Institution: University of Oxford		
Unit of Assessment: 1 – Clinical Medicine		
Title of case study: The Oxford-AstraZeneca COVID-19 vaccine		
Period when the underpinning research was undertaken: Jan 2012 – Dec 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Sarah Gilbert	Professor of Vaccinology	Jan 2000 – present
Andrew Pollard	Professor of Paediatric Infection and Immunity, Director of Oxford Vaccine Group	Aug 2001 – present
Adrian Hill	Professor of Vaccinology, Director of the Jenner Institute	Mar 1988 – present
Teresa Lambe	Associate Professor	Jan 2002 – present
Alexander (Sandy) Douglas	Postdoctoral Research Fellow	Oct 2016 – present
Catherine Green	Associate Professor	Oct 2012 – present
Katie Ewer	Associate Professor	Mar 2008 – present
Period when the claimed impact occurred: January 2016 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Oxford researchers have produced an efficacious vaccine to protect against SARS-CoV-2 infection. Oxford's experience in vaccine development and clinical trial design, combined with the technological expertise of AstraZeneca, resulted in emergency use authorisation of ChAdOx1 nCoV-19/AZD1222 vaccine in the UK and three other countries, by 31 December 2020. Over 11,000 participants in the Oxford COVID-19 vaccine clinical trials from the UK, Brazil, and South Africa, and 20,000 in the US, received the ChAdOx1 nCoV-19 vaccine; these individuals now have 70% reduced risk of COVID-19 and 100% reduction in risk of hospitalisation or death. Agreements were secured in 2020 for the supply of 2,678,900,000 vaccine doses on a not-for-profit basis worldwide, with half committed to LMICs. The underlying vaccine platform, ChAdOx1, has been licensed to companies worldwide and resulted in significant investment and business growth.

2. Underpinning research

In 2012, Gilbert and Hill published the design and construction of a new replication-deficient chimpanzee adenovirus-vectored vaccine, ChAdOx1 [1]. Adenoviruses are potent vectors for inducing strong cellular immune responses and the use from 2004 in Hill's lab at Oxford of various simian adenovirus avoided the widespread seroprevalence of neutralising antibodies to common human adenoviruses. Gilbert's team developed a ChAdOx1 vaccine for the MERS coronavirus in 2017, showing good immune responses in mice, camels, rhesus macaques and humans [2], providing critical insight into the biology of immunity and potential of the vaccine technology to provide protection against coronavirus diseases.

In response to the SARS-CoV-2 coronavirus outbreak in December 2019, Gilbert's team designed the novel coronavirus antigen to add to ChAdOx1 on 11 January 2020, as soon as the genetic code of SARS-CoV-2 was released. The genetic sequence of the spike protein of SARS-CoV-2, the surface glycoprotein responsible for receptor binding, fusion, and entry into the host cell, was codon-optimised and cloned into the ChAdOx1 vaccine. Together with Lambe, Gilbert produced the Oxford COVID-19 vaccine, ChAdOx1 nCoV-19, in their Oxford laboratory. The

initial doses were used to test immune responses in rhesus macaques at Porton Down, Public Health England (PHE), UK and Rocky Mountain Laboratories, USA where the team showed that ChAdOx1 nCoV-19 vaccine produced a strong immune response and prevented the development of pneumonia in rhesus macaques [3]. Gilbert and Green initiated and optimised good manufacturing practice (GMP) production of ChAdOx1 nCoV-19 in the Clinical Biomanufacturing Facility at the University of Oxford with Lambe and Douglas and Hill in preparation for Phase I human trials.

Pollard led the design and implementation of the Oxford COVID-19 vaccine clinical trials, at unprecedented speed and scale nationally and internationally. In parallel with animal studies [3], Pollard initiated a phase I/II clinical trial to assess the safety and immunogenicity of ChAdOx1 nCoV-19. Between April 23 and May 21, 2020, COV001 enrolled 1,077 participants between 18 and 55 years of age across five sites in the UK, including Oxford. By then Hill had identified key vaccine manufacturers, major industrial partners, and licensees. Volunteers were assigned to receive either ChAdOx1 nCoV-19 (n=543) or meningococcal conjugate vaccine, MenACWY (n=534). The Phase I/II trial showed no safety concerns and demonstrated that ChAdOx1 nCoV-19 induced both humoral and cellular immune responses in participants with neutralising antibody responses strongest after a booster dose [4]. The results supported large scale evaluation in Phase III trials. Immunogenicity to vaccines is often lower in older people. As older people are much more likely to suffer from severe COVID-19, a vaccine that protects this age group was crucial. Between May 30 and Aug 8, 2020, COV002 enrolled 560 participants across two sites in the UK (Oxford and Southampton), including 400 participants over the age of 55. The results showed that older people, including those over 70, produced a good immune response to the ChAdOx1 nCoV-19 vaccine and the vaccine was well tolerated across all ages groups [5].

Phase III trials were initiated in June 2020 across 19 sites in the UK, 6 sites in Brazil, 7 sites in South Africa (and an additional Phase I trial at 1 site in Kenya). Expansion of the clinical trials around the UK and to other countries increased the diversity of ethnicity and global generalisability of the results and provided a higher likelihood of catching a wave of disease and accelerating efficacy results. Interim analysis of the safety and efficacy of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2, from clinical trials in the UK (COV001, COV002), Brazil (COV003, phase III) and South Africa (COV005, phase I/II), was published in December 2020 [6]. The safety of the vaccine was assessed using all four trials and was shown to be acceptable with no hospital admissions or severe cases reported in the ChAdOx1 nCoV-19 arm. Interim efficacy of the vaccine was assessed using a global pooled analysis combining data from COV002 and COV003. Between April 23 and Nov 4, 2020, 23,848 participants were enrolled and 11,636 participants (7,548 in the UK, 4,088 in Brazil) were included in the interim primary efficacy analysis. Overall vaccine efficacy was 70·4% [6]. Additionally, Oxford research showed that a longer interval between the first and second vaccine dose promoted a stronger immune response [6].

3. References to the research (University of Oxford employees in bold, students in italics)

1. *Dicks MD*, **Spencer AJ**, **Edwards NJ**, Wadell G, Bojang K, **Gilbert SC**, **Hill AV**, **Cottingham MG**. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. *PLoS One.* (2012) 7:e40385. DOI: 10.1371/journal.pone.0040385
2. *Folegatti PM*, et al. (*22 Oxford authors, including* **S Gilbert, A Hill, T Lambe** and **K Ewer**). Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. *Lancet Infect Dis.* (Apr 2020) 20(7):816-826. DOI: 10.1016/S1473-3099(20)30160-2
3. van Doremalen N, **Lambe T**, et al (*18 Oxford authors including* **S Gilbert**). ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. *Nature* (Jul 2020) 586(7830):578-582. DOI: 10.1038/s41586-020-2608-y
4. *Folegatti PM*, **Ewer KJ**, et al (*25 Oxford authors including* **S Gilbert, A Hill, A Pollard, T Lambe, A Douglas, C Green**). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine

against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet.* (Jul 2020) 396(10249):467-478. DOI: 10.1016/S0140-6736(20)31604-4

5. **Ramasamy MN**, et al. (*46 Oxford authors including* **C Green, A Douglas, A Hill, T Lambe, S Gilbert, A Pollard**). Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* (Nov 2020) 396:1979-1993. DOI: 10.1016/S0140-6736(20)32466-1.

6. **Voysey M** et al. (3*5 Oxford authors including* **C Green, A Douglas, A Hill, T Lambe, S Gilbert, A Pollard,**). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 397:99-111 (Online 8 Dec 2020). DOI: 10.1016/S0140-6736(20)32661-1

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4. Details of the impact

Oxford vaccine technology underpins therapeutic and preventative applications

ChAdOx1 was patented in 2012 (PCT/GB2012/000467) and has been used in 11 vaccine programmes, including for malaria, influenza, Chikungunya, and MERS, showing a good safety profile and high immunogenicity. Recognising the potential for vaccine development using ChAdOx1, Gilbert and Hill founded Vaccitech in January 2016 to develop vaccine and T cell therapeutic products to improve global health. Vaccitech was spun out from the University of Oxford, and licensed intellectual property rights to the ChAdOx1 technology [1], raising GBP10,000,000 investment from Oxford Sciences Innovation (OSI) [A]. Vaccitech has subsequently attracted additional investment of GBP57,000,000 between Nov 2017 and Dec 2020 enabling programme development [A]. Vaccitech has grown from 1 employee in May 2017 to almost 50 employees in Dec 2020 [A], contributing to business development in the local area and has subsidiaries in Australia and the US to support global operations [A]. HAV Vaccines in London licensed ChAdOx technology from Oxford University Innovation (OUI) to develop a vaccine to treat and prevent infection by *Mycobacterium avium* subspecies *paratuberculosis* (MAP) which is responsible for the chronic gut inflammation in patients with Crohn's Disease. A phase 1 study on healthy volunteers [Bi] showed no safety concerns and patients with Crohn's Disease are being recruited into a follow-on phase 1 trial [Bii]. Aelix Therapeutics in Spain has also licensed the ChAdOx technology from OUI and is using the technology to develop a therapeutic vaccine for the treatment of HIV. Aelix Therapeutics launched a phase 1, randomised, double-blind, placebo-controlled safety, tolerability, and immunogenicity clinical trial in 45 individuals with HIV in July 2017 [C].

The Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1 nCoV-19/AZD1222)

Protecting people over four continents against COVID-19 through vaccination

Between 23 April and 4 November 2020, Oxford led clinical trials in geographically and ethnically diverse populations over three continents. 11,636 individuals were vaccinated with ChAdOx1 nCoV-19 in clinical trials in the UK, Brazil, and South Africa. Based on interim efficacy results [6], these individuals now have a 70.4% reduced risk of developing COVID-19 and vaccinated individuals are protected against hospitalisation with COVID-19. In August 2020, AstraZeneca began a Phase III clinical trial in the US to determine the safety, efficacy, and immunogenicity of AZD1222 [D], enrolling 32,449 participants, with two thirds receiving the COVID-19 vaccine and one third the placebo. Data from the US trial showed that the vaccine reduced risk of severe COVID-19 by 100%, of clinical COVID-19 by 76% and was 85% effective in older adults.

Informing regulators and UK vaccination dosing regimen

On 30 December 2020, following review of the Oxford clinical trial data by the Commission on Human Medicines, ChAdOx1 nCoV-19/AZD1222 was authorised for emergency use supply in the UK by the Medicines and Healthcare Products Regulatory Agency (MHRA) [E], the first viral

vectored vaccine against COVID-19 to be granted approval in Europe. Oxford research [6] was used to inform the Joint Committee on Vaccination and Immunisation (JCVI) decision on dosing regimen for the Oxford vaccine, and for the Pfizer-BioNTech mRNA vaccine that had received regulatory approval in the UK on 2 December 2020 and whose clinical trial data used a three-week dosing interval. Oxford research [6] showed that a longer interval between the first and second vaccine dose promoted a stronger immune response. On 31 December 2020, the JCVI recommended a two-dose schedule for the Pfizer-BioNTech and Oxford-AZ vaccines, with a maximal interval of 12 weeks between the first and second dose for both vaccines, based on the likelihood that immune responses to both vaccines were similar [F]. The Committee recommended prioritising delivery of the first vaccine dose as this was highly likely to have a greater public health impact, allowing more people to be vaccinated, and reduce the number of preventable deaths from COVID-19 [F]. Emergency use authorisation of ChAdOx1 nCoV-19/AZD1222 was granted in Argentina and El Salvador on 30 December 2020, and in Dominican Republic on 31 December 2020.

Securing access to vaccines for the UK population

The UK, through the UK Vaccine Taskforce (VTF), was the first country in the world to secure access to the Oxford vaccine, securing 100,000,000 doses (enough for 50,000,000 people) in May 2020, 7 months before the vaccine received regulatory approval. The former Chair of the VTF wrote that,

> "*The portfolio of Oxford's research on ChAdOx viral vectored vaccines was a critical factor for the VTF's decision to secure 100 million doses of the Oxford/AZ vaccine before it had received regulatory approval*" [G].

Guaranteeing doses of the Oxford vaccine helped the UK government meet its goal of securing access to COVID-19 vaccines for the UK population as quickly as possible [G].

Global partnership for worldwide distribution of ChAdOx1 nCoV-19

On 30 April 2020, the University of Oxford and AstraZeneca signed a landmark agreement for the global development, manufacture, and distribution of ChAdOx1 nCoV-19/AZD1222 [Hi]. Of crucial importance to the Oxford/AstraZeneca partnership was the joint commitment to ensure broad and equitable access to the vaccine on a not-for-profit basis for the duration of the pandemic and in perpetuity to low and middle income countries (LMICs) [Hii]. In June 2020, AstraZeneca was the first global pharmaceutical company to join COVAX (COVID-19 Vaccines Global Access), a global initiative led by CEPI, GAVI and WHO, aiming to distribute 2 billion vaccine doses to 92 LMICs at no more than USD3 per dose. As of 31 December 2020, agreements were in place for the supply of 2,678,900,000 doses of the Oxford vaccine worldwide [I], almost twice as many as any other vaccine developer globally, and notably with approximately half committed to LMICs via COVAX [J]. The Oxford vaccine has the significant benefit of being easy to manufacture, store in a fridge and distribute, allowing it to be rapidly deployed in LMICs.

AstraZeneca confirmed,

> "*The ChAdOx platform was particularly attractive for us as it enabled the rapid development and deployment of novel vaccines with a manufacturing process and supply chain that would enable the equitable and global rollout we all envisaged, without some of the limitations of mRNA vaccines*" [K].

Alongside expanding manufacturing capacity at AstraZeneca, the collaboration with Oxford also resulted in growth of

> "*a significant preclinical, clinical capability to support the vaccine programme. This now provides the platform for next generation vaccine development, not just for SARS CoV-2 but potentially for other important viral infections*" [K].

Driving UK vaccine development capabilities

The former Chair of the VTF said "*The development of the Oxford vaccine helped drive the growth of the UK's vaccine capability*" [G]. In May 2020, the UK government announced GBP131,000,000 investment to accelerate construction of the Vaccines Manufacturing and Innovation Centre (VMIC) at Harwell, Oxfordshire, and to create a virtual VMIC which could produce vaccine doses whilst VMIC was under construction [Li]. As of 31 December 2020, three

of the seven most advanced COVID-19 vaccines were being manufactured in the UK, including the Oxford vaccine [Lii].
The former Chair of the VTF stated,

"*The development of the Oxford vaccine has stimulated new investment in skills and training and dramatically expanded the UK's capacity to manufacture and fill vials across a range of bioprocessing and fill finish companies throughout the UK*" [G].

5. Sources to corroborate the impact

A. Testimonial from Chief Business Officer, Vaccitech stating the importance of ChAdOx viral vectored vaccines to Vaccitech's business growth

B. Clinical trials funded by HAV Vaccines Ltd: (i) ClinicalTrials.gov NCT03027193 A Study to Determine the Safety and Immunogenicity of a Candidate MAP Vaccines ChAdOx2 HAV and MVA in Healthy Adult Volunteers. https://clinicaltrials.gov/ct2/show/NCT03027193
(ii) A phase I clinical trial to investigate the safety and efficacy of two candidate Mycobacterium avium subspecies paratuberculosis (MAP) vaccines in patients with active Crohn's disease (HAV002, ISRCTN36126048) https://doi.org/10.1186/ISRCTN36126048

C. Clinical trial by AELIX Ltd: ClinicalTrials.gov NCT03204617. Safety and Immunogenicity Study of DNA.HTI, MVA.HTI and ChAdOx1.HTI in HIV-1-positive Patients (AELIX-002,) https://clinicaltrials.gov/ct2/show/NCT03204617

D. Clinical trial of AstraZeneca COVID-19 vaccine: ClinicalTrials.gov NCT04516746 Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults. https://clinicaltrials.gov/ct2/show/NCT04516746

E. Government Press Release; Oxford University-AstraZeneca vaccine authorised by UK medicines regulator, 30 Dec 2020. https://www.gov.uk/government/news/oxford-universityastrazeneca-vaccine-authorised-by-uk-medicines-regulator

F. JCVI statement of COVID-19 vaccination dosing regimen, 31 Dec 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103741

G. Testimonial from former Chair of the Vaccine Taskforce outlining contribution of Oxford's research to vaccine procurement decisions and the development of UK vaccine capabilities

H. Coverage of Oxford-AstraZeneca agreement: (i) Press releases announcing Oxford-AstraZeneca agreement for COVID-19 vaccine, 30 April 2020
(ii) News article by The Guardian on Oxford-AstraZeneca vaccine being sold to developing countries at cost price, 23 Nov 2020 https://www.theguardian.com/global-development/2020/nov/23/oxford-astrazeneca-results-covid-vaccine-developing-countries

I. Set of announcements of global agreements with AstraZeneca for a total 2,678,900,000 doses of the Oxford vaccine to the UK, US, LMICs (1,300,000,000), Brazil, China, Japan, Latin America, European Commission, Canada, Switzerland, Bangladesh, Thailand, Philippines and South Korea.

J. WHO news release: COVAX announces additional deals to access promising COVID-19 vaccine candidates, 18 Dec 2020, including advance purchase of 170,000,000 doses of Oxford/AstraZeneca vaccine with options for more. https://www.who.int/news/item/18-12-2020-covax-announces-additional-deals-to-access-promising-covid-19-vaccine-candidates-plans-global-rollout-starting-q1-2021

K. Letter from Senior Vice President and Global Head, Late Stage Respiratory and Immunology, AstraZeneca, confirming the benefits of the ChAdOx platform for vaccine development and global distribution, and the growth of AstraZeneca's vaccine capability.

L. (i) UKRI news report of government investment in VMIC, Harwell, 18 Sep 2020
(ii) UK Vaccine Taskforce 2020 Achievements and Future Strategy end of year report, Dec 2020 https://www.gov.uk/government/publications/uk-government-vaccines-taskforce-vtf-2020-achievements-and-future-strategy