme which funds collaborative research between academic institutions in Europe and pharma with multiple academic and pharma partners typically in each consortium – this was the vehicle for the development of the Johnson and Johnson Ebola vaccine in 2015/16. A number of funding schemes do encourage partnering with industry, such as the Medical Research Council's (MRC), Developmental Pathway Funding Scheme (DPFS).

101. A major obstacle to partnerships with industry is the perceived risk of conflict of interest for clinicians and researchers. To change this, there needs to be a better understanding of ways of working without conflict for all doctors in training in the NHS and academia, and leadership from doctors leaders, to promote working with industry. It should be obvious, that big pharma is essential for all of the lifesaving drugs and vaccines we use. Nevertheless, to maintain public confidence there must be clear, transparent and accepted guidance which is sufficiently specific to make it clear how to manage conflicts of interest and especially to avoid personal financial conflicts of interest and that this arrangement is consistently applied across institutions. Anecdotally, the problem currently is that the guidance from the General Medical Council (GMC) is often perceived as meaning that working with industry compromises patient care.

Obstacles encountered in relation to accelerated development, procurement, manufacture and approval of Covid-19 vaccines.

102. As discussed elsewhere there are a number of clear lessons from the pandemic that would facilitate development.

a) Early clarity on guaranteed funding and availability of funds from the outset (subject to appropriate milestones). This was a struggle in the UK, wasting time which would have been better spent on the development. In the US, each developer knew that had access to 1bn dollars.
b) Vaccine manufacturing capacity and capability in the UK to produce doses rapidly at moderate scale for clinical trials across a range of vaccine platforms. This was a major obstacle to initiating the clinical trials in the UK beyond phase I, which we could do in our small facility in Oxford. Furthermore, we should not rely on only one vaccine platform.
c) Investment in manufacturing science to build more efficient and more rapid platforms.
d) Having multiple shots on target (as organised by VTF) increases the chances of at least one success – we were fortunate in the UK to have AZ, Pfizer and Moderna in good time from the VTF long list. We need to ensure that we have a clear blueprint for success in future.
e) We did not have regulatory agreement on the design of clinical trials sufficiently early in the pandemic. we should now put in place principles to guide design of clinical trials for different scenarios (mortality, transmission, type of disease etc), so that rapid development can follow a plan (which should still be adaptable) that has already been scenario-tested.
f) We need to know more about the potential families of viruses and bacteria that could be future threat so that we are at least as prepared as we were for a coronavirus pandemic.
g) We need to maintain the flexible and enabling work of the HRA and MHRA that supports clinical trials in a pandemic and ensure that we have sufficient regulatory capacity.
h) Laboratory infrastructure has to be maintained to provide the support for licensure of pandemic vaccines by people knowledgeable about running assays to regulatory standards (i.e. not standard research laboratory work). Initiatives at UKHSA Porton Down have somewhat improved the situation when compared with 2020, but activity and expertise has to be maintained between pandemics.
i) Clinical trials infrastructure in the UK was shown to be responsive in the pandemic as a result of the NIHR funded networks across the NHS. We need

to sustain clinical research in the NHS for future pandemic responsiveness (this does not have to be vaccine-specific in peacetime.

j) There is no core investment in academic vaccine infrastructure across the UK in the way that this is provided in the US, and a more comprehensive and larger approach could be considered, considering microbes as a biological defence risk.

k) The UK needs strategic leadership in vaccine defence against biological threats.

Processes for feeding back experiences during Covid-19 pandemic to UKHSA and any other governmental bodies in respect of planning for future pandemics.

103. There is no forum for independent scientific advice to UKHSA or other Governmental bodies on pandemic vaccines in the absence of a pandemic, with the exception of Sir Chris Whitty's Vaccine R&D network which is focussed on funding of some vaccine development on a small scale. JCVI does not currently have a pandemic subcommittee to advise Governments on potential threats and to my knowledge there is no other *independent* scientific advisory committee to advise on pandemic vaccines, despite UK and international expertise in this area. Such a forum could ensure that the UK remains focussed in the decades ahead on emerging evidence on pandemic vaccines both in the UK and elsewhere and is better able to make technical decisions on response in future pandemics. NERVTAG does not provide vaccine expertise. A joint NERVTAG-JCVI committee has previously formed to address questions specifically on avian influenza vaccines.

Current state of contingency plans for development of vaccines for future pandemics.

104. Apart from discussions about avian influenza, as mentioned in my previous evidence, which are co-chaired by JCVI and NERVTAG, there is no formal external vaccine advisory committee on pandemics. The UK vaccines R&D network, chaired by Sir Chris Whitty provides oversight of funding for

outbreak vaccine development which may improve our planning for future pandemic vaccines.

Lessons learned relevant to preparing for and/or tackling a future pandemic in relation to the development, manufacture, procurement, approval and use of vaccines.

105. There is much discussed in this document which addresses this question. I believe that the UK needs to take the US approach to microbial threats (not just pandemics but also endemic diseases, infections that will increase as a result of climate change and AMR) which is to consider them in the same way as military defence, as I have outlined elsewhere in this report. This means that there should be strategic leadership on vaccines to defend our nation that is credible on the international stage with a properly funded ecosystem to invest properly to increase security and an individual leading who understands the broad areas of science that are essential for vaccine development and procurement. Despite some limited investment in UKHSA Porton Down I don't think we are close to this goal.

Vaccine roll-out

Advice to the UK Government on the practicalities of roll-out procedures for the Oxford-AstraZeneca vaccine.

106. I was not involved in the planning or logistics of the roll-out of the vaccine – policy decisions were dealt with by JCVI (from which I had recused myself) and logistics by the NHS. However, I was involved on the first day of the vaccine being used, personally receiving the 3rd dose of the Oxford-AZ vaccine in the roll-out to build public confidence in the vaccine as the developer and giving media interviews on the day of the first roll out, 4th January 2021.

How the scale up of the roll-out of the Oxford-AstraZeneca vaccine compared to scale-up of the roll-out of the Pfizer and Moderna vaccines.

107. The scale-up was led by AZ and so it would be more appropriate to ask them about this as I was not directly involved. Both vaccines were available in the UK and I believe that the initial roll out involved a roughly even split between the two vaccines but with AZ more used in older adults and Pfizer more used in younger adults. The AstraZeneca and Pfizer vaccines were deployed differently when first available because of the complicated requirements for the RNA vaccines for cold storage (required a -80 degree freezer) which meant that it was harder to deploy them in the community in GP surgeries or to take them to care homes.

Differences in the timing of rollout between the three main vaccines, any reasons for these differences, and any possible consequences to population immunity and deaths from Covid-19.

108. The main vaccines initially deployed in the UK were Pfizer and AZ. Pfizer trials were completed a few weeks earlier and therefore initial roll out could begin on 8th December whereas AZ roll out began on 4th January. However, it is worth noting that this did not result in a major difference in deployment of the two vaccines as supply was very limited at the beginning. The main differences in timing of the roll out are as a result slightly earlier licensure of the Pfizer vaccine. This was the result of faster accumulation of cases in the Pfizer trials which meant they had sufficient data to meet the statistical requirements to apply for a license a little earlier than we did.

Advice to the UK Government on decisions on eligibility, and prioritisation for the Oxford-AstraZeneca vaccine, including suitability for:

i. **Specific adult age groups;**
ii. **Pregnant and breastfeeding women;**
iii. **Children.**

109. Because I had recused myself from involvement in JCVI, I was not involved in any policy advice to Government on how the vaccine should be deployed. My role was to provide data on the trials of the Oxford vaccine that we had conducted and to ensure that this was communicated to JCVI and officials to use in developing policy. Our data showed good performance of the vaccine across all ages and these data were made available to MHRA and presented to JCVI to help with their deliberations.

Advice to the UK Government on appropriate dosage intervals for the Oxford-AstraZeneca vaccine.

110. The dosage interval question has received a lot of attention by non-vaccine scientists and the media. This attention is completely unwarranted as it is well known by vaccine developers and immunologists that longer intervals result in better immune responses with vaccines. This was not a new finding in the pandemic but was a well established fact. The question that needed to be addressed was not how long an interval is best, because longer is better….but the main question was whether there was sufficient protection after the first dose to wait to give the second dose and have a better response after a longer interval. This is a more complicated question than it seems on the face of it. If there is no virus circulating, such as during a lockdown, then a long interval is perfectly safe as there is no risk while awaiting the second dose and so longer intervals would always be preferred……but becomes a more important question if there is a wave of COVID19 passing through the population and the protection from one dose is insufficient. The second issue is to do with supply – if there is plenty of supply then public health officials have the luxury of deciding to go for a short interval for the earliest protection possible or a longer interval to give stronger protection than would be gained from a short interval. However, this was not the case in early 2020 when vaccines were being used as fast as they could be manufactured and so the calculation becomes one of whether it is best to give one dose to more people or 2 doses to a smaller number. The analyses being conducted at WHO and in many countries clearly showed that there was

so much gain in protection from the first dose that the best public health use of a limited supply was to give single doses to as many people and only give the second dose when there was more supply. A longer interval would always result from this policy approach, and would have the added benefit of meaning that the immune responses would be stronger when the (late) second dose was deployed.

111. Indeed we did have good data from the clinical trials to support the concept of a longer dose interval (around 3 months as recommended by JCVI). In the phase III trials in the UK we were able to recruit very rapidly to the Oxford vaccine studies and administered the first doses from the end of May 2020 with the plan to give second doses one month later. We had planned this short interval to maximise the earliest possible immune response as the modellers had indicated that many people would die during each COVID 19 wave and we had therefore hope to provide maximum protection as soon as possible with 2 doses close together (incorrectly assuming vaccine supply would not be an issue). Manufacturing of vaccines was being undertaken in several facilities at this time, now with added support from AZ. However, unexpectedly there was a delay in release of vaccine doses and so we were not in a position to give all of the doses on time as specified in the clinical trial protocol and so we ended up delaying the second dose while awaiting the next shipment, with a large number of doses given at a longer dosing interval than originally planned. The trial data clearly showed those with the longer dosing interval had a stronger immune response than those with a shorter dose interval.

Involvement in UK Government public messaging on the vaccine roll-out.

112. I was not involved in an official capacity on messaging about the vaccine roll out but I was frequently asked by the media to make commentary on various aspects of the roll out. I made every effort to engage with the media with up to date information to provide some expert commentary on the importance of being vaccinated, potential side effects and emerging safety signals.

Involvement in UK Government public messaging on advice to specific groups such as pregnant and breastfeeding women, children and specific age groups, in respect of whom recommendations were subject to change.

113. I was not involved in any of the Government messaging on specific groups as I had recused myself from policy advice. However, I did engage with requests from the media to provide personal commentary about vaccination in various groups throughout the pandemic. The lack of data on vaccination in pregnant women which led to delays in policy advice in this area does require some scrutiny. It has been a point of discussion for some years that pregnant women are excluded from clinical trials by vaccine developers and regulators until after licensure of products with safety cited as the rationale – this is because of potential risk to the mother baby and legal risk to the developer from an event in pregnancy that is either related to the product or perhaps unrelated but not possible to disprove. This has led to concerns that pregnant women may be excluded from life-saving vaccination and resulted in considerable discussion about risk of inequity of vaccine deployment in the Ebola outbreak in West Africa from 2014. In the COVID19 pandemic there was also a delay in many countries in advice for pregnant women because they were excluded from prelicensure trials and decisions were difficult in the absence of data. This is especially concerning given the severe outcomes in an unvaccinated group during the COVD19 pandemic. There should be active engagement with the MHRA to discuss how pregnant women could be better represented in earlier clinical studies to ensure that their health is not overlooked in future, this clearly is always a risk-benefit discussion, but given the tragic deaths in pregnancy with COVID19, this does need attention even for relatively low mortality pandemics.

114. I was not involved in the Government messaging about use of the vaccine in children. However, I did run a clinical trial of the Oxford Vaccine in children which showed that it induced excellent immune responses in children that were similar to those in adults and would likely have been protective and that there were no safety concerns. The Oxford vaccine was not used in the childhood programme in the UK (see AP11 - INQ000413056).

115. For the older adult vaccine programme, the decision by JCVI and DHSC to vaccinate was straightforward because there was a very low risk of side effects and huge benefit of vaccination to prevent hospital admission or death in individuals who were unvaccinated and thus far uninfected. However, at the time that the Government initiated the childhood programme in the UK, the benefit of the programme was much less clear and any gains had become marginal because the risk in childhood was already known to be vanishingly small, many children had already been infected and therefore had gained immunity from infection, those in risk groups for hospitalisation or death had already been offered the vaccine. With such marginal gains it is reasonable to take a view that vaccination is not good use of public resources, but also reasonable to take the alternative view that even a small benefit in a pandemic is worth it, whatever the cost. It is noteworthy that there was also a consideration that vaccination might help get children back to school, though not clear to me if any evidence of this important possibility was gathered. If formal Treasury cost-effectiveness analyses had been applied, as would be undertaken by JCVI in peacetime, I suspect it is unlikely that a programme in children would have gone ahead (because the very small cost to the NHS of COVID19 cases in children would not have met the normal thresholds for health spending). I was not involved in the decisions on childhood vaccination and I do not have direct access to the data which were available and were being considered at the time, but I think the uncertainty around the decision, which was presented to the public likely contributed to low uptake.

Key causes of vaccine hesitancy.

116. While vaccine hesitancy per se is often quoted as the chief reason for poor vaccine uptake, it is well known by public health experts that the biggest issue to tackle to improve vaccine coverage is access to vaccines. There are many challenges for individuals to get to immunisation services related to timing of vaccine clinics, distance to the clinics and other aspects of logistics for families

(especially for the young and elderly). For some it is simply a problem of access to a trusted health professional to talk through the importance and safety of immunisation in the process of making a decision – this is proper in all aspects of healthcare and is not hesitancy but just good judgement. Indeed tackling access, is an important issue for the decade ahead as we see vaccine coverage slipping across the UK. If we don't deal with this issue in peacetime, we certainly cannot fix it in the face of a pandemic. The recent polio transmission in London and measles outbreak in the West Midlands and London, and the rise in whooping cough cases and deaths shows that we have work to do in peacetime to ensure that everyone accesses and trusts NHS immunisation services. Multiple different solutions are required depending on the community and local knowledge is key to addressing the right solution in the right location.

117. Clearly, for some individuals, hesitancy per se is also an issue, but it is important to recognise that there are various underlying reasons for individuals to be hesitant and it is imperative that each of these is considered at the individual level and strategies developed to deal with them. We are currently better at identifying the presence of hesitancy than developing and using evidence to affect it.

118. Indeed, the issues affecting vaccine coverage in a non-pandemic period are likely to become important too in a pandemic. For example, we estimated in one study during the pandemic that about 10% of COVID19 vaccine hesitancy might relate to blood-injection-injury phobia (see AP12 - INQ000485227). Hesitancy is also associated with conspiracy beliefs that foster mistrust and erode social cohesion and conversely vaccine uptake is associated with recognition of the collective importance of vaccination (see AP13 - INQ000283335).

Measures that can be taken to engage with vaccine hesitancy and increase public trust in Covid-19 vaccines.

119. In the face of a pandemic, vaccine public information that highlights prosocial benefits may be especially effective overall but for the most strongly

hesitant (in this case about COVID-19 vaccines), provision of information on their own benefit reduced hesitancy more than information on collective benefit (see AP14 - INQ000485229).

120. At the population level it seems likely that improving understanding of science and scientific methods would prepare us all better to make informed choices about immunisation when faced with it. Decision-making is likely to be impaired when the decision is first made when needle is already in front of you. It is better to be fully informed and have an understanding of the importance of vaccination before entering the vaccine clinic. Tackling this in schools would provide better science literacy, education and understanding of risk and insights into the remarkable benefits of immunisation, and the dangers from the microbial world for us and our children if we don't get the jabs. It is also noteworthy that lower vaccine coverage is associated with higher levels of deprivation, and it is likely that reducing inequalities (which includes access to health and education) would improve understanding about immunisation and would likely reduce hesitancy – this is highlighted in research evidence showing higher immunisation uptake when families are better supported. It is also noteworthy that there are major differences in vaccine coverage by ethnicity and it is likely that this relates to differences in access to trusted information in different communities in our population. All of these issues seem to me to be solvable through better systems that are locally flexible to adapt to the needs of the community.

121. While we know there are multiple causes of hesitancy, there have been few studies to formally test interventions to reduce hesitancy and to work out which are the best strategies that are the most cost-effective for Governments to implement. However, failure to catalyse research in this area of social science now and build better strategies to reduce hesitancy, increases the threat from future pandemics.

Why the Astra-Zeneca vaccine was not included in the booster programme.

122. We collected data on use of the Oxford-AZ vaccine as both a 3rd dose and 4th dose booster vaccine. These studies did not raise any safety concerns

and showed that a good immune response was made following the booster dose. The vaccine was also tested in various mix-and-match studies with other vaccines in studies conducted in the UK and these studies also showed that the Oxford-AZ vaccine was suitable as a booster vaccine. I was not involved in the decision by JCVI on booster vaccines and so it is not possible to address the question directly and it would be better to put this to the chair of the JCVI COVID19 committee, Professor Wei Shen Lim. It may be that the changes in perception of the risk-benefit profile in a highly vaccinated population led to the decision. It is noteworthy that the rare serious side effects do not seem to occur (or are very unlikely) in second or subsequent doses of the Oxford-AstraZeneca vaccine.

Safety

Overview of the key stages in the clinical trials process for the Oxford-AstraZeneca vaccine, to include an explanation of the key elements of pre-clinical studies, Phase I, Phase II and Phase III.

Overview of the known risks associated with the Oxford-AstraZeneca vaccine, including but not limited to blood clots.

123. The preclinical studies involved various animal species and did not raise any safety concerns. Indeed, these studies provided confidence in moving to human clinical trials. Questions on these studies are best addressed to Dame Sarah Gilbert.

124. The different steps in the clinical trials are outlined earlier in this report

125. The clinical trials of the vaccine involved almost 25,000 individuals and this was sufficient to identify common side effects of the vaccine. These were similar to common side effects reported with vaccines in general. As expected, these side effects had onset mostly within 2 days of vaccination including fatigue, headache, malaise, muscle aches, joint pains, fever, nausea and chills. There

was also pain and tenderness at the injection site in some people. Of note these vaccine-related symptoms were more common with the first dose than with the second dose and we showed that these side effects were more common in younger individuals than older individuals. In the phase I and II trials there were no serious adverse events that were considered to be associated with the AZ vaccine. In the phase III trial there was a case of transverse myelitis reported which the site investigator thought could be related to the vaccine, but it was unclear of the significance of this event, i.e. whether it was coincidental rather than causal, since there were also cases reported in the control group and this condition also occurs in the absence of vaccination.

126. The study was paused on two occasions to review safety data following standard regulatory processes. In each case there was a detailed review by the independent data safety monitoring committee, the MHRA (and their independent advisors) and the study was restarted because no concerns were raised following extensive scrutiny. The second study pause received considerable media attention. Such pauses are appropriate and it is noteworthy that there was also a study pause in the Johnson and Johnson trials in October 2020 for safety review.

127. There was no evidence from the clinical trials that blood clots were associated with vaccination and no cases of the rare serious blood clots (thrombosis and thrombocytopaenia; also known as TTS or VITT) were identified in the Oxford clinical trials and were not anticipated prior to the vaccine roll out. This is because TTS was so rare that it could not have been picked up until millions of doses had been used.

128. The lack of information on very rare side effects in the clinical development of the Oxford-AZ vaccine is not surprising as clinical trials cannot detect very rare events.

129. Following licensure, Oxford University did not have access to or responsibility for safety monitoring and reporting as this is undertaken by a)

national regulators in countries in which a product is licensed (i.e EMA and MHRA in Europe) and b) the market authorisation holder (AstraZeneca in our case). The identification of the rare side effects that are not detected in clinical trials is only possible because of reporting of unexpected events by clinicians who become aware of cases that seem to be temporally associated with vaccination or that are unusual and have no explanation. Safety monitoring for certain conditions is also undertaken by regulators and academics using health records, but it is more difficult currently to detect patterns of conditions that are completely unexpected. Its easier to find patterns when you know what you are looking for. Safety monitoring is further complicated as the background rates of many rare conditions are unknown, so it is difficult to detect a signal of a change in rate if you don't know what is normal. Regulators and vaccine companies rely on reporting of events by clinicians or from databases and then have to assess whether the observed rates after vaccination are in excess of expected rates of the condition. Regulators tend to err on the side of caution in this inexact science and some apparent vaccine associations may be chance findings because of the uncertainty. This is made more difficult since doctors and the public are more likely to report an apparent new condition if they hear about it in the media leading to "reporting bias" and uncertainty about whether there is a true increase or simply an increase in reporting of the background rate that would have happened anyway. This inevitably means that any very rare signal has to be very carefully examined and this might not be possible immediately especially if collection of more data is required. Despite these difficulties in interpretation, the ability of systems to detect signals is far more advanced than it was in the two decades before the pandemic, and the identification of the TTS signal with viral vector vaccines and myocarditis with RNA vaccines provides some reassurance that rare events can be detected in the 2020s.

A chronology of when and how each of these risks first came to my attention.

130. I was not formally involved in the monitoring or review of safety signals following the AZ vaccine roll out. This was because the vaccine was licensed to AZ for manufacture, marketing and roll out and so they were required by

regulators to monitor safety and therefore would be best placed to outline the timelines and their formal response to the emerging signal as Oxford was (appropriately) not in the loop of these interactions. The main statutory responsibility for monitoring safety in the UK was for the MHRA and so they would be best placed to comment on the timing of signal detection and their decisions on use of the vaccine and how this was overseen. It might also be important to understand the process of decision-making by the JCVI COVID19 committee, led by Professor Wei Shen Lim. The key press briefing on the issue was given by DCMO, JCVI COVID19 chair, CEO if MHRA and chair of the commission on human vaccines on 7th April 2021.

131. I was clearly aware of the importance of safety monitoring and also the risks of misunderstanding a potential signal or getting the messaging to the public wrong and undermining confidence and followed the publicly available information on the emerging safety signal. I followed briefings in the media and by regulators closely. I was first aware from media reports of the very rare clotting disorder TTS around the time Denmark suspended use of the vaccine on 11th March 2021. I commented in the media on 15th March in support of the MHRA advice that they had in place a process of monitoring the signal and urging people to get vaccinated because any rare risk of the clotting disorder was likely to be far lower than the well-known risk from COVID19. Despite several countries suspending use of the vaccine while the issue was being investigated WHO took the same view as the MHRA (on 17th March) that from the evidence available the benefits of vaccination were outweighed by the risks of the coronavirus and that we should have confidence in the regulators to collect evidence and give advice on safety. Over the next few weeks regulators and AstraZeneca collected more data. Reports began appearing around 5th April that UK regulators were planning to restrict use of the vaccine in younger individuals because of a finding that the risk might be greater in younger individuals. The key press briefing on the issue was given by DCMO, JCVI COVID19 chair, CEO of MHRA and chair of the commission on human vaccines on 7th April 2021.

132. On 13th April the FDA paused the roll out of the Johnson and Johnson vaccine in the US over the same issue. On 16th April WHO reviewed all of the

safety data and said that the risk was about 4-10 per million.

133. The decision in the UK to continue vaccinating older adults with the vaccine, while supplies were limited of all vaccines, will have saved lives given the very careful analysis of risks and benefits that was undertaken – certainly for older adults at that time the risk of COVID19 was thought to be greater than any possible risk from the vaccine.

Whether any such risks disproportionately affected any identifiable groups or varied by age.

134. It is well documented that the mild common side effects mentioned above are more common in younger individuals than older individuals. It certainly appeared when the signal was first detected that case of TTS were more common in younger individuals and this information was presented in press conferences by the regulators including EMA and MHRA in April 2021. Clearly in the very elderly strokes and other bleeding or clotting conditions are common and so accurate rates of TTS in the elderly may be difficult to establish. However, a key issue was not their frequency in younger individuals but the risk of severe outcomes with COVID19 which became increasingly common with older individuals – this means that any risk of vaccine side effects should be balanced against the risk of the disease itself. It remains the case that in the time of supply shortage in the first half of 2021, vaccinating older adults saved lives.

135. Another observation has been geographic differences in risk of TTS with higher rates noted in Scandinavian countries than in the UK and the lowest rates noted in Southern Europe. There are also fewer reports from Asian countries or from Latin America or Africa, though this observation could be criticised because systems for surveillance are not as robust in some of the countries in these regions. There are some reasons to think that there are geographic differences but if these do exist it is unclear whether that is because of differences in the genetic background of individuals or environmental factors.

How knowledge of such risks fed into decision making on the Oxford-AstraZeneca vaccine, including advice if any given to the JCVI, MHRA and any other relevant UK Government body.

136. I was not involved in providing advice to JCVI, MHRA or other relevant Government bodies on the rare blood clots as I was not in a position to generate or analyse the data which was being collected by MHRA and other regulators and AZ. I did meet for an online discussion, which I convened, with Sir Chris Whitty and leading haematologists to discuss the condition but I do not have a record of that discussion. I am aware that a consortium was funded to undertake research into the condition but the Oxford Vaccine team was not involved because of the potential for a perceived conflict of interest.

Involvement in Government or non-Government public messaging on such risks.

137. I did not have any role in Government messaging on the risks but did provide some comment when asked to do so by journalists. Initially it was unclear if there was a real signal and once it was verified I commented that it was reassuring that the safety monitoring system was able to identify rare events and that the MHRA would provide advice.

Whether the current system for monitoring side effects and adverse reactions following Covid-19 vaccines is effective.

138. The fact that the system was able to identify a very very rare risk like TTS suggests that the system was functioning rather well. However, it is clear that with advances in technology and especially the use of AI, it should be possible in future to link vaccination status to a wide range of health data and pick up potential signals. However, this remains limited by a) the quality of data in the databases, b) the type of information available and c) access to the data which is restricted by the NHS. I am very worried that NHS concerns about data privacy

are making it more difficult to work with NHS data than is necessary. A key issue is ensuring that the health record is more complete and that data fields are standardised. So for example, it would be relatively straightforward to identify the many thousands of individuals admitted to hospital every year with clots on their hospital diagnosis records, but very difficult to identify a change in pattern with a few extra cases associated with low levels of the blood component, platelets (the hallmark of TTS), since these data are not so accessible in the usual extracts from the health record. Therefore, the system currently still relies on clinicians either spotting an abnormal pattern (such as clots in an unusual demographic) or an excess of cases and reporting it.

139. The yellow card system provides an alternative means of assessing safety signals passively. Yellow card reports are submitted to the UK regulator, the MHRA. This system relies on doctors or members of the public providing a report of any event that occurs after vaccination that they think could be associated with the vaccine. This results in a lot of reports, especially with new programmes, about conditions that would have happened anyway (eg an episode of pneumonia in a child, new diagnosis of diabetes or a condition like dementia) and the regulator therefore has to sort out the noise of normal conditions which happen around the time of vaccination from something new that may be caused by the vaccine. This is especially difficult with a pandemic vaccine roll out when everyone in the population has recently had a vaccine, and therefore any condition that arises in the months afterwards *could* have been caused by the vaccination. To make this assessment of what is noise and what is real, it is important to have good data on background rates of conditions, but the limitations of existing data show that for many conditions we just don't know. Furthermore, even where we do have good data, it can be difficult to assess whether the risk has changed. For example, if we take one type of clotting problem, deep vein thrombosis, where it is known that we should expect 60,000-100,000 cases per year in the UK, it would be very difficult to detect an increase of even a few hundred cases as this would still fall within the expected annual range.

140. Nevertheless, we can improve on safety monitoring by enhancing the quality and types of information in GP and Hospital electronic health records and building the technical and medical expertise in using these databases to monitor safety. Working with patient data is very challenging because of the information governance issues that provide substantial obstacles to access but this can be achieved, as has been done for example with OpenSAFELY, which is led by Ben Goldacre.

Effectiveness of the safeguards which exist to ensure both the independence and impartiality of MHRA and its advisers.

141. My experience of the MHRA is that they are impartial and independent. I also note that internally the MHRA department working with developers on clinical trials is separate from the department working on licensing, providing a further layer of independence within the organisation.

142. I have interacted with the MHRA over almost two and a half decades as an investigator on clinical trials of vaccines and have found the MHRA to be a tough but reasonable regulator of what we do. They review every trial protocol we submit to them in great detail and often refuse to accept the application until modifications are made or clarifications given to them. Over this time MHRA have also regularly inspected the clinical trial conduct at Oxford University in general, or my vaccine team at Oxford specifically, or inspected a particular aspect of our work or an individual trial to check compliance with the regulation. I have also sat on several MHRA committees, where there is a strict conflict of interest policy and members are regularly excluded from discussions if they have any connection to the issues under discussion.

Improvements that could be made to such safeguards.

143. From the perspective of an academic vaccine researcher, I don't see a problem in the independence/impartiality of regulators in the UK. The work of the MHRA is enshrined in law and there is a strong culture in the organisation and

amongst its advisors of independence and separation from the vaccine companies and academic developers where relevant. It is important not to confuse independence and impartiality with engagement. It is essential that we are able to maintain good engagement and dialogue between industry/academic researchers and regulators to ensure that the UKs role in development of vaccines is flexible, responsive and connected into the current issues. I believe that the MHRA managed this balance very well in the pandemic, facilitating pandemic vaccine development whilst also maintaining the highest standards and not cutting any corners.

Observations on the MHRA Yellow Card monitoring and reporting system.

144. The yellow card system is an important system to allow doctors and members of the public to flag rare events which may or may not be associated with recent receipt of a vaccine or drug. The system does allow the MHRA to monitor for patterns that might emerge. However, it produces rather noisy data which means it can be difficult to sort out true signals from coincidence and to avoid reporting bias (positive or negative). Also the presentation of the reports to the public is somewhat misleading in that the events are described as adverse reactions, even though there is no causality assigned in the list of reports and many are not "reactions" at all. We need better data on the expected rates of normal conditions so that an assessment can be better made when reports arrive at the MHRA that might or might not be important. This requires a concerted effort to link primary care and hospital data across the NHS and to ensure that the quality of the data that are collected are appropriate to allow better characterisation of rare conditions in our population.

Vaccine disinformation / misinformation

145. There were a number of examples of misinformation and disinformation around the Oxford-AZ vaccine. Some of the disinformation related to deliberate attempts to undermine the vaccine.

146. The clinical trials of the Oxford-AZ vaccine began on Thursday 23rd April 2020 and on Sunday 26th April a fake news website declared that the first volunteer had died, but in reality she was alive and well. The motive is not clear, but this was rapidly debunked in various media outlets led by the BBC through proof of life interviews.

AP15 - INQ000484810: UK vaccine trial volunteer says she is 'doing fine' after online death rumours | Coronavirus | The Guardian

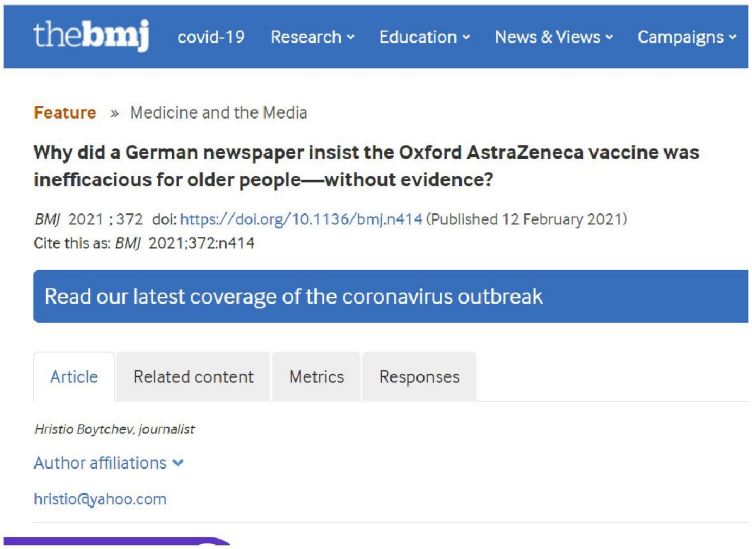
147. At the time of the first announcement of the interim results on 23rd November 2020, only the high level data were available and detailed analysis was still to come. Normally we would not press release data until publication of the results in a scientific journal, usually some time after the first analysis is available and more detailed interrogation of the data has been done. However, there was some more urgency in a pandemic as a result of public interest and the ongoing risk to life, and there was also an imperative from our industry partner because of potential insider trading rules. AZ, considered any results to be commercially sensitive and therefore had to be released publicly before the markets opened, about 36 hours after the first information was available. To report the results faithfully, we presented the initial high-level analysis without the

more detailed statistical analysis which was undertaken over the subsequent weeks. The initial data indicated that the efficacy was higher in one subgroup in the trial than the other. To be transparent and maintain integrity we presented the results from the two subgroups as well as the overall efficacy figure in the press release. With further analysis it is clear that the subgroup with the highest efficacy had the longest dosing interval, which gave an expected better result, but at the time of release we didn't have this information as that was still to be analysed. The media widely referred to the differences in efficacy results as being due to a dosing "error" which damaged confidence in the vaccine. The group with the longer interval between doses were also those who received a lower first dose in the clinical trials (we later showed that this didn't make any difference to immune responses after a full second dose if the interval was the same) and a full second dose. We did speculate that the lower first dose might have contributed to the improved protection in this subgroup as there is some existing immunological evidence that different doses may be more or less protective, but we later showed that this wasn't the case. The lower dose (lower than in the phase I/II trials) was given initially in the phase III clinical trials as the first dose to this subgroup because of a discrepancy in testing methods between 2 manufacturing facilities. The testing methods are used to establish the dose of vaccine and one facility gave a higher result on the dose than did the other one. In consultation with the MHRA, we therefore safely initiated the trials with the lower dose while investigation into the discrepant methods was ongoing, and then used the full dose for all subsequent vaccinations once we had established, with the MHRA agreement, which method should be used. By working closely through this difficulty with the MHRA we were able to continue safely moving ahead with the vaccine development to reach to ultimate goal of testing the vaccine. We later showed that the 2 different regimes of vaccination gave very similar immune responses and this was actually a non-issue. Having advice from the MHRA closely at hand through this process was exceptional and it is noteworthy that developers facing similar challenges in other countries stalled at such hurdles. What was declared in the media as an error was one of many pandemic vaccine development challenges which all developers had to overcome, and highlights the considerable tenacity required to get to the goal of

a vaccine for the world. This may be part of the reason why so few developers got there, but the headwinds in the media made it tough.

148.

149. When the vaccine was licensed a German government source is said to have reported to a media outlet that the vaccine was only 8% effective. There was no basis for this comment that we can find but it created a lot of media interest, it was not rapidly corrected, and likely added to misinformation about the vaccine performance.



150.

AP16 - INQ000484812 Why did a German newspaper insist the Oxford AstraZeneca vaccine was inefficacious for older people—without evidence? | The BMJ

AP17 - INQ000484807 Report of 8% vaccine efficacy for elderly is unreliable - Full Fact

151. President Macron claimed that the vaccine was "quasi-ineffective" in older adults. This statement caused a lot of concern among the public in many countries and undermined confidence in the vaccine. At the time of the interim analysis (Late November 2020) the body of data available clearly showed the vaccine to be safe and induce strong immune responses in older adults. Indeed the immune responses looked rather similar to those in younger adults, who had high levels of protection from the vaccine. However, there was a smaller number of older adults recruited at the time of the interim analysis in the phase III trial whose data could be included in the analysis, partly because the recruitment of this age group had been delayed by the independent data safety monitoring board (DSMB). The DSMB took the view that the trial team should await results of the small phase II study in older adults before allowing recruitment of a large number of older adults in phase III, which meant that older adult recruitment started later, even

though we had planned to recruit older and younger adults at the same time. So, although the vaccine performed very well in all age groups, there was less information to provide certainty at the time of licensure. However, vaccine experts making decisions in the UK (MHRA and JCVI) could be confident based on similarity of immune responses that protection should be similar to that seen in younger adults and did recommend use of the vaccine across all ages.

152.

AP18 - INQ000484797 Covid-19: Fact-checking Macron's over-65s claim about the Oxford-AstraZeneca vaccine - BBC News

153. A report in the Times outlined an attempt to persuade people that the vaccine would change people into chimpanzees because the vaccine was based on a virus that can infect chimps.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AP19 - INQ000484981 Russians spread fake news over Oxford coronavirus vaccine (thetimes.co.uk)

According to the report in the Times newspaper this was an attempt to undermine the vaccine in markets where the Russian vaccine was also likely to be used.

154. A channel 4 Dispatches documentary outlined evidence that medical representatives associated with Pfizer in Canada claimed that the AZ vaccine integrated into people's DNA and caused cancer. There is no evidence that this can occur and no such event has been reported by regulators despite billions of doses being used worldwide.

AP20 - INQ000484811: Watch Vaccine Wars: Truth About Pfizer: Dispatches | Stream free on Channel 4

The role played by the Science Media Centre in relation to the Oxford-AstraZeneca vaccine.

155. The science media centre played an important role in the pandemic by providing a forum for interaction between subject experts and science and health journalists through media briefings on many new research findings that were emerging as more became known about COVID19 during the pandemic. The SMC

also provided the science and health journalists with comments which could be used in media articles from their extensive network of experts in response to health and science issues that were appearing in the media.

156. In my view, much of the reporting around vaccines and vaccine development in the UK was better communicated by the media than in some other countries where it was often more sensational or politicised. It seems likely that the SMC played an important role in connection with the media to facilitate this. Most countries do not have a similar organization and in our communications elsewhere during the pandemic it was very difficult to provide any comment to media organizations outside of the UK, simply because there are so many and such a huge number of requests were coming to the University. At the peak of media interest the University had 18 staff members working on communications and managed up to 1000 contacts per hour from journalists. This meant that we were only able to engage with a handful of organisations in most non-UK settings whereas the SMC briefings made it possible for a very wide engagement with the UK media.

157. I think there are some important lessons that can be learnt from the media interactions during the pandemic and some recommendations have been nicely summarised by the science media centre themselves: AP21 - INQ000353459: The-Science-Media-Centres-recommendations-on-science-and-the-media-based-on-our-experience-during-the-COVID-19-pandemic-4.pdf (sciencemediacentre.org).

158. Some observations which are aligned with the science media centre thinking on this topic:

- It is important for scientist to maintain integrity and to be open about uncertainty that there is always in emerging data. There is a risk of trying to simplify public health messaging by giving certainty which then results in mistrust when the evidence directs a change in thinking or policy.

- News is immediate, perhaps more so than ever before and it is important to ensure that scientists understand the importance of timely responses to media

and public questions about emerging data or concerns – ensuring the best scientists who understand the data are among the voices commenting on the latest developments. We must train, encourage and support scientists to engage with the media and not leave a void where misunderstandings could take hold.

- Most of all scientists do need to be among the voices commenting in the media and not to hide away in their labs. Media or public engagement is not commonly part of training in science.

- To help with trust, it would make sense to enable unrestricted engagement with the media by independent scientists (whether they be advising Governments on SAGE or JCVI or just representing academic expertise).

- It is important to understand that scientific debate is a necessary part of the scientific process to test hypotheses and interrogate the data that arise from research, so that the best interpretation can be found and the gaps in knowledge identified so that the evidence-base can be improved. This is not the same as political debate where an ideological position is defended – science is about testing the evidence and potentially changing the position. A U-turn is welcome in science if the evidence says it fits the data better than a straight road.

159. As noted above, the University of Oxford's Public Affairs Directorate (PAD), led by Mr James Colman, had a pivotal role in the interactions with the media and in coordination with the SMC. The team also worked closely with the press office at AZ on the communication on vaccine development. PAD put considerable effort into communication with the public about vaccine development to ensure accurate and informative communication as part of the mission of a University. For example a cartoon video of how to make a vaccine has been widely viewed on YouTube

160. The PAD team were recognised in the communications and media world with multiple awards (AP23 - INQ000484795): Awards and recognition | University of Oxford

161. Perhaps less recognized, another important role that the Science Media Centre played, was their sharing of upcoming scientific publications with the scientific community. The reason for sharing information was to gather expert commentary for the media, but this also meant that their excellent research team were keeping busy researchers such as myself up to date with all the latest evidence in real-time, which would have been impossible without them.

162. For our vaccine development specifically, the SMC played a major role in facilitating interactions with the media. Here are links to some of the briefings undertaken by the Oxford-AZ team (for simplicity I have excluded Oxford briefings on the mix and match studies which were also hosted by the SMC):

163. 'Hear from the Oxford COVID-19 vaccine team', 17 April 2020 (AP24 - INQ000484798)

164. 'Results of the Oxford phase 1/2 COVID-19 vaccine trial', 20 July 2020 (AP25 - INQ000485237).

165. 'Phase 2 trial safety and immunogenicity data from the Oxford COVID-19 vaccine trial including in healthy older adults', 19 November 2020 (AP26 - INQ000485718)

166. 'AstraZeneca and University of Oxford media briefing', 23 November 2020 (AP27 - INQ000484794).

167. 'Lancet publication of the Oxford AstraZeneca phase 3 COVID-19 vaccine trial', 8 December 2020 (AP28 - INQ000484801).

168. 'Q&A with Oxford scientists on new preprint on the vaccine and the B.1.1.7 'Kent' coronavirus variant strain', 5 February 2021 (AP29 - INQ000484806).

169. 'Oxford vaccine data on long dose gap and third booster dose', 28 June 2021 (AP30 - INQ000484804).

170. ['Mixed vaccine schedules in people vaccinated with CoronaVac (SinoVac)', 21 January 2022 (AP31 - INQ000484803).

171. ['Willingness of children and adolescents to have a COVID-19 vaccination', 27 September 2021 (AP32 - INQ000484813).

172. *['Coronavirus – where are we now?', 7 February 2020 (AP33 - INQ000484796).*

173. *['Launch of the Pandemic Sciences Institute', 5 July 2022 (AP35 - INQ000484802).*

174. *['Q&A on vaccine manufacturing', 11 March 2021 (AP36 - INQ000484805).*

Vaccinology and 'all-in-one vaccines'

175. Various new approaches are being developed that attempt to provide vaccines which would be more broadly protective across a virus family. Such approaches could potentially be useful in producing prototype vaccines that "covered", for example, a wide range of different coronaviruses or alternatively future variants of SARS-CoV2. Pursuing this line of investigation is important as it could provide a potential for a new approach that allows for vaccines to be developed pre-pandemic and possibly stockpiled, perhaps for those in the front line, and buys time for a pandemic-specific vaccine to be developed for wider use. Some studies in animals have shown some promise, but it is important that such prototypes are tested in humans, since we have a very different immune system from that in a mouse.

176. Another approach is to develop vaccines which contain multiple components which are known to be protective – for example one protein is included in all influenza vaccines, the hemagglutinin (HA) and is known to provide protective immunity. A vaccine containing multiple influenza HA types could be a useful pandemic stockpile vaccine that could be used to prevent severe disease against whichever HA pandemic virus emerged. One of the obstacles to influenza vaccine stockpiles is that we don't know which HA type will emerge – currently we are concerned about the H5-type which began in a pandemic in birds and is now spreading in cattle in the USA, but there have also been concerns about H9, and most countries believe that they can't afford to have multiple individual stockpiles for H5, H9 etc. A single stockpile that covered the main threats in one vaccine may be more acceptable.

Statement of Truth

I believe that the facts stated in this witness statement are true. I understand that proceedings may be brought against anyone who makes, or causes to be made, a false statement in a document verified by a statement of truth without an honest belief of its truth.

Signed: Personal Data

Dated: 5/10/24