Witness Name: Professor Dame Sarah Gilbert
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UK COVID-19 INQUIRY

WITNESS STATEMENT OF PROFESSOR DAME SARAH GILBERT

I, Professor Dame Sarah Gilbert, will say as follows: -

1. I make this statement in response to a request under Rule 9 of the Inquiry Rules 2006 received from the UK Covid-19 Public Inquiry ("the Inquiry"), asking for information about my role, and that of the University of Oxford ("the University") and organisations and departments within and outside the University, in the development of a vaccine for the virus known as Covid-19.

2. I have structured this statement by reference to the areas of focus set out in the request received from the Inquiry, and I have adopted the headings used by the Inquiry in that request, and inserted my own sub-headings where appropriate.

3. The Inquiry has asked that my responses focuses on the period from 30 January 2020, when the first cases of Covid-19 were confirmed in the UK. However, intensive work began on developing a vaccine for Covid-19 several weeks before this, at the very beginning of January 2020, and so I have included material relating to this period in this statement.

4. I have not been asked to provide a corporate statement on behalf of the University or any part of it, and so I deal in this statement only with matters within my personal knowledge.

5. Given my extensive commitments during the period when I have been asked to prepare this statement, I deal with some areas briefly below. I have, after many of the events described in this statement, co-authored a book with my colleague Prof Cath Green, titled "*Vaxxers: The inside story of the Oxford AstraZeneca vaccine and the race against the virus*" and published by Hodder & Stoughton in 2021 (ISBN 9781529369885). In some

respects I have dealt in that book with the subject-matter of the questions raised by the Inquiry.

Structure, Role, People and Processes

Overview of my role at Oxford University

6. At the beginning of 2020 I was employed as a Professor of Vaccinology in the Jenner Institute, which is a sub-department of the Nuffield Department of Medicine (NDM) in the Division of Medical Sciences at Oxford University. In early 2020, the Jenner Institute had a staff of approximately 152. I am now employed in the Pandemic Sciences Institute, which is also part of the Nuffield Department of Medicine. I have been employed by the University since 1994 to undertake research, including the supervision of graduate students, not teaching of undergraduates. At the relevant time, my post, those of the staff in my group and all research expenses were funded by competitive grant funding.

7. At the beginning of 2020 I was working on the development of a vaccine against Middle East Respiratory Syndrome (MERS) which was originally funded by DHSC via the UK vaccines network but later received funding from CEPI, the Coalition for Epidemic Preparedness and Innovation. I was working on projects on vaccines against Lassa and Nipah viruses funded by CEPI, and an influenza vaccine funded by the Medical Research Council (MRC). I was also co-lead of Vax-Hub, a programme covering vaccine manufacturing research, along with a second co-lead at University College London.

8. I was one of the Principal Investigators (group leaders) in the Jenner Institute, working on projects developing vaccines against several pathogens with outbreak and pandemic potential. I was responsible for applying for funding for these projects, recruiting staff, supervising students and overseeing the research projects.

Interaction with UK Government

9. Throughout my involvement in the development of a vaccine for Covid-19 I had very limited personal contact with the UK Government. I do not hold written records of all such contact, whereas I anticipate that Parliamentary and ministerial records may provide a fuller account. However, and from memory, I recall the following:

    a. On or about 13 April 2020, I had a call with Alok Sharma, then the Secretary of State for Business, Energy and Industrial Strategy, during which I discussed with

Mr Sharma progress on developing a Covid-19 vaccine, and the funding which would be needed in order to continue the manufacturing for further clinical trials and more clinical development. I am not aware of whether a record of the content of this call was kept by the civil service.

b. On or about 19 April 2020, I, along with Prof Sir Andrew Pollard of the Oxford Vaccine Group, had a brief call with Matt Hancock, then the Secretary of State for Health and Social Care, during which we discussed the shortage of personal protective equipment (PPE) available for staff working on clinical trials of a Covid-19 vaccine.

c. I gave evidence to at least two Select Committee hearings, including, as far as I can recall:

    i. February 2020, when I gave evidence in person before a Science and Technology Select Committee;
    ii. 23 June 2020, when I gave evidence before the House of Lords Select Committee on Science and Technology.

10. On or about 18 April 2020 I became aware, from the media, of the UK Government Vaccines Task Force. I did not personally participate in the Task Force. However, and as I understand the position, Professor Sir John Bell, Regius Professor of Medicine at the University, was aware of progress with developing a vaccine and was in contact with the UK Government.

Development of the vaccine within Oxford University

11. I made the decision to start work on the vaccine at the earliest possible opportunity and work as quickly as possible. I wrote a grant application seeking funding from UK Research and Innovation in February 2020 in which I set out plans for the initial stages of vaccine development. However as it became clear that vaccine development would be more than an academic project reaching only as far as phase I trials, I discussed plans with Professor Sir Andrew Pollard who agreed to become Chief Investigator for the clinical trials, as he has a great deal of experience in that field. Professor Sir John Bell was also a strong supporter of the project. Once the project moved into the Clinical Biomanufacturing (CBF) Facility in February 2020 Professor Cath Green was responsible for overseeing all of the vaccine manufacture and testing.

12. At different stages in the development of the vaccine, different numbers of people were involved in the work.

13. The University has many processes in place for applying for and managing grant income, HR, contractual arrangements with outside bodies, intellectual property and applications to conduct clinical trials. All processes were followed, but with greater speed than usual.

14. However, I make the general point that the people involved and identified above were experts in their own field, all of whom had we had worked together in the past. The only formal body was a regular meeting organised by Professor Richard Cornall, head of the Nuffield Department of Medicine (NDM), to bring together NDM researchers who had all independently decided to work on a response to the pandemic. We each shared our recent news. As far as I can recall, the meetings were informal and were not minuted.

15. My impression and recollection is that all of the research staff I worked with at the University made the development of a Covid-19 vaccine our top priority and all worked as fast as we could in our own areas of expertise, collaborating where we were able to do so effectively. Meetings were organised as required, initially in person and then online.

16. Dealing with the specific question asked, I did not experience any challenges to the effective development of a vaccine arising from relationships with my colleagues.

Preparedness to develop vaccines

17. I can only comment on my own experience at the University, rather than for the UK as a whole. The Ebola outbreak in West Africa in 2014 had highlighted the fact that there are a number of highly pathogenic viruses which occasionally cause outbreaks, and the world does not have vaccines, therapeutics or diagnostics ready to use. The World Health Organisation (WHO) (as well as other organisations) put together a list of 'priority pathogens'. In the UK, the Vaccines Network (a project formed to advise the Department of Health and Social Care on research and development investment) produced its own list of priorities, and there was a Medical Research Council call for proposals to work on vaccines against the pathogens on the list, but open only to MRC units. I was based in the Jenner Institute at Oxford, which is not an MRC unit, but in about March of 2016 partnered with Vincenzo Cerundolo, head of the human immunology unit at the Weatherall Institute of Molecular Medicine in Oxford to submit an application for MERS vaccine development. My colleague Arturo Reyes Sandoval applied with the Glasgow

Centre for Virus Research to develop a Zika vaccine, and George Warimwe applied with the Uganda Virus Research Institute to develop a vaccine against Rift Valley Fever Virus. All applications were funded and work began.

18. The WHO asked for submissions to its 'R&D blueprint exercise' to propose platform technologies that could be used to advance development of vaccines, diagnostics and therapeutics. I applied in about January 2016 proposing the ChAdOx1 vaccine platform (see para 30 below concerning platform technologies). After the first round of presentations in Geneva I was invited to proceed to the second stage of the exercise, but recommended to partner with a pharma company. Janssen vaccines (part of Johnson and Johnson) were also applying and agreed to partner with us. The WHO approved our proposal to use ChAdOx1 to produce stockpiles of multiple vaccines against known outbreak pathogens. In parallel with the R&D blueprint exercise CEPI, a global consortium of public, private and other bodies was being formed to support the development of vaccines, with funding from multiple sources, and Oxford and Janssen were subsequently able to apply jointly to CEPI in response to the first call for proposals to develop vaccines against MERS, Nipah and Lassa viruses. The application was made in 2017 and a contract with CEPI was signed after a long negotiation period. Work on MERS was planned to continue the vaccine development already underway with UK funding, and begin work on Nipah and Lassa vaccines.

19. All of this work was aimed at developing vaccines against pathogens that are known to cause outbreaks, which in many cases had been contained rapidly, but occasionally caused larger outbreaks. The concept of 'disease X' was then added to the list of pathogens, to represent an outbreak by a pathogen not previously described. Whereas outbreak pathogen vaccine development was able to follow the usual slow, stepwise progression of vaccine development with multiple long pauses to seek additional funding, it became clear that this would not be acceptable if a new pathogen began to cause an outbreak, or epidemic. At the time, the emphasis was clearly on containing small outbreaks quickly, and not pandemic preparedness.

<u>CEPI Proposal</u>

20. CEPI put out a call for proposals on development of vaccines against 'disease X'. I was aware that we would have to change working practices to allow us to move more quickly. Previously my research group had produced small batches of vaccines for use in research labs to generate pre-clinical data which we would use in applications for

funding. If successful, perhaps one to two years later we would then work on producing a well-characterised stock of vaccine that could form the starting point for "Good Manufacturing Practice" (GMP) manufacture of the vaccine using a GMP-certified cell bank in a GMP manufacturing facility. That process could take months, as could the vaccine manufacture and quality control testing, followed by applications to regulatory and ethical bodies before a trial could start, even if all the funding was available from the beginning.

21. After discussion with colleagues in the University's GMP manufacturing centre, the CBF, I worked on a proposal to CEPI. It was not funded, but the planning that we had done meant that, by early 2020, we had conceived of a methodology for moving a vaccine rapidly from concept through GMP manufacture in readiness for clinical trials, using platform technology.

22. The methodology proposed reflected three factors which would allow us to manufacture a SARS-CoV-2 vaccine at increased speed.

23. First, drawing on years of experience in manufacturing novel vaccines, including multiple ChAdOx1-vectored vaccines, for first-in-human clinical trials. Over the preceding decade, procedures had been refined and staff had been trained and then gained experience. This allowed us to work as efficiently as possible, having already identified potential pitfalls and how to avoid them. Using a platform technology means that the same procedures can be followed again for a new vaccine, without having to develop a new manufacturing process, which can take many years. This also applies to the clinical trial that we proposed, since the dose that we would test had already been identified meaning that it was not necessary to start testing a low dose of the vaccine, study the response and then increase the dose in a further group of clinical trial participants.

24. Secondly, procedures were carried out in parallel rather than in series. Rather than complete part of the manufacturing process, stop and wait for the results of tests to find out if it had worked, we proceeded 'at risk', moving on to the next part of the process in parallel with conducting the tests on the first part. The extensive experience on the manufacturing process allowed us to do this, as in the past it was rare for any of the tests to fail. For example, we will test the first very small batch of vaccine that is made to see if it is sterile (no bacterial contamination) before continuing with the process, and these tests take three weeks to complete. If the procedures have been carried out correctly there will be no bacterial contamination. We moved directly to the next phase of manufacture while the tests were being conducted rather than stop and wait for the test

results. The tests were performed, no bacterial contamination was detected and work continued. Taking this approach carries a financial risk, since if we had detected bacterial contamination we would have wasted the material being used in the next part stage of manufacturing process. However the time saved makes this approach essential when speed is of the essence.

25. Thirdly, we developed and used a novel method for the initial generation of the ChAdOx1 vaccine seed stock at the beginning of the manufacturing process. Prior to 2020, there had always been a long delay between the first time a particular ChAdOx1-vectored vaccine was produced in a lab, and the manufacture of the vaccine in a clean room, whilst funding for the project was secured. In 2020 we tested a new approach to completing this part of the work very quickly, with the input of virologists and regulatory specialists. The details are highly technical and the process was not smooth, but was completed faster than ever before. Subsequent to the first manufacture, we continued to work on this part of the process and developed a faster and simpler way to initiate manufacture of a novel vaccine. This process was then tested to make candidate vaccines against some of the SARS-CoV-2 variants, one of which was then tested in a small clinical trial.

Lessons learned

26. The majority of viruses that cause epidemics and pandemics result in short-lived infections from which the infected individual either recovers or dies. In contrast HIV causes chronic infections, during which many different virus 'strains' may be present in the infected individual at any one time, or over time. This requires a different approach to vaccine development and I will not comment further as I have not worked on HIV vaccine development.

27. The main learning from other outbreaks is that there is a great deal that should be done in advance of a new outbreak of a known pathogen in order to be ready to respond quickly. Vaccines can be tested for efficacy in pre-clinical studies, manufactured for clinical trials and taken through phase I and Phase II clinical trials. A stockpile of the vaccine can be produced. Plans for testing the vaccine for efficacy in the event of an outbreak can be finalized. This should proceed in parallel with plans to develop and test diagnostics and therapeutics.

28. At present the WHO priority pathogen list is:

a. COVID-19
b. Crimean-Congo haemorrhagic fever
c. Ebola virus disease and Marburg virus disease
d. Lassa fever
e. Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
f. Nipah and henipaviral diseases
g. Rift Valley fever
h. Zika
i. "Disease X"

There are licensed vaccines for COVID-19 but not the other pathogens on the list.

29. For the unknown 'disease X' the best approach is to make sure that we understand how to make effective vaccines against all of the different viral families, as it is highly likely that any new outbreak will then be related to a pathogen for which we understand how to make a vaccine. It was beneficial to have worked on a vaccine against MERS coronavirus when we needed to produce a vaccine against a novel coronavirus in 2020.

30. The role of 'platform technology' in the development of new vaccines. Briefly, a "platform technology" provides a methodology for rapid and cost-effective vaccine development. This avoids the need to undertake certain parts of vaccine development for every new disease which emerges; a key feature of platform technologies is that the basic means of manufacture, as well as knowledge as to storage, dosage and effects, exists before a disease is identified. This differs from traditional vaccine development, which typically begins by using a pathogen, from which a vaccine could be developed, but which required very extensive work to develop each new vaccine. This does not eliminate the need for careful and phased safety testing, but it allows the design and development phase, and preparatory work for manufacturing, to be significantly shortened, and in the case of the Covid-19 vaccine allowed for stages to be undertaken concurrently, without compromising the safety or efficacy of the eventual vaccine.

The Oxford-AstraZeneca vaccine

Development, manufacture, procurement and approval

31. The first stage in the development, manufacture, procurement and approval of the Oxford-AstraZeneca vaccine was to design the vaccine, including making decisions about which

platform technology to use but also selecting precisely which DNA sequences will be required to express and encode the spike protein antigen. This work was complete by January 13th 2020.

32. Vaccine construction: after commissioning production of the required DNA sequence it is added into the ChAdOx1 sequence, and a first batch of the vaccine for use in preclinical testing was produced.

33. Immunogenicity testing in mice was completed and vaccine was sent to Rocky Mountain Labs (RML), National Institute for Health (NIH), USA, for testing in a non-human primate immunogenicity and challenge study. Data was received by April 22nd 2020 and shared with the MHRA.

34. DNA encoding ChAdOx1 nCoV-19 was transferred to CBF who made the 'starting material'.

35. CBF then produced the vaccine seed stock and clinical batch which completed all necessary testing.

36. The phase I clinical trial commenced on April 23rd 2020.

37. Subsequently phase II and phase III clinical trials commenced, interim primary readout of vaccine efficacy was announced on 23 November 2020.

38. The vaccine was licensed for emergency use by the MHRA on 30 December 2020

39. Vaccine rollout began on 4 January 2021.

40. I led the project through the initial stages and worked on the vaccine design along with two others. Staff in my research group produced the preclinical batch of vaccine and preclinical data. I organized the initiation of work at CBF, transfer of vaccine to RML NIH and transfer of data back to the UK, as well as further vaccine manufacturing for clinical trials at Advent. Professor Pollard was responsible for clinical development and AstraZeneca took over leadership of vaccine manufacturing for clinical trials as well as for vaccine rollout post licensure.

41. The development of the vaccine used the ChAdOx1 platform technology (a replication-deficient simian adenoviral-vectored vaccine), which I had been working on since 2012. I

had previously used this platform to make vaccines for influenza and MERS (Middle East Respiratory Syndrome, and, like Covid-19, a coronavirus). Others at Oxford had also used the platform to produce vaccines against different diseases and conduct clinical trials. Prior to April 2020, 12 phase I trials had been completed or were underway, so there was extensive experience in vaccine design, GMP manufacture, and preparation for and conduct of clinical trials in healthy individuals.

42. The existence of this platform meant that, as soon as we received the genomic sequence data of the emerging disease (which was made available on 10 January 2020) we could, and did, immediately begin work on designing a vaccine on the basis of the ChAdOx1 platform. Prior to obtaining the genomic sequence data, it was known that the emerging disease was a coronavirus, and so that a vaccine was required which would induce an immune response in humans to the spike protein which is the protein present on the surface of coronaviruses. We knew, from the experience in developing a vaccine for MERS, that the ChAdOx1 platform could be used to develop a vaccine for a coronavirus across a wide population group. Data from the MERS phase I trials indicated that the desired immune responses could be induced after a single dose of such a vaccine. Further work on administering a second dose of the MERS vaccine at either 4 weeks or 26 weeks after the first dose had been initiated but data was only available from three trial participants at the point when the trial was put on hold because of the pandemic, although the very limited data available did indicate that immune responses were boosted by the second dose.

43. Additionally, a preclinical vaccine efficacy study had demonstrated that a single dose of the MERS vaccine was protective against high dose virus exposure in non-human primates: **SG/1 -** INQ000475212. Thus although the efficacy of the ChAdOx1 MERS vaccine in humans was not known, the likelihood was that the vaccine would be effective and that other vaccines against coronaviruses produced in the same way would be expected to be effective.

Funding

44. As noted below, initial funding came from VaxHub which supports vaccine manufacturing research in general. This was followed by funding from CEPI to produce the vaccine starting materials, UKRI to manufacture the first batch of vaccine and conduct a phase I study and then the UK vaccine task force to fund further vaccine manufacture and clinical trials through to licensure. Additional funding for clinical trials in South Africa and Brazil was received from BMGF and Lehmann foundation (applied for by Professor Pollard).

During 2020 there were also philanthropic donations co-ordinated by the Oxford University Development Office via the Covid relief fund, and some of that funding was used to support the vaccine development.

45. The VaxHub funding was already in place. Both CEPI and UKRI had rapid response calls in early 2020, with expedited review times. At one stage, having been awarded the UKRI grant but not yet received the funds, the University provided an underwrite to allow signature of the vaccine manufacturing contract with Advent, in order to secure a vaccine manufacturing slot. Under normal circumstances the contract signature would have waited until the funding arrangements had been finalized. The vaccines task force then worked quickly to review our application and fund during April of 2020.

46. I have been asked to comment on the involvement of a number of other organisations in the development of the vaccine, and I summarise them below.

Oxford University

47. As is largely set out above, within Oxford University, my research was carried out within the Jenner Institute, which is a sub-department of the NDM. When we had prepared a vaccine which was ready to move to manufacturing, initial work was undertaken by the CBF, which is also part of the NDM.

48. The Oxford Vaccine Group is a sub-department of the Department of Paediatrics, which along with NDM is in the Division of Medical Sciences at Oxford University. Originally concentrating on studies of paediatric vaccines, producing data which fed into recommendations for their use in vaccine schedules in the UK, in recent years OVG has also worked on the development of novel vaccines, including some utilizing the ChAdOx1 platform. Professor Pollard is the head of OVG. In 2020 he became the Chief Investigator for the Oxford-led ChAdOx1 nCoV-19 clinical trials. Staff from OVG and the Jenner Institute all worked together on those clinical trials.

49. The vaccine knowledge project is a website set up by OVG, originally to provide accurate information about paediatric vaccines in use in the UK, in particular for parents of young children. In 2020 its remit expanded to provide information about Covid vaccines.

50. CCVTM is a building on the Churchill Hospital site, and the clinical trial unit to which OVG and the Jenner Institute both belong is based there. The first vaccinations for the ChAdOx1 nCoV-19 clinical trials took place there.

AstraZeneca

51. See 60-61 below. I was the Oxford Project Lead. Tonya Villafana was the AstraZeneca (AZ) Project Lead and as such, my main contact. Richard Turner at AZ took the lead on vaccine manufacturing.

UK Vaccine Taskforce ("VTF");

52. The VTF was set up to support development of Covid-19 vaccines in the UK. During April 2020 I provided some technical information on ChAdOx1 nCoV-19 and requested funding from the VTF. We received an initial £20M, but as the trials expanded we were able to request more funds. I was responsible for seeking approval from VTF/DHSC to publish each of the papers on ChAdOx1 nCoV-19 vaccine development.

UK Research and Innovation ("UKRI")

53. UKRI is the overall name for research councils which fund academic work in the UK. In February 2020 there was a 'rapid Covid response' call for proposals. I applied for funds to manufacture a first batch of ChAdOx1 nCoV-19 and conduct a phase I trial. The application was reviewed very rapidly, and approved.

UK BioIndustry Association ("BIA")

54. My colleague Cath Green had attended BIA meetings prior to 2020, in her role as head of the CBF. In 2020, the association offered assistance in preparing for scale-up of the ChAdOx1 vaccine manufacturing process.

Vaccines Manufacturing and Innovation Centre ("VMIC")

55. The CBF can manufacture a vaccine seed stock and the first small batch of a novel vaccine in readiness for phase I trials, but production capacity is low. Within the Jenner Institute we recognized the need for a larger facility which could receive the vaccine seed stock and produce sufficient doses for larger trials or for use in containing an outbreak. Following an

application for funding to UKRI, VMIC was established, some staff were in place and by 2020 plans were being made to build the manufacturing facility, which would be capable of manufacturing multiple vaccine technologies.

56. In February 2020 I visited the VMIC staff along with two senior staff from CBF to request assistance with planning the manufacturing of the ChAdOx1 nCoV-19 vaccine, which was then received. Funding for VMIC was increased and the facility was built, but before being used, was then sold.

57. The UK has no national capability in vaccine manufacturing, which VMIC would have provided. The CBF at the University of Oxford can currently only work on one vaccine manufacture at a time, and does not have space to take on all of the requests for work that are received. VMIC would have provided much more capability and could have produced much large numbers of doses of vaccines, which in some cases could be sufficient to respond to an outbreak without any other manufacturer being required. VMIC was set up to manufacture multiple types of vaccines (including viral vectored vaccines, recombinant protein and virus-like particles as well as mRNA) and could have supported the development of many vaccines outside of outbreaks or pandemics. The CBF has an excellent track record in successfully completing the first manufacture of a novel vaccines, including developing all of the tests that are required for regulatory submissions. However only small volumes of vaccines can be manufactured at CBF. The intention behind setting up VMIC was in part that virus seed stocks, manufacturing processes and testing protocols initially developed at CBF could be transferred to VMIC for larger scale manufacture. In addition, VMIC would have been able to work directly with other vaccine researchers in the UK.

58. Without VMIC, the only option is to use contract manufacturing organisations. Transferring all of the necessary expertise for the manufacture of a novel vaccine can be a lengthy process, (months or sometimes years) and most academic groups do not have the required expertise to do this.

Coalition for Epidemic Preparedness ("CEPI")

59. I had applied to CEPI, along with Janssen vaccines, in 2017 and we were funded to work on the development of vaccines against MERS (continuing work started with UK funding) Nipah and Lassa. In early 2020 I sought funding from CEPI for ChAdOx1 nCoV-19. I spoke with them on January 29th , and visited their London office of Feb 7th. CEPI put out a call for proposals for rapid response against the novel coronavirus, to which I applied: see

SG/2 - INQ000475210. I was awarded just under $350,000 which would enable CBF to make the 'starting material' for the vaccine. This would then be used to make the vaccine seed stock and phase I batch using funding from UKRI. There were many discussions with CEPI about further funding, but no more was agreed.

Vaccitech

60. Vaccitech is a University of Oxford spin out company founded by Adrian Hill and myself in 2016. In January 2020, one of the scientists at Vaccitech, who had formerly been employed by Oxford University in the Jenner Institute, worked with Teresa Lambe and myself on the precise DNA sequence to be used to encode SARS-CoV-2 spike protein in the ChAdOx1-vectored vaccine. Vaccitech was not subsequently involved in the vaccine development. The company was renamed Barinthus Biotherapeutics on Nov 6th, 2023.

VaxHub

61. As I mention above, I am a co-lead of VaxHub, which is a UK Government-funded programme, based at University College London, which is directed towards supporting research specifically on the manufacturing of vaccines, including international development of vaccines. VaxHub provided initial funding in January 2020 to enable us to produce a first pre-clinical batch of the vaccine, developed using the ChAdOx1 platform, and having received, after its publication on 10 January 2020, the genomic sequencing data of the emerging disease.

Advent Srl

62. Advent is a manufacturer, based in Italy, which I had worked with previously. In early 2020 the University entered into a contract with Advent in order to allow us to produce a batch of vaccine for clinical trials. We utilised manufacturing capability at both Advent and the University's own CBF (see above), with manufacturing at Advent, for the purposes of phase II clinical trials, beginning in late March 2020 and producing about 3,000 vials of vaccine for testing purposes.

Serum Institute India ("SII")

63. SII is a large-scale vaccine manufacturer in India. SII acted as subcontractors to AZ to manufacture the ChAdOx1 nCoV-19 vaccine at a very large scale, producing around half

of the 3 billion doses made in total. As there were minor differences in the manufacturing process, the SII vaccine was licensed separately, as Covishield rather than Vaxevria.

SK Bioscience

64. SK Bioscience are a South Korean vaccine company who AZ identified as manufacturers to join their manufacturing network.

Oxford Biomedica

65. Oxford Biomedica is a manufacturing facility in Oxford. Although I had no personal involvement in the arrangements, Oxford Biomedica was identified, during the development of the vaccine and preparation for testing phases, as being able to provide substantial new manufacturing capacity within the UK, and so formed part of the arrangements being entered into for large-scale manufacturing of the vaccine.

The initiation relationship between Oxford University and AstraZeneca.

66. I was not personally involved in identifying AstraZeneca as a potential partner for manufacturing and distributing the vaccine, the initiation or negotiation of the University's relationship with AstraZeneca, or the negotiation of the contractual terms of that relationship.

67. My involvement with AstraZeneca, following the agreement between the University and AstraZeneca, was focused on providing extensive information to AstraZeneca for the purposes of enabling them to develop the systems and facilities for the manufacture, storage and distribution of the vaccine at scale.

Innovations introduced and lessons learned

68. I have been asked to comment on a number of areas relating to innovations introduced in, and lessons learned from, the development of the vaccine.

Innovations introduced to accelerate the development, procurement, manufacturing and approval processes for Covid-19 vaccines

69. My knowledge and experience is principally directed towards the development of vaccines, as I have set out above, particularly at paragraphs 20 to 30, including in relation to the development and use of the ChAdOx1 platform. I was less directly involved in innovations relating to the manufacture of vaccines (for testing or approval purposes, or at scale for population vaccination).

70. Vaccines were developed at an expedited rate during the pandemic by using platform technologies, which meant that it was not necessary to develop new manufacturing processes. In Oxford, the team working on vaccine manufacturing and development had a great deal of experience and we worked as a team, with many meetings to discuss every stage of the process, identify possible difficulties and refine our approach. When it became clear that clinical development would need to move beyond Oxford, to other UK clinical trials sites and then overseas sites, we worked with known partners rather than needing to establish new relationships.

71. Additionally, many processes were carries out in parallel rather than series, and it was this that enabled huge time savings. The package of information that is submitted for ethical and regulatory review prior to the authorisation of a clinical trial is extensive. In 2020, we were able to use earlier submissions that had received approval to provide a template for the ChAdOx1 nCoV-19 dossier. Prior experience of working with the MHRA and ethics committees meant that we knew exactly what would be required, but as each document was finalised these were submitted as part of a rolling review process. This meant that when the final piece of information on the quality control of the vaccine batch was submitted, all other parts of the application had already been reviewed and approved, and full approval for the trial could then be granted rapidly.

72. The same approach was taken with clinical trials. Once the early data from the phase I study demonstrating the expected reactogenicity profile and strong immune response to SARS-CoV-2 spike protein in young, healthy adults, the larger phase II and phase III trials were initiated. For other vaccine development projects, the phase I trial would continue for a year, with blood samples being drawn after three, six and 12 months to continue to assess immune responses to the vaccine. The study report would then be written, a paper would be published and when possible, an application for further funding would be submitted, so that it would not be unusual for an interval of three years between initiation of the phase I and then the phase II trial. In 2020, the phase I trial of ChAdOx1 nCoV-19 began on April 23rd, with the phase II/III trial starting on May 30th.

73. In the early months of 2020 securing funding for the vaccine development was difficult, but a small amount of funding was received from CEPI in February followed by a larger amount from the UKRI rapid response scheme in March. However once the vaccines task force formed and began to fund the project during May, we were able to access the funding needed for the larger clinical trials in the UK without further delays. Additional funding had to be secured for trials in Brazil and South Africa.

74. I was not involved in the development of innovations for procurement or approval, beyond the fact that the use of platforms allows for development of vaccines which can be more rapidly ready for testing and approval: see my answer to Q7 above.

75. As I have set out above, the use of platform technologies allowed for a significant shortening of the time taken to develop, manufacture and test a vaccine.

76. The use of platforms was already under development worldwide prior to the emergence of Covid-19. Covid 19 provided an obvious illustration of the benefits of such technology in allowing for the rapid development, manufacture and testing of effective vaccines.

77. For viral vectored vaccine platforms such as ChAdOx1, there is a theoretical drawback that after vaccination there is a small immune response against the vaccine vector itself. That does not prevent the vaccine vector from being used again in the same person. However using the same viral vectored vaccine platform to make many different vaccines that are all used to vaccinate the same person could be disadvantageous.

78. Using viral vectored vaccines to produce stockpiles of vaccines against outbreak pathogens which cause outbreaks in different parts of the world will mean that different people are receiving the different vaccines.

79. This is not a drawback with mRNA vaccines. However more information is needed about the rare adverse events after vaccination with mRNA vaccines after repeated doses.

Public/private sector collaboration

80. Public/private sector collaboration is obviously of huge benefit – combining the broad knowledge base of academia with the ability to take new medical interventions into use by commercial organizations. This should be facilitated in future. There can be a very large gap between a University and a company in terms of translational research. Oxford succeeded in partnering with AZ because Oxford was able to bridge that gap. GMP

manufacturing and clinical development were underway in Oxford by April 2020. This is unusual for an academic organization.

Obstacles encountered

81. For the part of the process that I am concerned with, at the very beginning, the major obstacle is funding.

Contingency plans for development of vaccines for future pandemics

82. The UK is not well prepared to produce vaccines for the next pandemic. There is no co-ordination and no plan. There is no national capability. In 2020 vaccine development was done by individual academic teams (Oxford, Imperial, although others also made a start) or by companies outside the UK. The highly successful partnership between Oxford University and AstraZeneca formed only after the Covid vaccine development was well advanced, and there is no plan for this partnership to continue.

83. Using the ChAdOx1 platform again for a vaccine intended for widespread use in the UK or Europe is more complicated following the discovery of the rare but serious adverse event Vaccine induced thrombosis with Thrombocytopaenia (VITT). Gaining a fuller understanding of VITT may take some time, and although in the future it may be possible to redesign adenoviral-vectored vaccines or use alternative means of delivering adenoviral-vectored vaccines, it is not possible to predict the outcome of such studies. In Asian, South American and African countries VITT was either reported at a very low rate or not at all, and so adenoviral-vectored vaccines may continue to be used. However, in the UK and Europe, in a pandemic situation the benefits of using an adenoviral-vectored vaccine would outweigh the risks. There is not sufficient capacity to produce enough mRNA vaccines for the population.

84. In my view there is a great deal that we should be doing now in advance of the next pandemic, so that we are much better prepared. The viruses that are most likely to cause a pandemic spread through the air and infect the respiratory tract. Vaccinating to prevent such infections occurring, rather than preventing severe disease, could halt spread of an outbreak. However current vaccines, administered by intramuscular injection, do not achieve sufficient levels of immune response in the respiratory tract. In the UK there is much expertise in mucosal immunity, and investment into a consortium to develop improved vaccination regimens for respiratory infections, using a variety of vaccines, could

lead to better protection against seasonal influenza, other infections such as respiratory syncytial virus, and additionally make us better prepared to respond to a new pandemic.

85. There are many viruses that occasionally cause infections in humans, but may in the future cause a much larger outbreak. In 2020 we were hampered because the virus beginning to spread around the world was a coronavirus, and we do not have any other licensed vaccines against human coronaviruses. That meant that we had to make assumptions when planning to develop vaccines, and did not know what level of immune response would need to be induced by vaccination in order to protect people. It was therefore necessary to conduct phase III vaccine efficacy trials to formally test vaccine efficacy, which required tens of thousands of people to be recruited into the trials. Obtaining the necessary efficacy data from the trials took many months as the countries in which the trials were being conducted, including the UK, were in lockdown for part of the time. In order to determine vaccine efficacy it is necessary for some of the trial participants to become infected, and lockdowns obviously reduce the chances of that happening. Now that we have effective vaccines against SARS-CoV-2, we have a better understanding of what would be needed to develop vaccines against another novel coronavirus, should one begin to start causing infections in humans. However we need to develop the same level of understanding for other families of viruses. This type of work is being undertaken in other countries, but with the strong track record in vaccine development in the UK we should be continuing to play a part in acquiring this vital information.

86. The '100-day mission' does not allow for vaccine efficacy trials to be conducted. What is often not understood is that a great deal of knowledge must be acquired before any new vaccine in the future could be licensed for widespread use within 100 days, and even then, manufacturing capacity would not be ready to provide vaccines in sufficient quantity. However, at least for the viruses that we already know about, we should have vaccine stockpiles ready to use in an outbreak, with an approved clinical trial protocol in place, and data from phase I and II trials as well as preclinical vaccine efficacy studies. If all of those things were in place in advance of a new outbreak, we could deploy the vaccine stockpile and test vaccine efficacy very quickly. We should put these things in place.

Vaccine roll-out

87. I had no input into advice to the UK Government on, or giving effect to, the rollout of the vaccine, including suitability for particular groups, dosage intervals or messaging, generally or to particular groups.

88. I have been asked about vaccine hesitancy. I consider this to be an issue outside of my area of expertise. To the extent that I have made any public statements, including in the book which I co-authored with my colleague Prof Catherine Green and referred to above, I have simply sought to provide reassurance by setting out as clear and factual an explanation as possible of the means by which the vaccine was developed.

89. I have been asked about my understanding of why the vaccine was not included in the booster programme. I was not involved in any discussion about this and I am not aware of the detailed reasons for this, which I anticipate that others will be better placed to explain.

Safety

Overview of clinical trials

90. My colleague Professor Pollard led the process of undertaking clinical trials. However, I set out my understanding of the position in summary.

91. The first preclinical studies were to immunize mice and assess antibody and T cell responses to the SARS-CoV-2 spike protein. This provides evidence that the vaccine immunogenicity is as expected before committing to cGMP vaccine manufacture. Data is included in figure 1 of this publication: **SG/3 -** INQ000475214

92. The next stage was to immunize non-human primates (NHPs), confirm immune responses and also then expose the vaccinated plus some non-vaccinated animals to SARS-CoV-2. The clinical signs and viral load in both groups of animals were then assessed. This is chiefly a safety study. There is an adverse consequence of vaccination that has been observed with some vaccines in the past, particularly with a vaccine against respiratory syncytial virus (RSV) used in children in the 1960s. With that vaccine, the immune response resulted in worse outcomes for children who had been vaccinated than those who had not, when they then became infected with the virus.

93. The particular type of immune response associated with that phenomenon is now understood, and following a long period in which there were no vaccines for use against RSV, there are now approved vaccines. We know that the type of immune response induced by vaccination with ChAdOx1 is not associated with this adverse phenomenon, but it was still important to demonstrate that this was in fact the case. In the study which was conducted at the National Institutes of Health in the US, the vaccinated NHPs had

reduced viral loads and reduced clinical signs compared to the non-vaccinated animals. The abstract of the publication states:

> *"Vaccination with ChAdOx1 nCoV-19 (prime-only and prime-boost regimen) induced a balanced Th1/Th2 humoral and cellular immune response in rhesus macaques. We observed a significantly reduced viral load in bronchoalveolar lavage fluid and lower respiratory tract tissue of vaccinated rhesus macaques challenged with SARS-CoV-2 compared with control animals, and no pneumonia was observed in vaccinated animals. However, there was no difference in nasal shedding between vaccinated and control animals. Importantly, no evidence of immune-enhanced disease following viral challenge in vaccinated animals was observed. Safety, immunogenicity and efficacy of ChAdOx1 nCoV-19 against symptomatic PCR-positive COVID-19 disease will now be assessed in randomised controlled human clinical trials"* (exhibit INQ000475214)

94. This study was performed and data was provided to the Data Safety Monitoring Board (DSMB) for the phase I clinical trial, before any vaccinations were administered in the clinical trial.

95. I will leave it to Professor Pollard in his role as Chief Investigator for the clinical trials to describe the clinical development.

Overview of known risks

96. All vaccines are associated with some adverse events after vaccination. They can be divided into local reactions (at the injection site) and systemic reactions (felt throughout the body), and are a consequence of the vaccination itself, and the induction of an immune response by the vaccine. Typically they include soreness or muscle ache at the injection site, fatigue and sometimes headache. In placebo controlled trials these adverse events are often detected to some extent in the placebo group as well as the group receiving the test vaccine.

97. The adverse event profile of ChAdOx1 vectored vaccines in young healthy adults was known and has been described in a number of publications, following a number of phase I clinical trials that had already been conducted. For example the reactions after use of the ChAdOx1 MERS vaccine are described in **SG/4 -** INQ000475213.

98. In the first phase I trial of ChAdOx1 MERS, 92 (74%) solicited adverse events were mild, 31 (25%) were moderate, and all were self-limiting. All solicited adverse events were completely resolved 6 days after vaccination and 119 (96%) had their onset within the first 72 h after vaccination (66 [53%] at day 0, 48 [39%] at day 1, and five [4%] at day 2). Injection site pain was the most common local adverse event, reported by 18 (75%) of 24 participants and was predominantly mild in severity. Fatigue was the most common systemic adverse event, followed by headache and malaise.

99. In the second, phase I trial of ChAdOx1 MERS, which took place in Riyadh, Saudi Arabia, again most adverse events were mild (67, 74%) and moderate (17, 19%). Six (7%) severe adverse events were reported by two participants in the intermediate-dose group (two feverish, two headache, one joint pain, and one muscle pain). 'Feverish' means that the person reported feeling as though they had a raised body temperature, but did not have a raised body temperature that could be measured with a thermometer. Pain at the injection site was the most common local and overall adverse event, reported by 15 (63%) of the 24 participants. The most common systemic adverse event was headache, reported by 14 (58%), followed by muscle pain reported by 13 (54%). All adverse events were self-limiting and completely resolved by the second follow-up at day 7.

100. Any 'adverse event' that affects clinical trial participants must be reported, whether the participant considers it to be a consequence of vaccination or not. As these events can happen to people at any time, sometimes they will happen to clinical trial participants and it is then necessary to assess whether the adverse event is related to vaccination or not. Sometimes this is straightforward; being hit by a car and requiring hospitalization would be a serious adverse event not related to vaccination. In other case it can be more difficult to decide if the adverse event is a consequence of vaccination, particularly if it is only experienced by one participant in the clinical trial. All adverse events are recorded, reported to regulators and described in clinical trial publications.

101. As stated above, the expected adverse event profile was known prior to starting the clinical trials. As larger numbers of people, including older adults in who adverse events occur more frequently regardless of vaccination, a more detailed profile was built up, and submitted to the regulators at the end of 2020. Following rollout of the vaccine in the UK and other European countries in early 2021, a rare but serious adverse event which became known as vaccine induce thrombosis with thrombocytopaenia (VITT) began to be reported. This involved blood clots forming along with a very low platelet count in the days or weeks after vaccination.

102. Thrombosis with thrombocytopaenia is extremely rare, but can occur in the absence of vaccination with no known cause, or after treatment with heparin, which is also associated with the condition (it is then known as heparin induced thrombosis with thrombocytopaenia, or HITT. It was therefore necessary to understand if the number of cases detected after vaccination was greater than the number that would have been expected to occur without vaccination (the 'background rate'). Infections, including with SARS-CoV-2, are known to cause blood clots.

103. Haematologists in the UK worked together to provide information about this new phenomenon and to recommend the best course of treatment during the spring of 2021. VITT had not occurred during the clinical trials, but is so rare that it was only detected after multiple millions of people had been vaccinated. For Covid-19 vaccines in general, the clinical trials were larger than usual.

Risks and identifiable groups

104. Initially it was suggested that women were at greater risk of VITT than men. However, as the vaccine was being used widely in healthcare workers, who are more likely to be female, this finding was not borne out as more data became available. Risks did not appear to differ greatly by age, although there may have been some differences. In contrast the risks of SARS-CoV-2 infection increase greatly in older adults, meaning that the risk:benefit calculations for vaccination were then different for different age groups. Risk;benefit calculations also change over time. Smallpox is estimated to kill 30% of those infected. The vaccine is highly effective but itself has a fatality rate of around 1 in a million. If a smallpox outbreak occurs there is a clear benefit of vaccination, but now that smallpox has been eradicated there is no benefit and the vaccine, despite still being highly effective, is no longer used.

105. In early 2021, the risk to someone of being infected with SARS-CoV-2 was much higher than it is now, and that changes the risk;benefit calculation for use of the vaccine now compared to in early 2021.

Decision-making and risks

106. I had no input into advice given to the JCVI, MHRA or the UK Government.

107. I had no involvement in Government public messaging about the vaccine or actual or perceived risks. As I set out above, to the extent that I have made public statements, I have sought to provide clear factual information about the development of the vaccine.

Monitoring of side-effects and adverse reactions

108. I am not involved in the ongoing monitoring of side effects and reactions to vaccines and so am not able to offer an opinion on the effectiveness of such systems.

MHRA

109. I have no direct knowledge of, and am not qualified to comment on, the governance arrangements concerning MHRA.

Vaccine disinformation / misinformation

110. I have no specific personal knowledge or expertise as to the sources of and motivations for disinformation or misinformation concerning the vaccine, or as to unsubstantiated disinformation or misinformation relating to the vaccine and so any comment I make would inevitably be speculative.

111. I have not been involved in clinical research specifically directed towards disproving misinformation or disinformation about the vaccine. I became aware of some speculative, and incorrect, information, circulated about this and other vaccines, which was inconsistent with the known information about the composition and effectiveness of the vaccine, including as a result of information obtained from clinical trials. The scale, and diverse nature, of such misinformation is such that it is not possible to provide representative examples.

The role of the Science Media Centre

112. I did not have substantial personal involvement in the work of the Science Media Centre in relation to the vaccine.

Proactive vaccinology and "all-in-one vaccines"

113. The Inquiry has asked me to comment on a press release which refers to "proactive vaccinology". A copy of the press release is exhibited as SG/6-INQ000494258 copy of the paper referred to in the press release is exhibited as SG/5 - INQ000474234

114. In my view it is extremely important that in the UK we continue to work on vaccine development to increases our chances of a successful response to the next epidemic or pandemic that occurs. The press release from the University of Cambridge referred to a publication that it claimed described a technology which '*gives protection against other coronaviruses not represented in the vaccine – including ones that haven't even been identified yet*'.

115. However, the published paper to which the press release refers makes clear what was actually determined. 'Protection' in vaccinology means that a person or animal was vaccinated, then exposed to a pathogen either via deliberate exposure (a challenge experiment), or natural exposure (in a vaccine efficacy trial, typically a phase III trial), and failed to become infected or to develop symptoms of the disease. If a virus has not yet been identified, protection cannot have been demonstrated.

116. What the paper actually described is the induction of neutralising antibodies against a number of different known coronaviruses, including SARS-CoV-1, which was not included in the vaccine. Again, it is not possible to demonstrate that a vaccine is capable of inducing antibodies against a virus that has not yet been identified. Protection against a putative unknown virus has not been demonstrated, and nor has immunogenicity. Even if antibodies are induced, they may not be present at a high enough level to protect the vaccinated individual. Quantity as well as quality is required.

117. The main finding described in the paper was that it was possible to produce a vaccine containing parts of the spike protein from four different coronaviruses which were then assembled into small particles to make a vaccine, requiring only two separate components to be manufactured separately prior to assembly into particles. The particles were then administered to mice along with an adjuvant. The adjuvant increases the immune response to a vaccine. Typically, virus-like particles require an adjuvant, whereas viral-vectored vaccines and mRNA vaccines do not. The adjuvant used in the published study is not one that would be used in clinical trials in humans. Mice are typically used in early experiments to screen novel vaccine candidates, but there is a long way to go before the new approach can be assessed in clinical trials.

118. However, the publication does make the point that including components from multiple different, but related viruses may be a useful approach to inducing protective

immunity against more than one virus, and this should continue to be an area for research. The development of multivalent vaccines has a long history, and there are now pneumococcal vaccines which include 13, 15, 20, 23 or even 24 serotypes of *Streptococcus pneumoniae*. Unfortunately vaccine efficacy against all of the serotypes is not consistent, and as more serotypes are added into the vaccine, protection may be reduced or lost for others. This will continue to be an area of research.

119. When the Vaccines Task Force was formed in 2020, there was a decision to support multiple different vaccine technologies rather than backing only one. This should continue to be the approach for vaccine development for pandemic preparedness. We should also continue to address the many unanswered questions about what level or type of immune response vaccines must induce to protect people against different viruses. SARS-CoV-2 is a coronavirus, and the work that had been done on the early development of vaccines against MERS coronavirus prior to the pandemic was very helpful in designing new vaccines at the start of 2020. However, the virus that causes the next epidemic or pandemic could be an alphavirus, such as Chikungunya, an arenavirus, such as Lassa Fever, or something else. By completing the development of vaccines against these viruses as well as other known viruses we will increase our understanding of how to respond against a future virus from the same family.

120. It is respiratory pathogens, infecting the upper and lower respiratory tract and spread by airborne transmission that are highly likely to be the cause of the next pandemic due to the ease with which they spread and the difficulty of preventing transmission. With the exception of a nasal spray vaccine against influenza that is only used in children, vaccines against respiratory infections continue to be given as intramuscular injections. This is not the best way to create strong immune responses in the respiratory tract. The UK has researchers and facilities that provide us with an excellent opportunity to explore respiratory vaccination, which should also be a strong focus of research.

121. In my view, the most exciting development in the paper by Hills *et al.*, referenced in the Cambridge University press release related to a different approach to vaccine manufacturing which required only two components to be produced rather than nine in a previous version of the technology. This was completely overlooked in the press release. We must recognise that if we are to be able to produce vaccines for clinical trials, let alone widespread vaccine deployment, that research into improved methods for vaccine manufacturing must be prioritised. There is a need for vaccines to be affordable, since in a pandemic the whole world must be protected. It is easy to recognise the benefits of a vaccine that may be stored at room temperature, and delivered by a 'microneedle patch'

or a puff from an inhaler. To achieve this may well be possible, but will require investment into research and innovation.

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: 7th August 2024