Institution: University of Oxford		
Unit of Assessment: 1 – Clinical Medicine		
Title of case study: COVID-19 testing to understand and control transmission		
Period when the underpinning research was undertaken: February 2020 – December 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:**
Derrick Crook	Consultant in Infectious Diseases and Clinical Microbiology (Category C, OUH NHS)	1996 - present
Philippa Matthews	Clinical Research Fellow	Aug 2016 - present
(Ann) Sarah Walker	Professor of Medical Statistics and Epidemiology	Dec 2012 – present
Koen Pouwels	Senior Researcher	January 2019 - present
Gavin Screaton	Professor	October 2017 - present
David Stuart	Professor of Structural Biology	Oct 2000 – present
Tim Peto	Consultant Physician (Category C, OUH NHS)	1988 - present
Period when the claimed impact occurred: 1 March 2020 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Oxford researchers have driven the development, evaluation and implementation of antibody and antigen testing for SARS-CoV-2, tests that were non-existent at the start of the COVID-19 pandemic in February 2020. The Oxford ELISA has been used extensively to accurately inform seroprevalence levels across population groups (223,235 tests performed) and was rapidly commercialised. Evaluation of commercial lateral flow antigen tests by the Oxford team and PHE led to the government decision to roll out asymptomatic testing to the 18,000,000 people who were required to leave home to work, including critical groups such as NHS staff, breaking chains of transmission. Oxford researchers led the ONS COVID-19 Infection Survey, the largest community based COVID-19 survey in the UK, providing a vital source of information to guide UK government decision-making on local and national lockdowns to control infection levels that saved an estimated 37,000 lives in the UK.

2. Underpinning research

Development of the Oxford ELISA

In March 2020, research by the University of Oxford team led to the development of the Oxford ELISA (enzyme-linked immunosorbent assay) for SARS-CoV-2 [1]. The Oxford ELISA measures antibodies in the blood against SARS-CoV-2 trimeric spike protein. To meet the need for high throughput, low volume testing, the Oxford team developed a high throughput version of the ELISA [2]. Robotics and regression modelling enabled across-plate, across-batch comparisons. In partnership with Oxford University Hospitals NHS Foundation Trust (OUH NHS FT) Clinical Laboratories, the team developed systems to log and barcode samples, and an-end-to-end digital sample tracking system [2], essential for large studies such as serosurveillance (monitoring antibody levels in a population).

ONS COVID-19 Infection Survey

In April 2020, Walker (as Chief Investigator) led the design, implementation and analysis of the Department of Health and Social Care (DHSC) and Office for National Statistics COVID-19

Infection Survey (ONS CIS), a national research study to understand how many people of different ages across the UK had had COVID-19. The pilot study invited 20,000 households across England to take part and the survey was extended in August 2020 to include 400,000 individuals across England, Wales, Scotland, and Northern Ireland. All participants provided throat and nasal swabs that were assessed by PCR for presence of the virus, and 10% of participants also provided blood samples which were tested for the presence of antibodies using the Oxford ELISA. From May to August 2020, Walker was single-handedly responsible for the integration of the different data streams, then with Pouwels established methods for providing a weekly estimation of community infection levels in different age groups and geographical areas [3].

Lateral flow antibody tests (lateral flow immunoassays, LFIAs)

In May and June 2020, the DHSC commissioned the University of Oxford and Public Health England (PHE) to advise on a wide range of lateral flow immunoassays (LFIAs) and validate their utility for COVID-19 testing. LFIAs are small handheld devices, such as those used for pregnancy testing, that detect the presence of antibodies against SARS-CoV-2 in an individual's blood. The Oxford team created a large bank of serum and plasma samples from patients with confirmed COVID-19, including detailed clinical metadata, which was critical for successful validation of all types of tests. In addition, large banks of material collected pre-pandemic were acquired and collated through collaborations with NHS Blood and Transplant (NHSBT) and UK Biobank to provide a negative sample set. The Oxford team and PHE designed a protocol to test point of care LFIAs, selected by DHSC as the best available candidates at the time, and showed that these products failed to meet Medicines and Healthcare products Regulatory Agency (MHRA) 'target product profile' criteria for sensitivity and specificity [1].

Lateral flow antigen tests (lateral flow devices, LFDs)

In August 2020, to support Operation Moonshot, and subsequently NHS Test and Trace, the DHSC commissioned the University of Oxford and PHE to evaluate lateral flow antigen tests (lateral flow devices, LFDs) for mass community testing of COVID-19 infection [4]. Up to one third of individuals with COVID-19 display no symptoms and can therefore spread the disease unknowingly. Asymptomatic testing is therefore a vital tool to manage the pandemic. LFDs reliably detect high levels of viral proteins (antigens) in an individual's nasal or throat swab, whether the person has symptoms or not (low virus levels will not be detected using LFDs). People with high viral loads are at their most contagious and are therefore at high risk of infecting others. By combining cheap, rapid LFDs that do not require laboratory or logistics infrastructure to identify asymptomatic individuals with additional control measures such as self-isolation and contract tracing, transmission chains can be broken. The Oxford team, in collaboration with PHE, developed and delivered the infrastructure required to identify the most promising LFDs with the best performance characteristics [4]. In December 2020, the team assessed the effectiveness of LFDs to detect a new variant of SARS-CoV-2, VUI202012/01, and showed that all LFDs evaluated detected the variant [5].

3. References to the research

(University of Oxford authors in bold; **corresponding author*)

1. Adams ER *et al* (2020) (*72 authors of which 47 from the University of Oxford, including* **D Crook*, PC Matthews, DI Stuart, GR Screaton*, T Peto, AS Walker**) Antibody testing for COVID-19: A report from the National COVID Scientific Advisory Panel. *Wellcome Open Res* 2020, **5**:139. Journal article, DOI:10.12688/wellcomeopenres.15927.1
2. The National SARS-CoV-2 Serology Assay Evaluation Group *(131 authors, of which 76 from the University of Oxford, including* **D Crook, P Matthews, G Screaton, D Stuart**) (2020). Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison. *Lancet Infect Dis.* 20:1390-1400. Journal article, DOI: 10.1016/S1473-3099(20)30634-4
3. **K Pouwels*** et al and the COVID-19 Infection Survey Team (2020) (*106 authors, of which 25 from Oxford also including* **D Crook, P Matthews, AS Walker, G Screaton, DI Stuart, T Peto**). Community prevalence of SARS-CoV-2 in England from April to November, 2020:

results from the ONS Coronavirus Infection Survey. *The Lancet Public Health* 6:E30-38. First published online 10 December 2020.
Journal article, DOI: 10.1016/S2468-2667(20)30282-6

4. Preliminary report from the Joint PHE Porton Down & University of Oxford SARS-CoV-2 test development and validation cell: Rapid evaluation of Lateral Flow Viral Antigen detection devices (LFDs) for mass community testing.
Research report, made available 8 November 2020 at
https://www.ox.ac.uk/sites/files/oxford/media_wysiwyg/UK%20evaluation_PHE%20Porton%20Down%20%20University%20of%20Oxford_final.pdf

5. Report from PHE Porton Down & University of Oxford: SARS-CoV-2 lateral flow antigen tests: evaluation of VUI-202012/01, 23 Dec 2020. Research report, available at
https://www.gov.uk/government/publications/sars-cov-2-lateral-flow-antigen-tests-evaluation-of-vui-20201201

4. Details of the impact

Contributing to effective UK testing capacity: the Oxford ELISA

The University of Oxford research [2] showed that the Oxford ELISA met MHRA performance metrics for sensitivity and specificity with minor adjustments of assay thresholds. The work was published in the form of a government report [A]. On the basis of performance results [1,2] the Oxford team formed a partnership with Thermo Fisher in November 2020 to commercialise the Oxford ELISA as the OmniPATH Combi SARS-CoV-2 IgG ELISA Test [B(i)]. The test was CE marked by MHRA in November 2020 and was made commercially available in December 2020. The collaboration between Oxford and Thermo Fisher led to the rapid commercialisation of an accurate, widely used antibody test.

Thermo Fisher stated "*The last eight months has demonstrated the benefits of close collaboration between the academic knowledge and research capabilities of Oxford and the technology transfer and manufacturing expertise of Thermo Fisher. The commercialization of the assay in a new agile way of working has enabled accelerated time to market to serve in the pandemic response*" [B(ii)]. As of 31 December 2020,the Oxford ELISA had been used in population surveys (ONS CIS [C]; 88,120 tests performed), the Oxford COVID-19 vaccine programme (843 tests performed), screening programmes (Oxford-OUH Staff Testing Programme; 21,332 tests performed), by the UK Biobank (106,540 tests performed) and by RECOVERY (5,760 tests performed) and REMAP-CAP (640 tests performed) clinical trials. In total, 223,235 Oxford ELISAs were used to inform seroprevalence across these groups.

Optimising commercial testing capabilities

Oxford research [2] also showed sensitivity and specificity, with minor adjustments of assay thresholds, for four commercial ELISAs (produced by Abbott, DiaSorin, Roche and Siemens) which allowed the companies to better understand the performance of their assays and provided the insight required for them to modify to meet MHRA performance requirements. The Head of Medical Affairs at Roche stated that "*Research conducted and published by Oxford University* [1, 2] *provided important benchmarking to assess the performance of our COVID-19 antibody testing platforms*" [D].

Influencing global government decision-making: withdrawal of LFIAs

In early 2020, Oxford research [1], led directly to the withdrawal of the early LFIA testing kits nationally in the UK, in the US, Spain and Italy [E], preventing inaccurate tests being used to inform pandemic control. The former head of the UK DHSC Antibody Testing and Prevalence Studies (which went on to become NHS Test and Trace) stated

> "*Without this information, ministers would not have had the data to make informed decisions about which tests to procure and how relevant they were to policy ideas such as immunity certificates. It was the studies led by Derrick and team into the performance of the tests that resulted in decisions to delay mass deployment of antibody tests and the return of underperforming tests to their manufacturers*" [E].

Lateral flow antigen tests (LFDs) for community testing

The LFD evaluation study was published in the form of a report to government in November 2020 [4] and was used to inform test choice (Innova SARS-CoV-2 Antigen Rapid Qualitative Test) for a pilot COVID-19 community testing study of 300,000 people in Liverpool (6-16 November, alongside PCR testing. [F]). This pilot resulted in Liverpool moving from tier 3 to tier 2 restrictions and the subsequent deployment of 1,000,000 LFDs to 50 directors of public health on 16 November. The Community Testing Programme, including every local authority, was rolled out nationwide in December 2020 and offered local areas the opportunity to deploy large-scale testing to asymptomatic individuals in a way that best suited them and the needs of their communities. The evaluation of LFDs by the Oxford team and PHE led to the government decision to roll out asymptomatic testing to the 18,000,000 people who were required to leave home to work [G], including NHS staff (approximately 1,500,000 employees) and care home staff, reducing the risk of the virus being passed on to hospital patients, care home residents, colleagues and family members. The government also used rapid LFDs to offer asymptomatic testing at 126 universities across the UK, reaching 75% of the student population, providing assurance that they could travel home safely during the travel window (3-10 December) for the Christmas break and minimise the risk of transmission [H]. Oxford and PHE's research led to a successful application to the MHRA in December 2020 for using LFDs as a self-test, increasing deployment to settings that could not support supervised testing [G].

According to NHS Test and Trace data, between 26 November and 31 December 2020, 967,525 LFD tests were taken across England identifying 13,755 positive cases (number does not include healthcare workers). Subsequent confirmation and isolation of these cases contributed to infection control. Lord Bethell, Parliamentary Under Secretary of State (Minister for Innovation), who leads COVID-19 policy, confirmed that "*Oxford research enabled the development of mass community testing. These tests have successfully identified a significant number of individuals with SARS-CoV-2 infections who may otherwise not have been identified"* [I]. DHSC Deputy Director Testing Policy summarised; "*research conducted by Oxford has supported (and enabled) the widest deployment of asymptomatic testing in the western world*" [G].

Informing UK government pandemic control policy: infection survey

In April 2020, Walker led the ONS CIS nationwide survey to track COVID-19 in the population [3]. Since May 2020, the ONS CIS weekly reports using information from 400,000 individuals across England, Wales, Scotland, and Northern Ireland have been used by scientists and the UK government to manage the pandemic. Data from the ONS CIS directly feeds into the government's COVID-19 Task Force twice weekly meetings, providing real-time information to decision-makers [J]. ONS CIS data feeds into every Scientific Advisory Group for Emergencies (SAGE) meeting and helps shape its recommendations to the government [J]. Data also feeds into the SAGE sub-group Scientific Pandemic Influenza Group on Modelling (SPI-M) to model national and regional infection rates and estimate R (reproduction number).

Sir Patrick Vallance, Government Chief Scientific Advisor summarised the effects of this data:

> "*Several SPI-M groups use data from the ONS infection survey to inform their modelling, including estimating R… the Survey has been useful in informing and checking calculations of R and other key metrics used to understand the state of the epidemic, and therefore forms part of the critical evidence-base needed to make the best-informed policy decisions of national importance.*" [J].

Data from the ONS CIS has been used to inform tiering and national intervention decisions, to assess the effectiveness of non-pharmaceutical interventions such as face coverings and social distancing, and to advise key scientific groups such as SAGE and NERVTAG on epidemiological questions including new variants of SARS-CoV-2 [K]. Several models have been developed to estimate the number of lives saved as a result of national lockdown in the UK. Using data from the ONS CIS and comparing to data from Sweden where no lockdown was imposed, researchers at University College London estimated that lockdown on 23 March 2020 saved 17,700 lives in England and Wales to 7 August 2020 [Li]. Using data from the ONS CIS, researchers at London School of Health and Tropical Medicine modelled the effect of tiered restrictions in England introduced in October 2020 and showed that they had some effect in slowing transmission but

that a temporary lockdown (4 Nov – 5 Dec) provided the strongest effect in reducing COVID-19 deaths, saving approximately 20,000 lives between 1 October and 31 Dec 2020 [Lii].

Professor Sir Ian Diamond, National Statistician, highlighted the advancement in analytical capability of staff at the ONS through the collaboration with the Oxford team,

> "*The involvement of Professor Sarah Walker and Dr Koen Pouwels ... has significantly broadened the statistical infrastructure and capability in surveillance studies at ONS. ... The partnership has proven the success of flexible and innovative ways of working across sectors to provide vital evidence for key policy decisions*" [K].

5. Sources to corroborate the impact

A. Public Health England Report with the University of Oxford and OUH NHS Foundation Trust: Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays, July 2020. https://www.gov.uk/government/publications/covid-19-head-to-head-laboratory-evaluation-of-4-commercial-serological-assays

B. Corroboration of contribution to OmniPATH ELISA: (i) Press release announcing OmniPATH ELISA CE marking, 8 December 2020 https://thermofisher.mediaroom.com/press-releases?item=123524 (ii) Testimonial from Senior Director Global Marketing on benefit of Oxford-ThermoFisher collaboration.

C. Coronavirus (COVID-19) Infection Survey: characteristics of people testing positive for COVID-19 in England and antibody data for the UK: December 2020 https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19infectionsinthecommunityinengland/december2020

D. Testimonial from Head of Medical Affairs, Roche confirming importance of Oxford research [1, 2] in assessment of antibody testing platforms.

E. Testimonial from former DHSC Head of Antibody Testing and Prevalence Studies confirming importance of [1] on government decision making.

F. Press release from DHSC, 11 November 2020, announcing results of [4] and the use of the Innova test in the Liverpool pilot. https://www.gov.uk/government/news/oxford-university-and-phe-confirm-high-sensitivity-of-lateral-flow-tests

G. Testimonial from DHSC Deputy Director Testing Policy on benefit of LFDs on mass community testing.

H. Reports of asymptomatic testing for university students:
(i) Article in The Independent; 'Covid: Three quarters of university students in England covered by asymptomatic testing scheme', 1 December 2020;
https://www.independent.co.uk/news/education/education-news/university-students-covid-testing-asymptomatic-b1764215.html
(ii) Dept for Education blog, https://dfemedia.blog.gov.uk/2020/12/03/university-testing-your-questions-answered/, 3 December 2020.

I. Testimonial from Lord Bethell, Parliamentary Under Secretary of State (Minister for Innovation), on benefit of Oxford research on testing development and ONS CIS to government decision making

J. Testimonial from Sir Patrick Vallance, Government Chief Scientific Advisor, on benefits of ONS CIS to informing government decision-making.

K. Testimonial from Professor Sir Ian Diamond, National Statistician and Chief Executive of the UK Statistics Authority, corroborating benefits to ONS.

L. Journal papers estimating results of lockdown: (i) R Nyman & P Ormerod, How many lives has lockdown saved? *MedRxiv* 21 Aug 2020 DOI: 10.1101/2020.06.24.20139196;
(ii) NG Davies et al, Association of tiered restrictions and a second lockdown with COVID-19 deaths and hospital admissions in England: a modelling study,
The Lancet Infectious Diseases 4:482-492, first published 23 December 2020
DOI: 10.1016/S1473-3099(20)30984-1, especially Fig 3A.