OXFORD
POPULATION
HEALTH

Creating clarity
in a time of uncertainty

The Nuffield Department of Population Health's
contribution to the COVID-19 response 2020

"The University of Oxford has responded swiftly and effectively to the COVID-19 pandemic, with colleagues across the Medical Sciences Division delivering major breakthroughs in the research response.

NDPH focuses on providing reliable evidence on the causes, treatment and prevention of diseases that affect millions of people across the world.

It has drawn on its multi-disciplinary expertise and the strengths of partners within and beyond the University to answer some of the most important research questions and respond at speed to a challenge unlike any other we have experienced."

Professor Sir John Bell, Regius Professor of Medicine, University of Oxford

Introduction
Professor
Sir Rory Collins
Head of Department

OXFORD POPULATION HEALTH

UNIVERSITY OF OXFORD

The Nuffield Department of Population Health (NDPH) is uniquely placed to make a major contribution to the response to COVID-19 because it covers all aspects of population health and works at scale to provide clarity about the most important questions affecting human health.

The department delivers randomised trials, observational studies, ethics, health economics and health services research, and is supported by dedicated laboratory, IT, communications and administrative staff. NDPH is a key partner in the Big Data Institute (BDI), a cross-department initiative that focuses on the analysis of large, complex, heterogeneous data sets.

We have built on our track record of success in large-scale and global work and capitalised on our multi-disciplinary approach,

underlying infrastructure, and longstanding partnerships to respond to the pandemic.

For example, our two registered clinical trials units have longstanding experience in developing bespoke research systems and delivering innovative, streamlined clinical trials; we combined this experience with expertise in emerging viral infections in the Nuffield Department of Medicine (NDM) to deliver the first major breakthrough in the COVID-19 response.

The department is working with partners in the UK and across the world to help solve the problems that are having the greatest impact. For example:

→ In 2020, the RECOVERY trial delivered results on four potential COVID-19 treatments, changing clinical practice globally.

→ Our perinatal team is improving the care and treatment of babies and pregnant women directly and indirectly affected by COVID-19.

→ The Wolfson Laboratory team established the laboratory process for the biggest of the Lighthouse laboratories.

→ Our ethics expertise made a critical contribution to the development and introduction of mobile phone applications.

→ We are shining a light on the wider impacts of COVID-19 for patients with other diseases, such as heart disease and bowel cancer.

This report provides an overview of the work we have undertaken in 2020 to support the COVID-19 effort.

The important questions and our contribution

What are the risk factors and effective treatments?

How can diagnostic testing be delivered effectively?

What are the levels of infection and immunity?

How can we design effective containment strategies?

What are the longer term effects of SARS-CoV-2 infection?

How is COVID-19 impacting wider public health and services?

How can we inform decision-making?

Testing treatments in the biggest randomised trial of COVID-19 therapies

At the start of the COVID-19 pandemic, nobody knew which treatments would be effective. The RECOVERY trial is a large, randomised controlled trial of possible treatments for patients admitted to hospital with COVID-19.

The trial is focusing on testing treatments that are already used for other conditions. The trial is led by Professor Peter Horby in NDM which has world-leading expertise in infectious diseases, and by Professor Martin Landray in NDPH which has

RECOVERY in 2020

Randomised Evaluation of COVID-19 Therapy

176 hospitals

3 major results in 100 days

23340 participants

9 days to set up

828000 website visitors

15203 items of media coverage

pioneered novel approaches to delivering effective and streamlined randomised clinical trials.

Over 23,000 patients were randomised to nine treatment arms, or no additional treatment, in 176 hospital sites across the UK between March-December 2020.

The trial was set up at unprecedented speed; it took just nine days from conception to launch. Over 10,000 patients were recruited in just two months, making it the fastest ever recruiting individually randomised controlled trial. The trial is deliberately inclusive: the youngest participant was less than six months old and the oldest over 100 years, one-third are women, and one-sixth are of Black, Asian or Minority Ethnic (BAME) background.

In 100 days, the RECOVERY trial provided results enabling change

> **"The UK has done really well on the therapeutics side... largely because of the huge success of the Phase III trials and particularly the RECOVERY study."**
>
> Sir Patrick Vallance, UK Government Chief Scientific Adviser

in global practice three times. It showed that two drugs used to treat hospitalised COVID-19 patients throughout the world, hydroxychloroquine and lopinavir-ritonavir, do not improve survival, whilst one drug that was not recommended, dexamethasone, saves lives. The use of dexamethasone following the RECOVERY trial results is estimated to have saved approximately 12,000 lives in the UK and many more worldwide.

RECOVERY also found that there is no benefit from use of the antibiotic, azithromycin, in patients hospitalised with COVID-19. The trial is continuing to test other treatments, including Regeneron's antibody cocktail.

Given the success of the Phase III RECOVERY trial, the UK Government has increased investment so that new

treatments can be tested through RECOVERY+, including treatments tested in Phase II (smaller) and Phase III studies. The team are now preparing to deliver RECOVERY internationally, with new sites being set up in Indonesia and Nepal.

The trial is the best performing trial anywhere for COVID-19 and is being held up as the way forward for drug trials. Academics from across the world are drawing lessons from the pioneering design of the trial which minimises the impact on frontline teams by integrating the research with clinical care and making best use of national data sources.

The trial is also generating wider understanding of the importance of clinical trials in providing reliable evidence, and has been described as a 'beacon of excellence'.

Streamlining clinical trials to provide reliable evidence rapidly

Professor Sir Richard Peto (NDPH) and Professor Sir Rory Collins pioneered the concept of large simple trials for the International Studies of Infarct Survival (ISIS), a series of randomised trials that assessed the effects of widely usable treatments on survival following a heart attack. Around 140,000 patients participated worldwide between 1985 and 1993. To recruit as many participants as possible, the studies involved integrating the trials with clinical practice, simplifying the recruitment and data entry processes, and using government records for follow-up.

This innovative approach paved the way for other successful trials designed and delivered by NDPH and directly informed the design of the RECOVERY trial and of SOLIDARITY, the international COVID-19 treatment trial led by the World Health Organization (WHO). Both trials minimised the impact on frontline staff by using simple online enrolment, randomisation and follow-up forms, and embedding the research in clinical practice.

The SOLIDARITY protocol developed by Professor Sir Richard Peto, enabled over 400 hospitals in over 30 countries to randomise over 11,000 patients (from March-October 2020) to quickly and reliably answer critical questions.

The RECOVERY and SOLIDARITY trials have demonstrated that hydroxychloroquine, lopinavir (with or without) ritonavir, azithromycin, interferon beta-1a and remdesivir have little or no effect on mortality or other important clinical outcomes. In June, the RECOVERY trial announced that dexamethasone, a low-cost and widely available corticosteroid regimen, saves the lives of those with severe COVID-19.

> "The SOLIDARITY trial provides simplified procedures to enable even hospitals that have been overloaded to participate."
>
> Dr Tedros Adhanom Ghebreyesus, WHO Director-General

> "More than a third of trials have been too small to provide conclusive answers. You have to do things at scale as RECOVERY and SOLIDARITY have done."
>
> Sir Jeremy Farrar, Director of Wellcome

Drawing on their NDPH research, Professor Peto and Professor Hongchao Pan worked closely with the WHO principal investigator on governance and study conduct, and made a major contribution to analysis, interpretation and presentation of SOLIDARITY trial datasets.

Enabling the provision of outcome data to clinical trials

Clinical trials enable the development of new and improved treatments to transform patient lives. NHS DigiTrials was established in October 2019 to make it easier for trialists to establish and run clinical trials and for patients to participate in research.

A partnership between an NDPH team from the University of Oxford's Big Data Institute, NHS Digital, IBM and Microsoft, NHS DigiTrials was developed initially to enable trialists to undertake a rapid feasibility assessment of the number and location of eligible patients through secure analysis of clinical and demographic datasets. Recognising the urgent need to provide data

on clinical outcomes to COVID-19 researchers, the team, led by Professor Martin Landray, quickly refocused efforts on linking trial cohorts to NHS data sources, so that researchers could be provided with information on relevant medical events.

Data on clinical outcomes provided through NHS DigiTrials have been used to inform results from the RECOVERY trial. New identification and communications services are being piloted. The NHS DigiTrials

The RECOVERY trial and pregnant women

The UKOSS data collection system is being used to collect outcome data for pregnant women. The RECOVERY trial is ensuring that pregnant women have equitable access to trial treatments and is unusual in its commitment to them.

Co-development Panel have worked closely with the NHS DigiTrials team to ensure that patient and public feedback has been included in the design of this service.

Early insights on the impact on pregnant women and babies

COVID-19 in pregnancy

The impact of the SARS-CoV2 virus on pregnant women and their babies was unknown at the start of the pandemic. Reports of COVID-19 infection in pregnant women and their babies were emerging, so a rapid study of COVID-19 infection in pregnancy was important to inform prevention and treatment.

The COVID-19 in Pregnancy study is investigating the incidence of COVID-19 infection, and answering these critical questions:

→ What are the outcomes of COVID-19 infection in pregnancy for both mother and infant?

→ What are the characteristics of women who are hospitalised with COVID-19?

→ How does the treatment of COVID-19 infection in pregnancy influence outcomes for mother and infant?

The infrastructure was set up in 2012 in preparation for the possibility of a pandemic, to ensure accurate information could be collected to advise pregnant women, their midwives and doctors. It was activated immediately in March for COVID-19.

The team, led by Professor Marian Knight, carried out a rapid study

to get early insights, using the established UK Obstetric Surveillance System (UKOSS). The study found that pregnant women are at no greater risk of severe COVID-19 than other women. The majority of women who did become severely ill were in their third trimester of pregnancy, emphasising the importance of social distancing for this group.

Black pregnant women were eight times more likely to be admitted to hospital with COVID-19, while Asian women were four times as likely. This finding was communicated widely in the media, including all major UK outlets and international distributors. In response, the Chief Midwife in England wrote to all the maternity units in the country calling on them to take specific actions to minimise the additional risk of COVID-19 for BAME women and their babies. These included ensuring staff know when to admit pregnant women from a BAME background, and providing tailored support such as discussing protective vitamin D supplements.

The Royal College of Obstetricians and Gynaecologists (RCOG)'s report 'Guidance for maternal medicine services in the evolving coronavirus (COVID-19) pandemic', highlighted the need to be aware of the increased vulnerability of pregnant women from BAME backgrounds.

COVID-19 in newborns

There was very little information about how babies get COVID-19 infection, whether it transmits from mothers to their babies while they are still pregnant, during labour and birth, or whether the infection occurs following birth. Clinical guidance was variable.

Using the British Paediatric Surveillance Unit (a national surveillance system for disorders in childhood), researchers from the Policy Research Unit in Maternal Health and Care, led by Professor Jenny Kurinczuk, worked with colleagues in other institutions to investigate the incidence, characteristics, transmission, and outcomes of SARS-CoV-2 infection in neonates who received inpatient hospital care in the UK.

The study is one of few worldwide to collate comprehensive population-based data on babies affected by COVID-19. Researchers found that severe COVID-19 infection is rare in newborns, and only a small proportion of babies caught COVID-19 from their mother.

The research supports UK and international guidance to keep mother and baby together even when the mother is known or suspected to have COVID-19. Whilst a higher than expected proportion of the babies were from BAME backgrounds, COVID-19 infection was rare in babies from the BAME community, providing some reassurance to parents and prospective parents.

Making data available to researchers around the world

The emergence of new digital technologies has allowed huge quantities of information on health exposures and outcomes to be captured, stored, and analysed using advanced statistical techniques. It has also provided an opportunity to make large datasets accessible to researchers worldwide.

NDPH brings together epidemiologists, statisticians, computer scientists, and engineers to provide the infrastructure that facilitates large-scale epidemiological studies and the curation of clinical data. Led by Dr Alan Young, our computing team produces and maintains systems that meet the requirements of specific studies and can be adapted easily. The team have developed novel informatics tools which improve recruitment, data acquisition and analysis, as well as novel systems for storage, processing and accessing very large datasets. Examples include the use of touchscreen tools for patient-reported data, integration of MRI images, and linkage to NHS patient records.

Large cohort studies provide the opportunity to understand genetic and non-genetic risk factors for COVID-19. UK Biobank contains extensive phenotypic, genetic and health-record data on over 500,000 volunteer participants from across the UK.

Dr Young and his team have designed and built many of the clinical and data handling systems that enable the UK Biobank Data Analyst team at NDPH, led by Edward Horn, to receive, process and integrate a large and diverse array of health record data into UK Biobank on a regular basis.

In response to the pandemic, Professor Naomi Allen and the Data Analyst team have worked closely with Dr Young's team to make the following data on the health of participants available via UK Biobank, giving researchers an unprecedented opportunity to study COVID-19:

→ SARS-CoV-2 antigen test data, obtained through an existing collaboration between UK Biobank, Associate Professor Danny Wilson and Public Health England (PHE)

→ Cohort-wide GP (primary care) data which is being made available to researchers for the first time

→ Hospital inpatient data, including critical care, provided by NHS Digital

→ Death data provided by NHS Digital.

About 700 groups worldwide have already accessed these data, which are enabling a wide range of research into the relevance of genetic, lifestyle and medical factors on COVID-19 disease severity and the longer-term health effects of SARS-CoV-2 infection.

For example, Associate Professor Danny Wilson is working with groups at McGill University and the Broad Institute to contribute analyses of UK Biobank data on genetic risk factors for COVID-19 as part of the COVID-19 Host Genetics Initiative.

UK Biobank was among the first study to contribute a large volume of data, since the pre-existing Bugbank collaboration enabled it to respond swiftly to set up the linkage system. Graduate student Nicolas Arning and Professor Wilson are also using the diagnostic SARS-CoV-2 test data to develop a new approach to quantify the effects of lifestyle and medical risk factors for COVID-19 that accounts for uncertainty about which potential risk factors to consider.

Setting up the biggest of the Lighthouse laboratories - the national testing centres

The NDPH Wolfson Laboratory team, led by Associate Professor Mike Hill, provides critical and cost-effective support for large-scale observational studies and randomised trials conducted by NDPH and collaborating research groups. They moved quickly to support the UK Biocentre in Milton Keynes to set up a national testing centre.

The Department of Health and Social Care (DHSC) approached the UK Biocentre in mid-March to establish a swab testing centre; NDPH were asked to provide support. Several senior and specialist staff from the Wolfson Laboratory were seconded to UK Biocentre. They helped to establish the laboratory process and took the lead role in validating the testing process method and putting in place ongoing performance monitoring.

They also evaluated significant changes to the standard assay method, for example, using a half reaction volume which was adopted by other Lighthouse laboratories. The team worked with the national testing programme for evaluating new sample collection tubes for use across the network, evaluating the stability of different viral transport media and providing data to compare assisted versus self-administered swabbing.

Professor Hill also represented the UK Biocentre in the Pillar 2 testing Quality Leads group. NDPH staff established a structure for staff training in the

UK Biocentre Lighthouse laboratory, enabling rapid scale-up of volunteer and temporary workers to support high-throughput testing using liquid handling automation systems.

A testing process was established, and the first results delivered in two days. Within two weeks, a 'megalab' had been built; one million tests had been processed at the site within two

months. This was achieved through rapid validation of the testing process and documentation, and swift recruitment and training.

The scale of operation was expanded as the megalab and equipment became available and there was a move to 24/7 working. Over 400 volunteers had been recruited in the laboratories by the end of 2020. The UK Biocentre is the biggest of the Lighthouse laboratories and was typically receiving, preparing, analysing and reporting test results for 35,000-50,000 swab samples per day at this time. This figure is set to rise to over 220,000 test results per day with a further extension of the laboratory facilities and the addition of a new testing process. The laboratory is currently applying for ISO 15189 accreditation by the United Kingdom Accreditation Service.

Developing machine learning approaches for diagnostic screening

There is a need for reliable antibody detection approaches to support diagnosis, vaccine development, safe release of individuals from quarantine, and population lockdown exit strategies.

It can be difficult to distinguish SARS-CoV-2 in the early stages of the infection, and testing can take up to 48 hours. Working with colleagues from across the University of Oxford's Medical Sciences Division and Harvard University, Associate Professor David Eyre, developed two early-detection models to identify COVID-19.

The team used routinely collected data typically available within one hour (laboratory tests, blood gas and vital signs) during 115,394 emergency presentations and 72,310 admissions to hospital.

The models perform effectively as a screening test for COVID-19 in emergency departments and hospital admission units where rapid testing is unavailable. They provide a prediction of a patient's COVID-19 status, with more than 90% accuracy in less than an hour. Tools to implement these models in Oxford University Hospitals (OUH) are being developed.

Measuring the efficacy of antibody tests

At the start of the pandemic, a wide range of new COVID-19 antibody testing kits quickly launched onto the market, with millions being bought by governments. At the time, however, there was no evidence that these could accurately detect whether an individual has been exposed to coronavirus, and many kits subsequently proved insufficiently sensitive.

The DHSC approached Professor Derrick Crook's group in the NDM for support in validating the accuracy of COVID-19 antibody testing kits. Associate Professor David Eyre from NDPH played a leading role in designing the studies, performing the analysis and writing the subsequent papers. Dr Justine Rudkin supported the project, particularly in rapidly processing the thousands of blood samples required.

The team tested a wide variety of different kits, identified by the Government's overseeing committee as being fundamentally different enough to warrant a comprehensive assessment. Kits that passed preliminary tests were then tested on 100 patient blood samples. These included samples with varying levels of antibodies to test the sensitivity of the kits, besides historical samples from patients infected with similar viruses to confirm specificity.

Achievements from the group include:

→ **Demonstrating the limited sensitivity of early blood spot-based antibody tests.** These had been considered by the UK Government as a means to produce 'immunity passports' for previously infected individuals. Based on these findings, this policy was no longer pursued.

→ **Evaluating the performance of lateral flow devices.** The group found that available commercial rapid testing devices did not perform sufficiently well for individual patient applications. The results were used by the NHS and Civil Service to purchase better performing tests.

→ **Comparing performance characteristics of immunoassays.** This benchmark study gave a head-to-head benchmark comparison of different immunoassays for SARS-CoV-2. The results are being used to choose which devices are used for national mass testing.

→ **Evaluating enzyme-linked immunosorbent assay (ELISA) platforms.** This work was commissioned by Secretary of State Matt Hancock and delivered in collaboration with PHE Porton Down. The results demonstrated that ELISA testing was both highly sensitive and specific and were used by the UK Government to make purchasing decisions.

→ **Determining thresholds for antibody assays.** This study found that stringent thresholds for SARS-CoV-2 immunoglobulin G (antibody) assays result in under-detection of cases reporting loss of taste/smell.

→ **Setting up a novel diagnostic platform.** The group is the lead exemplar lab setting up LamPORE, a novel diagnostic platform for the detection of SARS-CoV-2 RNA. The platform has the potential to analyse thousands of samples per day on a single instrument, and will be replicated across 28 NHS laboratories.

Undertaking a large longitudinal study of SARS-CoV-2 antibody levels

In the early stages of the pandemic, there was little evidence about the proportion of people who had been infected or how long antibodies to coronavirus stay in the blood. A much better understanding of these questions was needed to help inform future Government strategy, including lockdown and social distancing measures.

UK Biobank, led by Professor Sir Rory Collins and Professor Naomi Allen, set up a seroprevalence study to track the extent of the coronavirus infection across England, Scotland and Wales. The study is measuring blood antibodies in volunteers to assess the extent of past infection in different population sub-groups, for example, by region, age, sex, ethnicity, rural/urban status and socio-economic deprivation. The study will also determine the extent by which antibody levels change over time within individuals.

UK Biobank's Health Data Linkage team, led by Dr Jo Holliday, was responsible for developing and implementing the participant materials, and the data analyst team were responsible for selecting a representative group of participants to take part. The epidemiology team, led by Dr Rishi Caleyachetty, collaborated with Professor Sarah Parish's team to analyse the data that have contributed to reports to the Department of Health and Social Care (DHSC) to help guide policy.

The study was launched in May and has successfully recruited 20,000 volunteers, a combination of existing UK Biobank participants and their adult children and grandchildren. These volunteers agreed to provide a finger-prick sample of blood using a kit sent to their homes every month for six months (June-November 2020).

UK Biobank COVID-19 antibody study

A major study to determine the extent of previous infection with coronavirus in different populations across the UK and how these rates change over time. These results will help inform the process of assisting in managing the pandemic.
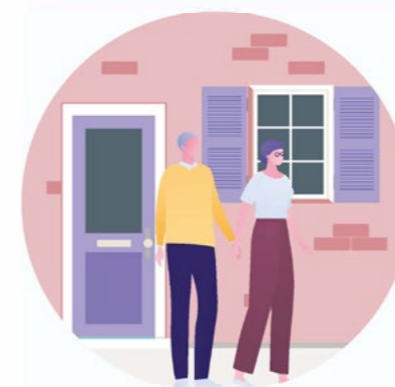
The study
We have recruited 20,000 volunteers, made up of UK Biobank participants and their adult children and grandchildren living in different households to provide generalisable evidence for the UK population.
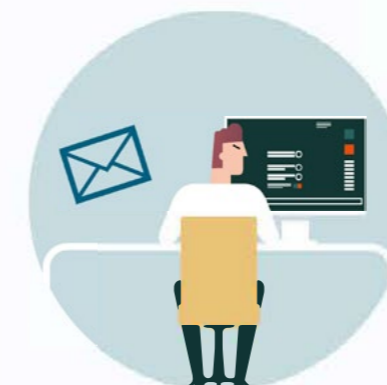
Samples
Participants are asked to complete a short survey about any **symptoms** they have experienced.

Participants receive **monthly collection kits**, and are asked to provide 0.5ml sample of blood from their fingertip.

Analysis
Samples are returned in protective envelopes to UK Biobank and **undergo validated antibody measurement** performed by the Target Discovery Institute based at the University of Oxford.

This study will provide vital information about changes in the rates of previous infection across the UK as we come out of national lockdown.

They were also asked to complete a survey about any symptoms they had experienced and potential risk factors for exposure (such as household size, employment, transportation, and use of protective measures).

Antibodies to SARS-CoV-2 in the blood samples are being measured in a laboratory at Oxford University's Target Discovery Initiative.

UK Biobank published the first results in July. It found evidence of previous infection in 7.1% of the study population, but with large variation in the rates between different parts of the UK and between different demographic groups. Detailed information available to UK Biobank on the participants will be used to assess the impact of age and other characteristics on the persistence of antibody levels and the presentation of symptoms. The final results were made available in early 2021.

> "This is a hugely important study, and we are incredibly grateful to the 20,000 people who have taken part or will do so in the future. The findings will help inform our future response to managing the pandemic."
>
> Lord Bethell,
> Minister for Innovation,
> Department of Health and
> Social Care

Developing a standardised UK-wide system for detecting SARS-CoV-2 in wastewater

Dr Koen Pouwels is determining the accuracy of estimates of SARS-CoV-2 in wastewater, as part of a project to develop a standardised UK-wide system for detecting SARS-CoV-2 in wastewater.

The system will provide an early warning of future outbreaks and reduce reliance on costly testing of large populations. By sampling wastewater at different parts of the sewerage network, public health officials will be able to quickly target interventions in those areas at greatest risk of spreading the infection.

The researchers will also determine whether there is a possibility for SARS-CoV-2 in wastewater and sludge to be infectious, and how environmental factors such as sunlight and temperature reduce infectivity. This will enable them to confirm whether current guidance protects workers at sewage plants, and also assess the risk to people and animals as a result of treated and untreated sewage discharge in rivers and seas.

The UK Wastewater Surveillance Programmes across England, Scotland and Wales have been actively monitoring wastewater since early summer 2020, building up an evidence base that has provided knowledge and support to the wider efforts for managing the pandemic.

Designing effective and ethical mobile phone apps to control the pandemic

A [team of medical research and bioethics experts at Oxford University](#) led by [Professor Christophe Fraser](#) (NDM/BDI) and [Professor Michael Parker](#) (NDPH) investigated the feasibility of developing a coronavirus contact tracing app to aid European governments in controlling transmission rates.

The team recommended that the mobile application should form part of an integrated coronavirus control strategy that identifies infected people and their recent contacts using digital technology. Besides

informing the UK Government's decision to pursue a digital contact tracing app, the research also provided the detailed parameters to maximise the impact, whilst upholding high ethical standards.

In January 2020, the research team began using the COVID-19 epidemiological data from China to explore the feasibility of developing a contact tracing mobile app for European governments. The researchers [proposed a contact tracing mobile app](#) that is instant, could be widely deployed, and that would be implemented with appropriate ethical considerations. They started developing a digital contract tracing app with NHSX from 7 March 2020, having shared the evidence with the UK Government.

Whilst the app was being developed, the research team investigated the [ethical considerations](#) and recommended: guaranteeing equal
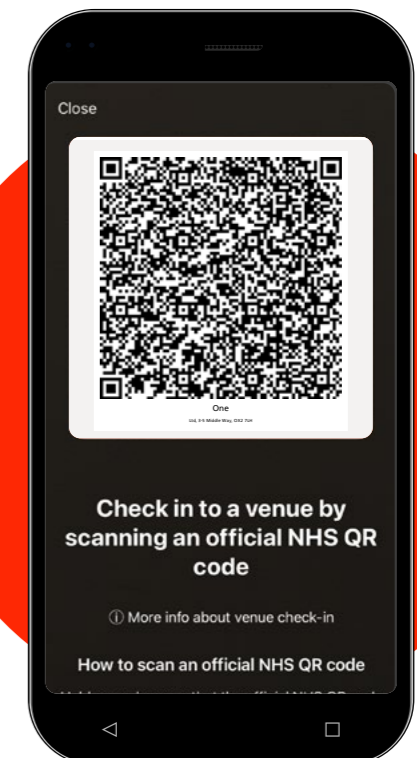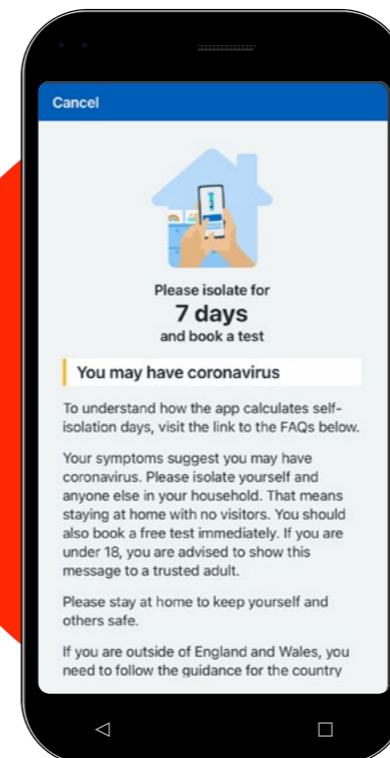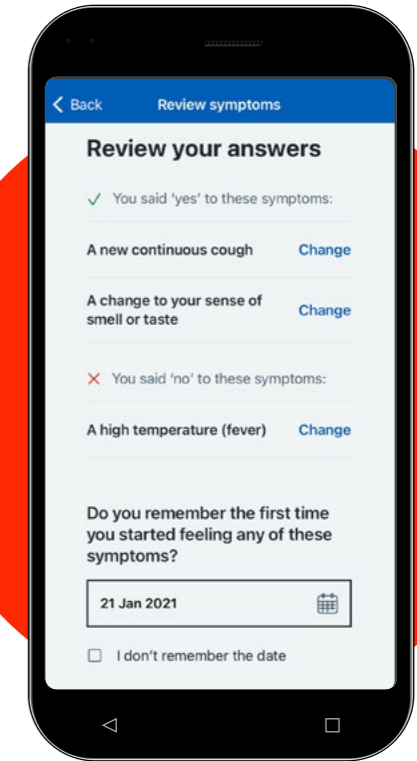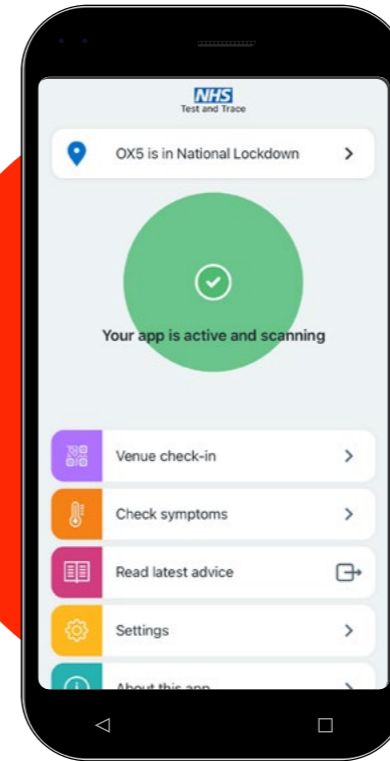
access and treatment; addressing privacy and data usage concerns; adopting a transparent and auditable algorithm; considering digital deployment strategies to support specific groups, such as health care workers, the elderly and the young; and, proceeding on the basis of individual consent.
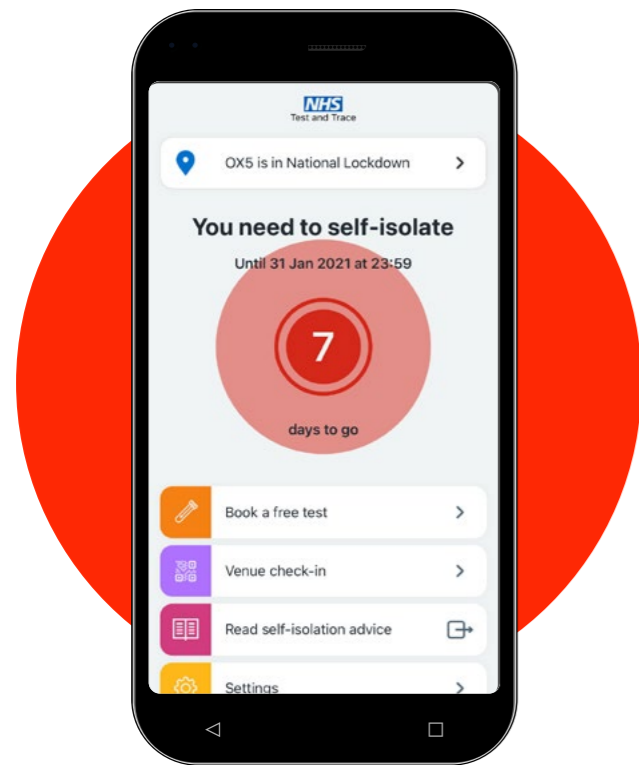
This work informed the WHO's Interim Guidance paper 'Ethical considerations to guide the use of digital proximity tracking technologies for COVID-19 contact tracing' and led to a UK pilot for a mobile contact tracing app, which was launched on the Isle of Wight on 7 May. An analysis by the research team found that the app was highly successful in reducing COVID-19 transmission rates, with the reproduction (R) rate reducing from 1.3 to 0.5. Based on the pilot, the Oxford team outlined five epidemiological and public health requirements that any COVID-19 tracing app should satisfy. These were: sensitively and specifically quarantine infectious individuals; high (60%) user uptake and adherence; rapid notification; integration with local health policy; and ability to evaluate effectiveness transparently.

Following the Isle of Wight pilot, the UK moved to the Google/Apple platform, which also now drives many other contact tracing apps worldwide. The five principles developed by the research team were used by the Google/Apple Exposure Notification developers as requirements for their app to meet before launch.

The UK NHS COVID-19 contact tracing app launched on 26 September 2020. It was downloaded by around six million people on the day of launch, and had been downloaded 20,739,925 times in England and Wales by 16 December. 775,191 QR posters had been generated through the GOV.UK coronavirus QR poster service, enabling NHS Test and Trace in England and NHS Test, Trace, Protect in Wales to contact multiple people when coronavirus outbreaks were identified in venues.

Professor Nina Hallowell, Dr Federica Lucivero and Dr Stephanie Johnson conducted a sociological analysis to gain an in-depth understanding of how stakeholders perceive the ethical debates associated with the NHSX app. This involved a media analysis and interviews with app users in the Isle of Wight and other stakeholders involved in the app development and assessment. The analysis explored issues such as safeguarding data; transparency and oversight; the role of 'Big Tech' companies; and who should access data.

Understanding antibody responses through a large healthcare worker study

Oxford University Hospitals NHS Foundation Trust (OUH) is working with Associate Professor David Eyre (NDPH) and collaborators from across the Medical Sciences Division to offer regular SARS-CoV-2 PCR and antibody testing to over 12,000 healthcare workers. Their study is tracking antibody responses over time, establishing who is at most risk of getting COVID-19, and whether previous infection protects against re-infection.

Their study was the first to comprehensively assess how SARS-CoV-2 prevalence varies among all staff groups across an institution, and the dynamics

> "This study is a fantastic example of how well-structured long-term cohort surveillance can produce hugely useful results. Studies like this one are absolutely vital in helping us to understand how this new virus behaves and what the implications are for acquired immunity."

Susan Hopkins,
Deputy Director,
National Infection Service,
Public Health England

and determinants of individual antibody responses. The results have been used to inform infection control and occupational health interventions. Initial results demonstrated that staff caring for COVID-19 patients were at greater risk, as were Asian and Black staff and those who had household members with the infection. Risk also varied across the hospital, with higher rates of infection seen in acute medicine staff; intensive care unit staff were relatively protected by a combination of infection control and PPE-related measures.

The researchers found that antibodies to SARS-CoV-2 nucleocapsid protein fall by half in less than 90 days, with antibody levels peaking lower and falling faster in younger adults and those without symptoms. Antibody levels peaked 24 days after the first positive test before beginning to fall. Those tested had lost their positive antibody result after an average of 137 days. However, antibodies to

SARS-CoV-2 spike protein, which may be important in protecting from re-infection, were stably maintained for up to six months in over 90% of individuals.

The study was used to perform the first large-scale assessment in the world of the extent to which antibodies against SARS-COV-2 are associated with protection against (symptomatic) reinfection. The results indicate that antibodies are associated with protection from reinfection for most people for at least six months. Over 12,000 healthcare workers were tested for antibodies to SARS-COV-2 to detect who had been infected, and were then tested on a regular basis over 30 weeks. None of the staff with antibodies developed a symptomatic infection, whilst 123 of the staff without antibodies did, suggesting that most people are unlikely to get COVID-19 again if they have already had it in the previous six months.

Addressing the lack of 'real-life' data on physical distancing measures

Physical distancing measures are now widely used to help contain the pandemic, but there was little evidence of their effectiveness. A team of UK and US researchers, led by Dr Nazrul Islam, set out to compare the change in new cases of COVID-19 before and up to 30 days after implementation of physical distancing measures.

The research showed that physical distancing measures are associated with a meaningful reduction in new COVID-19 cases. By gathering data from 149 countries and regions, the researchers were able to demonstrate that implementing lockdown restrictions earlier was associated with a greater reduction in new cases. Overall, the implementation of physical distancing interventions (such as quarantine) was associated with an average reduction of 13% in COVID-19 incidence.

The researchers provided information about the findings to the DHSC. The study and results were also cited in the WHO's Coronavirus Update 32 and Update 33, and a report for the Governing Board of the Organisation for Economic Co-operation and Development.

Evaluating testing strategies for care home settings

Long-term care facilities are particularly vulnerable to nosocomial (location-based) outbreaks of COVID-19, with high rates of transmission and mortality. Rapid epidemiological surveillance is essential to detect and respond to outbreaks, but this is restricted by asymptomatic transmission and limited testing facilities.

As part of a UK-French collaboration, Dr Koen Pouwels contributed to the design and analysis of a study which investigated how best to use limited testing facilities to monitor SAR-CoV-2 transmission in care home settings. This was one of the first studies to model nosocomial transmission of COVID-19 and used detailed inter-individual contact networks to describe patient-staff interactions.

The results demonstrated an important role for asymptomatic and pre-symptomatic transmission, and estimated a median delay of seven days from introducing an asymptomatic COVID-19-infected patient to the first presentation of COVID-19 symptoms among any patients or staff. The findings made a significant contribution to a limited evidence base for optimizing COVID-19 surveillance in healthcare institutions.

Understanding the longer-term effects of coronavirus

Although much is known about the short-term effects of SARS-CoV-2, very little is known about the longer-term effects of the virus on internal organs. A UK Biobank study is being set up to obtain information on antibody status from all 500,000 participants. The study is led by Professor Naomi Allen and Dr Jo Holliday, with IT support provided by Dr Alan Young and Allen Young, and data support from the Data Analyst team.

Antibody test kits will be sent to all 500,000 UK Biobank participants in early 2021 to allow assessment of the impact of past infection on later health outcomes by linking the results with health records. These tests will tell participants if they have antibodies to SARS-CoV-2 within about 15 minutes. Participants will inform UK Biobank of their results so that the information can be made available to the wider research community and used to inform research into the longer-term effects of infection.

UK Biobank collected magnetic resonance imaging (MRI) scans from about 50,000 participants before the COVID-19 pandemic occurred as part of a project to scan the brains, hearts, bones and abdomens of 100,000 participants. Data from the antibody tests will be used to invite back for a repeat imaging scan about 1,500 participants who have positive antibodies and 1,500 who are negative. This will generate a unique resource to enable scientists to understand how the SARS-CoV-2 virus affects internal organs (such as the heart, lungs, and brain) by comparing imaging data before and after infection.

This vitally important work will guide the development of approaches to managing the long-term health effects of SARS-CoV-2 infection. Combined with other information on UK Biobank participants, the scans will create a health resource of worldwide significance for many years to come.
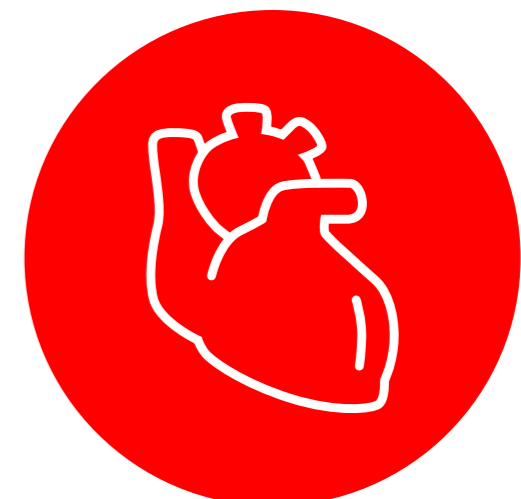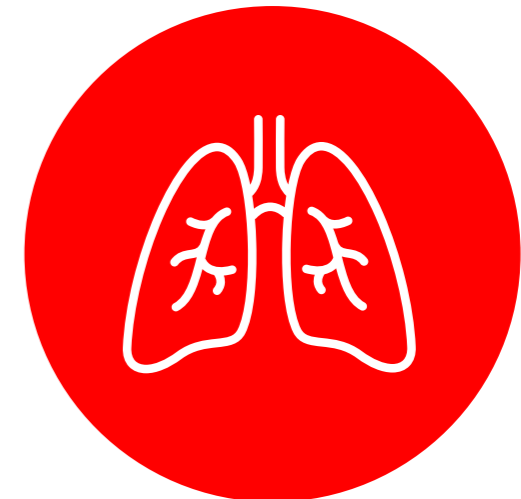
Understanding changes to admissions for acute coronary syndrome

Several countries affected by the COVID-19 pandemic had reported a substantial drop in the number of patients attending emergency departments with heart attack symptoms, and a reduced number of cardiac procedures.

Dr Marion Mafham and Professor Colin Baigent (NDPH), Professor Barbara Casadei (Radcliffe Department of Medicine) and colleagues worked with NHS Digital and colleagues from other universities and hospital trusts to understand the scale, nature, and duration of changes to admissions for different types of acute coronary syndrome in England.

The researchers found that the number of admissions to hospital with heart attacks fell by 35% between the middle of February and the end of March, compared with 2019 data.

Admissions with the most serious type of heart attack, caused by a complete blockage of an artery supplying part of the heart, fell by about a quarter, while rates of admission for heart attacks caused by a partial blockage of blood supply to the heart fell by 42%.

By the end of May, admission rates had partially recovered but, by that point, there had been about 5,000 fewer admissions with heart attacks in 2020 than would be expected, suggesting that many patients have missed out on lifesaving treatment.

The results were drawn to the attention of the British Cardiovascular Society and the British Heart Foundation, so that doctors and the NHS were alerted and guidance

> **"Medical societies, heart foundations, and governments have a responsibility to not only inform patients of the importance of seeking appropriate care, but also to ensure that a safe environment is provided for patients who are admitted to hospital because of a cardiovascular emergency."**
>
> Barbara Casadei, British Heart Foundation Professor in Cardiovascular Medicine at the University of Oxford, and former President of the European Society of Cardiology

could be given to encourage those with heart attack symptoms to go to hospital. The results were disseminated in other countries through the European Society of Cardiology. The team are continuing to monitor these trends and are posting updated results online every month.

Understanding the impact on colorectal cancer diagnosis

The coronavirus lockdown caused widespread disruption of NHS cancer services. Early diagnosis, however, is critical to give cancer patients the maximum chance of recovery and survival.

A study led by Professor Eva Morris investigated how the pandemic affected the number of patients referred for or diagnosed with bowel cancer, besides the treatment bowel cancer patients received. The study drew on NDPH's close working relationship with NHS Digital and methods developed to assess reductions in hospital admissions with heart attacks.

The researchers assessed the patterns of referral for bowel cancer investigation, diagnosis and treatment for NHS services in England from 1 January 2019 to 31 October 2020. The study revealed that bowel cancer diagnosis and treatment rates were significantly impacted by the first coronavirus lockdown.

Compared with an average month in 2019, in April 2020:

→ The monthly number of referrals by GPs to hospital clinics for investigation of possible bowel cancer reduced by 63%.

→ The number of colonoscopies performed fell by 92%.

→ The monthly number of people with confirmed bowel cancer referred for treatment fell by 22% and the number of operations performed fell by 31%.

The monthly rate had returned to 2019 levels by October, but did not exceed it, suggesting that, from April to October 2020, over 3500 fewer people were diagnosed and treated for colorectal cancer in England than would have been expected.

This was the first study to assess the impact of the COVID-19 pandemic on the diagnosis and management of bowel cancer across England. The results reflect a serious disruption in the normal identification and treatment of patients with bowel cancer, which likely extends to other types of cancer and chronic diseases.

Patients with symptoms of suspected cancer may have been reluctant to refer themselves for an assessment due to fears about catching coronavirus and the Government's call to 'stay at home' and 'protect the NHS'.

> "This research shows the clear impact of the pandemic on bowel cancer patients, and ultimately, their long-term chances of survival. It also highlights the unintended consequences of the 'stay at home' message and the impact of the temporary disruption to bowel cancer screening and diagnostic services."
>
> Genevieve Edwards, Chief Executive, Bowel Cancer UK

Revealing significant reductions in invasive bacterial infections

The bacteria *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* are leading causes of invasive diseases including pneumonia and meningitis, and of secondary infections post-viral respiratory disease. These are typically transmitted via respiratory droplets.

It was unknown whether the containment policies and public information campaigns during the early part of the COVID-19 pandemic had affected the transmission of these bacterial respiratory pathogens. To investigate this, Professor Angela Brueggemann and colleagues rapidly set up the Invasive Respiratory Infection Surveillance (IRIS) Initiative, a network of national reference microbiology laboratories in 26 countries across six continents. Nearly 100 collaborators are actively participating in IRIS.

A large invasive disease dataset of over 80,500 cases of invasive disease due to *S pneumoniae*, *H influenzae*, and *N meningitidis* and *Streptococcus agalactiae* (the latter as a non-respiratory pathogen comparator) from 1 January 2018 to 31 May 2020 was compiled.

In addition, the stringency of national policy decisions was quantified by the Oxford COVID-19 Government Response Tracker and the movements of people assessed using Google COVID-19 Community Mobility Reports.

The results indicated that the introduction of COVID-19 containment policies and public information campaigns reduced person to person transmission of these common respiratory bacterial pathogens, leading to a significant and sustained reduction in life-threatening invasive diseases. The incidence rate of *S pneumoniae* infections, for instance, was reduced by 68% at 4 weeks and 82% at 8 weeks, compared with 2018/19.

In contrast, there was no change in invasive diseases due to *S agalactiae*, suggesting that national reporting of invasive disease cases was proceeding largely as normal even in the midst of COVID-19. There was no evidence that school closures had an effect on invasive disease reductions. All participating countries experienced a significant reduction in invasive disease despite wide variation in the stringency of national containment measures. The timing of containment measures coincided with this rapid reduction in invasive diseases, and the mobility data suggested that people also voluntarily reduced their personal risks.

IRIS data collection is ongoing; this has revealed that the significant reduction in invasive diseases due to *S pneumoniae*, *H influenzae*, *N meningitidis*, and no change in disease due to *S agalactiae*, persisted throughout 2020. Phase II of IRIS is underway and whole genome sequencing of all of the bacterial isolates in IRIS will be performed, in part through a new collaboration with the Oxford Genomics Centre and BGI Genomics.

Evaluating the impact of maternity service changes on maternal deaths

Many health care services, including maternity services, have been impacted by COVID-19. A study, led by Professor Marian Knight, reviewed the care of all pregnant and postnatal women who died with SARS-CoV-2 infection or from mental health-related causes or domestic violence between 1 March and 31 May 2020.

The rapid report 'Learning from SARS-CoV-2-related and associated maternal deaths in the UK March-May 2020' was published in September by the MBRRACE-UK Confidential Enquiry into Maternal Deaths. The report concluded that:

→ Ten women died with SARS-CoV-2 infection, eight from COVID-19 and two from other causes, four women died by suicide and two due to domestic violence.

→ The majority of women who died from COVID-19 were from Black or other minority ethnic groups.

→ Some face-to-face services were withdrawn (particularly mental health); women with symptoms were unclear when to go to hospital; there was attribution of some COVID symptoms to pregnancy; safeguarding advice was not always appropriate.

→ Improvements in care could have made a difference in the outcome of 33% of the 16 women who died.

> "Through our collaborative working with the MBRRACE team throughout the pandemic, the clinical recommendations have already been incorporated into our guidance for women and healthcare practitioners."
>
> Dr Edward Morris, President of the Royal College of Obstetricians and Gynaecologists

The report recommended that pregnant and postpartum women with COVID-19 must receive coordinated care from physicians, obstetricians and midwives, and perinatal mental health services should be recognised as essential to maternity care even in the context of a pandemic.

Both the UKOSS and MBRRACE studies informed a joint statement from the Royal College of Midwives and Royal College of Obstetricians and Gynaecologists: 'Planning for Winter 2020/21: reducing the impact of COVID-19 on maternity services in the UK'. The MBRRACE report was also cited in the Royal College of Psychiatrists' guidance, 'COVID-19: Working with vulnerable people'.

Developing an ethical approach to redeploying staff to high-risk clinical roles

The severity of the COVID-19 pandemic has forced healthcare providers across the world to redeploy staff, particularly for intensive care and emergency department roles, but this can lead to concern that this places staff at increased risk of infection.

While health services have an overarching requirement to meet the needs of patients with severe illness, individual health professionals are not specifically obliged to provide treatment, creating a potential ethical dilemma.

Associate Professor Michael Dunn and Dr Mark Sheehan have been

working with collaborators from Oxford University Hospitals NHS Foundation Trust (OUH) and other areas of the University of Oxford to clarify these ethical issues, with the aim of identifying the key factors that need to be addressed when considering redeploying staff.

In May 2020, the group published an analysis of a range of ethical issues associated with changes to staff allocation processes in the face of COVID-19. This identified clear ethical tensions in reallocating healthcare professionals into positions that place them at risk of harm. The paper outlines the key questions that need to be considered within a justifiable process of reallocating professionals to high-risk clinical roles once those who are 'fit for reallocation' have been identified. This initial ethical analysis is informing decisions in NHS Trusts, including OUH via the Trust's Clinical Ethics Advisory Group.

Providing a comprehensive framework to help governments distribute a vaccine

NDPH researchers encouraged governments, researchers and the public to think early on about what should happen once vaccines were approved for use by regulators. Whilst evidence was emerging about the impact of COVID-19 on people's health and the economy, there was a need to bring this together into an evidence-based framework for understanding the potential benefits of adopting different vaccination prioritisation strategies.

Professor Philip Clarke, Dr Laurence Roope and colleagues provided a comprehensive framework to help governments distribute a vaccine effectively and fairly, and outlined the necessary decisions governments should make regarding allocation. Key considerations should include: the health impacts of COVID-19; reducing the rate of transmission; allowing the economy to return to normal; and equity (particularly as COVID-19 has been shown to have disproportionate impacts on socially disadvantaged groups).

In addition, their study suggested that governments should seek public opinion regarding several key aspects of vaccine distribution: whether governments allow their citizens to purchase a vaccine privately; the degree to which a vaccination prioritisation strategy should be focused on health versus wider benefits such as facilitating a safe return to education, and protecting jobs and the economy; and whether governments should randomly allocate the vaccine if there is not enough vaccine available to cover all individuals assigned the same priority.

Offering guidance on human challenge studies

The need to develop effective COVID-19 vaccines at speed created pressure to accelerate research pathways, including by conducting challenge studies in which participants would be intentionally exposed to the SARS-CoV-2 virus. Such trials are controversial, with concerns being raised about the social, legal, ethical and clinical implications of infecting healthy volunteers for research purposes.

Between March – May 2020, Dr Susan Bull acted as a consultant for the WHO Working Group for Guidance on Human Challenge Studies in COVID-19. The group provided guidance for scientists, research ethics committees, funders, policy-makers, and regulators on the key criteria that would need to be satisfied for challenge studies to be ethically acceptable. Their report on the key criteria for the ethical acceptability of COVID-19 human challenge studies was published in May. Criteria for conducting systematic risk evaluations of human challenge studies with SARS-CoV-2 were reviewed in research by Dr Bull, Professor Mike Parker and colleagues.

Whilst the rollout of vaccines was underway at the end of 2020, challenge trials were still being considered to test questions such as whether the vaccines prevent infections and how long that protection lasts.

Documenting the lockdown experiences of older people

The coronavirus lockdowns have highlighted the critical importance of meaningful, human interaction in our lives, as well as the risk of isolation and loneliness. A unique collaboration between London-based photographer Adam Isfendiyar and NDPH researchers, Dr Federica Lucivero, Mira Schneiders, Professor Michael Dunn, and colleagues Milly Farrell, and Dr Roderick Bailey, captured the experiences of older East Londoners during the spring 2020 lockdown as part of a new photography exhibition. INDOORS: Experiences of older people during lockdown combined intimate portraits and testimonies with reflections from the researchers on the themes of Isolation, Connectedness, Coping and Memories.

The exhibition was launched online as part of the Being Human Festival 2020. The public were invited to engage with the research team and Mr Isfendiyar at a dedicated event on 12 November. The exhibition is available to view indefinitely.
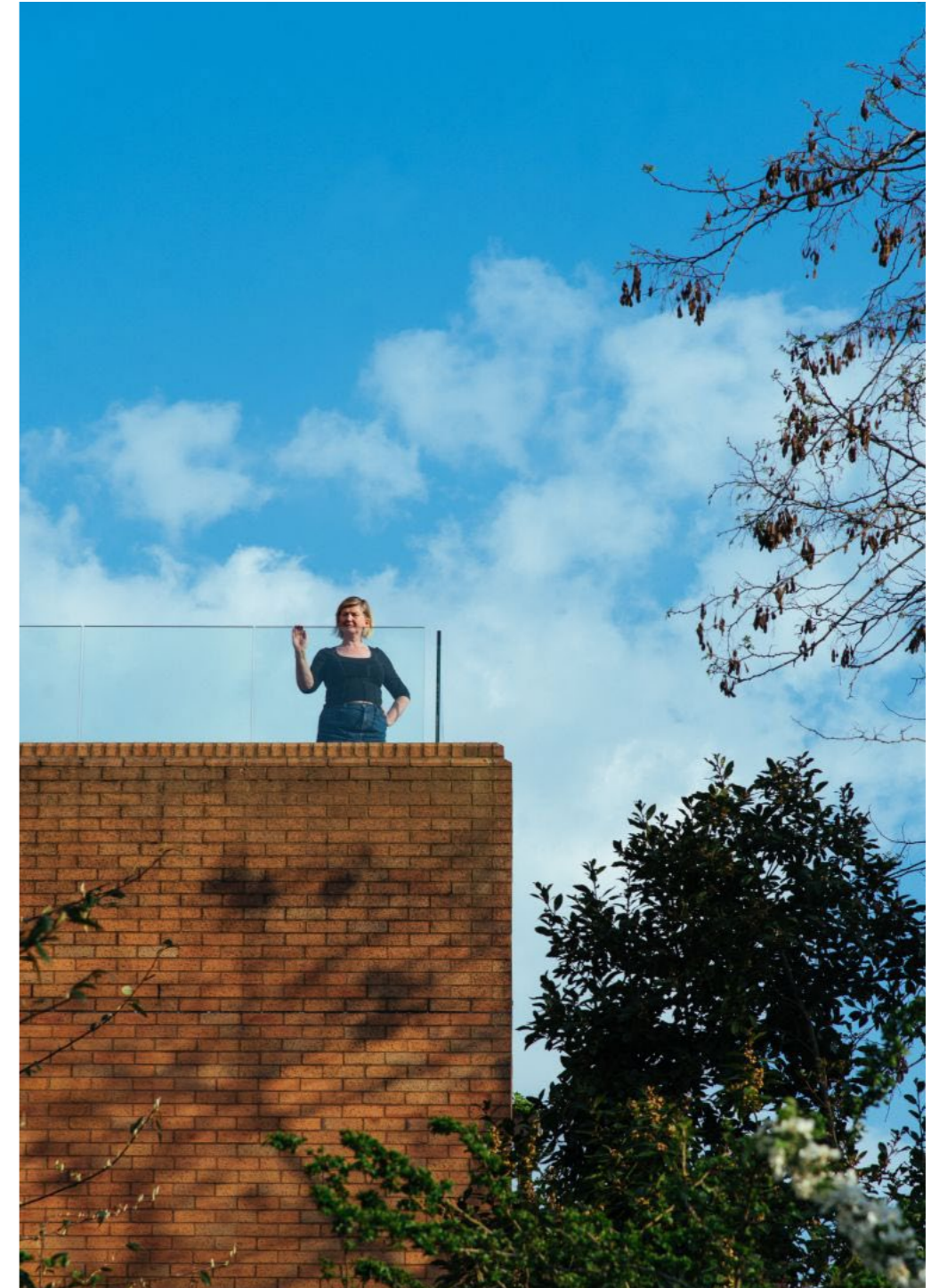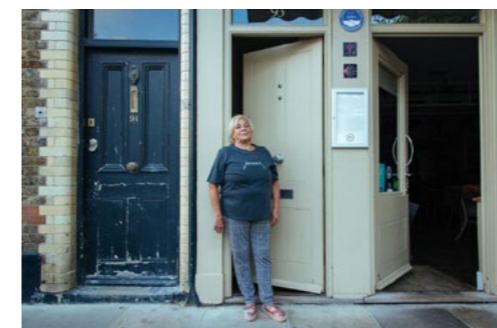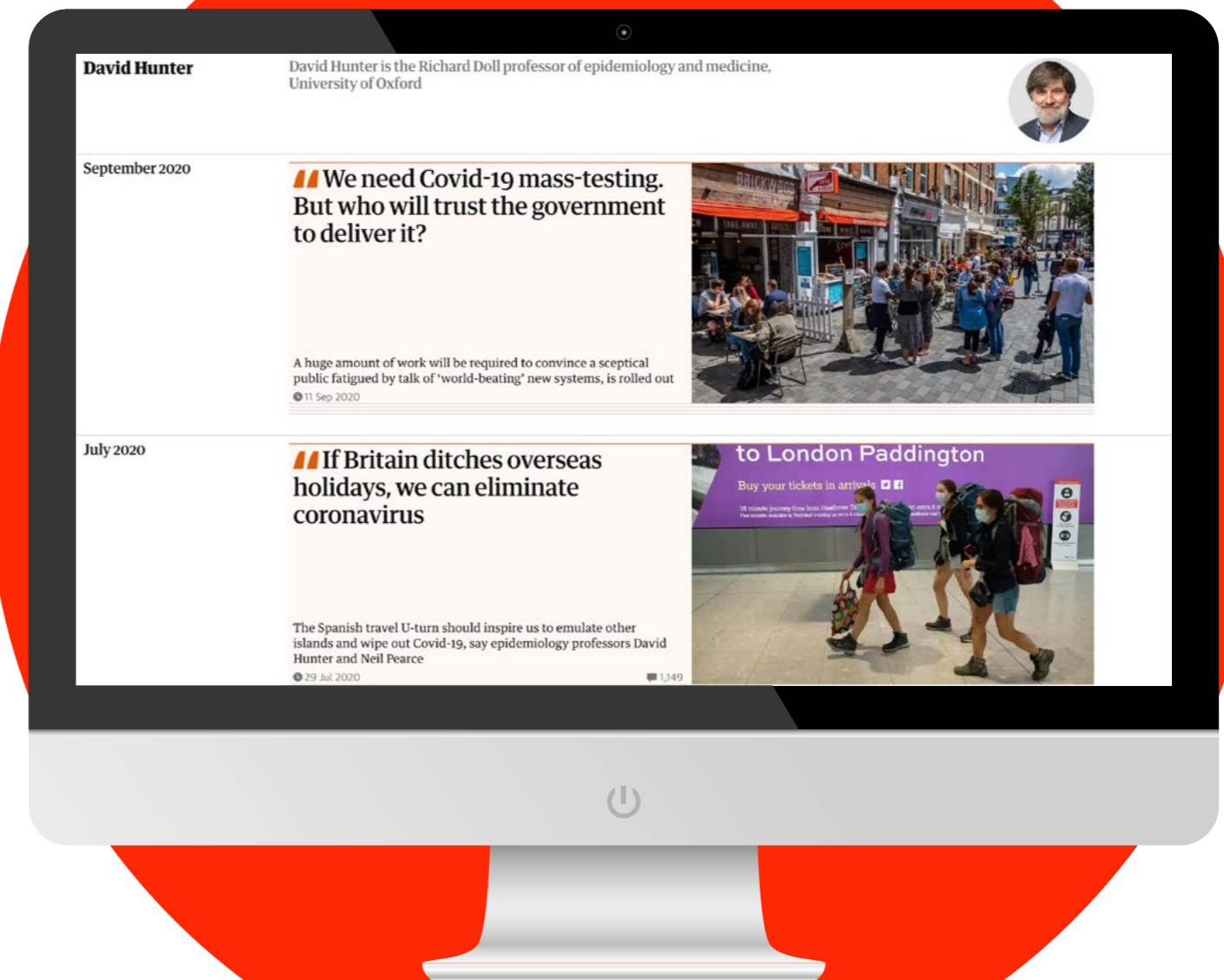
Reflecting on the UK's pandemic response

Professor David Hunter has contributed to public debate as a regular writer for *The Guardian* and other media. Opinion pieces included a call for test and trace measures to be stepped up when the system was launched in May; this piece accurately predicted a second wave in which the epidemic would resurge, 'Not because it had to, but because we did not push the virus closer to extinction.' Professor Hunter also discussed the risks of easing lockdown too early, allowing international travel in the summer, and failing to provide adequate support to those who test positive and are asked to self-isolate.

Prior to the first lockdown, Professor Hunter described, in a Perspective piece in the *New England Journal of Medicine*, the slow government response to the rapid growth of the epidemic, the reluctance to take obvious public health actions such as suspending mass gatherings, and the fact that the NHS was 'about to experience a challenge unlike any other in its 70 years of existence.' A recent Perspective provided comment on many of the topics of NDPH research, including the RECOVERY trial demonstrating the virtues of a 'single-payer system' in clinical trial implementation, the impact of the pandemic on non-COVID care, and the need for policy-makers to appropriately balance health and economic drivers.

Professor Hunter has been advising the University of Oxford on policies to ensure student and staff welfare during the epidemic as a member of the University's Health Measures Advisory Group.

David Hunter

David Hunter is the Richard Doll professor of epidemiology and medicine, University of Oxford

September 2020

We need Covid-19 mass-testing. But who will trust the government to deliver it?

A huge amount of work will be required to convince a sceptical public fatigued by talk of 'world-beating' new systems, is rolled out

11 Sep 2020

July 2020

If Britain ditches overseas holidays, we can eliminate coronavirus

The Spanish travel U-turn should inspire us to emulate other islands and wipe out Covid-19, say epidemiology professors David Hunter and Neil Pearce

29 Jul 2020

Acknowledgements

The work described in this report has been made possible thanks to the enormous effort, commitment, rigour and excellent work of NDPH staff, partners and funders, and the contribution of the thousands of participants in our studies. The work is far from done and we are continuing to work together to respond to the pandemic in 2021.

Funders