UKRI Medical Research Council
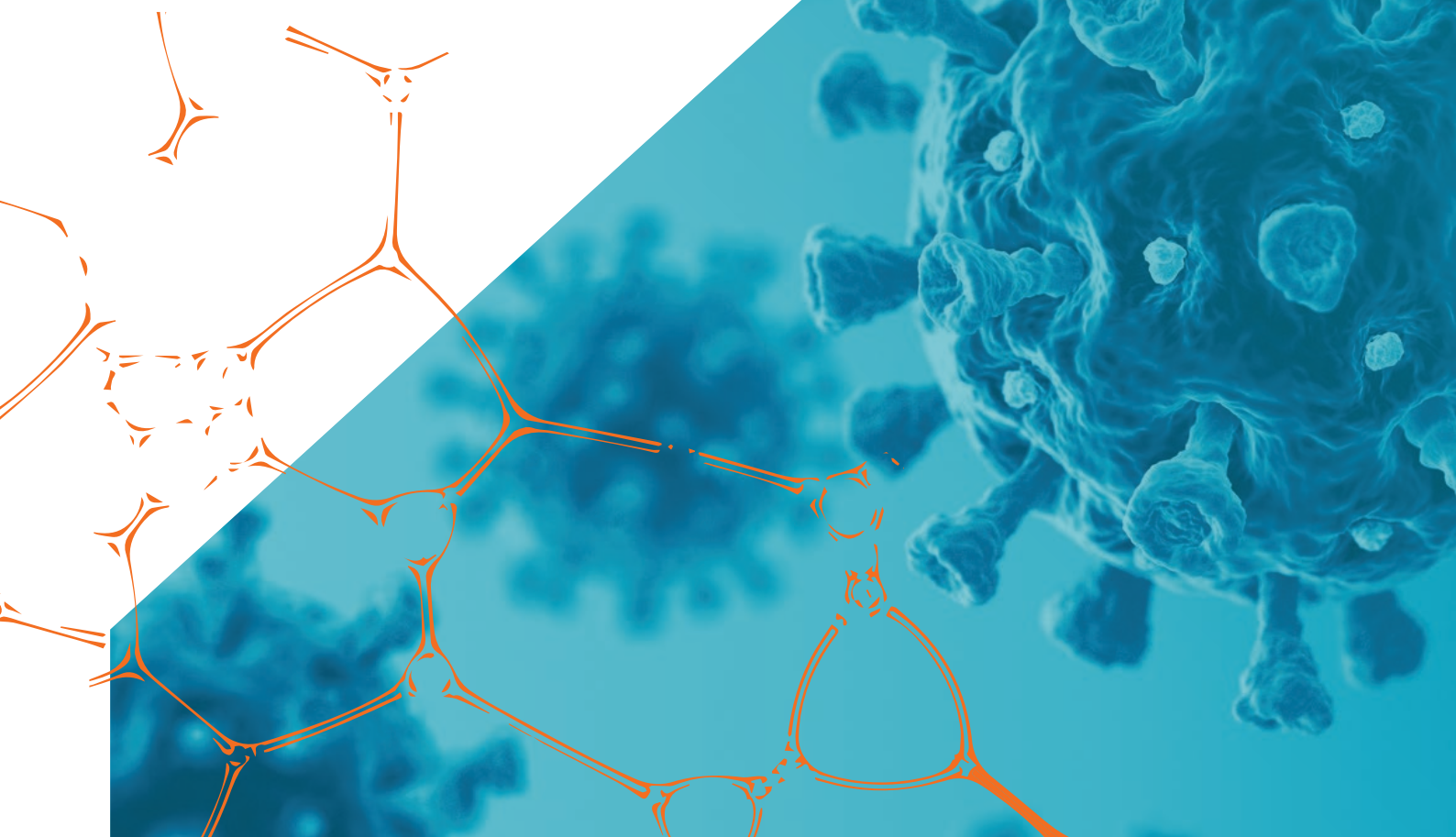
COVID-19 response interim report

Interim Report
(January 2020 to March 2021)

Medical Research Council
Evaluation and Analysis Team

Foreword

The intent of this report is to document the main activities undertaken by Medical Research Council (MRC), part of UK Research and Innovation (UKRI), and its community of researchers in response to the SARS-CoV-2 pandemic and to recognise the impacts and insights arising from these activities. As the response and outcomes will continue past 2021, this is an interim report covering January 2020 to March 2021. It is proposed that a final form of this report is produced in 2022.

The report is a collection of eight summaries of separate components of the MRC-led aspects of the UKRI COVID-19 response and their impact rather than a connected narrative of events. Highlighted blue and bold text provide links to more detailed descriptions either within the document and the Annexes or external webpages.

Methods and acknowledgements

Contents

Version 1.1 (03/08/2021) - updated with bookmarks to sections/annexes to aid navigation, and revised hyperlinks to WHO pages following their website revamp.

Executive Summary

The UK Biomedical research community has been in the forefront of the global response to the COVID-19 pandemic. Mobilising existing expertise, infrastructure and a knowledge base developed over decades of funding, the work of MRC-funded researchers provided global leadership and world leading research in clinical trial implementation, health data management, vaccine development, and genome sequencing throughout 2020.

MRC is now leading a £256m portfolio of COVID-19 relevant projects (£177m of which is funded from budgets managed by MRC). More than 60% of this funding will be spent by the end of 2021 and has been allocated to projects that have explicit objectives to have a rapid impact to prevent, treat and manage the pandemic.

The community response has been unprecedented, with more than 3000 applications submitted to MRC-led COVID-19 research calls in 2020. This was in addition to the business-as-usual submissions to MRC Research Boards and panels[1]. Researchers from across the MRC community have speedily formed collaborative research efforts both within and between research organisations. Three of the MRC supported COVID-19 research platforms include academics from more than 15 research organisations. From the outset of the pandemic, MRC's major strategic investments have worked collaboratively and individually re-aligning their work to progress hundreds of new COVID-19-relevant research projects. Additionally, the staff have delivered practical support for local clinical needs as well as providing analyses or compounds for research projects carried out by others. Some have built on their existing networks of laboratory expertise. For example, through the creation of the Protein Portal, a new international resource which provided key COVID-19 reagents for fellow investigators in the first year of the pandemic, the COVID-19 Protein Production Consortium contributed significantly to accelerating COVID-19 research.

The rapid development and scale up of production of the Oxford/AstraZeneca vaccine at unprecedented speed[2], has delivered an intervention that is suitable for global distribution. This assistance in bringing the global pandemic under control could provide benefits, in global income of almost 9 trillion dollars by end-2025[3]. The OECD has positively upgraded UK growth estimates specifically due to its successful vaccination programme[4]. The ongoing UK vaccination programme which primarily utilises the Oxford/AstraZeneca vaccine has, in combination with social distancing, brought the UK epidemic under control and provided considerable protection for the population against severe disease and future infection. The development of the Oxford/AstraZeneca vaccine was substantially founded on years of MRC-funded research, and publicly funded by MRC and partners in the early clinical studies.

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1. All applications considered by MRC research boards and panels in 2019/20 totalled 2169 and totalled 2070 in 2020/21.
2. Previously the four-year development of the mumps vaccine was the most rapid. (Why a coronavirus vaccine could take way longer than a year (nationalgeographic.com); Maurice Hilleman, M.M.R. Vaccine's Forgotten Hero - The New York Times (nytimes.com); Pinkbook | Mumps | Epidemiology of Vaccine Preventable Diseases | CDC)
3. IMF estimate Transcript of October 2020 World Economic Outlook Press Briefing (imf.org)
4. In December 2020 the OECD economic outlook estimated that UK total GDP growth in 2021 would be 4.2%, in March 2021 this estimate was revised to 5.1%, and then in May 2021 the estimate was further revised upwards to 7.2% https://stats.oecd.org/index.aspx?DataSetCode=EO.

In the year since the pandemic started, MRC UKRI-supported research has directly led to important societal impacts. COVID-19 targeted clinical guidance has been developed, effective treatments have been identified (as well as many proven to be ineffective), and these treatments implemented internationally. Validation of the effectiveness of dexamethasone therapy by the RECOVERY trial resulted in an estimated 12,000 lives saved in six months of implementation. The development of methodologies for efficient clinical trial management and coordination, along with the establishment of infrastructure for big data and health data management have positively impacted the research landscape. These investments will enhance our ability to face future pandemics and other population health challenges as well as continuing to support world-leading biomedical research.

UKRI-funded research has provided government and clinical policy makers with data to inform decision-making in several key areas. These include transmission, variant evolution, population group variance in vulnerability, patient metabolic responses, susceptibilities and mortality, and the population compliance and response to government restrictions as well as the mental health effects of the pandemic.

There is growing evidence that during the pandemic MRC researchers have engaged to a greater extent than usual with stakeholders to provide successful, rapid translation of knowledge into public policy or guidance. In surveys, MRC-funded researchers were able to tell us about the highly interactive relationships[5] developed between academic researchers and policymakers. They also demonstrated their ability to modify research questions and direction to serve the needs of policy makers in a rapidly changing COVID-19 knowledge base and public health landscape.
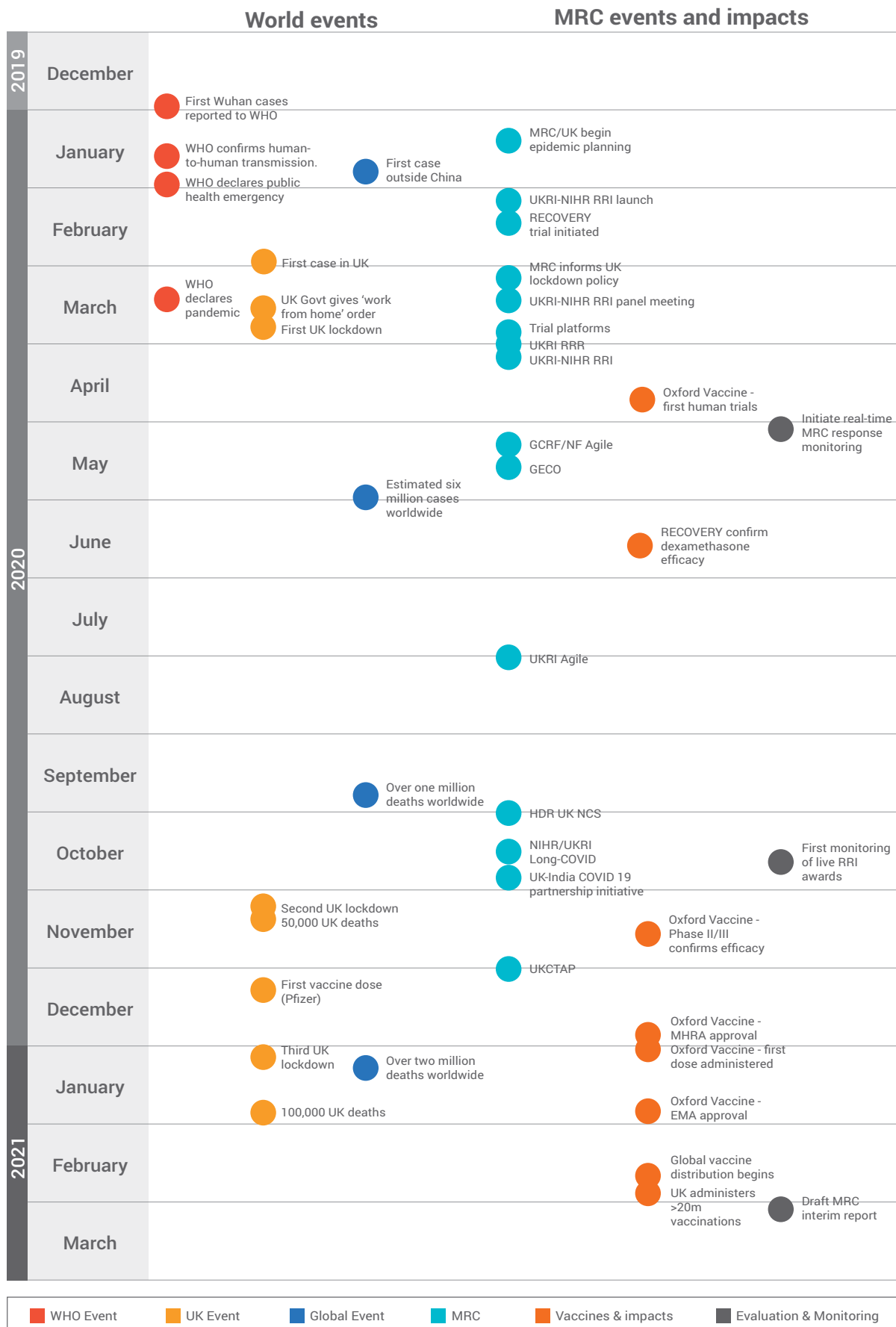
Working with other funders and leaders in the biomedical community, the MRC led efforts to brief the relevant government committees and integrate academic expertise from the community into the decision-making process. Central government had limited direct connection to the research community and lacked experience of what the research priorities might be. Strategic planning expertise was provided by MRC and UKRI senior staff, while specific epidemiological insight was drawn from leading MRC research teams supported by previous strategic investments. New coalitions of academic experts were convened from the MRC community; MRC used its convening skills, active connections, and good appreciation of the research landscape to bring researchers together. MRC staff served on the initial government task forces. MRC Centre for Global Infectious Disease Analysis (GIDA) was the first of several research Centres that redirected their attention to provide rapid, targeted and detailed data on SARS-CoV-2/COVID-19 transmission, and has been influential in providing the UK Government with modelling and surveillance data to support policy decisions on social distancing and movement during waves of increased transmission. MRC senior staff have continued to support the Government efforts to control the pandemic with research coordination and scientific expertise through development of a clinical trial management platform, UKCTAP, and administrative responsibilities for three of the six National Core Studies programmes. Directors of MRC Institutes and Units also provide expertise as members of government advisory bodies such as the Joint Biosecurity Centre Boards (HDR UK and MRC Biostatistics Unit).

In addition to its strategic role, MRC, in partnership with UKRI sister Councils, NIHR and/or other funders, funded 135 projects proposed by researchers from across the biomedical spectrum through seven initiatives (project details Section 4 and ANNEX 4.1) and has provided funding for an additional 40 COVID-19 targeted research activities in 2020. While the MRC staff at all levels rose admirably to the challenge of managing the large increase in workload — administering the new COVID-19 research calls, providing expert advice, maintaining and enhancing community interactions and relations, and processing double the amount of research applications — the effect on staff morale, data management and efficient team working left the MRC with challenges that will take some time to resolve.

It is evident that decades of past MRC investment in epidemiology, clinical trials, zoonotic diseases, immunology, data management, structural biology, and population health have provided a strong platform of knowledge and infrastructure. This enabled the effective and rapid scientific response to the COVID-19 pandemic in the UK. However, there were weaknesses in implementation, and some research areas, and these provide opportunities to learn lessons to better prepare us for similar crises.

5. 59 of 134 projects reporting in 2020 describe regular interactions with policy makers to provide bespoke data.

Timeline of pandemic-related events divided by world or background events, MRC activities and their impacts

World events | **MRC events and impacts**

2019

December
- First Wuhan cases reported to WHO (WHO Event)

2020

January
- WHO confirms human-to-human transmission. (WHO Event)
- WHO declares public health emergency (WHO Event)
- First case outside China (Global Event)
- MRC/UK begin epidemic planning (MRC)

February
- UKRI-NIHR RRI launch (MRC)
- RECOVERY trial initiated (MRC)

March
- First case in UK (UK Event)
- WHO declares pandemic (WHO Event)
- UK Govt gives 'work from home' order (UK Event)
- First UK lockdown (UK Event)
- MRC informs UK lockdown policy (MRC)
- UKRI-NIHR RRI panel meeting (MRC)
- Trial platforms (MRC)
- UKRI RRR (MRC)
- UKRI-NIHR RRI (MRC)

April
- Oxford Vaccine - first human trials (Vaccines & impacts)
- Initiate real-time MRC response monitoring (Evaluation & Monitoring)

May
- GCRF/NF Agile (MRC)
- GECO (MRC)

June
- Estimated six million cases worldwide (Global Event)
- RECOVERY confirm dexamethasone efficacy (Vaccines & impacts)

July

August
- UKRI Agile (MRC)

September
- Over one million deaths worldwide (Global Event)

October
- HDR UK NCS (MRC)
- NIHR/UKRI Long-COVID (MRC)
- UK-India COVID 19 partnership initiative (MRC)
- First monitoring of live RRI awards (Evaluation & Monitoring)

November
- Second UK lockdown 50,000 UK deaths (UK Event)
- Oxford Vaccine - Phase II/III confirms efficacy (Vaccines & impacts)
- UKCTAP (MRC)

December
- First vaccine dose (Pfizer) (UK Event)
- Oxford Vaccine - MHRA approval (Vaccines & impacts)

2021

January
- Third UK lockdown (UK Event)
- Over two million deaths worldwide (Global Event)
- 100,000 UK deaths (UK Event)
- Oxford Vaccine - first dose administered (Vaccines & impacts)
- Oxford Vaccine - EMA approval (Vaccines & impacts)

February
- Global vaccine distribution begins (Vaccines & impacts)
- UK administers >20m vaccinations (Vaccines & impacts)
- Draft MRC interim report (Evaluation & Monitoring)

March

Legend
- ● WHO Event
- ● UK Event
- ● Global Event
- ● MRC
- ● Vaccines & impacts
- ● Evaluation & Monitoring

Impacts arising from MRC supported COVID-19 research

MRC's research community has been in the forefront of the global response to the SARS-CoV-2/COVID-19 pandemic. Mobilising existing expertise, infrastructure and a knowledge base developed over decades of funding, the work of MRC-supported researchers provided global leadership and world leading research in clinical trial implementation, health data management, vaccine development and genome sequencing from early 2020.

RECOVERY, the first and largest clinical trial was approved as early as 11 March 2020 and in just under six weeks, had recruited a staggering 6000 patients in 170 NHS hospitals across the UK. It currently has 40,000 participants and 180 active sites across the world, has investigated 10 potential treatments and in its first year definitely ruling out four of these. RECOVERY was set up to identify COVID-19 treatments, and has saved an estimated 22,000 lives in the UK and one million lives worldwide through the early identification (June 2020) of dexamethasone, the first effect treatment for patients hospitalised with severe COVID-19[6].

The Oxford/AstraZeneca vaccine is the most widely used vaccine in the world due to early consideration of requirements for global use, with doses administered in 177 countries through the COVAX initiative. The UK has helped to raise $1 billion for the COVAX Advance Market Commitment (AMC) through match-funding other donors, which will help distribute one billion doses of coronavirus vaccines to 92 developing countries this year. The Oxford/AstraZeneca vaccine was the first vaccine deployed to LMICs through licensing agreements and emergency authorization use[7].

HDR UK has spearheaded the availability of patient and public health data within the UK as the coordinator of the UK Health Data Alliance, and taking the lead globally through facilitating collaborations and cutting-edge data science. HDR UK convened the International COVID-19 Data Alliance (ICODA), including 20 global public and private partners. They have established a co-ordinated international platform known as the ICODA 'Workbench', which enables researchers to access global patient data to drive rapid insights about COVID-19 and speed up the development of treatments. For example, the Workbench includes a perinatal dataset compiling information from over 100 researchers in more than 40 countries, including 22 lower- and middle- income countries (LMICs), with access to data on 2.4m births.

The COVID-19 Genomics UK Consortium (COG-UK) is a global pioneer in rapid, large-scale genome sequencing of the SARS-CoV-2 virus. COG-UK was launched in April 2020 and a year later almost half the world's sequences of SARS-CoV-2 were provided by the consortium. The virus is extracted from individual patients and the sequence data generated is paired with the anonymised patient data. This vital information allows governments and public health agencies around the world to mount a coordinated and rapid response to the pandemic, by identifying and monitoring the emergence, introduction and transmission of variants of concern. The knowledge informs policy decisions on transmission reduction strategies such as the introduction of travel restrictions or lockdowns as well as approaches for developing vaccine updates for emerging variants. To date, this systematic approach has generated nearly half a million virus sequences. To extend the global sequencing capability, COG-UK members have been supporting sequencing efforts in 28 countries, including 18 LMICs.

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6.   The lead investigators for the RECOVERY trial Professors Peter Horby and Martin Landray were both elected Fellows of the Academy of Medical Sciences in 2020, and Knighted in the Queen's birthday honours list in June 2021.

7.   The lead academic investigators responsible for development of the Oxford/AstraZeneca vaccine received recognition in the Queen's birthday honours list in June 2021, with Professor Sarah Gilbert receiving a Damehood and Professor Andrew Pollard a Knighthood.

In early 2020 MRC, in collaboration with NIHR and UK Government departments, began funding research platforms and projects whose objective was to provide immediate data and analysis to combat the SARS-CoV-2 virus threat. The MRC, as part of the UKRI response, is now leading a £256m portfolio of COVID-19 relevant projects (£177m of which is funded from budgets managed by MRC). More than 60% of this funding will be spent by the end of 2021 and has been allocated to projects that explicitly have the objective to make a rapid difference to preventive treatment and public health strategies to manage the pandemic. This represents a much nearer-term horizon for impact than the majority of MRC research, and a rapid expansion of research on a new disease[8]. The community response has been unprecedented, with more than 3000 applications submitted in 2020. This was in addition to the business-as-usual submissions to MRC Research Boards and panels[9]. Independent of organised funding calls, UKRI researchers across the UK undertook their own activities driven by the common purpose of addressing the pandemic crisis. Although the ease of application and speed of decision-making encouraged a large number of applications that were not always of the highest quality, there is robust evidence of substantial contributions made by MRC-supported researchers in 2020 to understand and tackle the COVID-19 threat.

The main contributions reported to date have been summarised[10] and grouped below into eight areas of impact:

■ Treatment (including the successful identification of new therapies now used in clinical care for patients)

■ Vaccines (including the accelerated development of the Oxford/AstraZeneca vaccine, now in use in over 130 countries)

■ Surveillance on viral transmission and its impact to inform Government policy

■ Modelling of the pandemic to inform Government policy

■ Data connectivity and co-ordination to support research and decision making in population health

■ Clinical care guidance for hospitalised COVID-19 patients

■ Public engagement and global communication

■ Understanding SARS-CoV-2 biology and pathology to support better control of transmission and identify potential treatments.

Treatment

Clinical trials

Health services around the world were faced with a highly transmissible virus that could cause severe disease, and as a new condition there were no treatments proven to improve patient outcomes. As a result, new clinical trials to test potential therapies were desperately needed. WHO and drug regulators had highlighted the need for a small number of relatively large, randomised trials that could provide meaningful knowledge about effective treatments[11]. In 2020, MRC and UKRI directly supported six platforms and projects which have validated efficacy or revealed inefficacy and have promoted effective trial development. This successful strategy will have important lessons for the way that clinical studies are supported over the long term.

In response to the global threat identified in January 2020, MRC in collaboration with other funders responded quickly to implement emergency planning and support the rapid roll out of the RECOVERY trial. During the early months of the COVID-19 pandemic, the UK therapeutics development pipeline

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8. Prior to 2020 the total MRC funding awarded for work relevant to coronaviruses following the SARS outbreak in 2002 was £13m https://questions-statements.parliament.uk/written-questions/detail/2020-03-17/30766

9. All applications considered by MRC research boards and panels in 2019/20 totalled 2197 and totalled 2137 in 2020/21.

10. Information about individual projects (ANNEX 4.1) and a fuller description of impacts is provided in and ANNEX 2.1 and ANNEX 2.2.

11. https://committees.parliament.uk/writtenevidence/17604/pdf/

focused on repurposing existing drugs that were affordable and readily available to rapidly identify effective treatments for immediate introduction into clinical care around the world. Notable successes include the identification of dexamethasone in early June 2020; treatment with this commonly prescribed steroid was shown to reduce mortality by a third in patients hospitalised with severe COVID-19, saving an estimated 12,000 lives in the UK between July and December 2020. Additionally, a MRC/UCL Clinical Trials Unit trial indicated that remdesivir shortens the recovery time in hospitalised patients.

Identifying ineffective treatments

UKRI-supported clinical trials have also been instrumental in the rapid identification of ineffective candidate treatments, allowing clinicians to focus on treatments that do work. RECOVERY demonstrated that there is no clinical benefit from hydroxychloroquine, lopinavir-ritonavir or convalescent plasma treatment in hospitalised patients with COVID-19.

Patient recruitment platform

The UK's investment in pandemic planning facilitated unprecedented recruitment for COVID-19 treatment trials.

ISARIC, formed in 2011, has a proven track record of helping to helped standardise protocols for the rapid coordinated clinical investigation of acute respiratory pathogens of public health interest around the world. It ensures that patients with a spectrum of emerging and unknown pathogens will be efficiently enrolled in clinical trials. ISARIC with other organisations, including WHO, have been preparing a pandemic response for the last nine years, enabling the researchers to start work immediately when the developing SARS-CoV-2 epidemic was first identified. ISARIC protocols included rapid trial recruitment plans that were implemented at the onset of the pandemic. The NIHR CRN (Clinical Research Network), a register of hospitalised patients, collects comprehensive data about patients and clinical research projects across the country. The success of the RECOVERY trial is primarily due to the efficient implementation of this clinical trial recruitment plan, and the infrastructure that was in place through the NIHR CRN. As of February 2021, RECOVERY has recruited 38,000 participants, and is the largest COVID-19 clinical trial in the world. This ready access to COVID-19 patients has also supported hospital-based studies such as the COVID-19 ISARIC GenOMICC (Genetics of Mortality in Critical Care) study.

Coordinating treatments for testing in clinical trials for COVID-19

UKRI has been instrumental in supporting clinical trials nationally and internationally to facilitate data sharing, best practice, and comparison of results. However, in early 2020, the UK had no coordinated system for identifying the appropriate treatments against various stages of COVID-19, for various sub-groups of the population, to be administered at the right time.

The COVID-19 Therapeutics Advisory Panel (UK-CTAP) was set up to facilitate the effective delivery of large-scale trials designed to identify treatments for all stages of COVID-19. A great many clinical trials were underway a few months into the COVID-19 pandemic, but these lacked a unified approach to addressing the disease challenge. In Spring of 2020, it was clear that better coordination was required to facilitate an efficient trial programme for the treatment candidates. ACCORD, a clinical trial platform with the aim of fast-tracking research into potential COVID-19 treatments, was originally launched to address this need. As the year progressed, limitations in the ACCORD platform were identified; the arising competition for sites nationally was inefficient and there was no consistent, transparent or strategic mechanism by which treatments would be allocated to trials. Rapid recognition of these limitations led to the suspension of ACCORD and informed the establishment of an independent panel, UK-CTAP by late Summer 2020. It was created to advise what treatments should be approved for testing through publicly funded clinical trial platforms, both in terms of the likely potential for success and the context of the national and international trial landscape. UK-CTAP provides a centralized approach for coordinating the treatments which enter these trial platforms. By having a single point of entry and a single point of recommendation, the process allows the panel of experts to identify both the suitable candidates and to target it to the appropriate stage of the trials pipeline. Currently, UK-CTAP coordinates COVID-19 drugs entering phase I, II and III trials in order to address the urgent need for effective drug treatments across all disease stages of COVID-19 including prophylaxis, post exposure

prophylaxis, hospitalised patients and most recently Long COVID. The UK-CTAP platform ensures minimal duplication of effort across the UK clinical trial landscape.

Decades of MRC-funded research has led or contributed to trial advancements, ranging from the methodology used for the adaptive clinical trials to the networks and organisations that coordinate clinical research across the world (for details see ANNEX 6.4).

Vaccines

The development of the Oxford/AstraZeneca COVID-19 vaccine was funded by MRC, UKRI, and others in February 2020 but was built on decades of global research and preparation. The development of protocols for rapid vaccine implementation in the face of a global pandemic caused by a novel pathogen has been supported by MRC and other global funders for more than a decade. MRC, with DHSC, supported previous work (details ANNEX 6.5) at Oxford to develop the ChAdOx vector vaccine platform against MERS (Middle East Respiratory Syndrome) caused by a related coronavirus. This knowledge base provided the advanced platform from which the AZD1222 vaccine (Oxford/AstraZeneca COVID-19) was developed, validated, and approved for human use in record time (11 months). Prior to 2020, the mumps vaccine had been fastest developed from viral sampling to approval, and this took four years[12].

The design of the Oxford/Astra Zeneca vaccine incorporated the requirements for global use; it can be stored, transported, and handled at normal refrigerated conditions (2-8°C) for at least six months and administered within existing healthcare settings. This foresight has led to Oxford/Astra Zeneca vaccine being described as the 'vaccine for the world'. The vaccine has been provided to COVAX[13] who delivered the first million doses to LMICs in February 2020 and 39 million have been provided to date. The IMF has estimated that the cumulative loss in output relative to the pre-pandemic projected path will grow from 11 trillion dollars over 2021-22 increasing to 28 trillion by the end of 2025[14]. However, if medical solutions such as vaccines and treatments can be made available faster and more widely relative to our current baseline, it could lead to a cumulative increase in global income of almost 9 trillion dollars by the end of 2025.

Another component of the preparations needed to face a pandemic was rapid vaccine manufacture. Over the last five years, the UKRI research councils including MRC have funded projects to improve the pace of vaccine manufacture. A small project was funded in March 2020 to accelerate mass manufacture of COVID-19 vaccines which contributed methodologies for improved efficiencies. Major improvements were made through the collaborative work of the team involved with developing the Vaccines Manufacture and Innovation Centre (a component of the ISCF Medicines Manufacture programme, launched in 2018), Vaccitech (an Oxford University spinout developed with DPFS and other MRC funding) and AstraZeneca. Additionally, the Future Vaccine Manufacture Research Hub (Vax-Hub) funded by EPSRC is building the UK the global centre for integrated discovery through to bioprocess manufacture of next-generation vaccines.

In 2021, UK are seeing another record-breaking feat in the implementation of the UK vaccination programme with 61 of every 100 people receiving at least one dose in the first four months. Researchers from MRC's major investments are volunteering their time to assist in managing the large volumes of people attending the vaccine centres and the Francis Crick Institute has partnered with UCL Hospital Trust to establish a vaccination centre on-site.

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12. Why a coronavirus vaccine could take way longer than a year (nationalgeographic.com); Maurice Hilleman, M.M.R. Vaccine's Forgotten Hero - The New York Times (nytimes.com); Pinkbook | Mumps | Epidemiology of Vaccine Preventable Diseases | CDC

13. the COVAX initiative for equitable global access to COVID-19 vaccines led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, the Vaccine Alliance (Gavi) and the World Health Organization (WHO), alongside key delivery partner UNICEF.

14. Transcript of October 2020 World Economic Outlook Press Briefing (imf.org) ANNEX 2.2, programmes: COV006; COV0659;

Surveillance

Many of the first awards made in early 2020 were funded to provide the Government with health surveillance data to inform decision-making (details in ANNEX 2.2). The community shared priorities were seen in the collaborative collecting and sharing of data and methodologies across and within the UK regions. In 2020, 14 projects supported by MRC and UKRI have provided surveillance data on all aspects of the COVID-19 threat to health and impact on the population. Over the year, these projects have reported to national and devolved nations' Government committees on various characteristics of viral transmission such as mechanisms of transmission (contacts, activities) and discontinuities in prevalence and susceptibility by region, ethnicity, life-stage, and occupation. These results have informed UK policy by providing data on the impact of the virus on hospital admissions, population health, and risk factors. Studies investigating the production of antibodies in response to SARS-CoV-2 infection in front line health workers led to rapid change in hospital policy in the Midlands, and an increased understanding of the vulnerability of BAME workers. Research on differential perceptions across ethnic groups and characterisation of UK population diversity is informing development of engagement strategies, particularly focusing on vaccine hesitancy. Most recently, the surveillance project EAVE II provided data on the 'real world' impact of the UK's vaccination programme, showing that hospital admissions were reduced by 85% and 94% for the Pfizer and Oxford/AstraZeneca vaccines respectively. MRC University Units are also contributing to the understanding of the virus epidemiology. For example, a SPHSU study into the impact of COVID-19 and associated responses on people who use or have used illegal substances informed revisions to Scottish Government policy on tackling drug deaths during the pandemic. A free smartphone symptom tracker App developed by the team at Kings College London (underlying science funded by MRC) is an impressive example of citizen science; it is credited with demonstrating the importance of several key symptoms in confirming COVID-19 infections, such as loss of smell.

Identifying SARS-CoV-2 variants is a global public health priority of the moment. The COVID-19 Genomics UK (COG-UK) Consortium is a group of researchers and research institutions funded by MRC along with all government and private biomedical funders in the UK. COG-UK tracks viral movement nationally and globally by sequencing the viral genomes from patient samples and identifying the changes in the virus' genome sequence. As of January 2021, COG-UK had sequenced more than 200,000 SARS-CoV-2 genomes, provided data on viral transmission and introduction in care homes, universities, hospitals and through international travel, enabled the tracking and analysis of viral variants and developed freely available bioinformatics and data sharing tools. This data has helped inform government policy on the efficacy of lockdown decisions, demonstrated the risks of travel and tourism and crucially, demonstrated the evolution of SARS-CoV-2 virus variants. These viral genome sequences, together with de-personalised patient data, is stored in COG-UK's central database called CLIMB-COVID-19. This database is provided by CLIMB (Cloud Infrastructure for Microbial Bioinformatics), funded by MRC, which hosts cloud-based computational, storage, and analysis tools for microbiologists across the UK, accompanied by a wide range of bioinformatics training activities. Many other programmes (CADDE in Brazil, MRC/UVRI and LSHTM Research Unit Uganda, CRUSH at CVR, and G2P-UK launched in Jan 2021) globally track how these variants impact on virulence and transmissibility. This has already sparked additional vaccine and booster development work to address these developing threats.

Modelling

The monitoring and surveillance data collected feeds directly into clinical and health policy decisions, but it also provides the data to create and test bespoke models to provide predictions and estimates about key COVID-19 pandemic questions. The five MRC-supported programmes (two University Units and three COVID-19 awards funded with NIHR) develop and modify models of transmission, pandemic impact on clinical care, and impact of government policy based on continually renewed evidence. These results were fed regularly into SPI-M, the modelling group that provides evidence to the Scientific Advisory Group for Emergencies (SAGE) and the wider UK Government.

The MRC Centre for Global Infectious Disease Analysis (MRC GIDA) is an international centre of excellence for research on the epidemiological analysis and modelling of infectious diseases (ANNEX 6.1) and has been a prominent government advisor since the pandemic outbreak. UKRI funded platforms and University Units[15] have also provided timely evidence-based modelling input to urgent policy questions. Much of the work is highly interdisciplinary, spanning statistics, mathematical modelling, epidemiology, genetics, intervention science and health economics.

Modelling provided to government includes:

- Understanding how new variants are spreading across the UK and developing statistical models to determine whether a new variant is causing more hospitalisations or deaths.

- Modelling the effectiveness of different testing strategies on virus transmission and suppression.

- Modelling the effect of vaccinations.

- Predicting outcomes from different scenarios (lockdown, track and trace, quarantine) of on disease prevalence and virulence.

- Understanding the impact of live attendance at schools.

- Predicting the health impact on residents of assisted living facilities.

(details provided in ANNEX 2.2)

A specific example is the work by the MRC Lifecourse Epidemiology Unit which provides a valuable template for the national expansion of testing in education, supporting schools and universities to retain face to face teaching while managing risks of COVID-19 transmission.

UKRI modelling contribution to policy making decisions will be continued and expanded by the JUNIPER programme, the 'Joint UNIversities Pandemic and Epidemiological Research' consortium brings together leading mathematical and statistical modelers from seven UK universities funded in late 2020 through the UKRI Agile call.

Data connectivity and co-ordination

The work to understand COVID-19 transmission, modelling and treatment efficacy requires access to and connectivity between a vast array of public health data. Linking clinical information held within the NHS to COVID-19 test results to contact tracing information to viral sequencing analysis to demographic data is required in near-real time to allow for an effective rapid response. This massive undertaking has been spearheaded by **Health Data Research UK (HDR UK)**. Their expertise has facilitated access, via the HDR Innovation Gateway, to 120 Covid-19 datasets alongside the UK's core Trusted Research Environments[16](TREs). The establishment of TREs – secure platforms for researchers to access sensitive, anonymised clinical and public health data – has been supported by MRC, and recently through HDR UK, over the past decade. This was supported with additional resource and expertise harnessed in response to the pandemic to establish the NHS Digital TRE, which was launched in November 2020. TREs are essential for managing risk for unauthorised access and/or re-identification of de-identified health data. These TREs provide rapid, safe, and trustworthy access to data to quickly answer COVID-19 related research questions thereby playing a leading role in the UK's COVID-19 response.

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15. ANNEX 2.2, programmes: COV006; COV0659; Virus Watch (CV220-094); Con-COV (COV0330); STORY (CV220-036; COV0331; CV220-046; EAVE II (CV220-091); CV220-194; in addition to MRC Units.

16. Trusted Research Environments (TREs) protect the privacy of individuals while facilitating large-scale data analysis to advance understanding of disease and improvements in health and care. Many of the perspectives expressed in this section were taken

HDR UK has been at the forefront of supporting the alignment and development of UK-wide TRE network, leveraging existing technical capabilities where available and aligning these capabilities to become interoperable. HDR UK has helped steer the availability of patient and public health data within the UK as the coordinator of the UK Health Data Alliance, a collaboration of over 50 leading healthcare and research organisations. For the management of global COVID-19 data, HDR UK convened the International COVID-19 Data Research Alliance (ICODA).

In addition, HDR UK leads the Data and Connectivity programme of the UK's National Core Studies (NCS) initiative, which aims to coordinate data management for the other five NCS programmes. The Data and Connectivity work consists of 180 projects that HDR UK staff and collaborators have established to answer key research questions about the pandemic. These research questions are in part generated via a communal Covid-19 activities + skills matching tool, allowing HDR UK to identify new collaborations and datasets whilst also allowing prioritisation of resources.

Beyond HDR UK, there are other coordination efforts made possible through UKRI support including:

- DECOVID – an enhanced database of individual clinical measurements, organised via the EPSRC-funded Alan Turing Institute and supported by MRC BSU, MRC HGU, MRC Harwell and MRC/Versus Arthritis Centre for Musculoskeletal Ageing Research (CMAR). This highly granular, near real time clinical database and research environment allowed bespoke answers to specific questions on critical care for 185,000 patients, accounting for >18 million hours of clinical care. The data generated by the consortium will now be used to assess additional projects, including thromboembolic events.

- Cohort datasets – a range of cohorts run through or used by MRC investments are being integrated into COVID-19 research. Some cohorts are targeted for specific research projects (e.g. a pandemic-specific survey of participants to ULHA's National Survey of Health and Development) or creating additional COVID-19 arms to pre-existing cohorts (e.g. Crick's involvement in the Posthumous Evaluation of Advanced Cancer Environment (PEACE) trial – a national autopsy-based study of cancer and drug resistance is adding 100 autopsies from COVID-19-positive patients to help understand the pathology).

- The Liverpool COVID-19 Drug Interactions Database retains information on, currently, 26 COVID-19 drugs compared against over 500 potential co-medications. Their interactive website and published charts of known or potential drug interactions has been recommended in many clinical treatment guidelines around the world and helping healthcare professionals with clinical decision making.

The ability to collate information to allow COVID-19 surveillance, monitoring and modelling to happen also requires the computing infrastructure to support it. The Cloud Infrastructure for Microbial Bioinformatics (CLIMB) supported by MRC since 2014 provides an essential national capability for microbiologists in the UK, serving more than 900 users and over 300 research groups scattered across at least 85 research institutions. Crucially, CLIMB now provides COG-UK with the technological support and IT infrastructure for COVID-19 viral sequence analysis, with further MRC support.

Clinical care guidance

Over the year, eight projects funded in the UKRI-NIHR Rapid Response initiative have already developed effective communication links with NICE, PHE, NHS England, CSO, CNO, and CMOs in England, Wales, Northern Ireland and Scotland. Through these links, they have provided policy briefings, established clinical guidance and influenced health care regimes (details in ANNEX 2.2): for nursing care of hospitalised COVID-19 patients, for use of standard drugs in COVID-19 patients (e.g. corticosteroids), in palliative care, for mental health in the context of the pandemic and in hospice practice. Early research rapidly identified the critical role played by comorbidities (e.g. obesity and cancer) and the patient's immune response (organ specific immunopathology) in the disease trajectory which dictated distinct care and treatment procedures. Projects have developed systems to support clinical decision making: a prognostic scoring regime for assessing COVID-19 patients and a dataset to inform clinicians on the outcome of drug interactions in COVID-19 patients.

Public engagement and global communication

Public awareness and interest in biomedical research have soared in the wake of the COVID-19 pandemic. Some have suggested that public interest in science is greater than at any time since the moon landing. Many researchers and their work were thrust into the public spotlight, and the scientific community has been instrumental in helping inform the public about the complexity of the research effort. From social media to op-eds on national newspapers, from TV interviews to radio broadcasts, UKRI-funded scientists are engaging directly with the public. This has been particularly key given the fast-paced 'science by press-release' trend that contrasts with the traditional peer-reviewed journal publications for disseminating results from research projects. The public engagement work carried out by scientists like Neil Ferguson (GIDA), Sarah Gilbert (University of Oxford), Devi Sridhar (University of Edinburgh), Sharon Peacock (COG-UK), the scientist of UK-CIC, and many others continues to be vital for strengthening public trust in science and tackling misinformation and conspiracies around topics such as the origins of the SARS-CoV-2 virus as well as vaccine safety and development. Engagement efforts have also extended internationally with the MRC Epidemiology Unit's project to crowd-sourced translations of WHO facts on Coronavirus into as many African languages as possible.

COVID-19 targeting research has been launched around the world at a rapidly increasing rate from the outset of the pandemic. The need for globally accessible datasets recording and cataloguing the diversity of projects was immediately apparent. MRC has contributed to this effort through its Unit investments, funded projects and in partnership with Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). The COVID-19 Research Project Tracker created by the UK Collaborative for Development Research (UKCDR) and GloPID-R has been collating world-wide award data and categorising projects against the WHO roadmap for COVID-19 research. MRC took a leading role facilitating UKCDR's data gathering through our network of international funder collaborations and providing methodology to allow UKCDR records to be incorporated into Europe PubMed Central's own Covid-19 dataset. As of 01 April 2021, the details of almost 8,000 projects (totalling $3.8 billion from ~101 funding agencies from 136 countries) have been accessed over 25,000 times. A year on from the pandemic being declared, the portfolio shows that the global R&D response has been comprehensive, rapid and of unprecedented scale. However, the value of tracking these investments, despite the likelihood of be gaps in coverage (e.g. research in Asia, particularly China, being under-represented), has been clear. Emerging findings highlight the lower investment in research conducted in lower and middle-income countries, the increasing need (given limited resources) for improved co-ordination of studies worldwide, and that unfortunately many research studies are under-powered or unable to achieve their aims. Since April 2020, a RRI (UKRI-NIHR COVID-19 Rapid Response Initiative) project has provided a global hub/showcase of COVID research, tools and methodologies sharing outputs in real time for researchers from 195 countries. Additionally, the MRC Lifelong Epidemiology Unit (LEU) has supported the COVID-19 Open Research Dataset (CORD-19) an open, text-minable dataset of (primarily) publications related to Covid-19 backed by NIH and the White House.

Understanding SARS-CoV-2 biology and pathology

Exploiting UKRI's historical support for development of structural biology methodologies (ANNEX 6.2), the current research has played a key role in understanding how the SARS-CoV-2 virus causes infections. The virus contains four main structural proteins (S, E, M, and N) and entry into host cells is mediated by the Spike glycoprotein (S protein). It is therefore an attractive antiviral target, and many of the vaccines currently authorised for use (e.g. AZ/Oxford vaccine, Pfizer/BioNTech and Moderna) focus on the Spike protein as the antigen to generate an immune response to.

MRC and UKRI-supported scientists have contributed to the understanding of the SARS-CoV-2 structure resulting in several key impacts that have informed rapid translation of knowledge into new interventions (preventative and treatment) against COVID-19 and provide a deeper understanding of the zoonotic origins of the virus.

- In October 2020, the LMB opened a new Containment Level 3 laboratory that was fast-tracked to enable use of live virus for rapid responsive COVID-19 research into SARS-CoV-2 infection and immunity that could help future vaccine development.

- LMB scientists have applied cryo-electron microscopy and tomography to image intact SARS-CoV-2 virions and determine the high-resolution atomic structure, conformational flexibility, and distribution these Spike proteins on the surface of the virus. This information is vital for understanding the interactions of the Spike protein and neutralizing antibodies, either through infection or vaccination.

- LMB scientists showed that chronic COVID-19 disease leads to viral evolution and reduced sensitivity to neutralizing antibodies in an immunosuppressed individual treated with convalescent plasma, through mutations in the Spike protein.

- A team at the Francis Crick Institute in London used cryo-EM to determine the structures for the spike proteins of both SARS-CoV-2 and a related bat coronavirus. The results showed that the bat coronavirus spike protein would be unable to bind to the human ACE2 receptor and enter human host cells, demonstrating the possible involvement of an intermediate host for zoonotic transfer to have occurred.

Strategic activities[17]

Leading an agile research response

At the start of 2020 the WHO was taking its first steps to understand the report of a cluster of pneumonia cases in Wuhan, China[18], but the development was already a topic of active discussion in the UK biomedical academic community and with research colleagues and collaborators across the world. MRC head office staff began to consider how the medical research community could be supported to respond to a potential public health emergency. Academic colleagues in China had shared with UK academics first-hand accounts of the rapid transmission and severity of this new disease, and ideas were swiftly forming about how UK strengths in immunology, epidemiology, and molecular biology could be harnessed to fill important knowledge gaps and lay the foundation for containing and combatting the outbreak. MRC's recent experience in responding to the Ebola (2014) and Zika (2016) epidemics, our response to SARs (2002), and work to strengthen preparedness for an influenza pandemic in the years in-between, had highlighted the importance of research to those responses and that research teams could usefully pivot to studies that would make a rapid difference. During January and February, MRC staff conferred and established strong working relationships with academics, other funders and government groups, briefed MRC research boards, MRC Strategy Board and Council, and the UKRI CEO, developed and refined research priories in the evolving knowledge landscape, initiated a series a research calls and coordinated research consortia to address the COVID-19 challenge. Executive action was taken to provide immediate additional support to the MRC Centre for Virus Research (CVR) in Glasgow and the MRC Centre for Global Infectious Disease Analysis (GIDA) at Imperial College, London, both having active research programmes with clear relevance to the problem. By the end of January, and with the first cases identified in the UK, it was clear that the risk of an epidemic spreading globally was rising significantly. On 04 February 2020, two funding calls were launched, in partnership with DHSC, for new research directed to the COVID-19 pandemic. The first call invited short-term projects for vaccines and therapeutics for rapid clinical development, while the second call invited projects for diagnosing and understanding Covid-19. The way that these calls were run were a notable departure for both MRC and NIHR, with no pre-defined expectations about the scale of funding for each award (awards ranged from £50,000 to £7m), a focus on results within 18 months (MRC normally funds work for 3-5 years), a requirement to share data and tools immediately, and lastly while all proposals underwent expert peer review, the allocation decisions lay with the Government's Chief Medical Officer (Chris Whitty)[19].

Forward planning and relationship building

MRC has a track record of addressing the discovery science requirements in emerging diseases and epidemics and could draw on its intramural expertise and wider research community connections immediately. Central government needed to rapidly access this direct connection to the research community and gain advice on research priorities. Working with other leaders in the biomedical community, strongly connected to international bodies such as WHO, the UKRI led on efforts to brief

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17. Many of the perspectives expressed in this section were taken form staff interviews in spring 2020 which were included in the Management Board Paper dated 28 July 2020, *MRC's COVID-19 Response: Lessons Learnt* by Rebecca Barlow

18. Pneumonia of unknown cause – China (WHO Disease Outbreak News, 5 January 2020) http://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229

19. https://blogs.bmj.com/bmj/2020/07/29/fiona-m-watt-covid-19-a-new-disease-has-forced-a-re-think-of-how-we-fund-medical-research/

the relevant government committees and integrate academic expertise from the research community into the decision-making process.

Strategic planning expertise was provided by MRC and UKRI senior staff while specific epidemiological insight was drawn from leading MRC research teams and new coalitions of academic experts were rapidly convened from the community. Jonathan Pearce (MRC Director COVID-19 response) served as the deputy chair for the UKRI research co-ordination group, contributed to the vaccine taskforce, the setting up of COG-UK, and has led the setting up of three out of the seven programmes within the National Core Studies for COVID-19. In coordinating pan-UK consortium, MRC and UKRI maintained its commitment to providing funding assistance across the four nations. Jonathan Pearce[20] was praised for confirming nation-wide inclusion in the PHOSP-COVID consortium through ensuring involvement of the devolved administrations. This was problematic given the parameters of the NIHR (a funding partner) remit.

UKRI staff served on several of the initial government task forces initiated in March 2020 (see figure below), although the strategic landscape took several months to develop and has now expanded significantly[21]. MRC GIDA was the first of several research Centres that redirected their attention to provide rapid, targeted, and detailed data on COVID transmission and it was partly the modelling from this Centre through SPI-M and SAGE directly that influenced the Government's decision to introduce the first national lockdown measures late March.

The success of the initial rapid response call was largely attributed to the foresight of MRC's IIB team. This was strengthened by the development of an extremely productive relationship with NIHR forged and managed by the then Head of IIB (Jo Jenkinson[22]). Both groups were willing to share freely their understanding of the health and political situation and work together to serve the collective needs. The time required for government advisors to assimilate the medical briefing and the details of its impacts on public health initially created significant challenges in communicating the call scope to the community without delay.

Engagement with stakeholders is a key element of successful, rapid translation of knowledge into public policy or guidance. In surveys, MRC-funded researchers were able to tell us about the highly interactive relationships developed between academic researchers and policymakers as well as the barriers to engagement or progress. Colleagues at MRC and at NIHR have been able to quickly pick up on reported barriers and facilitate resolutions to these, actively supporting the research community (ANNEX 2.3). MRC funded researchers have provided weekly briefings or regular reports to government committees concerned with public health policy and clinical policy and guidance including SAGE (and its subgroups such as the Environmental Monitoring Group), Public Health England, NHS Digital, NICE, NHS England, regional NHS Clinical Commissioning Groups, and the World Health Organisation, as well as a great variety of clinician groups.

20. Dr Jonathan Pearce's contribution, with partners from across MRC and NIHR, to establishing the UKRI-NIHR COVID-19 rapid response initiative, while supporting UKRI leadership in understanding the challenge posed by COVID-19 and potential priorities for the response was recognised in the Queen's Birthday Honours 2020, with the award of an MBE for services to COVID-19 research.
21. SAGE now has several additional ad-hoc working groups, networks and sub-groups to consider areas such as COVID-19 transmission in children, ethnicity issues etc. https://www.gov.uk/government/publications/scientific-advisory-group-for-emergencies-sage-coronavirus-covid-19-response-membership/list-of-participants-of-sage-and-related-sub-groups
22. Dr Joanne Jenkinson's contribution to setting up the COVID-19 rapid response was recognised in the Queen's Birthday Honours 2021, with the award of an MBE for services to COVID-19 research.

Scientific Advisory Group on Emergencies (SAGE) and related expert groups
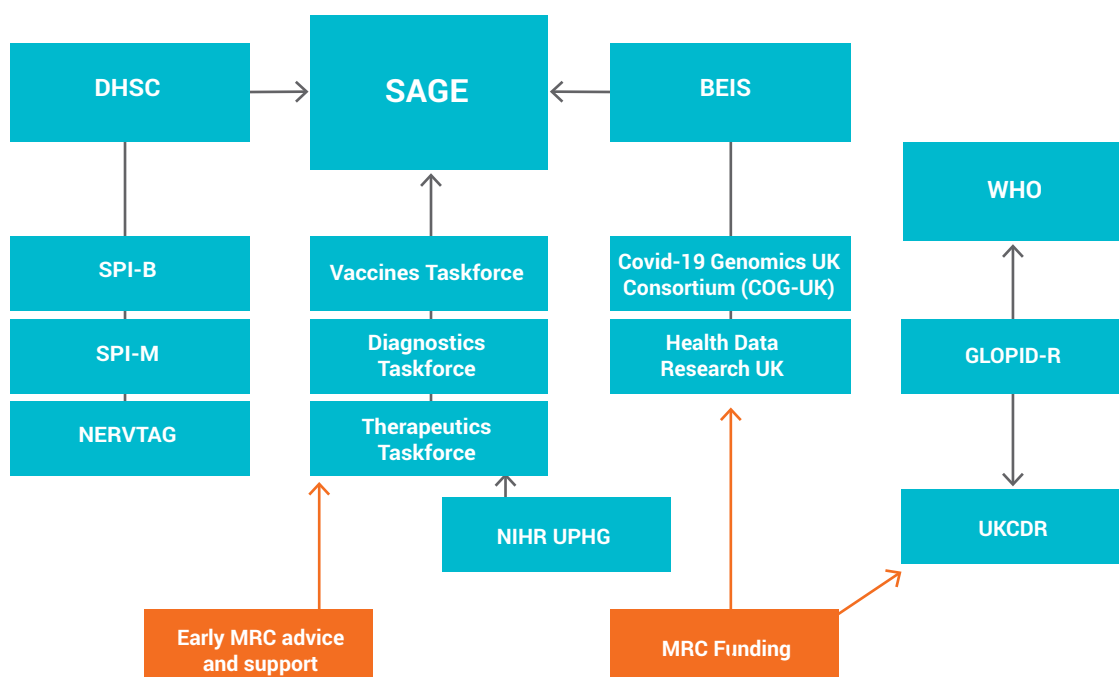
- The Government Scientific Advisory Group on Emergencies (SAGE) provides expert input into the meetings held in the Cabinet Office Briefing Room (COBR), when the nature of the emergency requires this. SAGE has been activated temporarily on eight occasions prior to the COVID-19 pandemic and is chaired by the Government's Chief Scientific Advisor, Sir Patrick Vallance.

- Scientific Pandemic Influenza Group on Behaviours (SPI-B) provides advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts. Depending on the agenda SPI-B has drawn on over 40 experts during 2020.

- Scientific Pandemic Influenza Group on Modelling (SPI-M) provides advice to DHSC on matters of infectious disease modelling and epidemiology, almost 70 experts have been drawn on to help with the SPI-M agendas during 2020.

- New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) is chaired by Peter Horby, Oxford it is a standing committee advisory to the CMO, and in this crisis has been regularly consulted by SAGE.

- The Therapeutics Taskforce was established in April 2020 and initially chaired by Patrick Chinnery, Cambridge/MRC with support from Glenn Wells, MRC, it is now chaired by the Deputy CMO. It focuses on ensuring that research to develop new therapeutics continues at pace and has been central to the setting up of several clinical trial platforms such as MRC funded RECOVERY trial.

- NIHR Urgent Public Health Group (UPHG) is chaired by Nick Lemoine, Medical Director of the NIHR Clinical Research Network and was set up to provide clinical intelligence for the selection, prioritisation, setting up and delivery of studies relating to COVID-19. It works closely with the Therapeutics Taskforce to ensure that COVID-19 studies continue to be supported within the NHS throughout the pandemic.

- **The Diagnostics Taskforce** is chaired by Mike Ferguson, Dundee and the secretariat initially provided by UKRI it focused on the development of serological tests for COVID-19.

- The Vaccines Taskforce is chaired by Kate Bingham, SV Health Partners and focused on driving forward the development and delivery of a COVID-19 vaccine.

- COG-UK is supported by the UK Government, through a rapid response fund administered by UKRI, DHSC and the Wellcome Sanger Institute. It is focused on large-scale, rapid whole-genome sequencing of SARS-CoV-2 and led by Sharon Peacock, Cambridge.

- HDR-UK was established by MRC in 2017, and is led by Andrew Morris, University of Edinburgh. As the national institute for health data, HDR-UK is championing the use of health data to respond to COVID-19.

- Global research collaboration for infectious disease preparedness (GloPID-R) is a network of research funding organisations in the area of infectious disease preparedness research. It has performed a unique role in the current pandemic activating unprecedented levels of cooperation between research funding agencies within our network and beyond.

- UK Collaborative on Development Research (UKCDR) is a group of UK Government departments and research funders working in international development. UKCDR has worked closely with GloPID-R and with its members to support coordination of UK research funding in response to COVID-19.

Clarity on the setting of research priorities and identifying gaps in the research landscape

Early in the pandemic there needed to be clarity on and transparency of government and SAGE priorities. There were challenges to SAGE developing a clear approach to identifying research priorities, with such a paucity of data and the urgency of the problem. When priorities were shared, UKRI was often not permitted to share the information further, meaning it was unable to build them into call scopes or issue highlight notices to better direct the response of its research community. MRC's perspective on research priories sometimes aligned with those of government and SAGE but also sometimes diverged. It was suggested that UKRI could have worked more closely with GO-Science[23], that MRC should have made better use of the researchers and contacts who contributed to SAGE discussions at all levels and that this leverage was therefore not explored to positively influence priority setting activities. The issue of process, particularly for developing therapeutics, was also a challenge. Operationalising an effective oversight process for prioritising and coordinating development of treatment for this novel disease proved difficult to work through at speed with the diversity of stakeholders involved: DHSC, MRC, WT, NHS, CMO, CNO, trialists and other researchers. MRC's reputation for integrity and the trust of the community developed through the personal way of working with researchers was identified by a key component of the resolution to some of these snags. It served to help create some improvements in trial coordination as the year progressed, seeing the evolution of ACCORD[24] followed by UK CTAP as a working system to manage therapeutic development.

The first deadline for the second joint UKRI/NIHR call for researcher-led investigations, in March 2020, was set such that the WHO coordinated global research mapping could be incorporated into the call scope. This promoted potential linkage between the UK and global SARS-CoV-2 research outputs. The

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23. The Government Office for Science (Go-Science) provides advice to the Prime Minister (e.g. through the Council for Science and Technology) and members of the cabinet (e.g. via SAGE) which reflects the priorities of the Government Chief Science Advisor https://www.gov.uk/government/organisations/government-office-for-science/about

24. ACCORD, funded by UKRI and DHSC, brought together a single, UK-wide clinical trial platform provided by the clinical research company IQVIA, and the UK's leading research expertise through the NIHR. Strategic coordination of the programme was through an Oversight Group chaired by the Secretary of State for BEIS, meeting regularly to update, address potential barriers to progress and ensure that the work was being taken forward at pace and with ambition.

WHO roadmap, published March 2020, tightened the scope of the global priorities and set standards for how the priorities should be approached: highlighting affordable and equitable access as well as speed. These standards mirrored those of MRC-funded research historically and over the course of the current pandemic. This is particularly true of vaccine development. The principles of globally accessibility had been integrated into MRC-funded MERS vaccine development which has provided the springboard from which the Oxford AZ vaccine has been validated and globally distributed with such speed. The WHO roadmap states that

> *"Given that at present there are no vaccines, no curative treatments and a strong need for more rapid diagnostic tests, the roadmap unites the global community around a common research agenda and common ambition to accelerate timely, adequate, affordable and equitable access to any innovation and medical countermeasures."*

Balance of bottom-up and top-down funding mechanisms

MRC and UKRI deployed a variety of different approaches to funding COVID-19 work. It was clear that the COVID-19 knowledge gaps in early 2020 needed a range of different scales of activity and networking, from small pilot work to national consortia (e.g. ISARIC-4C, GenOMMIC COVID-19 study, COG-UK, CIC, Protein Portal). Some research teams were already actively addressing the issues and making progress, while other teams needed a strategic push. MRC used its convening skills, active connections, and good appreciation of the research landscape to bring researchers together. The most urgent research questions justified allocating funding with expert review and a sound business case, but without competition, although most of the support for COVID-19 projects was allocated in competition. Options and associated risks were assessed to enable selection of the most effective mechanism to deliver the intended outcome. However, in considering opportunities for refinement, the convening of a more formal oversight review group may have achieved smoother coordination of the evolving portfolio.

Funding activities included:

- **Response-mode funding through the rapid response and rolling call.**
  - Rapidly established the key research questions for the community attracting diverse approaches to focused areas identified in the WHO roadmap.
- **Highlight notices to encourage applications in specific areas of need.**
  - Established research and policy stimulated research activity- particularly in areas not attracting sufficient activity via response-mode.
- **Commissioning research or helping to facilitate the creation of consortia or groups to address specific research questions.**
  - Rapidly established a critical mass of researchers, appropriately powered in key areas (six identified and agreed with SAGE).
- **Direct commissions from the UKRI CEO.**
  - Extremely rapid deployment of existing consortium, harnessing organisation expertise, instant allocation of funds. Responding to the most immediate demands without the luxury of time.

Efforts to encourage the wider research community to collaborate (e.g. seeking joint submissions from epidemiologists and immunologists) were found to be challenging, and this underlined the limitation of relying on a bottom-up approach to funding in some areas. It was accepted that projects funded through the commissioned, top-down route would not have occurred organically.

There was also a perception that the general research community were less familiar with delivering answers to applied questions (such as describing the minimum effective dose of the virus, or basic research on the use of PPE), finding it difficult to link in with more applied research. This highlighted the need for strategic action from MRC, to overcome siloed working and to connect the discovery research effectively with those in the implementation landscape.

MRC's community of board and panel members were regularly consulted to test the wording of the scope of calls and worked hard to pragmatically balance the rigour of their usual approach to selecting the most excellent proposals with the pressing need for immediate answers to very tightly defined research questions: rapid vaccine development, effective, readily available treatments, transmission rates and patterns, population vulnerabilities, etc. UKRI benefited from the way that these expert assessors rose to the challenge of the need for rapid review. Early in the pandemic, it was relatively straightforward to match proposals to the gaps and opportunities, as these were wide and numerous. Applications could be brief and review quick. As the funded portfolio built up it obviously became more involved to determine what each proposal would contribute, more details were needed, and review became more onerous.

The UKRI-NIHR Rapid Response calls were formulated, launched, and processed through highly effective co-working between MRC IIB team and NIHR. When, by mid-February, it became clear that this call would be of a much larger scale than originally anticipated, these teams established a "College of Experts" which allowed them to hold three separate March panel meetings in parallel to deal with the demand on the call. In addition, they had employed the services of a specialist AV company to better facilitate panel members joining via Zoom (the meeting was held the day after the UK was advised to avoid unnecessary travel and contact). This was the first panel meeting employing the virtual meeting Zoom system and it established the protocol for all subsequent funding meetings which have had to be held virtually. This rapidly devised and implemented process has allowed MRC funding panels and Boards to continue business-as-usual as well as the novel COVID-19 rolling panel initiatives without a pause throughout 2020 and into 2021.

An important constraint to funding additional covid-19 work was clarity over MRC's budget to do this. Although there had been an initial emergency allocation from Treasury to support covid-19 research, this was for the 2020/21 financial year only. As early as March 2020, MRC Strategy Board discussed using their budget to support the knock-on effect of the proposals that could not be funded through the £20m rapid response call (because they had a longer than 12-month time horizon for impact). These proposals were expected to put additional pressure on the funding available from MRC's Infections and Immunity Board. Uncertainty over the 2021/22 funding position continued until an allocation was made following the Government's spending review in June 2021, and only clarified the position for that financial year.

International coordination

MRC and UKRI has contributed to the co-ordination of international research efforts via two international coordinating bodies formed to improve the global response to epidemic threat: The WHO's Global Coordinating Mechanism for Research and Development (GCM) and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). In addition, MRC's Units in Africa received additional funding in early 2020 to contribute to local monitoring and treatment efforts as well as to global SARS-CoV-2 monitoring and surveillance datasets.

The UKCDR started work early in the pandemic to compile a database of all COVID facing research projects being carried out throughout the world. UKCDR is a crucial part of the UK international development landscape. Its work is to promote coherence and link up development research funding in the UK, and its collaboration with GloPID-R has led to the establishment of COVID CIRCLE working globally to map opportunities, share resources and learning about COVID-19. MRC contacted UKCDR to assist in encouraging funders worldwide to submit details of the awards they were making relevant to COVID-19 as soon as possible. This was done by working through our contacts at the Heads of

International Research Organisations (HIROs), colleagues at World RePORT and other networks. The aim being to ensure that there was a complete view of work underway, to avoid unnecessary duplication and to help strategic planning. The COVID-19 Research Project Tracker grew quickly to ~2,000 COVID-19 research awards by July 2020, and as of 14 May 2021 has reached over 10,000 awards. MRC and UKRI also facilitated the extract, transform and load process to provide the UKCDR dataset as a specialised search within Europe PubMed Central, which provides much richer search functionality and linkage to publications arising from the work, with the support of colleagues at the European Bioinformatics Institute.

MRC funding response to the COVID–19 pandemic

Activities Summary

In January of 2020, UKRI took an active role early in the UK-wide response to the unfolding COVID-19 crisis. Over the next six months, MRC led or participated in the planning and establishment of the UK's biomedical research response to the public health threat posed by the pandemic. In the spring of 2020, as the high transmission rate and virulence of the SARS-CoV-2 virus became clearer, MRC and UKRI focused its role in co-ordinating and expanding the research efforts to address the most immediate public health concerns and refining the pathways of communication between research knowledge and government and clinical policymakers (see Section 3) . In addition to its strategic role, MRC and UKRI, in partnership with NIHR and/or other funders, funded 165 projects proposed by researchers from across the biomedical spectrum through seven initiatives[25]. These calls attracted 3008 applications of which 135[26] were funded, a 4.7%[27] award rate. The streamlined application process that was introduced specifically for the COVID-19 calls may have encouraged many applications that were not sufficiently considered, which was reflected in the success rate. MRC and UKRI contributed funding, coordination, and expertise for two pan-UK consortia, clinical trial platforms and in government research oversight groups (Therapeutics and Vaccine Task Forces, UK COVID-19 Therapeutics Advisory Panel (UK-CTAP), and the National Core Studies programmes). The MRC-supported community of Institutes, Units and Centres initiated hundreds of research projects and provided practical support for local clinical needs and research projects carried out by others (Section 3). Over the course of 2020, MRC and UKRI managed[28] £256m in research funding (£177m MRC commitment) to combat the COVID-19 crisis. In total, more than 165 projects, platforms and programmes have been supported.

MRC supported COVID –19 research

MRC and UKRI funded research projects to rapidly provide data and analysis to fill the broad diversity of knowledge gaps in 2020 concerning the COVID-19 pandemic and its effects both in the UK and globally. These were funded through a variety of bespoke funding coalitions.

Funding calls – summary and abbreviations

MRC and UKRI supported eight main funding calls throughout 2020. Detailed descriptions of each call, its intent and a summary of its award details are found in ANNEX 4.1.

- RRI - UKRI-NIHR COVID-19 Rapid Response Initiative
  - Calls 1+2 (February 2020)
    - *Call 1: Vaccines and therapeutics*
    - *Call 2: Diagnosis and understanding of COVID-19*
  - UKRI-NIHR Rapid Response Rolling call (April 2020)

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25. Initiative and project details in ANNEX 4.1

26. An additional 20 awards were funded through calls run by other funders and 10 COVID-19 awards were funded through the Boards

27. This is the award rate for all COVID-19 applications managed by MRC staff. This will include applications that were excluded, post- staff assessment, as out of remit. The success rate for reviewed applications with be higher.

28. Data from 26APR21 COSTED COVID Awards finance calculation.

- **RRR** – UKRI COVID-19 Rapid Response Rolling call (March 2020)
- **EDCTP RR** – EDCTP COVID-19 Response call (April 2020)
- **GCRF/Newton Agile** – UKRI GCRF/Newton Agile Response call (May 2020)
- **GECO** – Global Effort on COVID-19 Health Research COVID-19 (May 2020)
- **Agile Rolling** – UKRI COVID-19 Agile Rolling call (August 2020)
- **UK-India RR** – UK-India COVID-19 partnership initiative (October 2020)
- **Long COVID** – NIHR-UKRI Long-term COVID-19 effects in non-hospitalised individuals (December 2020)

Other COVID-19 awards

- **Boards**
  - Three projects awarded from direct submission to Board (37 apps)
  - Six projects approved through requests for change of research direction from existing Board awards (12 apps)
- **Strategic Priorities Fund (SPF)**
  - Two awards through the Adolescent Mental Health and the Developing Mind initiative
  - One award through the Nucleic Acid Therapy Accelerator

MRC and UKRI co-ordinated/supported research knowledge infrastructures

In early 2020, the COVID-19 research environment was rapidly evolving; the WHO road map was produced in March 2020 outlining research priorities. These were further developed by SAGE to establish UK COVID-19 research priorities. To address these, MRC and UKRI funded, and often initiated, a broad spectrum of research platforms in early 2020. These platforms established a methodological infrastructure focused on a specific facet of the COVID-19 challenge: to test drug and vaccine candidates, techniques, or concepts as they were identified, sequencing and analysis platforms, or databases. These consortia of researchers came together rapidly through collaboration across the academic and clinical research community, through MRC's active networking of community expertise, or through multi-funder initiatives. Many arose within the community of MRC's large investment infrastructures, and some were established through the early UKRI-NIHR Rapid Response Initiative (RRI).

Vaccine development

Two vaccine development programmes were funded through the RRI. First, the ChAdOx1 vaccine platform, already shown to be safe and effective through a previously funded Phase 1 trial against a related coronavirus, was quickly adapted to develop a vaccine candidate against SARS-CoV-2 and launched human trials by April 2020. The second vaccine programme focused on developing a novel technology utilising a self-amplifying RNA sequence to provoke an immune response. In parallel, project funding was provided to investigate and develop more efficient vaccine manufacture processes, in addition to the ISCF Medicines Manufacture's Vaccines Manufacturing Innovation Centre establishment was already in progress (for more details, see Section 2 and ANNEX 4.1).

Clinical Trial and clinical observational study platforms

While vaccine clinical trials were funded through the RRI to develop infection prevention capability, the need for therapies and interventions for patients who had already become infected with SARS-CoV-2 was pressing. In January 2020, MRC and UKRI provided funding for the RECOVERY trial, which utilised a previously established pandemic trial recruitment plan (part funded by MRC). This trial and those that followed were designed to identify the appropriate treatments against various stages of the disease, for various sub-groups of the population, to be administered at the right time. As such, it required the rigorous testing of many different treatment protocols in clinical trials. By June 2020, 28 independent interventional trials and 19 clinically based observational trials were registered in the UK. 10 of these were supported

by MRC (ANNEX 4.1) in combination with other funders. To ensure efficient governance, many of these clinical trials were merged and brought under a coordinated umbrella (UK-CTAP) to facilitate patient recruitment, data sharing, best practice for shared protocols, and comparison of results.

Earliest clinical trials funded by MRC/NIHR:

- **RECOVERY** – Phase III adaptive large-scale trial platform for currently available, affordable drugs for the treatment of COVID-19 patients funded through the RRI.

- **PRINCIPLE** – Phase II trial testing potential COVID-19 treatments in the community in patients with mild to moderate COVID-19 who are aged over 65 or aged 50 to 64 with an underlying health condition.

- **TACTIC-R** – Phase III randomised, parallel arm, open-label platform trial for investigating potential treatment for COVID-19. This study proposed to assess the efficacy of immunomodulatory agents that target the dysregulated immune response linked to the severe lung, and other organ, damage seen in patients with severe COVID-19.

- **CATALYST** – Phase II multi-arm multi-stage initial trial platform to test currently available promising drugs for hospitalised SARS-CoV-2 patients in small trial populations. This adaptive trial has developed into a filter and 'springboard' for the larger-scale phase III COVID-19 trial platforms.

Major platforms to provide data for population health and clinical policy decisions

Primarily through the UKRI-NIHR RRI, research platforms (details ANNEX 4.2) were organised and funded to spearhead the programme to **understand the COVID-19 epidemiology, disease progression and population health impacts**.

- **ISARIC 4C**: International Severe Acute Respiratory and Emerging Infection Consortium's dedicated **Coronavirus Clinical Characterisation Consortium**.

- **UK-CIC:** The UK Coronavirus Immunology Consortium is a UK underpinning platform **to study immunology and immunopathology of COVID-19**.

- **Virus Watch**: Understanding community incidence, symptom profiles, and transmission of COVID-19 **in relation to population movement and behaviour**.

- **HICC**: Humoral Immune Correlates for COVID19 will study the humoral immune response of two cohorts; **NHS workers and hospitalised patients**.

- **PHOSP-COVID**: Post-hospitalisation COVID-19 study is a national consortium to understand and **improve long-term health outcomes**.

- **CONDOR**: COVID-19 National DiagnOstic Research and Evaluation Platform evaluates how new diagnostic tests perform **in hospitals, general practices and care homes**.

- **OpenSafely**: A secure analytics platform for electronic health records in the NHS **for data analysis during the global COVID-19 emergency**.

- **CoMMinS**: COVID-19 Mapping and Mitigation in Schools will create new knowledge and tools to help schools deal with the practical challenges of **preventing and coping with an outbreak of COVID-19**.

- **OWLS:** Optimising Wellbeing during Self-isolation will explore how people with severe mental ill health experienced the pandemic restrictions and **how they dealt with the social consequences of lockdown**.

- **Con-COV**: Controlling COVID-19 **through enhanced population surveillance and intervention**.

- **CO-CONNECT**: COVID – Curated and Open aNalysis aNd rEsearCh platform will support researchers to link **COVID-19 cohort, serology and other health and non-health datasets**.

- **COVID-CNS**: The COVID-19: Clinical Neuroscience Study seeks to understand how brain injuries during COVID-19 infection occurs **and to develop strategies to prevent and treat them**.

- **Coronavirus STORY**: Serum Testing of Representative Youngsters aims to collect sufficient childhood and teenage serum samples for near real-time monitoring of **increases in paediatric COVID-19 infections**.

- **EAVE II**: early assessment of COVID-19 epidemiology and **vaccine/anti-viral effectiveness**.

MRC community platforms

- **COG-UK** – **COVID-19 Genomics UK Consortium** – to deliver large-scale and rapid whole-genome virus sequencing to local NHS centres and the UK government (established by Professor Sharon Peacock, Cambridge University, with funding from MRC and others).

- **COVID-19 Protein Portal** – **a consortium of leading centres of protein engineering and production** to allow UK scientists to access protein reagents needed for critical research relating to SARS-CoV-2 free of charge (MRC and WT funded).

- **GEL-GenOMMIC** study on COVID-19 Established April 2020, this project focused on severely affected COVID-19 patients and was integrated into the already active work to understand individual increased vulnerability to serious illness of the **GenOMICC consortium**.

MRC support for strategic initiatives

Therapeutic Task Force to oversee the development of policy around of identification and deployment of safe and effective treatments for COVID-19. MRC provided secretariat services and expertise during the initial response. Subsequently, UKRI role has transferred into management of **UK CTAP**: overseeing the appropriate inclusion of new treatment candidates and oversight of the clinical trial portfolio.

The **National Core Studies** are composed of **six themes of research** to respond to the near-term strategic, policy and operational needs of the UK response to COVID-19. MRC and UKRI manages three of the six. The start-up phase of these programmes ran from October 2020 to MArch 2021 continuing with Phase 1 funding through financial year 2022/23.

- COVID-19: **Data and Connectivity** – National Core Study (D&C-NCS) £8.3m (+ £15.2m Phase 1 funding).

- COVID-19: **Longitudinal Health and Wealth** – National Core Study (LWH-NCS) £9.9m (+ £9.0m Phase 1 funding).

- COVID-19: **Immunity** – National Core Studies (IMM-NCS) £7.2 (+ £6.7m Phase 1 funding).

International coordination

The **COVID-19 Research Project Tracker** by UK Collaborative for Development Research (UKCDR) (**ANNEX 4.1**) and Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) took an early lead in March 2020, usefully categorising all projects against the **WHO roadmap for COVID-19 research**. MRC is a member of GloPID-R and not only part-funds the UKCDR alongside Wellcome but also took a leading role facilitating this project tracking effort. This collaboration brings a regularly updated funding database of COVID-relevant work to a worldwide audience; the WHO (and associated COVID-19 research priority area groups) and research groups regarding its use and the **living mapping review**.

MRC COVID-19 portfolio

In 2020/21, MRC and UKRI managed ~£256m funding commitment (~£177m MRC administered budgets) for the COVID-19 response through a variety of budgets: UKRI to MRC C-19 Core allocation, MRC Core R&D, SPF, GCRF, HMT/NCS and MRC WCL[29]. This included £133.2 for competitive calls, £16.4 additional support for MRC major investments, £102.7 COVID-19 strategic initiatives, and £3.9m for COVID-19 extensions to studentships.

Award process

Rapid Response Initiative, the GECO call and the Long COVID call were jointly funded by UKRI (MRC) with DHSC (NIHR). NIHR managed the offline receipt of applications and peer review via a College of Experts and MRC organised the funding panel and processing of awards (details in ANNEX 4.2). To support and capture outputs of the live RRI awards, regular communication was established through quarterly surveys. This provided a unique opportunity to assist researchers in addressing impediments to impact in the rapidly changing COVID-19 public health landscape.

UKRI COVID-19 Rapid Response rolling call and UKRI COVID-19 agile call (rolling call part two) applications were initially received by the EPSRC who distributed them by remit to the RCs. The RC staff assessed the applications for suitability for remit and project requirements then managed the review and panel assessment of the grants (details in ANNEX 4.2).

UKRI GCRF/Newton Agile COVID-19 was administered by UKRI central with MRC providing panel expertise.

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29. UKRI to MRC C-19 Core allocation, MRC Core R&D, Strategic Project Fund, Global Challenge Research Fund, HM Treasury/ National Core Studies and MRC World Class Laboratories.

MRC administrative responsibilities in response mode COVID-19 funding calls[30]

Research call	# applications MRC processed[31]	#awards	MRC administered Commitment (£m)		Expected spend by 2022 (£m)
			MRC	Total funding	
RRI 1+2	270	27	12 .8 (50%)	25.9	22.1
RRI Rolling	698	52	23.4 (50%)	47.1	37.0
RRR	800[32]	8	2.5	N/A	2.5
Agile Rolling	279[33]	18	16.6	N/A	13.6
GCRF/Newton Agile	–	9	0		
GECO	850[34]	19[35]	5.8 (50%)	11.7	8.0
Board awards	47	4	1.2 (100%)	1.2	0.6
Repurposed awards	10	6	0.9	0.9	0.9
NPIF funding (SPF)	25	3	0.5	0.5	0.5
UK-India C19 (FIC)	30	4	–	2.7[36]	N/A
EDCTP COVID-19 emergency call	–	11 (projects with UK researchers from the 20 awards)	2.0	–	2.0
Long COVID	46	4	9.3 (50%)	18.6	17.6
COVID Urgency	–	3	0.08	0.08	0.08

30. Data from 26APR21 COSTED COVID-19 AWARD finance calculation.

31. Applications received and assessed by MRC staff. Due to confused communications, many were out of remit for MRC or the call.

32. 349 applications reviewed

33. 115 applications reviewed

34. 136 applications reviewed

35. Substantial adjustments to commitment were made post panel 3 award decisions to allow for the 2021 ODA funding restrictions. Ten projects were awarded but with substantially reduced funding and length of award. Commitment numbers to be confirmed May 2021.

36. Funding provided by FIC with contribution from the Indian Government, DBT.

Geographic distribution of MRC funded COVID-19 UK researchers
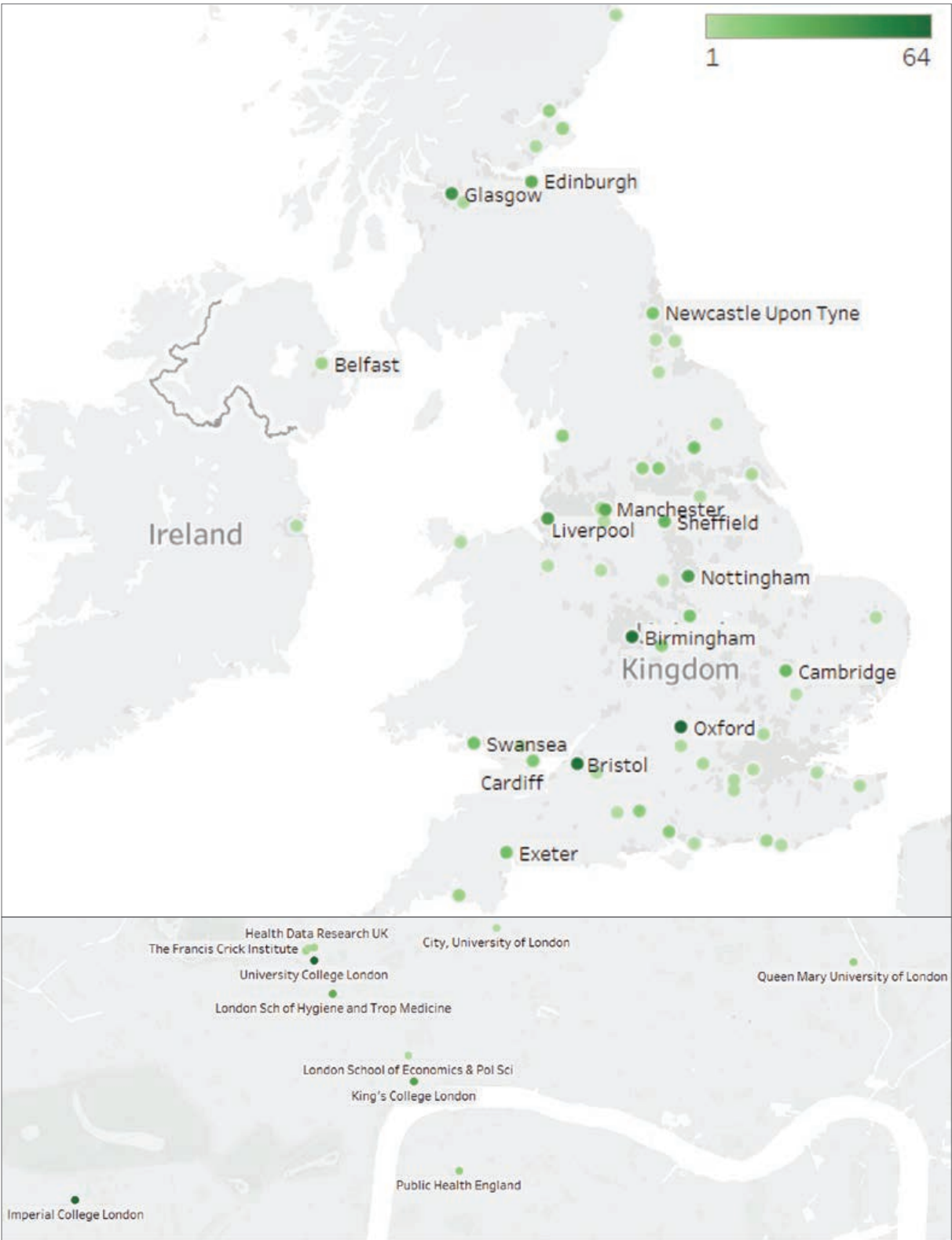
The COVID-19 platforms funded at the outset of the pandemic brought together a diverse collection of expertise stretching across the UK. Three different projects each convened researchers with a diversity of expertise from more than 15 research institutions to create interdisciplinary approaches COVID-19 epidemiology and surveillance. A third of the COVID-19 research programmes brought together five or more research organisations to address the programme objectives.

MRC and UKRI COVID-19 portfolio classification

HRCS classification

The research funding committed by MRC and UKRI to combat the COVID-19 crisis was considerably different from the usual spectrum of disease priorities before 2019.

MRC has used the Health Research Classification System (HRCS) since 2004 as a mechanism by which to compare our funding over time, nationally and internationally. The most recent nationwide assessment using HRCS criteria was in 2018 the UK Health Research Analysis 2018 (UKHRA2018). The HRCS Research Activities provide an indicator of the type of research being conducted. As data from the UKHRA series has indicated, the proportion of funding for translational research expenditure remains focused on basic science (64% of total spend in 2018) despite a slow increase seen since 2004. Instead, the COVID-19 awards were more focused on translational areas of research, particularly in Disease Management and Health Services where considerably more funding was allocated than a typical MRC portfolio. Aetiology spending was similar to 2018 and the spend on Underpinning was far lower[37]. This is indicative not just of the increased emphasis in funding on research with rapid impacts, but also that those early impacts are more likely to be seen in areas of policy and health systems.

Distribution by HRCS Research Activity as proportion of total spend for calendar year 2018 and the COVID-19 award portfolio


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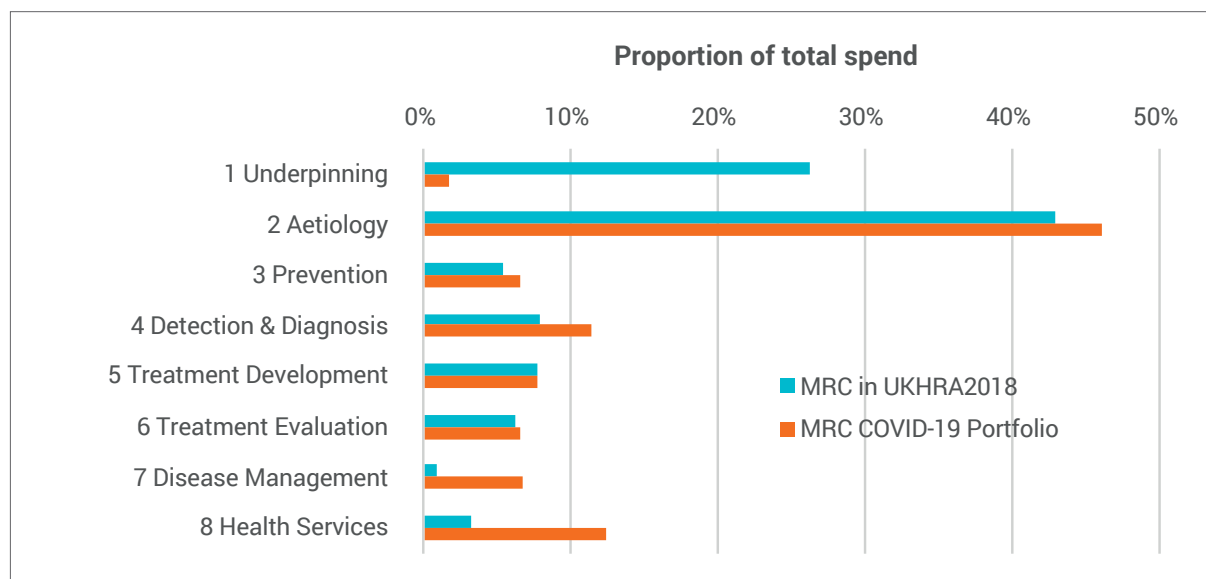
37. Again, HRCS methodology may play a factor here. Aetiology - research into the cause, risk or development of disease – is used for all fundamental basic research on infectious diseases, whereas Underpinning is only applied to the study of normal/healthy functions which, by definition, a pathogen-derived condition is not.

The proportion of MRC spending by health category on Infection was 75.5% in the MRC COVID-19 portfolio as compared to the 2018 level of 16%[38]. A full comparison of Health Classification is found in ANNEX 4.3.

MRC and UKRI COVID-19 portfolio classification by WHO priority research areas

The classification against WHO priority research areas (see ANNEX 4.4) is conducted by the UKCDR as part of their efforts to create a COVID-19 Research Project Tracker of COVID-19-related awards. This added value to centralise classification has significant potential for analysing 'who is funding what and where' over the course of the pandemic, albeit with some caveats around data availability and levels of funding[39].

The distribution of MRC and UKRI spending across WHO priority research areas is focused on the SARS-CoV-2 virus and transmission (33%), candidate therapeutics (19%) and clinical characterisation (12%). The remainder of UKRI has a strong focus on social science (32%), virus transmission (18%) and infection prevention and control (15%). Across all other international funders in the UKCDR tracker there was a greater focus on clinical characterisation (31%), virus transmission (18%) and candidate vaccines (17%).

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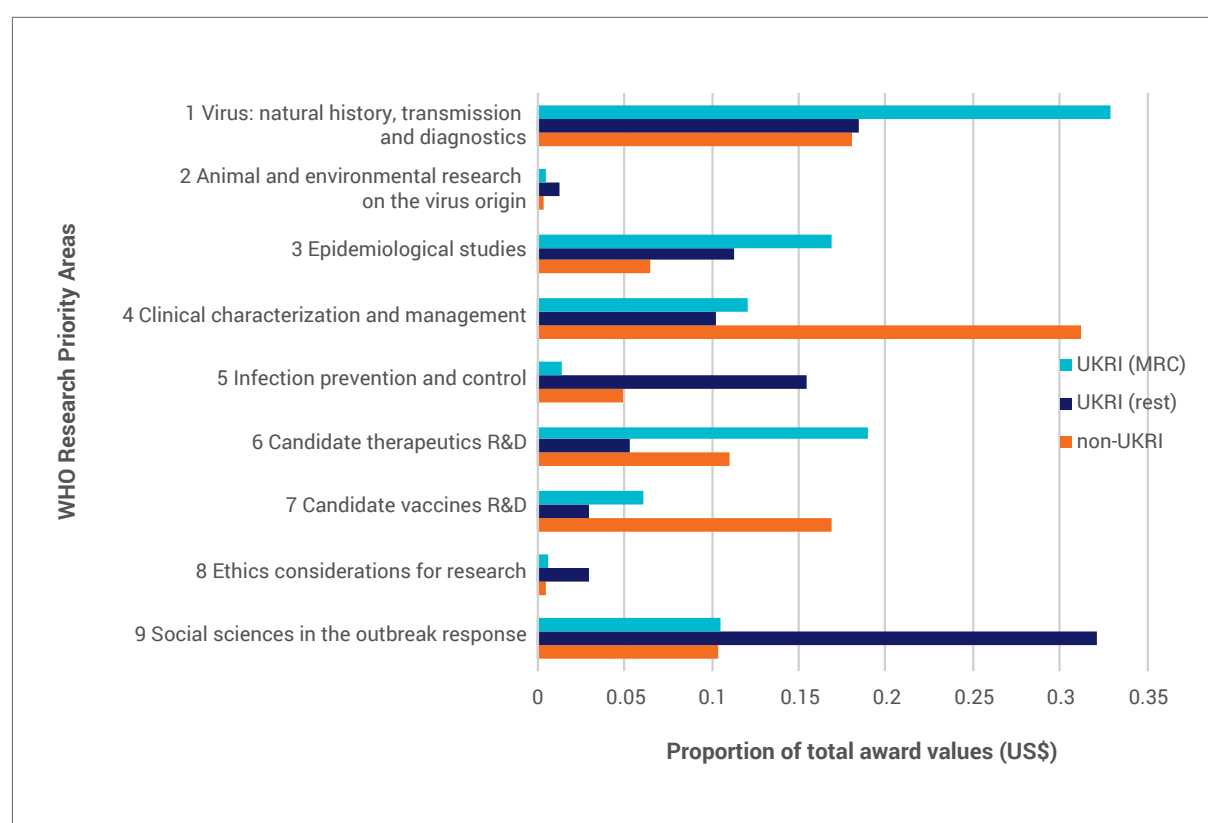
38. It may seem odd that 24% of COVID-19 spending was in other areas. The methodology of HRCS assigns equal weighting to awards with more than one Health Category, so although all awards in the portfolio were classified as 'Infection' additional codes for 11 (or a possible 20) further Health Categories were also applied.

39. The UKCDR source their data on MRC awards via the UKRI website, so only awards formally announced publicly are included in this dataset. In addition, ~35% of UKCDR-tracked awards do not have an award value available, often because not all funders publicly announce award values. Values are compared using US Dollars as the UKCDR converts local currency to allow cross-comparisons. Weighting of classification is applied using the same methodology as HRCS; 50% for two codes, 33% for three etc

COVID-19 response from the MRC community of major investments

MRC makes long-term investments in partnerships, institutes, units, and centres which provide national centres of scientific expertise and a synergistic density of researchers within specific research areas. This community has been able to quickly apply their expertise, researching SARS-CoV2 and providing advice and resource relevant to managing the COVID-19 pandemic.

Research initiated within partnerships, institutes, units, and centres

MRC partnerships, institutes, units and centres engaged in a wide range of COVID-19 facing research activities (project details in ANNEX 5.1). Over 200 projects have been reported by MRC major investments in 2020. They have redirected their expertise and infrastructure to address a broad spectrum of pandemic issues:

Understanding virus biology and immune responses

Research projects and support for researcher carried out by other groups is contributing to the understanding of the virus structure, the genetic similarity with other infectious diseases and biological pathways of transmission and severity of the disease. For example, tightly targeted projects on resistance monitoring are being led by groups at CVR and PPU and other Units support for COVID-19 researchers through the provision of the Coronavirus toolkit.

Modelling disease outbreak and understanding transmission

Investments in platforms for research into epidemiology and modelling such as UK Biobank, MRC GIDA and MRC Biostatistics Unit have rapidly redirected their substantial infrastructure and expertise to gather and provide data and modelling analysis to support into government decision making.

Societal and psychological impacts of COVID-19

The community has responded to the increasing effects of the virus and the government restrictions both in research to describe and investigate the underlying components of the effects and in efforts to mitigate or lessen the effects on society. UK DRI and MRC CTU have been active investigating the neurological effects of the virus itself while MRC CBSU, SPHSU, and CEH are monitoring the effects on domestic and social life in the UK.

Understanding the global context

International Units, as well some UK based Units, have been supporting efforts in sub-Saharan Africa to understand, track and treat the disease in the geographical context as well as linking up with global efforts to disseminate COVID-19 public health messages and virus surveillance.

Coordinating big data

Two major investments in big data management, storage and analysis, HDR UK and CLIMB, focused their significant expertise and infrastructure to address the pandemic data needs with substantial impact. HDR UK has been instrumental in supporting the collation, interoperability and secure access to vast amounts of clinical and epidemiological data collected to bring the pandemic under control. CLIMB was established as a database for microbial genomic data in 2014. With enhanced support it has provided the data support for COG UK, enabling the most comprehensive virus monitoring and tracking in the world. The MRC Biostatistics Unit has teamed up with Universities and NHS trusts to employ the real time clinical database, DECOVID, to improve patient care.

Refinements to diagnostic testing and vaccine delivery

Programmes have been launched to create and refine methodology for virus diagnostic and detection systems in both Institutes and Units.

The rapid response of the community was marked in both the University based researchers as seen in the applications to funding calls and in the researchers based in MRC major investments with 95 projects underway or in planning by April 2020. By August 2020, 194 projects were reported in progress (49 (20%) in planning) and 203 research active projects reported (69 (24%) in planning) in December. At least 68 of these projects have attracted additional funding for their COVID-19 work or are co-investigators on larger programme awards.

MRC-supported community response: other support activities

While not all MRC investments have the specific expertise for virology or public health emergencies, they are still skilled researchers with a variety of other methods to contribute.

At least 30 of the 47 institutes, units and centres undertook non-research supportive activities at the onset of the pandemic. Clinical staff were re-deployed to the COVID-19 front lines within the NHS, while non-clinical staff volunteered to help establish the first lighthouse labs. Several of these newly established testing centres also benefitted from qPCR machines and other equipment and consumables loaned/donated from MRC-funded research centres. Meanwhile others began distributing their stocks of PPE (personal protective equipment) to local hospitals.

Several investments contributed to diagnostic testing, either to help local capacity or to enhance capacity or methodologies.

■ The **UK Dementia Research Institute** at Imperial College established a Pillar 2 Lighthouse Lab contracted to deliver 3,500 tests a day for DHSC; they have completed more than 16,000 tests to date. This effort includes refining methodologies for low-cost, high throughput testing such as trialling sample pooling and software for the robotic platforms used.

■ Nick Gilbert at the **MRC Human Genetics Unit** developing a new serology test, "First generation tests use linear peptides as antigens. We have developed a new-generation of serology test, using 3D protein modelling and high-throughput production of glycosylated modified immunogenic SARS-CoV-2 antigens to profile patients' antibody 'fingerprint'. We are using antibody fingerprints to predict infection rates, resistance to disease and effectiveness of vaccines.".

■ The **MRC Unit, The Gambia at the London School of Hygiene & Tropical Medicine** and **MRC/UVRI and LSHTM Uganda Research Unit** have become a vital component for their nation's diagnostic testing and public health data analysis.

■ A postdoc at **London Institute for Medical Sciences** (LMS) volunteered with OpenCell, a company specialising in converting shipping containers into biolaboratories, to help create mobile COVID-19 emergency testing labs. The postdoc's expertise with LMS' Opentrons OT2 robot was used to help set up OpenCell's own equipment and LMS also loaned their OT2 to other OpenCell collaborators.

Other investments formed collaborations to provide DNA clones, proteins, and antibodies to aid research on viral structure or as reagents for developing diagnostic testing. There are many individual examples of researcher-driven altruism as well as the more coordinated efforts, including the COVID-19 Protein Portal and **Coronavirus Toolkit** whose impact are described in more detail in ANNEX 2.2.

Beyond these volunteering efforts or re-distribution of laboratory expertise, researchers have put their other skills to good use, both as science communicators to the general public and as subject-specific experts to policymakers. Advisory roles range from local authorities to devolved administrations to Parliamentary Select Committees to SAGE.

To assist in providing accessible health data to everyone, a member of the MRC Epidemiology Unit's Global Diet and Activity Research (GDAR) Network has led an Engage Africa Foundation project to translate information on preventing the transmission of COVID-19 into 19 languages spoken across Africa. The 'Found in Translation' resources are freely available for download and are now being disseminated through community networks and international organisations across Africa.

Knowledge platforms — prior investments and research themes

Previous work funded by UKRI research councils have informed many aspects of MRC's COVID-19 response. This previous funding includes both researcher-led programme funding and strategic investments into areas identified as key priorities over the past several decades. The foresight of these funding decisions has been made evident by the rapid mobilization and impact of the UK's scientific community in targeting COVID-19. This has been possible because of the strength of these existing knowledge platforms, as a result the starting point for the current research was considerably advanced.

These knowledge platforms have been vital at key stages of the pandemic:

Epidemiology

MRC's historical investment into epidemiology (ANNEX 6.1), particularly disease modelling was instrumental in developing the methodology that was used to provide information to government advisory committees and influenced policy at the start of the pandemic and continues to do so as restrictions are gradually eased. Large-scale population cohorts, also funded through epidemiology investments provide the established infrastructure that is invaluable for revealing 'before' and 'after' pictures of the pandemic, helping to answer questions on COVID-19 and the long-term consequences — on health, wellbeing, human behaviour and socioeconomic factors.

Structural biology

Decades-long investment into structural biology (ANNEX 6.2) has helped develop techniques needed to image biological molecules at atomic resolution, and nurture world-leading expertise in this field, allowing scientists to quickly determine the structure of the SARS-CoV-2 virus and the structural changes arising from the steadily evolving variants.

Tracking pathogen development

Strategic investment into tackling AMR (antimicrobial resistance) and infectious/zoonotic diseases (details in ANNEX 6.3), refined through overseeing the research responses to outbreaks of Ebola in 2014 and Zika virus in 2016, helped establish the rapid response funding model. This was key to effectively mobilising the UK's research response to COVID-19 over an incredibly short timescale.

Clinical trial methodology

Refinement of trial methodology — now embedded into the UK's clinical trials landscape — and optimising patient recruitment (ANNEX 6.4) has allowed the speedy evaluation of treatments for COVID-19, with impact on clinical practice through identifying life-saving therapies.

Vaccine development

Key advances from several decades of investment into genetic technology and immunology research has formed extensive networks of expertise and a strong knowledgebase in vaccine development (ANNEX 6.5) for infectious diseases. Work to develop a vaccine for a related coronavirus (i.e. Middle East Respiratory Syndrome or MERS) had been funded in 2012 as a follow-up to MRC funded research first directed at developing a broadly useful influenza vaccine and this research was at an advanced stage when the SARS-CoV-2 pandemic struck in December 2019.

Health data science

The UK's health data science capability has been supported through the establishment of HDR UK Institute in 2017, which has been vital for coordinating and connecting research efforts related to COVID-19. The UK's data science expertise has been instrumental in establishing coordinated international platforms to enable researchers to access global data and inform effective and appropriate measures to prevent and control the spread of SARS-CoV-2 and the management of COVID-19 and its consequences.

Infrastructure

Sustained investment into infrastructure capabilities have provided researchers with advanced equipment, facilities, and technologies that underpin the UK's world-leading reputation for research and innovation. These include high-resolution microscopy capabilities through the establishment of cryo-EM networks that have been vital for virus research, novel MRI techniques such as hyperpolarised MRI that can monitor lung damage in COVID-19 patients and large-scale vaccine manufacturing capability.

Pathogen surveillance

MRC founded pathogen surveillance networks and genomic sequencing capabilities, supported through sustained investment over the past two decades, have helped identify the emergence of new variants of the virus and monitor their spread within the community, the UK, and the world.

COVID–19 response implications for MRC resources

As a core component of the UK knowledge and research resource for health and more particularly for immunology, MRC and its community had a responsibility to be part of the first wave of response to the COVID-19 threat. The sudden appearance and rapid transmission of the virus required an equally rapid response to increase knowledge about the virus, the control of transmission and the treatment and prevention. The growing recognition of the gravity of the COVID-19 crisis in early 2020 highlighted the need for an immediate roll out of research in a variety of disciplines and a plan to bring together the relevant expertise from across the UK Biomedical community. While the rationale was clear and compelling, the implementation of the streamlining of the granting process combined with the doubling of the application workload within 2020 have had implications for staff resources, procedural rigour, and data management.

UKRI and the UK research community have put in place a wide variety of research activities to address the pandemic in 2020. Over the year, UKRI-led COVID-19 facing funding calls would attract c.3000 applications designated as MRC's remit. MRC's initial research funding for multiple areas of COVID-19 science was organised, launched, and awarded between the end of January and mid-March. These first two calls attracted 270 applications which required internal and external review and processing within a month's time. For context, all four MRC Boards would process ~900 applications over the course of a year. These first two calls were rapidly followed by a rolling call which attracted a further 700 applications which were assessed by 18 funding panels convened between April and July. This rolling funding process had never previously been used by MRC. MRC also attracted a very large proportion of the applications received by the UKRI Rapid Response Rolling and Agile calls (25% initially allocated pruned to 8% for review); to cope with this influx, 800 applications were considered by MRC staff and six funding panels were convened within seven weeks. The staff involved commented that the Matrix working could not be applied because there were insufficient experienced staff to provide consistency. This placed all the burden on a very small number of colleagues.

The demands of managing the COVID-19 initiatives happened in parallel with the business-as-usual demands. The usual processes of funding non-COVID research and managing MRC investments was continued through 2020 to minimise the damage to ongoing research activity, to protect the careers of researchers and to reassure our research communities. Despite the large volume of additional COVID-19 research applications, the 20/21 volume of applications received to MRC Boards was similar[40] to that of the previous year (see table below). These too required management by MRC staff.

FY (Call Closing Date)	All Applications	IIB	MCMB	NMHB	PSMB
2019/20	2170	201	200	256	181
2020/21	2020	215	226	282	209

One positive outcome of the COVID-19 pressure in 2020 was the establishment of virtual board and panel meetings (both COVID-19 and BAU). The rapid staging of the first semi-virtual panel in March 2020 with only 24hr notice was a triumph by MRC staff. They have continued to be broadly perceived as a success and a credit to MRC and UKRI, with staff pulling together across the entire office to deliver meetings to the same high standard. While there are limitations in virtual panel member interaction, the model will provide useful insights for the convening of post-COVID panel meetings.

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40. All applications considered by MRC research boards and panels in 2019/20 totalled 2197 and totalled 2137 in 2020/21. The table above reports applications received for review.

The demand for rapid funding resulted in a streamlining of the funding process. This included an abbreviated application, a manual application process (not using Je-S or Siebel) as well as modifications in the review process. Initially, this was perceived by some to be effective 'bureaucracy busting' however the complications arising from this truncated process have become apparent over time. Using an offline, shorter application process resulted in sharply increased demands on the data and finance staff to capture award and application data. Approximately an FTE of additional resource was required to manually keep track of and coordinate COVID-19 facing funding across the administrative processes. Centrally gathering information on the who, what and how of our funding process is now proving impossible for many aspects of the COVID-19 response. The minimal funding data gathered in the streamline process has limited our ability to understand the characteristics of our portfolio as well as to produce the required reporting e.g. EDI data. The most severe effects resulted from the absence of unique identifiers for the applicants. Additionally, the rudimentary abstracts and inadequate Case for Support resulted in increased demand on staff resources to iterate with applicants to ask for further information. The rapidly produced, shorter application may not have allowed sufficient consideration of time needed to complete the project objectives; to date, 20% of the earliest awards have applied for extensions. However, the continuing request for extensions may also reflect the real-world challenges of carrying out robust research during a pandemic. The extensions also place additional burden on staff to consider the applications and on researchers to revise their projects to fit the time allowed.

In retrospect, the abbreviated applications may have been appropriate for the initial call when almost nothing was known about the virus and any advance on our understanding was valuable, but this period was brief. The strong virus and immunology research base in the UK rapidly provided a great deal of information applicable to the COVID-19 pandemic. Our understanding of what existing tools and methodologies might be brought to bear on the current pandemic became apparent within weeks of the outbreak. The fast-changing COVID-19 research landscape required larger and/or more tightly focused projects as knowledge increased. The limited the amount of information applicants could provide on the shorter applications became insufficient for panels to make a robust assessment. The small percentage of fundable applications, those deemed suitable for panel assessment and receiving a panel score of seven or greater may have been a result of the abbreviated application process.

Looking at the data from the UKRI-NIHR COVID-19 Rapid Response initiative, Panel meeting notes and data show that initially the weekly (on average) panel meetings were carried out effectively and with significant enthusiasm and good will. Over time the application numbers increased and both administrative, reviewer and panel fatigue began to appear. As the months went by, the number of applications for which three reviews could be obtained decreased. The application success rate for this initiative was 8%. The chart below indicates the increasing burden and challenge in processing and reviewing the applications.
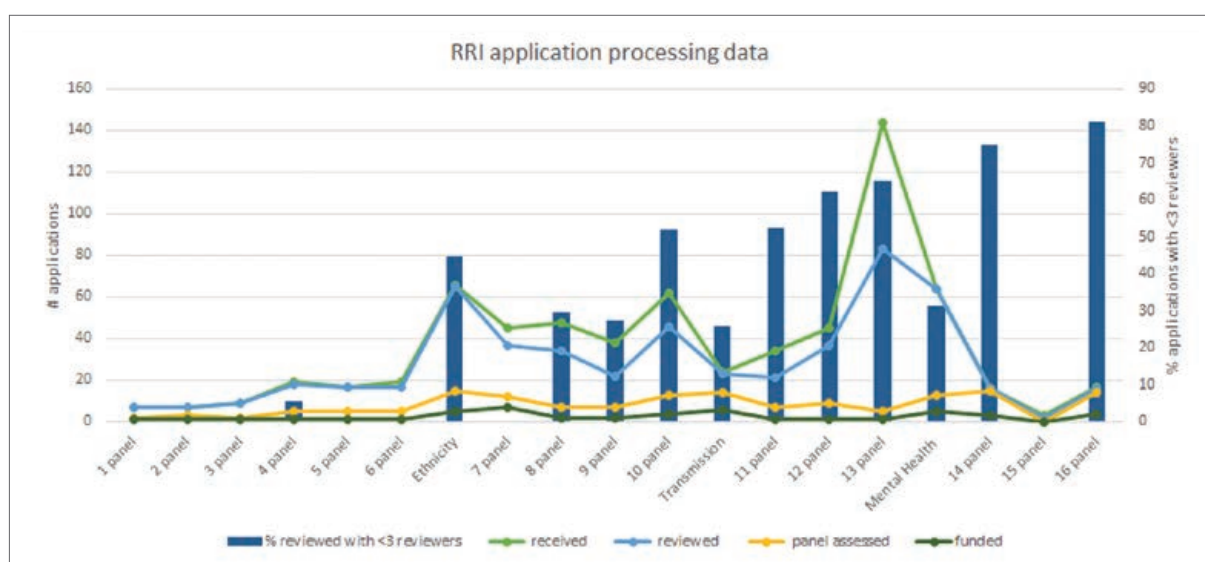
A recent assessment of peer review for MRC business-as-usual funding indicates that although there were areas where obtaining reviews was problematic these were dealt with by board staff. The established system for applications processed through Seibel and the standard processes were flexible enough to cope with scarcity of expert viewers in specific disciplines or research areas, although not without extra effort.

MRC's Management Board Paper dated 28 July 2020, M*RC's COVID-19 Response: Lessons Learnt* by Rebecca Barlow provided an excellent review of the cost and benefits of the early MRC response. I have restated many of the points she raised in this summary of implications.

MRC is seen to be light on resource as compared to many other Councils within UKRI. While MRC is an efficient organisation, its leaner structures and siloed working do not make for resilient teams as there is limited latitude to absorb additional work. The July 2020 report stated, *"There was a consensus that staff are accepting of taking on increased workloads and working longer hours to deliver high-priority projects, and the initial rapid response call was flagged as a good example of this this kind of working. However, it was noted that the lack of resource in the Infections and Immunity Board (IIB) team had been flagged before the launch of the rapid response call in February"*. The report highlighted the increasing staff fatigue in early 2020; efforts were made to increase staffing levels in Autumn 2020 with limited success. With the ongoing rollout of funding schemes, the heavy burden on staff resources at all levels continued throughout 2020. For example, the predictable increase in applications in response to the announcement of closure of the UKRI Agile call in December again resulted in staff working longer hours to ensure applications could be reviewed and assessed before the end of the financial year.

Such a precipitous change in the demands on staff time, unsurprisingly, resulted in communication gaps within MRC and with UKRI Central. Within MRC, there was a significant delay in understanding and substantively addressing the developing staff resourcing issues, in sharing information across the various workstreams, and in co-ordinating efforts to work effectively with UKRI central. With the focus on the primary task of reviewing and funding applications, communication between the differing areas of responsibility was neglected resulting in the loss of established efficient MRC process. The simultaneous launch of the UKRI-NIHR Rolling Call and the distinct UKRI Rolling call in early April caused substantial confusion for applicants resulting in additional work for researchers, UKRI staff and RO staff. Given that much of the COVID-19 research fell within MRC's remit, it was necessary to keep the biomedical research community informed of the research undertaken and research progress to reduce duplication and promote productive collaboration. The volume of this information overwhelmed the UKRI Comms and web content capacity. Options such as a blog posts and making use of the external comms channels of Units and Institutes were not explored in depth until May. It was suggested that secondments of the Central team to Councils could be a way to share best-practise and cultivate a better working relationship with the Central team. However, developing a working strategy to resolve the issues of external communication took many months and the issue is yet to be fully resolved.

Lessons learned: Impediments to research progress during the first year of the COVID-19 pandemic

Surveying the researchers over 2020 has highlighted a variety of impediments to research progress during the pandemic. Their comments are listed in ANNEX 8.1 and are summarised below.

Access to materials or equipment or other resources

Extremely successful efforts were made to provide access to key reagents and COVID-19 research materials from the outset of the pandemic through the Protein Portal and other networks. However, some projects were significantly delayed. Additionally, the demand on PPE for clinical staff resulted in limited availability for research staff. In addition, laboratory capacity was significantly reduced due to lockdowns or limitations on occupancy in both academic and clinical laboratories, which slowed research progress for some projects.

Co-ordination

Again, there have been many examples of successful coordinated working across disciplines and sectors in 2020: e.g. in improved efficiency in vaccine manufacture, in COVID-19 surveillance (COG-UK), in efficient implementation of the RECOVERY trial. However, there were many areas of communication in both research knowledge and national health and care strategies which could have been improved. Patient distribution for recruitment into the myriad of trials and clinical studies that were launched in early 2020 became bogged down and eventually broke down as the year progressed.

Funding

The extent of the knowledge gap at the onset of the pandemic meant that there were far more potentially vital avenues of investigation than there was funding available.

Staff well-being

In many areas of COVID-19 facing work, the demand on staff was extreme. Many researchers noted the extended periods of increased workloads leading to staff burn out. Additionally, the clinical demands on clinical staff allowed little time for coordinating with clinically based studies.

Bureaucracy

Delays resulting from access to patient data or the delay resulting from gaining patient consent were identified by some researchers as a major impediment. Clearly some projects found efficient mechanisms to deal with these impediments and there may be an opportunity to codify and share best practice going forward. Several projects were funded to make patient data more accessible, and these have made progress on this front over the year.

Annexes

Note some materials have been extracted directly from award data, Researchfish® and other documents.

For Section 2

ANNEX 2.1 Details of impacts resulting from COVID-19 targeted clinical trials and vaccines

- Clinical Trials
- Demonstrating effective treatments (and identifying ineffective treatments)
- Establishment of a national platform for clinical trials
- Vaccine for the world

ANNEX 2.2 Details of project impacts

- PREVENT – which encompasses modelling transmission and vaccine development
- DIAGNOSE – developments in testing and diagnostics
- TREAT – new treatments for COVID-19 and the progression of clinical trials
- UNDERSTAND – key breakthroughs on virus structure and the pathophysiology of COVID-19

ANNEX 2.3 Support provided for 'live' awards

For Section 4

ANNEX 4.1 Details of COVID-19 facing funding initiatives

- MRC supported research calls:
  - UKRI-NIHR COVID-19 Rapid Response Initiative (RRI) (February 2020)
    - Platforms: development of vaccines and treatment
    - Clinical studies and epidemiological surveillance and analysis
  - UKRI COVID-19 Rapid Response Rolling call (RRR) (March 2020)
  - EDCTP COVID-19 Response call (April 2020)
  - UKRI COVID-19 Agile call (Agile) (August 2020)
  - UKRI GCRF/Newton Agile Response call (May 2020)
  - Global Effort on COVID-19 Health Research COVID-19 (GECO) (May 2020)
  - UK-India COVID-19 partnership initiative (October 2020)
  - NIHR-UKRI Long-term COVID-19 effects in non-hospitalised individuals (Long COVID) (December 2020)

- Individual initiatives:
  - COG-UK
  - GenOMMIC study of COVID-19
  - Protein Portal
- International coordination
- National Core Studies

ANNEX 4.2 COVID award funding process
- UKRI-NIHR COVID-19 Rapid Response Initiative (RRI) (February 2020)
  - UKRI-NIHR COVID-19 Rapid Response Call 1 and Call 2 (Feb 2020)
  - UKRI-NIHR COVID-19 Rapid Response Rolling Call (April 2020)
- UKRI COVID-19 Rapid Response Rolling call (RRR) (March 2020)
- EDCTP COVID-19 Response call (April 2020)
- UKRI GCRF/Newton Agile Response call (May 2020)
- Global Effort on COVID-19 Health Research COVID-19 (GECO) (May 2020)
- UKRI COVID-19 Agile call (Agile) (August 2020)
- UK-India COVID-19 partnership initiative (October 2020)
- NIHR-UKRI Long-term COVID-19 effects in non-hospitalised individuals (Long COVID) (December 2020)

ANNEX 4.3 COVID-19 research portfolio analysis
- Classification of the total MRC COVID-19 award portfolio – by HRCS Health Category and Research Activity

ANNEX 4.4 WHO Research Priorities

For Section 5

ANNEX 5.1 MRC community COVID-19 response programme and project details
- Understanding virus biology and immune responses
- Modelling disease outbreak and understanding transmission
- Societal and psychological impacts of COVID-19
- Understanding the global context
- Coordinating big data
- Refinements to diagnostic testing and vaccine delivery

ANNEX 5.2 Survey methodology for pandemic activities: MRC partnerships/institutes/units/centres.

For Section 6

For Section 8

Annex 2.1

Details of impacts resulting from COVID-19 targeted clinical trials and vaccines

This annex consists of four segments:

■ Clinical Trials

■ Demonstrating effective treatments (and identifying ineffective treatments)

■ Establishment of a national platform for clinical trials

■ Vaccine for the world

Clinical trials

Over the last decade, the UK and other countries, have been involved in developing a strategic approach to planning for and responding to a global pandemic. The approach is multi-faceted and includes a register of hospitalised patients (Clinical Research Network, CRN) developed through international consultation with organisations such as ISARIC. These plans were taken advantage of during the COVID-19 pandemic, and the NIHR CRN register helped to facilitate the gamut of clinical trials that were subsequently launched. During the early months of the COVID-19 pandemic, the therapeutics development pipeline focused on repurposing existing drugs, to rapidly identify effective treatments for patients. Notable successes include the identification of dexamethasone which was shown to reduce mortality by a third in patients hospitalized with severe COVID-19, and remdesivir which shortens the recovery time in hospitalized patients.

MRC-funded research has enabled the development of many of these advancements, ranging from the methodology used for the adaptive clinical trials to the networks and organisations that coordinate clinical research across the world (for details, see ANNEX 6.4).

Demonstrating effective treatments

UKRI, with DHSC, have funded clinical trials that identified three drugs being used to treat COVID-19 patients. These were the first drugs proven effective against COVID-19 during the first year of the pandemic and have thousands of lives world-wide.

The **RECOVERY** trial platform ('Randomised Evaluation of COVid-19 thERapY'), launched in February of 2020, was the fastest growing trial in medical history, enrolling 1,000 patients at 132 hospitals within its first 15 days. Results from RECOVERY showed that dexamethasone reduces deaths in COVID-19 patients with severe respiratory complications by a third. A recent study estimated that the potential number of lives saved between July and December 2020 from this intervention would be 12,000 in the UK and approximately 650,000 lives globally. Another RECOVERY trial arm demonstrated that the anti-inflammatory treatment Tocilizumab reduces the risk of death when given to hospitalised patients with severe COVID-19, shortens the time until patients are successfully discharged from hospital, and reduces the need for a mechanical ventilator.

ACTT-EU/UK (Adaptive COVID-19 Treatment Trial) launched at the start of April 2020 was an international randomised trial to evaluate the safety and efficacy of the anti-viral drug remdesivir, as a treatment for COVID-19. ACTT-EU/UK has recruited more than 1000 patients globally, with the MRC/UCL Clinical Trials Unit coordinating the trial in the UK and Greece. Preliminary results just a month after the trial launch showed that the speed of recovery for hospitalised COVID-19 patients treated with the drug was 31% faster than for those patients who had the placebo. These results were instrumental for the EMA in authorising remdesivir for use in patients with COVID-19.

Identifying ineffective treatments

Clinical trials funded by UKRI/DHSC have also been instrumental in the rapid identification of treatments that are ineffective for COVID-19, allowing clinicians to focus on treatments that do work. RECOVERY demonstrated that there is no clinical benefit from hydroxychloroquine or lopinavir-ritonavir in hospitalised patients with COVID-19. In early January 2021, RECOVERY showed that there is no clinical benefit to convalescent plasma treatment for patients hospitalised with COVID-19. The **PRINCIPLE** (Platform Randomised trial of Interventions against Covid-19 In older peoPLE) trial investigates treatments outside of hospital, stopping people's symptoms from worsening at an earlier stage of the disease. The PRINCIPLE trial has so far determined that the antibiotics azithromycin and doxycycline are not effective treatments during the early stages of Covid-19. The trial continues to investigate budesonide, an inhaled corticosteroid, in people aged over 50.

## Establishment of a national platform for clinical trials

Since March 2020 there has been a gamut of clinical trials for identifying effective treatments for COVID-19. By summer 2020 it was clear that a coordinated approach for developing a treatment portfolio for tackling all stages of COVID-19 was needed. Establishment of a development pipeline for feeding novel candidate treatments into clinical trials was necessary to promote discovery of more effective treatments for COVID-19.

ACCORD (Accelerating COVID-19 Research & Development), a Phase II clinical trial platform with the aim of fast-tracking research into potential COVID-19 treatments, was launched in April 2020. ACCORD was designed to reduce the time taken to set up clinical studies and enable multiple new therapies to be tested in parallel. If positive results were seen, these drugs would then advance rapidly into the large-scale trials in progress across the country. Initially ACCORD had four arms, which were comparing potential new treatments against NHS standard of care. By May 2020, the data science company IQVIA joined ACCORD to establish a single research platform across the UK to facilitate multiple clinical trials regardless of sponsor.

COVID-19 Therapeutics Advisory Panel (UK-CTAP)

As 2020 progressed, limitations in the ACCORD platform were identified; the arising competition for sites nationally was inefficient and there was no consistent, transparent, or strategic mechanism by which treatments would be allocated to trials. Rapid recognition of these limitations led to the suspension of ACCORD and informed the establishment of an independent COVID-19 Therapeutics Advisory Panel (UK-CTAP) over the summer of 2020. UK-CTAP is chaired by Professor Patrick Chinnery, and MRC provide secretariat services: programme management, and scientific due diligence to the independent panel. All candidate treatments nominated to be tested through publicly funded trials in the UK are assessed through UK-CTAP. This ensures a consistent, transparent, and integrated process of independent assessment for proposed COVID-19 therapeutic candidates. UK-CTAP then advises the Therapeutics Taskforce, responsible for the end-to-end provision of treatments from trials to delivery of treatments at scale to the patient population. The final decision on which treatments will be included in these trials will lie with the Chief Investigators (who have ultimate responsibility for the delivery of the trials) and the Chief Medical Officer (Professor Chris Whitty). By having a single point of entry and a single point of recommendation, the process allows the panel of experts to identify both the suitable candidates and to target them to the appropriate stage of the trials pipeline. The UK-CTAP platform ensures minimal duplication of effort across the UK clinical trials landscape.

UK-CTAP process for candidate treatments[41]
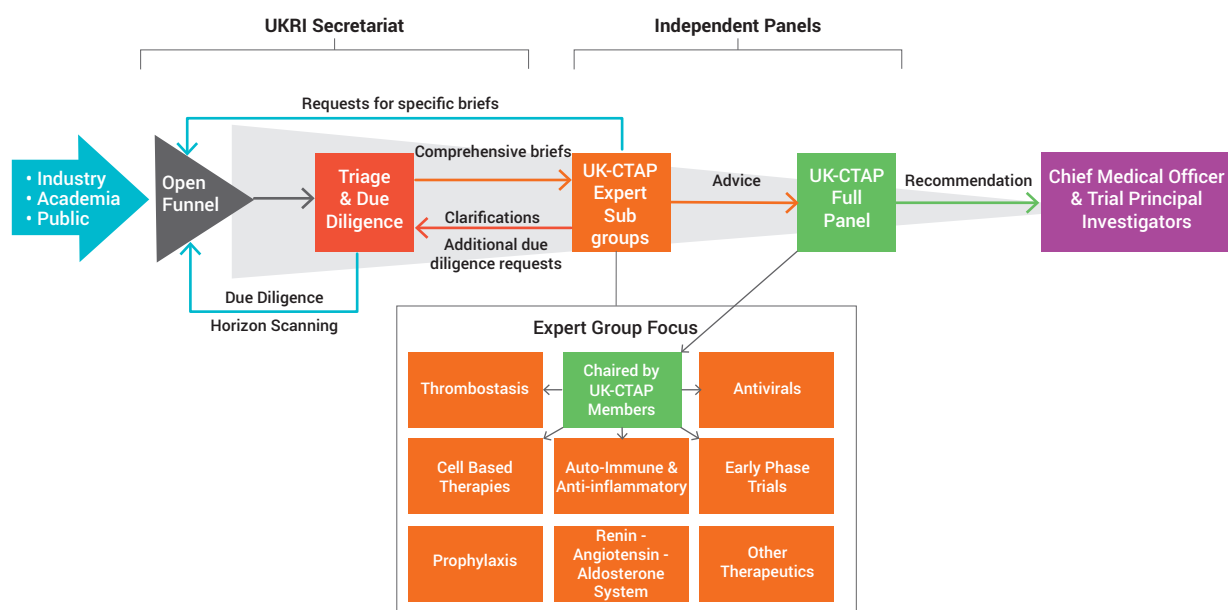
Seven main clinical trials are being supported to test Phase II and III COVID-19 therapeutic and prophylaxis candidates. These are:

■ **REMAP-CAP.** Established prior to the outbreak of COVID-19, REMAP-CAP is an international clinical trial testing a range of supportive care and specific interventions in patients admitted to ICU with severe community acquired pneumonia (CAP). A new arm specifically for COVID-19 was added to the trial and is currently testing potential COVID-19 treatments in critically ill patients in hospital settings, including in intensive care units.

■ **RECOVERY+:** RECOVERY+ is testing potential COVID-19 treatments in hospital settings in patients with moderate to severe COVID-19. This is an expanded platform following the success of RECOVERY, which will operate for the next 24 months and will include new treatments tested in Phase II and Phase III studies which will now be delivered through the RECOVERY+ platform in patients admitted to hospital. Colchicine, Regeneron's antibody cocktail, Aspirin, and the rheumatoid arthritis drug Baricitnib are currently being trialed for effectiveness. MRC committed £9m/ NIHR £9m.

■ **PRINCIPLE:** PRINCIPLE is testing potential COVID-19 treatments in the community in patients with mild and moderate COVID-19 who are aged over 65; or aged 50 to 64 with an underlying health condition.

■ **AGILE:** AGILE is a Phase I/II1 trial that tests the safety and efficacy of promising therapeutics for further evaluation in a Phase II/III trial. It bridges the gap between non-human trials and large-scale testing, so potential new treatments can go through the important testing stages in a matter of months rather than years, while maintaining a high level of safety at all times.

■ **PROTECT CH:** A community trial designed for testing treatments for post exposure prophylaxis in care homes

■ **PROTECT V:** A community trial for identifying treatments for post exposure prophylaxis in vulnerable immunocompromised patients.

■ **HEAL:** A community trial for identifying treatments for patients discharged from hospital and suffering from Long COVID.

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41. Figure provided by UK-CTAP

UK-CTAP treatments in UK publicly funded trials[42]

PHASE I & IIa Safety in healthy individuals	PHASE IIb Efficacy and safety in COVID-19 patients	PHASE III Efficacy in large numbers (1000s) of target patients			LONG COVID	PROPHYLAXIS	
AGILE	RECOVERY+	PRINCIPLE	RECOVERY	REMAP-CAP	HEAL	PROTECT V	PROTECT CH
Hospital/ Community

Currently trialling: EIDD-2801 VIR-7831 and VIR-7832 Niclosamide | Hospital

Currently trialling: Dimethyl Fumarate | Community

Currently trialling: Inhaled Budesonide Colchicine

Scheduled to trial: Favipiravir Adalimumab | Hospital

Currently trialling: Neutralising antibodies (REGN10933 + REGN10987) Aspirin Colchicine Baricitinib Methylprednisolone* Immunoglobin* Hydrocortisone* Anakinra* *Paediatric use only

Scheduled to trial: Namilumab Infliximab | ICU

Currently trialling: Lopinavir/ritonavir Interferon-beta Anakinra Simvastatin Anti-platelet arm (aspirin, clopidogrel, prasugrel and ticagrelor)

Scheduled to trial: Namilumab Infliximab | Community

Patients post-discharge for COVID-19

Scheduled to trial: Atorvastatin Apixiban | Community

Pre-exposure in vulnerable immuno-compromised patients

Scheduled to trial: Ciclesonide Niclosamide | Community

Post-exposure prophylaxis in care homes

Scheduled to trial: Ciclesonide Niclosamide |

Such work will continue to be critically important as new variants emerge and as we learn more about patient populations who may be unable to generate a full response to the vaccine who will be in need of effective therapeutics.

ISARIC Platform

The pandemic preparedness plans underpinning the UK rapid response to COVI-19 was developed over the last decade in part by the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC). It was funded in 2011 by MRC, Institut National de ma Santé et de la Recherche Médicale (INSERM), the Bill and Melinda Gates Foundation, and Wellcome Trust. Developing into a global federation of 55 research networks spanning 111 countries. These networks work to a) generate the evidence necessary for improving clinical care and public health responses to infectious disease epidemics and b) support the development and evaluation of new diagnostics, treatments, and vaccines. Since its inception, ISARIC has worked closely with WHO, responding to MERS-CoV, avian influenza A/H7N9, Ebola virus, and Zika virus. ISARIC has helped standardise protocols for the rapid coordinated clinical investigation of acute respiratory pathogens of public health interest around the world, to ensure that patients with a spectrum of emerging and unknown pathogens will be enrolled in clinical trials. Arising from preparedness planning, the NIHR Clinical Research Network (CRN) supports patients, the public and health and care organisations across England to participate in high-quality research by providing the Study Support Service, which helps researchers and industry plan, set up and deliver high-quality research. This process ensures that national platform clinical trials testing Phase 1, 2 and 3 COVID-19 therapeutic candidates have access to COVID-19 patients. This infrastructure for providing open access to clinical data and samples from COVID-19 patients was instrumental in facilitating recruitment at unprecedented speed for clinical trials such as RECOVERY and hospital studies such as the ISARIC GenOMICC (Genetics of Mortality in Critical Care) study.

42. Figure provided by Professor Patrick Chinnery, UK-CTAP

A vaccine for the world

The Oxford/AstraZeneca vaccine developed by Professor Sarah Gilbert and her team at the University of Oxford is now part of the UK COVID-19 vaccines delivery plan for the largest vaccination programme in British history. The vaccine was rapidly developed by utilising the replication-deficient chimp adenovirus platform (ChAdOx) and built on results from the previously funded Phase I trial for the related MERS coronavirus.

The vaccine can be stored, transported, and handled at normal refrigerated conditions (2°C-8°C) for at least six months and administered within existing healthcare settings. It does not contain any human or animal products, so that it can be administered without marginalising communities that may have religious or cultural objections to animal-derived vaccine components, such as traditional egg-based technology as seen with flu vaccines or pork gelatine used as a stabiliser for nasal vaccines.

The Oxford team obtained agreement from pharmaceutical partner AstraZeneca that the vaccine will be made on a not-for-profit basis so long as COVID-19 is classified as a pandemic and will remain so when sold to developing nations. In February 2021, the vaccine was granted Emergency Use Listing (EUL) by WHO which enables global access to the vaccine during the pandemic. Global vaccine manufacture and supply will be managed by AstraZeneca and the Serum Institute of India, who will work with the COVAX Facility, a global mechanism for accelerating the development, production and equitable access to new COVID-19 tools across the world for all participating countries, regardless of income level. This will allow them to begin supplying the vaccine around the world, with the majority going to low and middle-income countries as quickly as possible. In the first half of 2021, it is hoped that more than 300 million doses of the vaccine will be made available to 145 countries through COVAX, pending supply and operational challenges. These doses will be allocated equitably according to the COVAX Allocation Framework. The IMF has estimated that this year $11 trillion has been lost to the global economy due to the pandemic and could cost $28 trillion by the end of 2025. If that estimate is translated to a daily figure, the roll out of globally suitable vaccines that speeds up the end of the pandemic by even one day could cut more than $13m from the cost to the global economy.

The recently published EAVE II study showed that the vaccine is highly effective; by the fourth week after receiving the first dose, the Oxford-AstraZeneca vaccine was shown to reduce the risk of hospitalisation from COVID-19 in up to 94% of people.

Annex 2.2

Details of project impacts

The details of the impacts of specific programmes[43] have been self-provided through surveying the live programmes, surveying major investment activity, and Researchfish® data. Some impacts were gleaned from review of news stories and website information. Below are the impacts reported in 2020 during the initial phase of the programmes, grouped into broad categories based on their intent:

■ PREVENT – which encompasses modelling transmission and vaccine development

■ DIAGNOSE – developments in testing and diagnostics

■ TREAT – new treatments for COVID-19 and the progression of clinical trials

■ UNDERSTAND – key breakthroughs on virus structure and the pathophysiology of COVID-19

Note that many programmes have had impact in multiple areas.

Outputs reported in Researchfish® from 135 COVID-19 facing projects in 2020.

Publications	Policy Influence	Medical Products	Research Tool	Data Set	Software	Further funding for COVID-19 research
295	34	13	27	25	7	42 (£37.3m)

Ten researchers reported national and international awards for their COVID-19 work in 2020.

Communication with policy makers

Surveys of the RRI awards in January 2021 provided detailed descriptions of highly interactive relationships with UK policymakers in 52 of the 70 projects that had started in 2020. These included regular, monthly or weekly, reports, presentations to government committees, advisory roles on government and clinical policymaking groups and adjustments to project objectives or methodology to address specific data requests from decision makers. Communication with directors and senior staff at MRC major investments providing COVID-19 indicated similarly strong links.

PREVENT

MRC Centre for Global Infectious Disease Analysis (GIDA) led in providing government ministers, departments, and COVID-19 committees with analysis to inform policy decision. The have focused on outbreak size, severity, intervention policy and genetics. Additionally, their research has provided insight to the UK government and WHO assessing impact of interventions, health impacts, and transmission patterns. They have tailored their research focus and methodology to provide rapid, open access, real-time modelling and assessment analysis targeted at the needs of policy makers. One example was the accurate prediction of the decrease in R, 2.6 to 0.6, as result of lockdown. Oriole Global Health, a GIDA spin-out from GIDA is part of the group of organisations running the ASCEND programme – a flagship £200m FCDO NTD programme – which had a role in advising LMICs on their COVID-19 response.

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43. The earliest programmes were funded in February 2020 and all the programmes reported below began before December 2020.

Linking clinical information held within the NHS to COVID-19 test results to contact tracing information to viral sequencing analysis to demographic data is required in near-real time to allow for an effective rapid response. This massive undertaking has been spearheaded by **Health Data Research UK (HDR UK)**. Their expertise has facilitated access, via the HDR Innovation Gateway, to 120 Covid-19 datasets alongside the UK's core Trusted (or Trustworthy) Research Environments (TREs); highly secure data repositories for researchers to access sensitive data. The establishment of TREs for clinical data, particularly those for the four national health administrations of the UK, has been supported by MRC, most recently through HDR UK, over the past decade. In response to the pandemic, additional resource and expertise provided by HDR UK were instrumental in establishing the NHS Digital TRE for England, which was formally launched in November 2020. Aligned to similar TREs for Scotland, Wales and Northern Ireland, the NHS Digital TRE is led by HDR UK to provide rapid, safe and trustworthy access to data in a transparent way that accelerates the pace of quality research, playing a leading role in the UK's COVID-19 response.

HDR UK has been at the forefront of supporting the alignment and development of the UK-wide TRE network, leveraging existing technical capabilities where available and aligning these capabilities to become interoperable. HDR UK has helped steer the availability of patient and public health data within the UK as the coordinator of the UK Health Data Alliance – a collaboration of over 50 leading healthcare and research organisations – and via the UK's National Core Studies (NCS). The latter consists of six programmes, with HDR UK leading on the Data and Connectivity NCS; 180 projects that HDR UK staff and collaborators have established to answer key research questions about the pandemic. These research questions are in part generated via a communal Covid-19 activities + skills matching tool, allowing HDR UK to identify new collaborations and datasets whilst also allowing prioritisation of resources. Professor Andrew Morris, Director of HDR UK, is a member of the Data Science Advisory Group for the Joint Biosecurity Centre (JBC). The JBC was established in summer of 2020 to provide targeted, timely and actionable information to decision makers at all levels.

HDR UK has also taken the lead internationally through coordinating collaborations and cutting-edge data science. In the management of COVID-19 data, HDR UK has convened the International COVID-19 Data Research Alliance (ICODA); an international collaboration of 20 public and private partners – to create a co-ordinated international platform – the ICODA 'Workbench' – to enable researchers to access global data to drive rapid insights about COVID-19 and speed up the development of treatments. ICODA has already commenced work on two Driver Projects:

- Efficacy and safety of COVID-19 treatments – supporting pharmaceutical companies of the COVID-19 R&D Data Alliance alongside academic institutions to contribute their data into the ICODA Workbench for researchers to analyse.

- International Perinatal Outcomes in the Pandemic (iPOP) study – The iPOP Study currently involves over 100 researchers in more than 40 countries, including 22 lower- and middle- income countries (LMICs), with access to data on 2.4m births. The team working on the study includes obstetricians, neonatologists, epidemiologists, public health researchers, environmental scientists and policymakers. The study protocol is now available online via Wellcome Open Research.

To identify further data research priorities, in December 2020 ICODA launched its Grand Challenges COVID-19 Data Science initiative[44], funding awards up to $100,000 for 6–12-month studies beginning in June 2021. The initiative aims to unite data and develop processes, analytical tools and infrastructure to achieve rapid scientific progress and impact and is a pilot for the ongoing Grand Challenges that seek to develop global collaboration and innovative approaches to major health challenges.

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44. 'Grand Challenges' is a family of initiatives supported by the Bill & Melinda Gates Foundation (BMGF), which also supports ICODA itself via a grant from the COVID-19 Therapeutics Accelerator; another large-scale initiative initiated by BMGF alongside Wellcome, Mastercard with additional support from Minderoo Foundation.

MRC Biostatistics Unit has been regularly nowcasting and forecasting COVID-19 infections and deaths throughout 2020. They provide this information to SAGE through the Scientific Pandemic Influenza sub-group on Modelling (SPI-M), to the regional Public Health England teams and to WHO supporting both UK and global population health policy decisions. The Biostatistics Unit has also provided regular guidance regarding work in mathematical modelling, statistical modelling and computer science to the Joint Biosecurity Centre (JBC). The JBC was established in summer of 2020 to provide targeted, timely and actionable information to decision makers at all levels.

CV003- start date April 2020)

- developed safe effective vaccine for 18- to 50-year-olds with this funding (insufficient funding for all age groups)

- effective engagement with clinicians and policy makers and private sector (all relationships were previously existing)

- publications

CV 205: start date March 2020)

- increased efficiencies in vaccine manufacturing process

- very good links with decision-makers at all levels and directions

- publication

MRC and Glasgow University Centre for Virus Research (CVR) have a continuing programme to provide data on the spread and risk of the evolving pandemic to UK government policy makers. They have rolled out the CRUSH programme which collects and provides data from:

- Screening the antiviral activity of drugs and therapeutics (e.g. monoclonal antibodies) against SARS-CoV-2, the virus responsible for COVID-19

- Identifying and characterising the emergence of potential drug-resistant viral mutations following treatment with antiviral drugs

- Monitoring the global incidence of SARS-CoV-2 strains with potential drug-resistant mutations and making this information openly available.

The data on the emergence of potential drug-resistant variants are available through CoV-GLUE, an open-access analytical software package.

The **Francis Crick Institute** in collaboration with the UCL NHS Hospital Trust has allocate part of its building and released many of its staff to become a vaccination Centre. Vaccinating hundreds of London citizens every day. Additionally, it provides resources to process COVID-19 samples for the UCLH COVID-19 testing centre.

MRC Unit The Gambia at the London School of Hygiene & Tropical Medicine and **MRC/UVRI & LSHTM Uganda Research Unit** have coordinated with their respective governments to rolled out COVID-19 testing and vaccination programmes.

COVID-19 Genomics UK Consortium (COG-UK: start date April 2020)
Providing data on transmission and viral mutation to inform government decision-making. They have sequenced more than 350,000 Sars-CoV-2 genomes which supports the genomic epidemiology to understand transmission patterns and enable epidemiological surveillance.

They have provided:

- Informed understanding of viral transmission and introduction in care homes, hospitals, and universities
- Assessment of effectiveness of government policy on reducing transmission: lockdown and international travel
- Identification of new variants and coordinate with other researchers to identify variant of concern and their susceptibility to the vaccine programmes.

In addition to informing policy makers, the COG UK data underpins pandemic research globally. It is openly accessible, released almost as soon as it is created, and linked to rich clinical data. The workflow supported by MRC CLIMB ((MR/V020498/1 and MR/T030062/1) for COG-UK has used 123 years of compute time. Their data is heavily accessed, 5 million API requests. The comparison international picture can be seen at GSAID. In 2020, the US has only deposited 150k sequences, and the median time to deposition is just about the shortest (half that of the US).

CV0659: start date September 2020

■ Data on:

- characterising/modelling effect timing of track and trace

■ Reporting to SAGE via SPI-M

CV046: start date March 2020

■ Data on:

- lockdown behaviour and adherence
- self-isolation
- on rate of infection
- shielding strategy

■ Publications: TBC

CV194: start date April 2020

■ Data to understand and predict:

- the burden and impact of the epidemic on healthcare
- probability of severe hospital outcomes (ICU admission, death)
- Evidenced the decrease in the lengths of stay in hospital and ICU wards over the first wave of infection in March to June 2020

■ Reports on data analyses provided to PHE and the SPI-M and SAGE government advisory groups

■ Inputs to the joint PHE/MRC Biostatistics Unit (MRC-BSU)'s nowcasting and forecasting of the epidemic through transmission modelling

■ Provides nowcasting data to the Joint Biosecurity Centre

■ Data in use to understand the granularity of COVID-19 'risk'

■ Publications

COV0006: start date May 2020

■ Impact: modelling support to feed into government decision-making

■ Provided requested data for government committees

■ calculation of the effective reproduction number and growth rate by region

■ short- and medium-term forecasts that are used to inform the UK government contingency planning

■ development of models:

  – strategies for re-opening schools in June

  – optimal policies to ensure a safe return to workplaces

  – estimating a suitable spatial scale for the introduction of local lockdown policies

  – understanding the effectiveness of the "rule of six".

  – role of circuit breakers to mitigate the impact of the epidemic.

    • This circuit breaker work was considered by SAGE and similar policies were adopted by the Scottish and Welsh governments: to consider multiple circuit breakers of varying strengths and timings, to determine the optimal strategy to minimise impact, considering both direct impacts to public health of the virus, indirect health impacts of control and economic impacts of any intervention.

  – reduce the pressure on the national health service

  – time to improve test and trace effectiveness.

■ Publications: TBC

CV152: start date July 2020

■ Data on:

  – characterisation of vulnerabilities to COVID in BAME community and by socioeconomic criteria

  – BAME susceptibility and comorbidity characteristics cited in PHE guidance

■ Input to PM advisors, SAGE; publications

CV0076: start date May 2020

■ Data on:

■ COVID risk factors

  – severity indicators

  – treatment effectiveness and safety

  – ransmission models validity

■ Adjusted plans at request of CSO and NHS England

■ fed through insights to CSO and NHS England and central policymakers

■ publications

CV091: start date April 2020)

■ Data on:

  – vaccine monitoring

    • Showed the first 'real world' evidence of a substantial reduction in the risk of Covid-19 admissions to hospitals following vaccination through linking vaccination records with subsequent health records for the Scottish population. The study makes use of data that are already collected as part of routine care. EAVE II study data will remain within the National Safe Haven of Public Health Scotland, with access strictly controlled.

- Impact of COVID-19 on accident and emergency and planned hospital admissions

- changing demographics of infected people and forecasts for hospital admissions

- healthcare burden

- risk prediction

- pandemic modelling (testing profiles by age and sex, and positive tests by age, sex, rurality, and deprivation)

■ Analyses are informed by prioritised needs of Scottish Government CMO Covid-19 Advisory Group, its Data Intelligence Network and Shielding Team and other national decision makers.

■ publications

CV094: start date April 2020

■ Data on:

- efficacy of track and trace (1 of 5 contacts)

■ Insight:

- The community incidence of acute respiratory infection syndromes in August, September, October 2020 was substantially lower than that in the same period of 2018 indicating that measures to control spread of COVID-19 have also impacted on other respiratory illnesses.

- The number of contacts prior to illness is substantially higher than that recorded in the national Test&Trace programme indicating that this programme has substantial under ascertainment of contacts.

- The frequency of activities is substantially greater in the week before illness in Virus Watch participants than in the Test&Trace Case-Control Study indicating substantial under ascertainment of exposures in cases in the case-control study.

■ links with UK gov committees, PHE, and WHO

■ Publications

CV0330: start date July 2020

■ Development of a data platform used for epidemiology and eval of interventions in Wales

■ Data to adjust mortality risk for care homes in Wales

■ Real-time spatial health surveillance: mapping the UK COVID-19 epidemic

■ Report regularly to Welsh Government COVID-19 groups, SAGE, NERVTAG, and have fed into policy decisions.

CV036: start date April 2020)

■ Insights:

■ Most children have no evidence of SARS-CoV-2 infection and those that do have few symptoms.

■ Higher risk in BAME children independent of material deprivation quintile

■ report provided to WHO and PHE

CV0331: start date August 2020

■ Data on characterisation of rate of seroconversion in regions and ethnic differences

■ Insights: double rate of infection risk for blacks

■ Good evidence of pull thru and impact on midlands clinical policy.

■ evidence from project publication has impacted on guidelines for healthcare workers in some localities.

CV0143: start date July 2020

- Insights: Identifying key differences in perception, attitude, and behaviour in the face of COVID-19 between our target populations (Black and South Asian communities)
  - Within the Black community, there is evidence of perceived mistrust because of historic racism and discrimination and immigration status.
  - This contrasts with the South Asian community where whist this feature is not as evident there is however fear originating from multi-generational households, acquiring, and spreading COVID-19 with the family setting.
- Data on:
  - diversity of BAME community and initial characterisation of the diversity
- engaged/advised PHE, NHS England and Cabinet Office

CV0479: start date August 2020

- Data on:
  - care of people mental ill health in the context of CovID
- regular updates requested by PHE and DH

CV145: start date April 2020

- Data on:
  - vulnerability of platform and delivery workers to C-19 and their impact on transmission
- Insight:
  - Preliminary data demonstrated compliance with safety measures and little evidence of increased susceptibility
- publication

CV143: start date April 2020)

- Data on:
  - survival on virus on surfaces and in the environment
- Studies have been requested by and results provided to by government departments and SAGE, SAGE EMG and PHE Guidance cell.
- shared results with international collaborators through WHO GLOPRID
- Publication

MRC/CSO Social and Public health Sciences Unit (SPHSU) (C19-IUC-284) has provided analysis of National Surveys of Sexual Attitudes and Lifestyles (Natsal) data which has informed Scottish Government policy on sexual health and blood borne viruses. Additionally, their work on the impact of Covid-19 and associated responses on people who use or have used substances (C19-IUC-239) have informed revisions to Scottish Government policy on tackling drug deaths in light of the pandemic.

ZOE COVID Symptom Study tracker: an early success in better understanding COVID-19 came from the wide use of a free smartphone symptom tracker App developed by the team at Kings College London, Department of Twin Research, Guys and St Thomas' Hospital and Zoe Global Health Ltd (an MRC spinout). The KCL team has benefited from substantial Wellcome funding, but also several MRC awards key to establishing their epidemiological approach. The App supported the quick self-reporting of data related to COVID-19 exposure and infections and was launched in the UK on 24th of March 2020 (garnering one million downloads in 48 hours). Additional UK Government funding continued this momentum, and the App now has 4.5 million UK users. This impressive example of citizen science is credited with demonstrating the importance of several key symptoms in confirming COVID-19 infections, such as loss of smell.

DIAGNOSE

CV0051: start date May 2020

- Identified and prioritised use cases for COVID-19 rapid tests in primary and secondary care and care homes to map out current diagnostic pathways while identifying potential new use cases for invitro diagnostics

- informed NICE economic modelling and CONDOR's clinical evaluations.

- evaluate in vitro diagnostics for two DHSC advisory groups: Viral Detection Test Approvals Group (VTAG) and the New Tests Approvals Group (NTAG)

- Our results were to be used to influence national procurement decisions

- worked with LVG to contribute to the 'moonshot' evaluation of lateral flow tests

- rapid implementation of new rapid tests for COVID-19 in the NHS (e.g. early adopter scheme for the LumiraDx antigen test)

MRC Cancer Unit (C19-IUC-225) have instigated increased use of cytosponge – a 'pill on a string' diagnostic test – as a mechanism to streamline urgent cancer referrals due to the reduced procedure time and staff resources needed for this diagnostic test vs traditional endoscopy. After initial trials the team are expanding efforts with NHS Innovation/NHS England to do a pilot across three Cancer Alliances to reduce the secondary care endoscopy backlog.

MRC Lifecourse Epidemiology Unit's evaluation of the expanded Southampton pilot study (Phase 2) for use of saliva-based lamp testing in asymptomatic populations (C19-IUC-424) provides a valuable template for the national expansion of testing in education, supporting schools and universities to retain face to face teaching while managing risks of Covid-19 transmission.

TREAT

CV074: start date April 2020

- An adaptive platform design to test at home treatments for COVID-19

- Demonstrated that Doxycycline and azithromycin are not effective treatments

- strong links and steady comms with DHSC, PHE, NHS Digital

- publications

CV0011: start date April 2020

- Provided guidance on palliative care response to COVID-19 and end of life care.

- Data on the role of palliative care and hospices in the COVID-19 pandemic

- Produced 3 policy briefs.

- publications

CV0243: start date July 2020

- developed unique protocol/guidance for care of COVID-19 patients

- have engaged with 24 NHS Trusts to implement uptake and Chief Nurse's Office and HEE to facilitate further dissemination

CV0058: start date June 2020

■ compiled a COVID-19 section on their drug interactions website (www.covid19-druginteractions.org)

■ Published drug interaction recommendations for COVID-19 treatment

■ COVID-19 drug interactions website has been recommended in many clinical treatment guidelines around the world and helping healthcare professionals with clinical decision making

■ 26 standard drugs used in treating COVID-19 patients divided into adjunct (3; Aspirin, Dalteparin, Enoxaparin), Anti-viral (11; inc. remdesivir, HCLQ) and immune therapies (12; inc. dexamethasone) from which there are at least 114 instances where pharmaceuticals should not be co-administered and hundreds more where potential interactions are highlighted for closer monitoring.

CV0090: start date June 2020

■ Improved guidance about ethnic component for COVID trials adopted by NIHR

   – "NIHR has confirmed that it will link to the site from the NIHR Standard Application Form guidance, meaning grant applicants see it at the grant preparation phase"

■ extending the Ethnicity Framework idea to three other underserved groups: people with low incomes; those with cognitive impairments; LGBTQ+.

CV0283: start date August 2020

■ characterisation of immune response to COVID-19 infection

   – Inflammatory profile

   – Effect of variants on neutralisation

   – Immune markers/predictors of severity

■ 'The UK-CIC PI continues to write Immunity Update reports for HMG SOs

■ UK-CIC researchers Drs Ane Ogbe, Leo Swadling and Ryan Thwaites hosted a Reddit AMA ('Ask Me Anything'), an open interactive interview with a Question and Answer format that allows the general public to submit questions for the researchers. The team answered questions from the public around COVID-19 infection, the immune response, and the action and safety of the vaccine. In total the AMA generated 490 comments and over 3200 upvotes from the Reddit community.

■ publications

CV169: start date March 2020

■ prognostic score for COVID-19 patients

■ improve corticosteroid use in UK clinical practice

■ identified multiple genes that underlie critical illness in Covid-19, including several that lead directly to potential therapeutic targets

■ immune system response to many different parts of the SARS-CoV-2 virus (for vaccine development)

■ effect of ethnicity on outcomes in hospitalised patients, revealing the effect of comorbidities in mediating part of the increased susceptibility in some ethic groups

■ a primary role for the host immune system in causing fatal disease

■ obesity is an important risk factor

■ weekly briefings for government committees, PHE, etc; feed through to clinical guidance

■ The preparation work over the last decade has resulted in facilitated recruitment and establishment of an integrated analysis platform:

   – 206378 patients at Tier Zero case report forms (CO-CIN)

   – 2307 patients at Tier 1/2 (host/viral multi-omics)

- 12516 critically-ill patients can also be recruited to a sister study, the ISARIC GenOMICC study
- an open-access integrated analysis platform for linked clinical data from across the NHS for a range of studies, including ISARIC4C, GenOMICC, PHOSP, COG-UK and UK-CIC

■ publications

CV0607: start date August 2020

■ Data on characterisation of differential susceptibility of young people with cancer to death from COVID-19

■ initial cancer data feeding into development of policy at the Association of Cancer Physicians

CV0617: start date August 2020)

■ initial characterisation of organ specific immunopathology in fatal COVID

■ ICECAP feed directly into Crown Office and Procurator Fiscal Service to give guidance on post-mortem diagnosis of SARS-CoV-2 infection.

MRC Clinical Trials Unit at UCL (C19-IUC 164 & -298) are involved in over 15 clinical trials for COVID-19 treatments and demographics studies of risk factors. This includes the rapidly rolled out adaptive COVID-19 Treatment Trial (ACTT) which allowed the antiviral drug remdesivir to be fast tracked into clinics by May 2020 and the combined remdesivir and baricitinib therapy to be authorised by the FDA in December 2020. CTU continues to be involved in the global, multi-centre study Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV).

MRC Toxicology Unit (C19-IUC-333) demonstration of efficacy of remdesivir: *"report the use of remdesivir in a patient with COVID-19 and the prototypic genetic antibody deficiency X-linked agammaglobulinaemia (XLA). Despite evidence of complement activation and a robust T cell response, the patient developed persistent SARS-CoV-2 pneumonitis, without progressing to multi-organ involvement. This unusual clinical course is consistent with a contribution of antibodies to both viral clearance and progression to severe disease. In the absence of these confounders, we take an experimental medicine approach to examine the in vivo utility of remdesivir. Over two independent courses of treatment, we observe a temporally correlated clinical and virological response, leading to clinical resolution and viral clearance, with no evidence of acquired drug resistance. We therefore provide evidence for the antiviral efficacy of remdesivir in vivo, and its potential benefit in selected patients."* Published Dec 2020.

UNDERSTAND

The **COVID-19 Protein Portal** is an open science initiative that enables UK scientists to share protein reagents relating to SARS-CoV-2. The portal itself is the brainchild of the COVID-19 Protein Production Consortium (CPPC), a collaboration of MRC Units and Institutes (principally CVR, PPU and LMB) which also developed the Coronavirus Toolkit, have distributed around 350 antibodies, 200 mg protein and 100 clones worldwide to researchers in the UK and across the globe including Australia, Korea, USA, Japan, Finland Switzerland and Canada. We have also supplied to the NHS, NIH, and other National medical authorities. Provision of specialised reagents has contributed to the success of many COVID-19 research projects in the UK and around the world.

Accelerating global research – The resources and technologies available in the toolkit have been made openly available to research groups worldwide to accelerate research. The toolkit has already been used in several high-profile studies into the virus.

MRC and Glasgow University Centre for Virus Research provided the complete genomic sequencing and analysis of the COVID-19 virus from Scotland's first confirmed case.

CV201: start date April 2020

- global hub/showcase of COVID research, tools and methodologies sharing outputs in real time

- The COVID Hub is being used by researchers from over 195 countries, with almost 400,000-page views as of mid-September. The hub enables health professionals and researchers to discover the most relevant information, guidance, and resources to their research, role and setting

- evidence of global participation of both the research and policy/government communities

MRC Laboratory for Molecular Biology (LMB) has used high resolution microscopy and structural biology to describe how the virus enters and replicates in cells.

Francis Crick Institute has provided insight on the underpinning biology of the virus, the production of recombinant proteins from the virus, immunological responses, and chemical inhibitor screening.

The **UKRI-NIHR Rapid Response Initiative** launched in February 2020 with projects starting from March to December. The projects were tasked to get rise to societal impact within their 12-18 months lifetime. These calls were surveyed quarterly with the intent to track and support project impact. In 2020, 26 of 67 project surveys reported some societal impact through interventions, data for government policy making or clinical guidance.

The projects supported through other funding initiatives are being surveyed in 2021 and their impacts will be reported in the next iteration of this report.

The **UKCDR's** second update to the living review was published on 01 April 2021 in which over 7,500 awards collated via UKCDR, with a value of $3.8bn, are assessed. Within this dataset, UKRI represents $252m (~8%) of this combined spending on pandemic, of which MRC contributes $93m (~3%). Roughly $3.8 billion had been invested globally to support new research relevant to the WHO roadmap. A year on from the pandemic being declared the portfolio shows that the global R&D response has been comprehensive, rapid and of unprecedented scale. However, the value of tracking these investments, despite there likely to be gaps in coverage (e.g. research in Asia, particularly China, being under-represented), has been clear. Emerging findings highlight the lower investment in research conducted in lower and middle-income countries, the increasing need (given limited resources) for improved co-ordination of studies worldwide, and that unfortunately many research studies are under-powered or unable to achieve their aims.

Annex 2.3

Support provided for 'live' awards

The survey process for the UKRI-NIHR Rapid Response initiative (RRI) provided and opportunity for a relationship between PI and monitoring PM to develop. This enabled the collection of information on the state of progress in the project and any impacts as they occurred. More importantly, it allowed the Principle Investigators to communicate impediments to progress in a timely manner. In many cases, NIHR or MRC colleagues were able to assist in resolving the issue and promote efficient project progress. During 2020, much of this assistance has involved straight forward shared information as outlined below. As the pandemic challenge has evolved from the time when the projects were designed, the funders have needed to engage in more complex assessment of where the research infrastructure established can still provide value insight and where programmes can be modified to meet new knowledge priorities.

In 2020, funders were able to provide assistance to researchers requests in the following areas:

Priority status or clinical contacts to facilitate patient access for trials and clinically based studies

- For example, in summer 2020, PHOSP COVID: Post-hospitalisation COVID-19 study was struggling to recruit patients. Support in applying for UPH status has improved the pace of recruitment.

- MRC's lead in shaping the UK CTAP structure has organized and rationalised the progress of a group of trials: coordinating of trial management, developing consensus of the trial leaders, structuring of treatment needs to address the SARS-CoV-2 pandemic and prioritizing candidate treatments.

Linkages or contacts with appropriate government committees or policy makers for use of the project outputs

- For example:

  – Prognostic models for COVID-19 to support risk stratification in secondary care had been unable to find the appropriate office in government to share her outputs with. NIHR were able to connect her to the NHS England and Improvement office who have found the data very useful.

  – COVID-19 detection assay details were disseminated to the appropriate government stakeholders.

Data management and access expectations

- Most of the Principle Investigators (PIs) requested further information about data storage, management, and public accessibility in the survey.

- MRC staff member, RK, reviewed survey responses for (i) findability, (ii) long-term storage, and (iii) independence/transparency in the data access process. From 69 responses she found:

  – 14 responses were inadequate (13 only stated that arrangements would be made in due course and 1 was unsure about sharing individual-level data). We are contacting these 14 award holders to provide support for data sharing.

  – 27 responses were partially acceptable; key issues were a lack of findability (13 had no plans to list the dataset/metadata in a catalogue; 3 were relying on their study website only), and that the access process was not clearly independent or transparent (8). We are contacting these 27 award holders to suggest improvements to their data management plan, such as providing lists of metadata catalogues, appropriate repositories, and guidance on data access committee independence and transparency.

- 28 responses were detailed with adequate plans or a statement that data could not be shared (2 were preclinical data; 5 used data from sources that did not permit onward sharing). Six award holders who requested advice have been emailed confirmation that their plans are satisfactory; any further queries will be followed up.

■ The result has been that the PIs have received targeted data management information, and their compliance will be monitored, and the funders have a clearer picture of where and how we need to support better understanding of management of research data.

Dissemination

■ Many projects have requested our support in dissemination of their publications, guidance, or other information materials. We have been able to assist through NIHR's Centre for Engagement and Dissemination, highlighting on the MRC website, and retweeting the publications as they are published.

■ For example, Professor Terweek's project Ensuring that COVID-19 trials consider ethnicity: the INCLUDE Ethnicity Framework for randomised trials developed the ethnicity framework which NIHR's Standard Guidance for Applicants signposts to applicants applying for HTA funding and the MRC's blog links to the framework.

Oversight/steering groups/ system

■ MRC or NIHR staff are observers on oversight or steering groups for the larger programmes. This has provided the opportunity to ensure strong communication between programmes to promote data sharing and limit redundant efforts.

Project focusing or realignment support

■ Some projects struggled with changing conditions such as school closure or access to NHS trusts because of clinician fatigue which severely limited the progress. The ongoing relationship with the researchers has facilitated productive discussion on best to restructure and redirect research as well as when to terminate the programmes. The truncation of the other two vaccine development projects is an example of the latter.

Annex 4.1

Details of COVID-19 facing funding calls

■ MRC supported research calls:

- UKRI-NIHR COVID-19 Rapid Response Initiative (RRI) (February 2020)
  - Platforms: development of vaccines and treatment
  - Clinical studies and epidemiological surveillance and analysis
- UKRI COVID-19 Rapid Response Rolling call (RRR) (March 2020)
- EDCTP COVID-19 Response call (April 2020)
- UKRI COVID-19 Agile call (Agile) (August 2020)
- UKRI GCRF/Newton Agile Response call (May 2020)
- Global Effort on COVID-19 Health Research COVID-19 (GECO) (May 2020)
- UK-India COVID-19 partnership initiative (October 2020)
- NIHR-UKRI Long-term COVID-19 effects in non-hospitalised individuals (Long COVID) (December 2020)

■ Individual initiatives:

- COG-UK
- GenOMMIC study of COVID-19
- Protein Portal

■ International coordination

■ National Core Studies

A summary of this activity is found in Section 4. Further details about award funding processes can be found in Annex 4.2 and impacts arising in 2020 are reported in Annex 2.2.

MRC supported research calls[45]

UKRI-NIHR COVID-19 Rapid Response Initiative (RRI) (February 2020)

Includes UKRI-NIHR COVID-19 Rapid response calls 1 and 2 and the UKRI-NIHR Rapid Response Rolling Call (distinct from the similarly titled UKRI COVID-19 Rapid Response Rolling Call, RRR, see below).

UKRI-NIHR Rapid Response calls 1 and 2

To rapidly engage the expertise of the UK research community in the fight against COVID-19, on February 4 MRC, in partnership with sister UKRI councils and the Department of Health and Social Care (DHSC) launched the UKRI-NIHR COVID-19 rapid response initiative to support research (up to 18 months) to understand, prevent, treat and control the disease. The initiative had two calls: (i) active intervention development including vaccines and therapeutics, and (ii) diagnosis and understanding of COVID-19. 28 new projects (270 applications) totalling £25.2m were funded.

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45. In this interim report, all the projects funded through calls described were funded through the RRI (UKRI-NIHR COVID-19 Rapid Response call 1 and call 2 and UKRI-NIHR COVID-19 Rapid Response Rolling call). The final funding decisions for the other calls were made too late for inclusion in this report but will be part of the final report.

These projects were closely link to the COVID-19 research priorities recently identified by the government advisory committee, SAGE (Scientific Advisory Group for Emergencies), and the WHO. They included work to develop new vaccines, treatments and diagnostics, research to understand the epidemiology and pathology of the disease, and to increase understanding of the biology of the virus and its transmission. In addition to the usual assessment of scientific quality, applications were assessed for whether or not they would have a public health impact within the period of the award; whether they addressed priorities identified in the WHO R&D Roadmap; and their contribution to a coordinated research response/portfolio of COVID-19-relevant research.

UKRI-NIHR Rapid Response Rolling Call (March 2020)

This follow-up to the initial COVID-19 rapid response calls was established to harness the breadth and enthusiasm of the UK biomedical research community to develop knowledge and inform policy making to combat the enfolding pandemic. In early April 2020, UKRI launched the rapid response rolling call in partnership with DHSC for projects of 12-month duration to make a significant contribution to the understanding, prevention and/or management of the COVID-19 outbreak. *Note: this call was administered by NIHR and MRC, and is distinct from the similarly titled* UKRI COVID-19 Rapid Response Rolling Call *(RRR, see below).*

■ Awarded 51 programmes, MRC committed £23.2m (£46.3m with NIHR) (698 applications)

■ Included three highlight notice sub-panels assessing Mental Health, Transmission or Ethnicity focused projects for funding.

The Mental Health highlight notice (5 awards; ~£17m) aim was to reduce the emergence of new, and exacerbation of existing, mental health problems, and to improve outcomes for those whose mental health has already been adversely impacted by the COVID-19 pandemic. The intent was to improve understanding how the measures imposed to reduce the spread of the virus in the UK stand to impact on immediate mental health, and the role of other factors, including but not limited to, SARS-CoV2 infection, stress, stigma, isolation, bereavement and trauma (including trauma following ICU treatment in COVID-19 patients with severe illness). Proposals could take a whole population view or focus on groups who may be more vulnerable such as frontline health and social care staff and other groups of key workers, people with existing mental health problems, those who recover from COVID-19, BAME populations and those experiencing social inequality such as lack of employment, housing or existing health inequalities.

The Ethnicity highlight notice (5 awards; ~£3m) aim was to improve our understanding of the links between COVID-19 and ethnicity. These projects will seek to explain and mitigate the disproportionate death rate from COVID-19 among people from Black, Asian and minority ethnic (BAME) backgrounds, including BAME health and social care workers. The projects were launched following emerging evidence showing that BAME people are nearly twice as likely to die of COVID-19 than white people, after taking account of age and other sociodemographic factors. Researchers were intended to collaborate with other MRC investments including the UK Biobank and the MRC Lifecourse Epidemiology Unit.

The Transmission highlight notice (4 awards; ~£1.8m) aim was to improve understand of the epidemiology of the disease, including its prevention and control will be critical for mitigating the severity of the COVID-19 pandemic. These projectswere intended to complement the existing portfolio of platforms addressing UK population transmission.

To help inform policy decisions about COVID-19 − including possible decisions about infection prevention strategies and any relaxation of existing containment measures − there is an ongoing need to better understand the epidemiology of the disease, specifically:

■ the transmission of disease

■ risk factors for both disease transmission and acquisition

■ levels of exposure to the COVID-19 virus within certain priority groups (SARS-CoV-2) i.e. seroprevalence.

The RRI (UKRI-NIHR Rapid Response initiative) funded tightly focused research projects as well as research platforms designed to monitor, analyse and assess COVID-facing research topics with interdisciplinary expertise e.g. vaccine trials, clinical trials, clinical studies and epidemiological surveillance and analysis.

Platforms: development of vaccines and treatment

Vaccines

MRC has a strong foundation in vaccine development, supporting a portfolio of research relating to genetic technology and immunology. Professor Sarah Gilbert at the University of Oxford and Professor Robin Shattock at Imperial College London were both awarded funding under the UKRI-NIHR Rapid Response Call to develop candidate vaccines against COVID-19. The results of the Oxford vaccine Phase III trial were published in December, confirming that the vaccine is safe, effective, and gives good protection with two different dose regimens, resulting in an average efficacy of 70.4%. The Oxford vaccine is now being used to roll out an ambitious plan to vaccinate all UK adults by Summer 2021. Additionally, the Oxford team are set to begin to assess their safety and effectiveness when inhaled into the lungs. Work on the Imperial College vaccine, based on self-amplifying RNA, after poor results in efficacy trial has been discontinued.

The speed at which these COVID-19 vaccine projects have progressed demonstrate how previous work funded by research councils including MRC, BBSRC, and EPSRC have laid the strong foundations necessary for the rapid deployment of UK scientific expertise in tackling this pandemic.

MRC and BBSRC provided strategic support for early vaccine development through the Global Challenges Research Fund Vaccine R&D Networks (£12.4 m), which seek to address gaps in discovery and pre-clinical development of vaccines. Later stage development is supported by MRC and BBSRC through the DHSC-led £120m UK Vaccine Network (UKVN).

Clinical treatment trials

- **RECOVERY trial** ('Randomised Evaluation of COVid-19 thERapY') (supported through UKRI-NIHR RRI and subsequent awards; £2.1m in the initial phase; additional £19m in 2020 for maintenance of the platform). The RECOVERY trial is a large, randomised controlled trial of possible treatments for patients admitted to hospital with COVID-19. It is the fastest growing trial in medical history, enrolling 1,000 patients at 132 hospitals within its first 15 days. It is a Phase III adaptive large-scale trial platform for currently available, affordable drugs for the treatment of COVID-19 patients. RECOVERY demonstrated the rapid implementation of plan for highly efficient patient recruit developed previous by ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium and others.

- **PRINCIPLE** – (funded through RRI: £1.6m) Phase II testing of potential COVID-19 treatments in the community in patients with mild to moderate COVID-19 who are aged over 65; or aged 50 to 64 with an underlying health condition.

- **TACTIC-R** – mulTi-Arm Therapeutic study in pre-ICU patients admitted with Covid-19 -Repurposed Drugs (TACTIC-R AGILE- a randomised, parallel arm, open-label platform trial for investigating potential treatment for COVID-19 disease. This study proposed to assess the efficacy of immunomodulatory agents that target dysregulated immune response that drive the severe lung, and other organ, damage.

- **CATALYST** – a randomised adaptive trial for new drugs for SARS-CoV-2+ patients initiated in early 2020 (MRC committed £0.45m). It is a phase II multi-arm multi-stage initial trial platform to test currently available promising drugs for hospitalised SARS-CoV-2+ patients in small trial populations. This adaptive trial has developed into a filter and 'springboard' for the larger-scale phase III COVID-19 trial platforms.

- **ACTT-EU/UK** – (MRC Clinical Trial Unit (CTU) partnership) Adaptive COVID-19 Treatment Trial launched at the start of April 2020 is a globally organised randomised trial that aims to evaluate the safety and efficacy of the anti-viral drug remdesivir, as a treatment for COVID-19. ACTT-EU/UK has recruited more than 1000 patients globally, with the MRC CTU coordinating the trial in the UK and Greece. It is a Multicentre, Adaptive, Randomised Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalised Adults.

- **ACCORD** (Accelerating COVID-19 Research & Development) is a Phase II clinical trial platform launched in the UK to fast-track research into potential COVID-19 treatments.

Vaccine and treatment trials impacts are described in ANNEX 2.1.

Clinical studies and epidemiological surveillance and analysis

- **ISARIC 4C**: ISARIC Coronavirus Clinical Characterisation Consortium

- **UK-CIC**: A UK underpinning platform to study immunology and immunopathology of COVID-19: The UK Coronavirus Immunology Consortium UK Coronavirus Immunology Consortium

- **Virus Watch**: Understanding community incidence, symptom profiles, and transmission of COVID-19 in relation to population movement and behaviour

- **HICC**: Humoral Immune Correlates for COVID19

- **PHOSP-COVID**: Post-hospitalisation COVID-19 study: a national consortium to understand and improve long-term health outcomes

- **CONDOR**: COVID-19 National DiagnOstic Research and Evaluation Platform

- **OpenSAFELY**: a secure analytics platform for electronic health records in the NHS for data analysis during the global COVID-19 emergency

- **CoMMinS**: COVID-19 Mapping and Mitigation in Schools

- **OWLS**: Optimising Wellbeing during Self-isolation

- **Con-COV**: Controlling COVID19 through enhanced population surveillance and intervention

- **CO-CONNECT**: COVID – Curated and Open aNalysis aNd rEsearCh plaTform

- **COVID-CNS**: The COVID-19: Clinical Neuroscience Study

- **Coronavirus STORY**: Coronavirus Serum Testing of Representative Youngsters

- **EAVE II**: Early Estimation of vaccine and Anti-Viral Effectiveness II

ISARIC4C: (ISARIC Coronavirus Clinical Characterisation Consortium) is a COVID-19 focused section of the ISARIC programme. The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) is a global federation of 55 research networks spanning 111 countries. These networks work to a) generate the evidence necessary for improving clinical care and public health responses to infectious disease epidemics and b) support the development and evaluation of new diagnostics, treatments, and vaccines. Founded in 2011 by MRC and other global funders (background details in Section 6.6), ISARIC has become the largest study of COVID-19 in the world. ISARIC4C is funded through UKRI and NIHR (£5m funded through UKRI-NIHR RRI). ISARIC4C provides a foundation for other studies through the immediate deployment of sample and data collection expertise since the first UK cases of COVID-19 were reported. As of March 2, 2021, data from 188,708 patients have been collected.

ISARIC's purpose is to prevent illness and deaths from infectious disease outbreaks. They are a global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious diseases. COVID-19, a new virus (SARS-CoV-2), is an example. It causes a disease termed COVID-19 that may be mild but can also be severe, leading to viral pneumonia; about one in 100 infected people are expected to die of it. ISARIC 4C tackle many urgent questions that need answering to help control the outbreak and treat patients in the UK:

- how long are people infectious, and what body fluids are infectious?

- what puts people at higher risk of severe illness?

- what is the best way to diagnose the disease?

- who should we treat early with drugs, and which drugs cause harm?

- does the immune system in some patients do more harm than good?

- what other infections (such as pneumonia or flu) happen at the same time?

Over the last 8 years ISARIC and other organisations have been preparing for such a major outbreak; developing expert teams to immediately deploy.

UK CIC: The UK Coronavirus Immunology Consortium (£6.5m provided through UKRI-NIHR RRI) is an underpinning platform to study immunology and immunopathology of COVID-19. It brings together leading immunologists from 17 research institutions to coordinate an agile national research programme to increase our understanding of how the immune system interacts with SARS-CoV-2. The scientists aim to develop better tests to define immunity, to study the body's immune response to SARS-CoV-2 and to understand why some people suffer from severe life-threatening COVID-19 while others have mild or asymptomatic infections but can still transmit the virus. Importantly these studies will determine when and how immunity persists or whether people can become re-infected.

Virus Watch: Understanding community incidence, symptom profiles, and transmission of COVID-19 in relation to population movement and behaviour. (£3.2m provided through UKRI-NIHR RRI).

To prepare and respond to the novel strain of Coronavirus (COVID-19) we need to know how many people become infected, how many of them become ill, what their symptoms are, how many seek health care, how commonly they transmit to household contacts, what proportion need hospitalisation and what proportion die. We need to understand how the population responds e.g. hand washing, behaviours during and after coughing, sneezing or nose wiping, and whether people restrict their movements and social contacts. Since many of those infected will have relatively mild symptoms and not seek medical advice the only way to accurately obtain this information is to conduct large scale community studies. Virus Watch follows up members of the public and contacts of cases using regular online surveys of symptoms and behaviours, secure tracking of participant movements, and testing for COVID-19 and other respiratory infections to build a detailed picture of how the virus spreads and the population responds. They share this data with participants, health service and public health planners and the general public to help minimise the impact of the virus.

HICC: The Humoral Immune Correlates of COVID-19 (HICC) consortium (£1.6m provided through UKRI-NIHR RRI). study the humoral immune response – molecules produced by the immune system to fight infection, including antibodies – by focusing on two cohorts: NHS workers – in collaboration with SIREN – to track immunity over 12 months, and hospitalised patients.

The research improves understanding of the differences between beneficial – or protective – antibody responses versus those that cause disease. This helps to determine why early indications suggest that people with stronger antibody responses may have had more life-threatening disease and what types of antibody responses are more effective in preventing severe infection.

It is also hoped that the study will inform treatments for COVID-19 patients at different stages and with different severities of the disease, including whether targeting the over-activation of the innate humoral immune response – known as the 'complement system' – to SARS-CoV-2, could provide a unique approach to reducing severe COVID-19-related disease and death.

PHOSP-COVID: Post-hospitalisation COVID-19 study: a national consortium to understand and improve long-term health outcomes (£8.5m provided through UKRI-NIHR RRI). The COVID-19 pandemic has tragically led to severe acute illness, hospitalisation and death. Beyond the health of those affected, it has had widespread economic, psychological and societal effects. The clinical spectrum is broad, ranging from those with no or minimal symptoms to severe pneumonia in 15-20% with evidence of widespread disease beyond the lung. As we emerge from the first wave of the pandemic, we have new insights into the acute phase of this disease but very little information concerning long term effects of COVID-19 and the ongoing medical, psychological and rehabilitation needs of these patients. Phosp-COVID established a national consortium and a research platform embedded within clinical care to understand and improve long-term outcomes for survivors following hospitalisation with COVID-19. They have built the consortium from existing expert groups across the UK and shall use standardised assessments of patients, including advanced imaging, recording of information and collection of samples. This study will provide a comprehensive understanding of the impact on the health of those that have been hospitalised with COVID-19. This will enable trials of new strategies of clinical care including personalised treatments to improve the long-term outcome of current and future COVID-19 survivors.

CONDOR: COVID-19 National DiagnOstic Research and Evaluation Platform (£1.2m provided through UKRI-NIHR RRI). The CONDOR platform is a multicentre national programme of research that will evaluate how new diagnostic tests perform in hospitals, general practices and care homes. CONDOR is funded by the NIHR, UKRI, Asthma UK and British Lung Foundation and will create a single national route for evaluating new diagnostic tests in hospitals and in community healthcare settings. This programme of research brings together experts who are highly experienced in evaluating diagnostic tests and generating the robust evidence required for a test to be used in the NHS.

OpenSAFELY: is a new secure analytics platform for electronic health records in the NHS, created to deliver urgent results during the global COVID-19 emergency (£1.3m provided through UKRI-NIHR RRI). It is designed to deliver analyses across millions of patients' full pseudonymised primary care NHS records. All our analytic software is open for security review, scientific review, and re-use. OpenSAFELY uses a new model for enhanced security and timely access to data: we don't transport large volumes of potentially disclosive pseudonymised patient data outside of the secure environments managed by the electronic health record software companies; instead, trusted analysts can run large scale computation across near real-time pseudonymised patient records inside the data centres and secure cloud environments of the electronic health records software companies. This pragmatic and secure approach will allow delivery of our first analyses in just weeks from project start.

CoMMinS: COVID-19 Mapping and Mitigation in Schools (£2.8m provided through UKRI-NIHR RRI). This project will create new knowledge and tools to help schools deal with the practical challenges of preventing and coping with an outbreak of COVID-19. Our project builds on a well-established, strong partnership between the University of Bristol and Bristol City Council, Public Health England, local schools and other city stakeholders. The project will test for infection in the school environment and test whether staff and pupils have current or past COVID-19 infection, over a 6-month period. We will use staff and pupil postcodes to identify the areas of the city with most infection, so that they can be given targeted support for infection control. We will improve systems for rapid and effective contact tracing, using digital support. We will work with staff, pupils, and parents at school and outside school. Finally, we will assess the impact of returning to school on pupil and staff mental wellbeing, and their attitudes to this project.

OWLS: Optimising Wellbeing in Self-isolation study (OWLS) will explore how people with severe mental ill health experienced the pandemic restrictions and how they dealt with the social consequences of lockdown. It will also investigate the impact of coronavirus on their physical health (£200k provided through UKRI-NIHR RRI).

People with severe mental health problems are at increased risk of being affected by COVID-19 and the pandemic restrictions. This is because they are more likely to live in impoverished circumstances and are less likely to be able to access the internet. Many people with mental health problems have physical health problems also which may mean they are in a group that needs to isolate for long periods of time.

In this project we want to look at how people with mental health problems are affected by the current pandemic. We want to know whether people can access health services when they need to. Whether they can use the internet to access services and contact friends and if they are feeling lonely. Finally have they made any changes to reduce the risk of COVID-19 such as stopping smoking. The project involves completing questionnaires and taking part in interviews. We will invite people who took part in the Health and Wellbeing Survey and said they were interested in taking part in future research. The results of the study will be used to make recommendations about how best to support people with severe mental illness during a pandemic.

Con-COV: Controlling COVID-19 through enhanced population surveillance and intervention: a platform approach (£830k provided through UKRI-NIHR RRI). The virus has had an unprecedented effect on the global population in a very short space of time meaning international governing bodies and health care provisions have had to devise their responses to fight the virus and protect people, in real time based on ever evolving information. In Wales a specialist research team made up of representatives from; Welsh Government, Public Health Wales, academia, and the public have come together to develop a project which will rapidly analyse data from numerous sectors including primary and secondary care. The project will ensure; 1) policy makers and health care providers are kept informed and have a detailed insight into the evolving pandemic; 2) interventions which are being used to fight and control the virus are evaluated for their effectiveness; 3) the general public are kept informed. Each week the project will provide a report to Welsh Government COVID19 Technical Advisory Group (TAG) and British Government's SAGE; this will help inform evidence-based strategies to control the virus, safeguard the general population and bring the UK out of lockdown.

CO-CONNECT: COVID – Curated and Open aNalysis aNd rEsearCh plaTform (£4m provided through UKRI-NIHR RRI). Project will support research into the COVID-19 antibody response by connecting COVID-19 data derived from patient blood samples. CO-CONNECT will help scientists across the UK to access the data they need more easily to help develop potential therapies and treatment for COVID-19.

The UK has rich, globally important COVID-19 datasets, including large serology cohort studies funded by UKRI, Wellcome, DHSC/NHS, NIHR and the devolved administrations. However, this breadth of data creates a risk of fragmentation, inconsistent structure and access processes, severely limiting utility, timeliness, and impact. Our vision is to transform UK COVID-19 diagnostic datasets to be Findable, Accessible, Interoperable and Reusable (FAIR) and couple this with expert data engineering, enabled by Health Data Research UK (HDR UK), to catalyse responsible and trustworthy use of the data for research and innovation.

They propose to support PIs and data custodians to link COVID-19 cohort, serology and other health and non-health datasets. This longitudinal linkage is vital to derive new scientific insights and deliver informed decisions about how best to control the spread of SARS-CoV-2. At present there are >30 independent studies with no streamlined approach to linkage to other health and non-health related datasets, lack of data standardisation, and no strategic approach to synthesise analyses across studies.

SAGE (9th June) requested HDR UK to work with partners to develop the UK-wide serology and testing data research asset that is linkable to other data sources. They have bought together 41 leaders from 29 different organisations and 44 data sources to address a major data engineering challenge by building upon existing UKRI investments, including the HDR UK BREATHE Hub, to create a 'one-stop' service for trustworthy, multi-stakeholder utilisation of curated COVID-19 data for public, private and third sector benefit.

COVID-CNS: The COVID-19: Clinical Neuroscience Study (£2.3m provided through UKRI-NIHR RRI). COVID-19 patients frequently suffer brain problems during the infection and can be left with symptoms of brain injury. Similar problems have been seen in previous pandemics, including Spanish influenza over 100 years ago, but how and why this occurs is poorly understood. We have already been notified of 800 UK patients with these complications due toCOVID-19. We have a unique opportunity to understand how these problems occur and develop strategies to prevent and treat them. The questions we will ask include in whom does COVID-19 cause injury? Does it do this by invading the brain? Or by

triggering excessive immune responses or interfering with the blood supply to nervous tissue? We will answer these questions through in depth clinical, laboratory, and imaging studies of these 800 patients in comparison to 500 control patients (hospitalised during the pandemic with COVID-19 [400] or without COVID-19 [100]). Without this understanding, we cannot determine whether anti-viral medication, or treatments that modulate the immune system or that improve blood supply will help, and if so in which patients. We will apply this understanding through our World Health Organisation-commissioned Task Force (co-Chair Michael) to develop clinical care guidelines, identify patients for targeted clinical trials, and ultimately improve patient outcomes.

Coronavirus STORY: Coronavirus Serum Testing of Representative Youngsters (£570k provided through UKRI-NIHR RRI). This COVID-19 paediatric sero-epidemiology study adapts an existing national research network and ethically approved NIHR-funded study to collect sufficient childhood and teenage serum samples for near real-time monitoring of increases in paediatric COVID-19 sero-positivity rates across the UK in 2020. The importance of sero-epidemiological monitoring is emphasised in the Public Health England (PHE) pandemic influenza protocol, currently being adapted in response to the COVID-19 threat. This requires the monthly collection of 1000 serum samples, including 100 per month in each of the 0-4, 5-9, 10-14 and 15-19-year-old age-groups. This is essential to understanding the rates of symptomatic and asymptomatic infection in children, a population that are the predominant transmitters of most respiratory viruses. This information is in turn crucial to understanding the severity of COVID-19 disease in children, as well as modelling the spread of this virus through the community and planning an effective public health response. The challenge of obtaining blood samples from representative cohorts of children (rather than residual sera from sampling for clinical purposes) had already led to the Oxford Vaccine Group (OVG), PHE and seven regional partners throughout England establishing the 'What's the STORY (Serum Testing of Representative Youngsters)' network to evaluate antibody levels against vaccine-preventable diseases. This study will form a rapid, responsive and crucial component of the UK response to this emerging global threat. An important way of tracking the spread of a new viruses like the novel coronavirus (COVID-19) is to study the blood-born immunity against that virus in the general population. Measuring this at the beginning of an outbreak can determine what proportion (if any) of the population already have immunity, and ongoing monitoring for any increase in this proportion can show how many people are getting new infections. This is especially important for children, who are often responsible for spreading respiratory infections to others. Accordingly, Public Health England plan to study the concentrations of antibodies (a marker of immunity) against COVID-19 in 400 children and teenagers per month for the duration of the COVID-19 outbreak.

EAVE II: Early Estimation of vaccine and Anti-Viral Effectiveness II (£450k provided through UKRI-NIHR RRI). EAVE I was a NIHR-funded project on pandemic influenza, which created a Scotland-wide cohort of 227,000 individuals recruited from 40 general practices together with stored serology samples from 1,000 individuals. This established a national electronic cohort though linking health data sets from general practice, prescribing, hospitalisations and virology testing using the unique Community Health Identification (CHI) number for residents of Scotland. We plan to repurpose and expand this cohort to collect electronic data from 1.2m individuals living in Scotland to study COVID-19. We will augment the cohort by collecting and storing residual sera samples and by sequencing virus from patient specimens. Both are being taken as part of routine care from a sample of these individuals. We will track the progress of the COVID-19 epidemic in near real-time using the EAVE II cohort. We will be able to model the full course of the epidemic from genome sequence data. Once a serological test becomes available, we will be able to refine this model and provide precise estimates of the attack rates in different sub-populations and accompanying hospitalisation and fatality rates. EAVE II will help to identify the clinical features of the epidemic and, in due course, provide estimates of the effectiveness of any vaccines and anti-viral therapies deployed. Ethical and Privacy Committee approval has previously been given for the EAVE study and we anticipate the same approvals will readily be obtained for this follow-on study.

Scotland is an ideal place to carry out this research as there is a unique reference number for every individual. This makes it easy to link together different health datasets and construct an electronic cohort based upon data from 250 general practices and 1.2m individuals (22% of the population). Such

a large cohort gives wide regional coverage and permits investigation of subgroups such as children aged under 5 or adults over 65.

These data are already being collected for routine care – information on GP consultations, prescriptions, out of hours' consultations, use of accident and emergency and hospital admissions. It also includes laboratory tests to diagnose a person with coronavirus and specifically COVID-19. Individuals will be having routine blood tests and a sample of unused blood will be stored and eventually tested for the presence of COVID-19 antibodies to work out the proportion of the population exposed during the epidemic. We will also sequence virus genomes from a sample of patients. The analysis of these data is carried out in a safe haven using anonymised data so that individuals cannot be identified.

This cohort will be followed up to monitor the progress of the COVID-19 epidemic and to evaluate which interventions are effective for treating and preventing the virus.

UKRI COVID-19 Rapid Response Rolling and Agile rolling call (April 2020)

The **UKRI COVID-19 Rapid Response Rolling** (RRR) call funded urgent applications on a wide range of coronavirus pandemic-related research and innovation projects addressing and mitigating the health, social, economic, cultural and environmental impacts of the COVID-19 outbreak in an 18-month timeframe. The RRR call was launched April 2020 and closed in July with new and deferred applications going to the **Agile rolling call** which ran from September to December 2020. The distinction between the two parts of the rolling call was primarily administrative.

The call supported excellent proposals up to 18 months duration, in any subject area within UKRI's remit, which meet at least one of the following:

- new research or innovation with a clear impact pathway that has the potential (within the period of the grant) to deliver a significant contribution to the understanding of, and response to, the COVID-19 pandemic and its impacts
- supports the manufacture and/or wide scale adoption of an intervention with significant potential
- gathers critical data and resources quickly for future research use.
- Projects can be up to 18 months long, of any scale and can demonstrate it will deliver impact in the project length.

26 grants fully within MRC remit were awarded.

EDCTP Emergency funding of COVID-19 research call (April 2020)

This funding is for collaborative clinical research studies to support research activities in sub-Saharan Africa to manage and/or prevent the spread of the current COVID-19 outbreak.

The intent of the research is to:

- Address urgent research questions in the context of the current COVID-19 outbreak, in line with the research priorities of the Global Research Roadmap and the WHO R&D Blueprint for rapid activation of R&D activities during epidemics.
- Strengthen national and local research capacity.
- Coordinate and collaborate with other research and/or humanitarian activities operational in the countries affected.
- Comply with International Council on Harmonisation – Good Clinical Practice (ICH-GCP), regulatory and ethical standards.
- Commit to open access and data sharing principles.

Global effort on COVID-19 (GECO) health research call (May 2020)

Research proposals addressing COVID-19 in low- and middle-income countries (LMICs) – supported by National Institute for Health Research (NIHR) and UKRI. Global Effort on COVID-19 (GECO) health research is a new cross UK government funding call aiming to support applied health research that will address COVID-19 knowledge gaps. The focus is on understanding the pandemic and mitigating its health impacts in LMIC contexts. The call prioritises epidemiology, clinical management, infection control and health system responses.

The funds form part of the UK's Official Development Assistance (ODA). Support will be available to address the impacts of COVID-19 in LMICs for research which has a direct and primary focus on improving health in LMIC countries. Applications will be accepted from eligible institutions based in the UK or in LMICs. This call builds on the NIHR and MRC/UKRI COVID-19 Rapid response UK-focussed rolling call to facilitate a coordinated research approach and will be run as a series of calls: three consecutive rounds of the call taking place on a rolling basis.

The call specification is based on the World Health Organisation (WHO) COVID-19 global research roadmap priorities identified through a consultative process that involved experts from across the world. In addition, we have taken into consideration the African Academy of Sciences research priorities for COVID-19, and input from external experts, for example DHSCs Global Health Research Independent Scientific Advisory Group and MRC's Applied Global Health Research Board.

As well as projects addressing direct impacts of COVID-19, projects investigating the indirect consequences of the pandemic through other health issues will be considered, such as (but not limited to):

■ mental health

■ domestic violence

■ inter-personal violence

■ water and sanitation

■ maternal and neonatal health

■ nutrition

■ chronic conditions

■ the wider impact on the health system or health service delivery.

Implementation science and operational research will be supported across the four thematic areas where appropriate to ensure a focus on practical application of findings.

Areas three, four, five and nine from the WHO roadmap are in scope:

■ Thematic area three: Epidemiological studies

■ Thematic area four: Clinical management

■ Thematic area five: Infection prevention and control including health care workers' protection

■ Thematic area nine: Social sciences and humanities in the outbreak response.

The reduction in ODA funding in early 2021 required a revision in the awarding decisions resulting in only 19 awards being made (850 applications).

UKRI GCRF/Newton Agile Response call (May 2020)

Proposals are invited for short-term projects addressing and mitigating the health, social, economic, cultural, and environmental impacts of the COVID-19 outbreak in Low- and Middle-Income Countries. This call is funded through the Global Challenges Research Fund (GCRF) and the Newton Fund. These Funds address global challenges through disciplinary and interdisciplinary research and strengthen capability for research and innovation within both the UK and developing countries, providing an agile response to emergencies where there is an urgent research need. Researchers holding existing UKRI GCRF grants should in the first instance consider whether they could repurpose that funding to address the objectives of this call.

UKRI will support excellent proposals which meet at least one of the following:

- New research or innovation with a clear pathway to impact on policy or practice that has the potential (within the period of the award) to deliver a significant contribution to the understanding of, response to, and recovery from the COVID-19 pandemic in a developing country context.
- Supports the manufacture and/or wide scale adoption of an intervention with significant potential for impact in developing countries.
- Gathers critical data and resources quickly for future research use.

Nine awards were made.

UK-India COVID-19 partnership initiative (October 2020)

This initiative provided awards for researchers in the UK and India. UKRI and the Indian Department of Biotechnology (DBT) will fund research collaborations that, in the COVID context:

- study related ethnic groups in different environments
- explore the role of external influences and demographic variables in influencing COVID-19
- improve our understanding of the differential outcomes in populations of similar ethnic origin.

The research should focus on south Asian populations and can involve:

- mechanistic studies of the disease and its long-term effects
- virology, immunity, and pathophysiology
- epidemiology.

The call received 30 applications.

NIHR-UKRI Long-term COVID-19 effects in non-hospitalised individuals (Long COVID) (November 2020)

Research funded to address the causes (biological and environmental), mechanisms and management of the longer-term physical and mental health effects of COVID-19 infection as well as reducing health inequalities in non-hospitalised individuals. Projects may draw upon the learnings from other conditions or syndromes that might have some similar symptoms encountered by long COVID (for example, stroke, multiple sclerosis, chronic fatigue syndrome or myalgic encephalomyelitis, and post-traumatic stress disorder) and their management.

While the scope of the funding call is on the longer-term biological and health impacts of COVID-19, proposals may capture or consider societal factors and demographic characteristics that influence these outcomes, and any downstream social and economic effects (for example, returning to work, impacts on carers).

Example areas that the research may address include but are not limited to:

■ determining whether long COVID is a distinct syndrome or a set of syndromes.

■ identifying whether an identifiable subgroup of symptoms exists.

■ determining the prevalence of long COVID.

   – understanding factors that increase or diminish the risk of long COVID, this might include viral titre, age, gender, ethnicity, socioeconomic status, or comorbidities.

      • comparison with other cohorts, for example, seasonal influenza.

   – understanding the trajectory and how people experience long COVID over time including any biological, social, or ecological interactions that impact on the severity of symptoms.

■ determining the pathogenesis of long COVID.

■ developing and assessing the effectiveness of approaches to reduce the risk of long COVID or interventions and therapies to address its impacts.

■ management of long COVID in primary care and social care settings.

Four awards were made from 46 applications.

Individually coordinated initiatives

COG-UK

Established in March 2020, the COVID-19 Genomics UK Consortium (COG-UK) brought together NHS, Public Health Agencies, the Wellcome Sanger Institute, and numerous academic institutions to delivers large scale, rapid sequencing of the virus and share intelligence with hospitals, regional NHS centres and the government.

By looking at the whole virus genome in people who have had confirmed cases of COVID-19, scientists can monitor changes in the virus at a national scale to understand how the virus is spreading, whether different strains are emerging, and whether changes in the virus affect the severity of disease. The MRC Human Genetics Unit (MRC HGU), as well as many other researchers and major investments from within the MRC community, partner with the COVID-19 Genomics UK Consortium. (Initially ~£20m funding from across UK and government funders, including a £5m in-kind contribution from the Wellcome Sanger Institute (MRC committed £6m); subsequent additional support £12.2m DHSC and £1.2m MRC additional support for CLIMB (COG data and analysis management)).

The COG-UK Consortium is identifying SARS-CoV-2 variants, the global public health priority of the moment. Professor Sharon Peacock, head of COG-UK, realised that mutations and variants could pose a potential threat in late 2019. In March 2020, she led the development of COG-UK. She successfully sought funding and support from Sir Patrick Vallance, the UK government's chief scientific adviser, Professor Chris Whitty, chief medical officer for England, UKRI and Sir Mike Stratton, director of the Wellcome Sanger Institute. The COG-UK network of experts, from virologists to immunologists, analyse up to 30,000 genomes from positive tests a week. "We are ready to carry on identifying important variants that threaten the effectiveness of vaccines" says Prof. Peacock.

GEL-GenOMICC COVID-19 study

Established April 2020, this project was integrated into the already actively work to understand individual increased vulnerability to serious illness of the GenOMICC consortium. Working with Genomics England this project will sequence the genomes of thousands of patients with COVID-19 to understand how genetic makeup can influence susceptibility to the virus. Genomics England was initially setup to sequence 100,000 whole genomes from NHS patients with rare diseases and common cancers. Funded by MRC, NIHR, NHS England, Wellcome and CRUK. Genomics England is now working with the GenOMICC consortium to sequence the genomes of thousands of patients with COVID-19 to understand how genetic makeup can influence susceptibility to the virus. This includes up to £3m MRC/UKRI investment targeted

at younger individuals with severe symptoms but no underlying health conditions. GenOMICC, initiated in 2016, is a global community of doctors and researchers funded by MRC with Wellcome, Sepsis Research and the Intensive Care Society. The initial study was designed to investigate emerging infections including SARS and MERS and is therefore well placed to respond to the COVID-19 pandemic.

COVID-19 Protein Portal

Established May 2020, the Covid-19 Protein Portal, an initiative led by UKRI major investment institutes, Wellcome and UKRI, allows UK scientists to access protein reagents needed for critical research relating to SARS-CoV-2 from a consortium of leading protein production laboratories. MRC funded Institutes and Units including the MRC Protein Phosphorylation and Ubiquitylation Unit, the Francis Crick Institute, the MRC Laboratory of Molecular Biology and the MRC-University of Glasgow Centre for Virus Research are partners in the Protein Production Consortium, with vast expertise in protein and reagent production. The Portal has the potential to accelerate vital research towards delivery of effective clinical management of COVID-19. The portal was used extensively in 2020 and closed in 2021 as the need diminished.

International coordination

MRC is also contributing to the co-ordination of international research efforts via three international coordinating bodies formed to improve the global response to epidemic threat: The WHO's Global Coordinating Mechanism for Research and Development (GCM), the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) and the UK Collaborative on Development Research (UKCDR). The **UKCDR** is co-funded by UKRI alongside the Wellcome Trust and forms a crucial part of the UK international development landscape promoting coherence and link up development research funding in the UK. To that end, UKCDR supports an Epidemics Preparedness and Response Group, helping to coordinate UK research efforts against COVID-19; this group involves five UKRI councils (MRC, AHRC, BBSRC, ESRC and NERC), DHSC, DIFD, Wellcome and the Academy of Medical Sciences.

A key aspect of the UKCDR's preparedness groups work was to establish, with support from GloPID-R, the COVID-19 Research Project Tracker. Beginning in early March 2020, the team behind the tracker aimed to collate information on new research awards made internationally: a significant undertaking in data collation with added benefits such as centrally categorising awards against the WHO roadmap for COVID-19 research (see ANNEX 4.4). MRC took a leading role facilitating this project tracking effort, ensuring that details of UKRI projects were rapidly submitted to this dataset, wrote to hundreds of funding agencies worldwide to encourage similar participation and coordinated with UKRI Central teams to ensure UKRI data was harmonised and presented accurately. MRC also proposed linking this dataset to the new COVID-specific grant finder within Europe PMC and continue to provide data feeds between the European Bioinformatics Institute team and UKCDR. This collaboration brings a regularly updated funding database of COVID-relevant work to a worldwide audience.

National Core Studies

The National Core Studies programme is enabling the UK to use health data and research to inform both our near and long-term responses to COVID-19, as well as accelerating progress to establish a world-leading health data and research infrastructure for the future. The COVID-19 National Core Studies consists of six programmes, of which three (Data and Connectivity; Longitudinal Health and Wealth; Immunity) are supported by MRC.

COVID-19: Data and Connectivity: National Core Study (D&C-NCS) led by HDR UK (£8.3m + £15.2m Phase 1 funding: spend from April 2021). The Data and Connectivity study sits across the other National Core Studies and aims to build a national health data research capability to support COVID-19 research questions, ensuring datasets are discoverable and accessible and linkages are established to answer the priority research questions from the other five National Core Studies. Making data available for wider research use will increase the scope of benefits beyond the specific studies above, leading to unexpected benefits and boosting UK research capacity more generally, increasing return on investment for the NCS programme. Data integration and harmonisation of methods and standards will enable rapid research and development of new interventions and technologies across the spectrum of COVID-19, and knowledge and technology transfer to other clinical and public health areas.

October 2020-March 2021 the Data and Connectivity study will:

- Map the initial high priority COVID 19 datasets required by the National Core Studies.

- Deliver the necessary data infrastructure and services (quality and timely data, ability to link the data and provide access to data for multiple researchers) in 5 Trusted Research Environments across the UK to allow the initial high priority research questions to be answered efficiently in a transparent and trustworthy way.

- Deliver a single "shop window" for the COVID-19 National Core Studies to ensure the priority datasets for COVID 19 research are findable, accessible, interoperable, and reusable (FAIR) by enhancing the UK Health Data Research Innovation Gateway.

Collation and linkage between datasets is critical to bringing the core studies together, ensuring that each of them can deliver against their policy priorities e.g. hospital data may not currently be linked with GP data and wider community data (e.g. socioeconomic data or data on housing and the built environment). Access, cleaning, linkage and use of these datasets together is needed to fully understand links between these factors and outcomes. Delivery of the COVID-19 Data and Connectivity Study will involve close interaction with data custodians, the public and patients, and providers of UK-wide national Trusted Research Environments (TREs) to ensure the required data is stored safely and securely, made readily available to approved researchers and is associated with compute, analytical and data services that make it easier to address priority research questions in a transparent and trustworthy way.

COVID-19 Longitudinal Health and Wealth: National Core Study (LWH-NCS) led by Prof Nishi Chaturvedi at UCL (£9.9m + £9.0m Phase 1 funding: spend from April 2021). The Longitudinal Health and Wellbeing National Core Study will improve understanding of C-19 infection risk factors, examine the physical and mental health consequences of asymptomatic to hospitalised cases, and assess the impact of population scale mitigation policy. We will unite distinct, but complementary, longitudinal studies already engaged in C-19 research, including UK representative population and hospitalised cohorts, household panel surveys, and national primary care registries. These will be enriched with health and administrative data linkage. Linkage, self-reporting and repeat serological assessment will allow greater precision in case assignment. This collective resource will be mined by a consortium of experienced analysts linked to these resources to provide rapid answers to existing and emerging priority research questions. For the first 6 months, these include short- and medium-term physical and mental health impacts of those who have had C-19 infection, risks of re-infection and role of risk factors, health effects of interruption to health care services, and the interplay between socioeconomic and health effects of viral suppression policies. Our outputs will include briefing notes as well as scientific reports to optimise policy influence.

This study will generate greater understanding of risk factors related to Covid-19 outcomes (e.g. from individual risk factors to wider environmental risk factors), as well as information on the burden of both short- and long-term health and wider outcomes related to Covid-19 and interventions. This information is required to:

- better manage individual cases,

- understand and balance the impact of interventions

- stop direct Covid-19 transmission and,

- manage health impacts against unintended or negative effects of these on e.g. physical and mental health.

This will enable more targeted policy interventions that better consider overall outcomes. Further studies will aim to examine the mechanisms under which different health outcomes are experienced and where best to target public policies.

October 2020-March 2021:

- Establish the determinants of C-19 re-infection in the community
- Identify the short- and medium-term health (physical and mental) health impacts of those who have had C-19 infection
- Establish the impacts of NPIs on health behaviours (e.g. exercise, diet), and on health (e.g. obesity, mental distress)? These outputs will specifically help:
- identify high risk groups that may require protective measures
- determine target interventions to avoid or diminish health effects of infection in high risk groups
- Quantify the early health risks of viral suppression measures and inform policy to mitigate these risks.

COVID-19 Immunity: National Core Studies (IMM-NCS) led by Prof Paul Moss at the University of Birmingham (£7.2m + £6.7m Phase 1 funding: spend from April 2021). Understanding immunity against Covid-19 to inform back-to-work policies. This study will coordinate research programmes and infrastructure to ensure key questions on immunity are being answered, from basic understanding of the immune response, through duration and nature of immunity, to the impact of pre-existing immunity to other coronaviruses on Covid-19. It will build on results generated by previous UKRI studies but will not delve into new areas of research which falls under the UKRI agile call. This information is required to inform specific policies related to immunity in individuals and policies that are impacted by the level and dynamics of immunity in the population. As we enter winter the answer to these questions is vital to restrict spread of Covid-19. It will inform policy relying on the results of specific antibody tests, and/or policies related to the likelihood of those who have previously been infected experiencing severe disease again. This risk is increased in the next 6 months.

October 2020-March 2021:

- What are historical infection rates in patients who have been shielding and which clinical groups will be at specific risk from Covid-19? How can we minimise and control this challenge? Policy Outcome: DHSC. Guidance on shielding policy

- What are the features of the SARS-CoV-2 specific immune response and how does this differ in asymptomatic and severe infection? How can we use this information to improve protective immune responses in patient groups? Policy Outcome: DHSC, UKRI. Building immunity into the power of the NCS cohorts to develop new prognostic and therapeutic opportunities for severely ill patients

- How does the magnitude, profile and duration of immunity compare within different demographic groups, and does it prevent re-infection? Policy Outcome: DHSC, UKRI. Insight into protection and potential transmission from different age groups, e.g. children and younger adults.

- Do immune responses contribute to early and late complications of SARSCoV-2 infection, is this related to the severity of the first infection and how can this be managed optimally? Policy Outcome: DHSC, Treasury. What will be the policy and cost implications of management of late-disease complications including 'long-Covid'?

- What are the optimal cellular assays to measure immunity to Covid-19?

Development of reliable and effective tests to support policy of 'immune protection'. Immunity underpins susceptibility, severity of disease and protection. These proposed studies of immunity have been designed to build around associated NCS investments (e.g. surveillance, data, transmission) to offer solutions 'at scale' that could NOT be addressed through traditional UKRI support mechanisms.

Annex 4.2

COVID award funding process

Over 2020, MRC managed COVID facing calls attracted 3000 applications of which 135 were funded, a 4.7% success rate.

The applications were processed through nine different call processes:

- **UKRI-NIHR COVID-19 Rapid Response Initiative (RRI) (February 2020)**
  - UKRI-NIHR COVID-19 Rapid Response Call 1 and Call 2 (Feb 2020)
  - UKRI-NIHR COVID-19 Rapid Response Rolling Call (April 2020)
- **UKRI COVID-19 Rapid Response Rolling call (RRR) (March 2020)**
- **EDCTP COVID-19 Response call (April 2020)**
- **UKRI GCRF/Newton Agile Response call (May 2020)**
- **Global Effort on COVID-19 Health Research COVID-19 (GECO) (May 2020)**
- **UKRI COVID-19 Agile call (Agile) (August 2020)**
- **UK-India COVID-19 partnership initiative (October 2020)**
- **NIHR-UKRI Long-term COVID-19 effects in non-hospitalised individuals (Long COVID) (December 2020)**

A summary of this activity is found in Section 4. Further details about awards can be found in Annex 4.1.

**UKRI-NIHR Rapid Response Initiative processes (February 2020)**

The initial design for the UKRI-NIHR Rapid Response Initiative (RRI) was created in February 2020. The remit for the initiative was to support research to understand, prevent, treat and control COVID-19. The first two calls addressed: **Call 1: active intervention development** including vaccines and therapeutics and **Call 2: diagnosis and understanding** of COVID-19. Both calls were launched in late February with applications reviewed, triaged, and brought to panel in March. In addition to the usual assessment of scientific quality, applications were assessed for the likelihood of the work having a public health impact within the period of the award; whether they addressed priorities identified in the WHO R&D Roadmap; and their contribution to a coordinated research response/portfolio of COVID-19-relevant research.

The rapid turnaround time placed a significant demand on staffing resource to manage review, organise and convene the panel, and process the assessment of the extensive response from the research community. Call 1 received 59 applications with the panel funding 6 projects and Call 2 received 213 applications of which 21 were funded. The diversity of research fields covered by the applications for Call 2 required an extremely broad set of expertise for the initial review, from which 213 applications were triaged to 62, and three panels for final assessment: diagnostics (16 applications), epidemiology (25 applications) and social sciences (21 applications).

In response to the high level of engagement of the research community, a **novel** rolling call was added to the RRI. From April to July, 718 applications were received and processed by the Programme Managers, 546 were sent for review and triaged and 152 were assessed by 19 expert panels (no data for panel 17). An external peer review college was established by NIHR and 20 expert peer review panels were convened by to make the award decisions. In additional to the 17 panels convened to assess general COVID-19 research applications, 3 expert review panels were convened to assess applications

submitted in response to highlight notices in Ethnicity (66 applications), Mental Health (64 applications), and Transmission (24 applications). NIHR was given right of refusal for all award decisions.

Panel meeting notes and data indicate that initially the weekly (on average) panel meetings were carried out effectively and with significant enthusiasm and good will. Over time the application numbers increased and both administrative, reviewer and panel fatigue began to appear. The chart below indicates the increasing burden and challenge in processing and reviewing the applications.
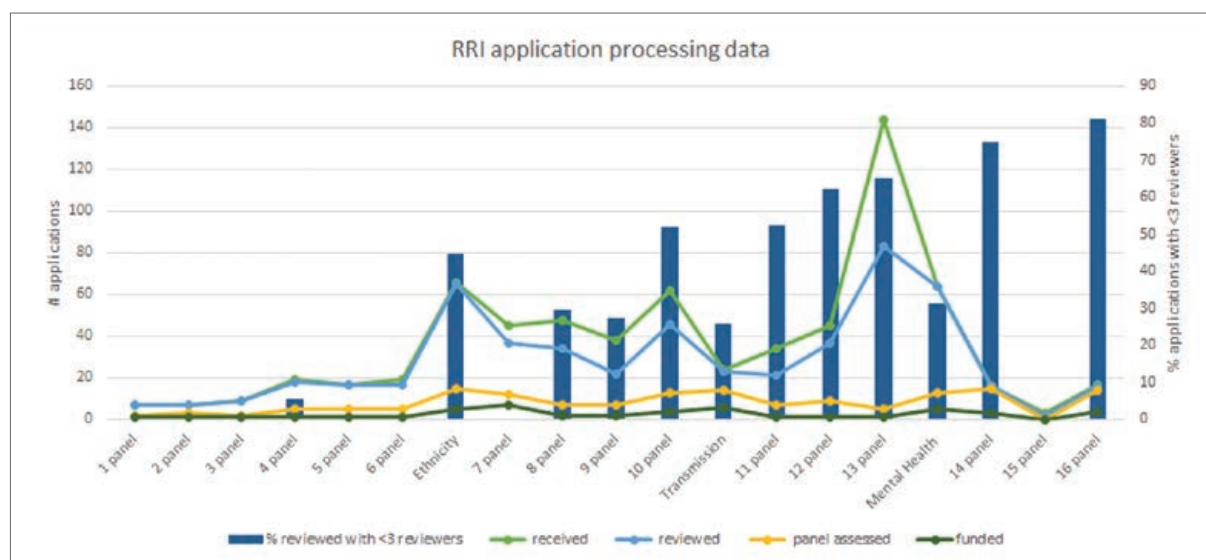
Over four months (excluding panel 17), 691 applications were received, 540 external peer-reviewed, 152 assessed by panels and 46 awarded. This is a success rate of 7% with ~65% of applications receiving 3 or more external reviews. While the exact data for panel 17 is still being compiled, ~ 29 applications were considered and 6 were awarded bringing the total to 79 awards from ~992 applications (8% success rate) over 7 months. For context, all four MRC Boards, employing an automated system, standard procedures, and an experienced team of staff, would process ~900 applications over the course of a year with current success rates around 10%. Only 10 of the awards not funded scored a 7 or higher at panel assessment indicating a large volume of substandard applications.

It appears, from early panel meeting notes, that all clinically based trials and studies were considered for UPH badging in the discussions, but this happened less consistently in later panels resulting in clinically based studies being significantly impeded by limited access to patient groups.

UKRI COVID-19 Rapid Response Rolling and Agile call processes (April 2020)

The UKRI COVID-19 rolling call awarded projects on a wide range of coronavirus pandemic-related research and innovation projects addressing and mitigating the health, social, economic, cultural, and environmental impacts of the COVID-19 outbreak in an 18-month timeframe. The **UKRI Rapid Response Rolling** call was launched April 2020 and closed in July with new and deferred applications going to the **Agile rolling call** which ran from September to December. The combined parts of the rolling call received 3999 applications with 482 (this number is still being confirmed) awarded funding.

Applications were initially received by the EPSRC UKRI who allocated them to the sister Research Councils based on researcher designation. In total, 1079 (27%) applications were distributed to MRC staff for suitability for remit and the call requirements. Across all Councils, the UKRI Rolling call had a 12% award rate while MRC had a 6% award rate (27 of 460 applications within the MRC remit).

Those within remit were triaged by review and the remaining grants submitted for panel assessment. For the **UKRI COVID-19 Rapid Response Rolling** call, MRC and UKRI convened 6 funding panels in 7 weeks during spring and early summer. MRC staff processed ~800 applications over four months. 696 were within MRC remit, 349 applications with agreed MRC lead responsibility and 347 with MRC interest to be handled by other Councils. Reviews were solicited and applications triaged before panel meetings. 9 applications were awarded with MRC as lead Council.

To facilitate rapid response to the pandemic, the RRR applications were processed manually off-line. At the end of summer 2020, the application submission process returned to normal and applications were submitted to Je-S. There was an administrative transition which was marked by the close of the RRR process in July and the initiation of the Agile call process in August. The **Agile call** assessment began with 56 applications rolled over from the RRR process call; an additional 279 applications distributed to MRC for remit assessment by the December cut-off date. 141 applications were determined not to have an MRC interest or out of scope and in 27 applications the MRC had a minor interest and provided referees to the lead council panel. The Agile panel met monthly from September through March 2021 considering 167 applications. The applications were externally reviewed and triaged by head office staff before the panel meeting. The panel provided detailed assessment of the subset of applications triaged by external review; they were also given the opportunity to assess the applications that were triaged out and include them in the subsequent panel assessment it was deemed appropriate. This process served through January.

The announcement of the end of the rolling call resulted in a large influx of applications at the end of December necessitated a resource intensive and expedited triage process for the February and March panel meetings. Head office staff reviewed all applications received in December (~260 apps) over the Christmas break, determined which were within MRC remit, prioritised projects requiring rapid decisions (e.g. vaccine monitoring in population subgroups), and convened a panel triage meeting to trim down the applications for assessment to a manageable 18.

Of the 325 applications processed through the Agile call, 17 grants were awarded within the MRC remit.

EDCTP COVID-19 Rapid Response Call process (April 2020)

This call was run by the EU EDCTP staff with applications reviewed, triaged, and assessed by an expert panel. NIHR and MRC contribution to the funding was distributed across the 11 projects (of 20 awarded) with UK researchers. MRC contributed £2m.

UKRI GCRF/Newton Agile Response call process (May 2020)

This call and awards are managed by UKRI central staff with MRC providing area expertise, an advisory role to ensure complementarity with the GECO call, and representation on the funding panel. Nine awards were funded.

Global Effort on COVID-19 (GECO) Health Research initiative process (May 2020)

The GECO initiative was designed to support applied health research that will address COVID-19 knowledge gaps. The focus is on understanding the pandemic and mitigating its health impacts in LMIC contexts.

The call was launched May 2020 with applications accepted through September. The applications were assessed and sent for review by head office staff, triaged and presented to the award panel over three meetings. The funding was equally divided between NIHR and MRC GCRF funds.

Three awarding panels were convened:

- July 2020:
  - 31 applications considered (out of 147 submitted, 18 out of remit)
  - 12 awards agreed committing ~£7.65m
  - 5 awards to research organisations in LMICs

- September 2020
  - 24 applications considered (out of 202 submitted, 32 out of remit; 25 applications were deferred from Rounds 1 and 14 were deferred leaving 181 applications to be processed for panel)
  - 9 awards agreed committing ~£5.25m
  - 2 awards to research organisations in LMICs
- January 2021
  - 501 applications considered: 77 out of remit
  - 21 awards were determined appropriate for funding
  - Awarding suspended February 2021

The decision to sharply reduce ODA funding in early 2021 necessitated a review of funding available for any new awards. As of March 2021, only 19 of the 850 applications will be able to be funded.

UK-India COVID-19 partnership initiative process (October 2020)

This was to be a collaboration between UK and Indian Research funders: MRC and Department of Biotechnology, Government of India (DBT) with the UKRI funds derived from the Funding International Collaboration Strategic Opportunities budget. The call was run jointly between MRC and DBT. 30 applications were received, reviewed, and assessed by an expert panel; 4 awards were made. The changes in ODA rules in the UK and changing economic conditions in India held up the awarding decision significantly. Adjustments to the proportion of funding provided by each partner had to be made.

NIHR-UKRI Long COVID process (November 2020)

The call for research into the causes (biological and environmental), mechanisms and management of the longer-term physical and mental health effects of COVID-19 in non-hospitalised individuals was co-funded by MRC and NIHR. 46 applications were received in 2020, reviewed and assessed by an expert panel in January 2021. Four programmes have been funded with a commitment of £18.9m.
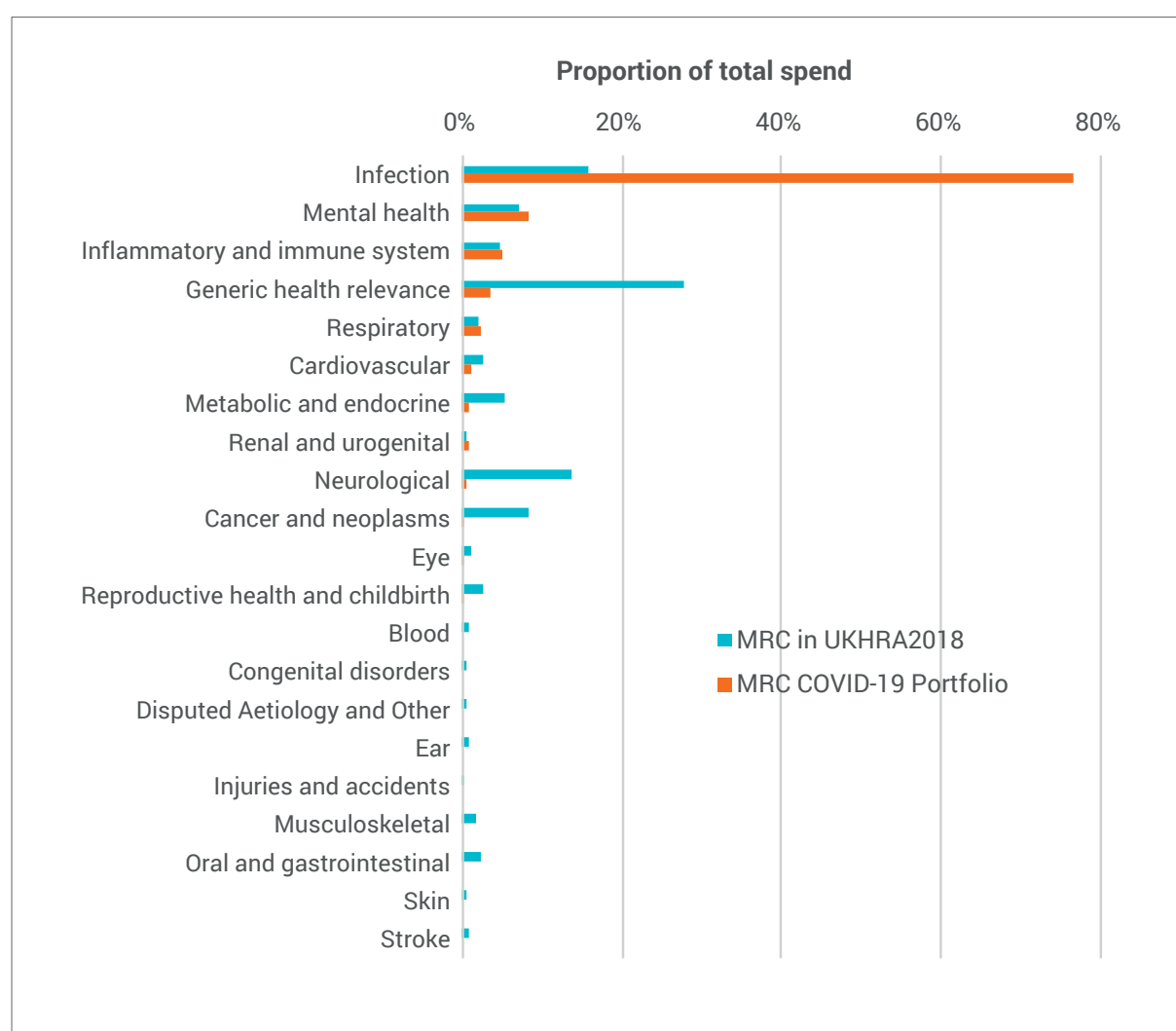
Annex 4.3

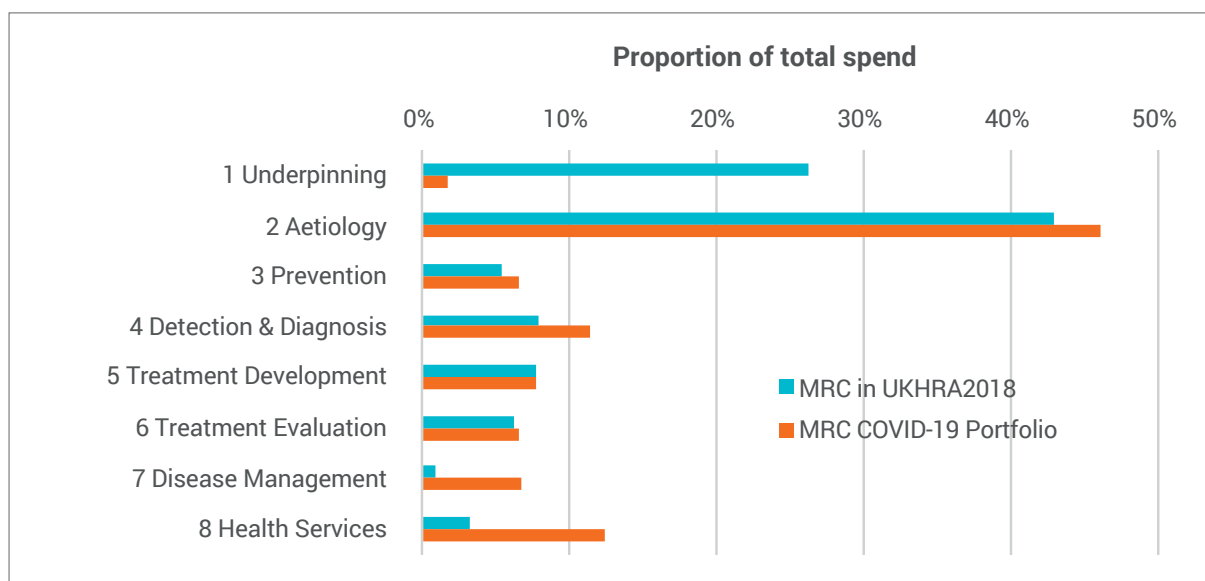## COVID-19 research portfolio analysis

Classification of the total MRC COVID-19 award portfolio

COVID-19 portfolio HRCS classification in comparison to MRC2018 portfolio

(i) Proportion of spend by HRCS Health categories

(ii) Proportion of spend by HRCS Research Activities

Proportion of total spend

Annex 4.4

WHO Research Priorities

(used to classify MRC-supported COVID-19 portfolio in ANNEX 4.3)

World Health Organisation: A Coordinated Global Research Roadmap: 2019 Novel Coronavirus, March 2020[46]

1	Virus: natural history, transmission and diagnostics
1.a	Support development of diagnostic products to improve clinical processes.
1.b	Understand virus compartments, shedding and natural history of disease.
1.c	Develop tools and conduct studies to monitor phenotypic change and potential adaptation.
1.d	Characterize immunity (naturally acquired, population and vaccine-induced, including mucosal immunity).
1.e	Develop disease models (animal models and 3Rs approaches)
1.f*	Virus stability in the environment

2	Animal and environmental research on the virus origin, and management measures at the human-animal interface
2.a	Investigation of animal source and route of transmission
2.b	Socioeconomic and behavioural risk factors for spill-over
2.c	Risk reduction strategies at the human-animal environment interface

3	Epidemiological studies
3.a	Transmission dynamics – Clarify the relative importance of pre-symptomatic/asymptomatic transmission (including distinction between virus shedding and infectious transmission)
3.b	Disease severity – Identify groups at high risk of severe infection; Determine the role of different age groups in transmission
3.c	Susceptibility – Determine if children are infected, and if so, are they infectious?
3.d	Control and mitigation measures – Predict the most effective measures to reduce the peak burden on healthcare providers and other societal functions; Estimate the effects of social distancing measures and other non-pharmaceutical interventions on transmissibility

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46. https://www.who.int/blueprint/priority-diseases/key-action/Coronavirus_Roadmap_V9.pdf?ua=1

4	Clinical characterization and management
4.a	Prognostic factors for severe disease (Different populations – pregnancy, young children, risk groups – immunosuppressed)
4.b	Understand pathophysiology of COVID-19 infection, including understanding mild disease and the role of co-infections / infection, transmissibility, viral shedding
4.c	Optimal endpoints for clinical trials
4.d	Improve processes of care, including early diagnosis, discharge criteria; Determine interventions that improve the clinical outcome of infected patients (Steroids, High flow oxygen therapy)
4.e	Optimal adjuvant therapies for patients (and contacts)
4.f*	Develop core clinical outcomes to maximize usability of data across range of trials

5	Infection prevention and control, including health care workers' protection
5.a	Effectiveness of restriction of movement of healthy exposed and infected persons to prevent secondary transmission (home, congregate setting, geographical restriction vs nothing)
5.b	Effectiveness of specific PPE to reduce the risk of COVID-19 transmission among HCWs, patients and individuals in the community
5.c	Effectiveness of activities to minimize the role of the environment in COVID-19 transmission
5.d	Factors and methods influencing compliance with evidence-based IPC interventions during outbreak response

6	Candidate therapeutics R&D
6.a	Develop in vitro and in vivo testing to identify candidates
6.b	Evaluate efficacy and safety in prophylactic use
6.c	Promote adequate supply of therapeutics showing efficacy
6.d	Evaluate efficacy and safety of therapeutics through randomised clinical trials
6.e	Investigate combination therapies

7	Candidate vaccines R&D
7.a*	Identification of candidates for clinical evaluation in addition to the ones already prioritized.
7.b	To develop and standardize animal models to evaluate the potential for vaccine effectiveness and to understand the potential for enhanced disease after vaccination. Results from animal models are expected to be important prior to large-scale efficacy studies and prior to studies in which enhanced disease is considered a significant possibility.
7.c	To develop and standardize assays to support vaccine development, particularly to support the evaluation of immune responses and to support clinical case definition. Basic reagents should be shared to accelerate the development of international standards and reference panels that will help support the development of ELISAs, pseudovirion neutralization and PCR assays.

7	Candidate vaccines R&D
7.d	To develop a multi-country Master Protocol for Phase 2b/Phase 3 vaccine evaluation to determine whether candidate vaccines are safe and effective before widespread distribution, using methodologically sound and ethically acceptable vaccine trial design. Vaccine efficacy trials should be done if such are feasible to implement.
7.e	To develop potency assays and manufacturing processes to rapidly enable the production of high-quality large quantities of clinical grade and GMP materials.

8	Ethics considerations for research
8.a	Articulate and translate existing ethical standards to salient issues in COVID-19
8.b	Sustained education, access, and capacity building
8.c	The impact of restrictive public health measures (e.g., quarantine, isolation, cordon sanitaire)
8.d	Public health communications and the 'infodemic'; ensuring accurate and responsible communications
8.e	Ethical governance of global epidemic research

9	Social sciences in the outbreak response
9.a	Public Health — What are relevant, feasible, effective approaches to promote acceptance, uptake, and adherence to public health measures for COVID-19 prevention and control; and how can secondary impacts be rapidly identified and mitigated?
9.b	(Clinical) care and health Systems — What are the relevant, acceptable, and feasible approaches for supporting the physical health and psychosocial needs of those providing care for COVID-19 patients?
9.c	Media and communication — How are individuals and communities communicating and making sense of COVID-19? What are the most effective ways to address the underlying drivers of fear, anxieties, rumours, stigma regarding COVID-19, and improve public knowledge, awareness, and trust during the response?
9.d	Engagement — What are the relevant, acceptable, and feasible approaches for rapid engagement and good participatory practice that includes communities in the public health response.?
9.e	Sexual and reproductive health — What are the relevant, acceptable, and feasible approaches to communicating uncertainty regarding mother to child transmission of COVID-19, and possible sexual transmission?
9.f	International cooperation — What international coordination mechanisms can optimize the international response to COVID-19?

* These sub-priorities were added from "key milestones" or "other research priorities" listed in the document to help classify the data

Annex 5.1

MRC community COVID-19 response programme and project details

MRC partnerships, institutes, units and centres with notable COVID-19 activity during 2020

Full Official Name	(Internal) Acronym
MRC London Institute of Medical Sciences	LIMS
MRC Laboratory of Molecular Biology	LMB
Francis Crick Institute – virus biology and vaccine delivery	Crick
Health Data Research UK	HDRUK
UK Dementia Research Institute – social and data	UKDRI
MRC Biostatistics Unit	BSU
MRC Cancer Unit	CU
MRC/CSO Social and Public Health Sciences Unit, University of Glasgow	SPHSU
MRC Clinical Trials Unit at UCL – social and data	CTU
MRC Cognition and Brain Sciences Unit	CBSU
MRC Epidemiology Unit	EU
MRC Human Genetics Unit at the University of Edinburgh	HGU
MRC Human Immunology Unit at the University of Oxford	HIU
MRC Integrative Epidemiology Unit at the University of Bristol	IEU
MRC Lifecourse Epidemiology Unit, University of Southampton	LEU
MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee	PPUU
MRC Toxicology Unit	TU
MRC Unit The Gambia at the London School of Hygiene & Tropical Medicine	Gambia
MRC/UVRI and LSHTM Uganda Research Unit	UVRI
MRC-University of Glasgow Centre for Virus Research – virus biology & global	CVR
MRC Harwell Institute	MHI
Research Complex at Harwell	RCaH
MRC Centre for Medical Mycology at the University of Exeter	CMM
Wellcome – Medical Research Council Cambridge Stem Cell Institute	CSCI
MRC Versus Arthritis Centre for Muskuloskeletal Ageing Research	CMAR
MRC Centre for Global Infectious Disease Analysis	GIDA
MRC Centre for Environment and Health	CEH
UK Biobank – virus biology & transmission	UKBB

Notes on project references and sources

The details of these projects have been drawn from self-reported data, publications, and news stories from respective MRC investment websites. As these are ad hoc projects initiated by the research centres, we have used an internal identifier (C19-IUC-xxx) when referring to specific projects.

Details on active projects are incorporated into UKRI's COVID-19 Research Grant Tracker alongside new awards made by MRC and other UKRI partners.

Below are some examples of research projects involving MRC investments, grouped into six areas of scientific interest/expertise:

■ Understanding virus biology and immune responses

■ Modelling disease outbreak and understanding transmission

■ Societal and psychological impacts of COVID-19

■ Understanding the global context

■ Coordinating big data

■ Refinements to diagnostic testing and vaccine delivery

Understanding virus biology and immune responses

The pioneering UK BioBank, primarily funded by MRC and Wellcome, tracks the health of 500,000 volunteers in Great Britain aged 50-80+, by gathering data on blood biomarkers and genetics, along with healthcare data including cancer registrations and deaths. It is an invaluable resource for health research with information on genetic and other risk factors and is therefore well placed to help answer a wide range of questions about the COVID19 pandemic. Because UK BioBank data can be accessed by about 10,000 registered researchers in close to 80 different countries, it is making a major contribution to the global research effort on COVID-19. In addition, UK BioBank is involved in a dynamic linkage study (C19-IUC-226) that has enabled COVID-19 positive participants to be rapidly identified. This means that severe infections requiring hospitalisation can be investigated intensively to quickly identify genetic and other risk factors for severe infection. As of January 2021, UK Biobank now seeks to send antibody test kits to all 500,000 volunteers to allow investigations into the long-term health effects of infection across the full disease spectrum, such as "long-COVID" (C19-IUC-403).

The MRC Centre for Virus Research at the University of Glasgow (CVR) represents the UK's largest grouping of human and veterinary virologists. The Centre has contributed expertise to recent Ebola outbreaks, and is now working on the SARS-CoV2 virus with £0.5m of supplementary funding. Most recently, the CVR has established the COVID-19 Drug-screening and Resistance Hub (CRUSH) that will utilise their state-of-the-art containment facilities, drug screening pipelines, and technological platforms such as real time genomic sequencing and cryo-electron microscopy (C19-IUC-270). More details can be found on the dedicated CRUSH website. The CVR is also participating in a multicentre study on the use of Remdesivir to treat moderate and severe disease, funded by Gilead (C19-IUC-023), and will lead a clinical trial on Favipiravir. In addition, the trial will be linked to studies aimed to understand the viral and immunological correlates of clinical severity and response to anti-viral therapies. The study is funded by the Scottish Chief Scientist's Office.

The MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee, working in partnership with the MRC-University of Glasgow Centre for Virus Research (CVR), have developed the Coronavirus Toolkit, a resource comprising of expression plasmids, proteins, and polyclonal antibodies against each of the SARS-CoV-2 and related coronavirus proteins (PPU C19-IUC-108, CVR C19-IUC-025)). Researchers can use the toolkit to easily and immediately order materials such as antibodies and genetic tools via an online portal. The toolkit is important for many avenues of COVID-19 research, including characterising new variants of the SARS-CoV-2 virus. It will also help researchers to monitor vaccine efficacy and evaluate additional treatment options for Covid-19. To date, over 120 DNA clones,

70 proteins, and 42 antibodies have been produced and made available to researchers worldwide (for more details, see project impacts in ANNEX 2.2).

"The development of vaccines for Covid-19 is encouraging, but there is still a lot to learn about this virus. The simple genetic tools we've made available to the community will help scientists understand the role of individual changes in new variants of SARS-CoV-2 (which often contain multiple individual changes) – and our online toolkit and portal will allow scientists to access antibodies and other tools for research, at cost, at the click of a few buttons." – Dr Sam Wilson, Senior Research Fellow, CVR

The MRC Laboratory for Molecular Biology (LMB) is deploying its world-leading expertise in high resolution microscopy and structural biology to interrogate how the virus enters and replicates in cells. This includes making different kinds of disabled viruses, so-called 'pseudotyped' viruses, that contain the spike protein from SARS-CoV-2, which is used for cellular entry, but no viral genes, to allow scientists to safely study how the spike protein gets the virus into cells (C19-IUC-257). In addition, LMB teams are studying how the immune system responds to the spike protein, and other viral proteins which are important for vaccine and therapeutic antibody design.

In parallel, teams at the **Research Complex at Harwell**'s Diamond Light Source have examined the structure of SARS-CoV2 viral proteins, with a particular interest in the receptor binding domains of the spike protein and polymerase (C19-IUC-119). The whole complex is a science-led national resource, supported by several UKRI partners, and provides not only access to the synchrotron but also to the research hubs that surround it. Those hubs conduct their own research projects, including the development of nanobodies against SARS-CoV-2 spike protein for research, diagnostics, and therapy. The technology available at the complex allows for designing nanobodies against new variants, and to assess the structure of antibodies isolated from convalescent plasma (projects C19-IUC-119, -439 and -440 respectively).

The Francis Crick Institute has initiated a multidisciplinary research response to the COVID-19 pandemic, deploying their researchers' wide-ranging expertise in studying the underpinning biology of the virus, the production of recombinant proteins from the virus as a resource for immunological studies, chemical inhibitor screening, mechanistic studies, and their work in identifying the most effective treatments for people with severe disease. Researchers at the Crick have characterised the structure of the SARS-CoV-2 spike protein, as well as the spike protein of a closely related bat coronavirus; these structures provide valuable insights into the zoonotic origins of this novel virus, and could help inform vaccine design. More information can be found here on the Crick website.

The Wellcome MRC Cambridge Stem Cell Institute has a number of researchers involved in COVID-19 projects, including identifying genetic and structural similarities between SARS-CoV-2 and the Rubella virus, with implications that the MMR vaccine may provide protection against COVID-19 (C19-IUC-221).

MRC Human Immunology Unit (HIU) at the University of Oxford began investigating the immune response and immunopathology of the virus from its initial emergence in Wuhan, China. One such projects provides multi-dimensional high-throughput analyses of SARS-CoV2 immune responses and those elicited by vaccination using mass cytometry and flow cytometry. This will provide crucial early data to inform next steps in vaccine design and testing and will help identify T cell clones for future diagnostics and understanding disease pathogenesis (C19-IUC-177).

The **MRC Centre for Medical Mycology** is the UK lead for an international BRACE study, assessing the use of BCG vaccination to reduce the impact of COVID-19 in healthcare workers (C19-IUC-409). Although developed for TB, the BCG vaccination provides an off-target boost to the immune system and is already used as part of treatments for other diseases including bladder cancer.

Researchers at the **MRC Human Genetics Unit** (HGU) in Edinburgh launched CORONAGENES; recruiting from existing cohorts to associate human genetic variation and the spectrum of COVID symptoms – from very mild to severe – via an app-based survey (C19-IUC-095).

Modelling disease outbreak and understanding transmission

The MRC Centre for Global Infectious Disease Analysis (GIDA) is at the forefront of delivering timely analysis to inform policy responses to emerging infectious disease threats, and was rapidly awarded an additional £0.5m to support their real-time analysis and modelling of the SARS-CoV2 pandemic and the impact of COVID-19.

The MRC Biostatistics Unit (BSU) in Cambridge is also contributing to a wide variety of coronavirus-related projects, from clinical trial data to the impact of the pandemic on cancer treatments. In particular, the BSU have developed a methodology for real-time tracking of the COVID19 pandemic – or "nowcasting" (prediction of the present). Working closely with Public Health England (PHE), the researchers are using a transmission model, data on daily COVID-19 confirmed deaths and information on the risk of dying and the time from infection to death, to reconstruct the number of new COVID-19 infections over time (C19-IUC-397). This will help to estimate a measure of ongoing transmission (R); and predict the number of new COVID-19 deaths in different regions and age groups to help inform the public health response to the outbreak, by providing the R0 and attack rates by region.

The UK Biobank SARS-CoV-2 Serology Study (C19-IUC-227) sought 20,000 participants to measure the extent of coronavirus infection in different regions across the UK. They had over 116,000 volunteers allowing the researchers to select 20,000 individuals representative of the UK population. The volunteers provided monthly blood samples for at least six months so that their levels of immunity (antibodies in their blood) can be measured. Results published in February 2021 showed by the end of November 2020 8.8% of the participants had been previously infected and that antibodies were retained for at least 6 months in 88% of cases. UK Biobank plan to follow up this work with a repeat MRI scanning on a further 3,000 volunteers – half with COVI-19 antibodies, half without – to enable research into the effects of SARS-CoV-2 on internal pathophysiology (C19-IUC-404).

The **MRC Toxicology Unit** has identified a correlation between air pollution – specifically nitrogen oxides – and COVID-19 mortality and infectivity. In addition, Particulate matter with an aerodynamic diameter <2.5μm (PM2.5) correlated with an increase in COVID-19 cases after adjustment for socioeconomic, demographic, and health-related variables (C19-IUC-247).

Societal and psychological impacts of COVID-19

The impact of the COVID-19 pandemic on mental health will be investigated through six new projects worth a total of £2 million, awarded by UKRI and NIHR. These six projects will focus on reducing the negative effects on the mental health of at-risk groups such as healthcare workers, children, and younger people, and those with serious mental health problems.

The MRC Cognition and Brain Sciences Unit (CBSU) in Cambridge is carrying out a range of projects focusing on the psychological impact of COVID-19. For example, the Resilience in Education and Development (RED) Study will explore the impact of the COVID-19 pandemic on child development, education, and mental wellbeing. Baseline assessment data for this study was already collected before the pandemic, and now detailed information about family life in lockdown is being collected, with follow-up assessment data collection when children return to school. CBU scientists are also planning the Isolation Tracker project, to understand the effects of social isolation, and how different behaviours such as exercise, sleep, or technology use could mitigate or exacerbate these effects. The results from this project will be shared quickly to ensure that the learnings lead to the appropriate policy recommendations on which behaviours to encourage during the crisis.

The UK Dementia Research Institute (UKDRI) are characterising the neurological and cognitive effects of SARS-CoV-2 and using remote technology to assess people with dementia and carers in their homes. A rapid, robotics testing platform has also been developed and used by the Institute, to assess the COVID-19 infection rates in several care homes. The study highlights high rates of infection and death from the virus, and urges specific, tailored measures to manage the spread of disease.

DRI has 13 COVID-19 facing research projects, including:

- REACT – Paul Elliot – largest population study of seropositivity
- Neuro-COVID – Dr Patterson (DRI @ UCL)- effect C19 on brain
- UK Biobank population study of the effects of Covid-19 in brain and multiple organ systems.
- Prof Paul Matthews (UK DRI at Imperial) has jointly led 10 research (tools, effects, epidemiology), 3 contributing testing/analysis equipment/expertise to other programmes

The **MRC/CSO Social and Public Health Sciences Unit** (SPHSU) has been particularly active in the pandemic, examining the effects of COVID-19 restrictions on a range of demographic populations; children/education, mental health, healthcare staff, and socioeconomic inequalities. SPHSU, using data from UK Biobank, have recently published a study that indicated how some minority ethnic groups have a higher risk of confirmed SARS-CoV-2 infection, which was not accounted for by differences in socioeconomic conditions or baseline self-reported health or behavioural risk factors.

The **MRC Clinical Trials Unit** (CTU) is also coordinating an observational study called CoroNerve that aims to rapidly report neurological features of acute COVID-19 infection in the UK. Another study coordinated by the CTU is ICOS, an international study looking at understanding the disease progression in individuals with SARS-CoV-2 infection who do not require immediate hospitalisation.

The **MRC Integrative Epidemiology Unit** at the University of Bristol has not only contributed to a number of epidemiological cohort studies of COVID-19 but has also produced a COVID-19 Response Map, plotting social and community support efforts against the demand for such support, using a variety of open data sources and social media. This live map can quickly highlight areas that might be more vulnerable due to an imbalance between community support and community need, allowing for more effective allocation of limited social resources (C19-IUC-048).

The **MRC Centre for Environmental Health** (CEH) has – thanks to its extensive prior experience with environmental and demographic data – collaborated with many studies around COVID-19. Air pollution and social inequalities are recurring themes, but the centre has also been involved in other aspects of the pandemic, including the availability of local parks, the only available out-of-home space option for many citizens, and the impact on social distancing. While their research showed 87% of the population is within 10 minutes' walk of a public park, 19-50% of parks – primarily in high population density urban areas – would be unable to maintain minimum social distancing space if used at capacity (C19-IUC-195).

The **MRC Cancer Unit** at the University of Cambridge is assisting with the significant backlog of routine diagnostic testing within the NHS by assessing the role of the 'pill on a string' cytosponge as a quicker, cheaper alternative to traditional endoscopy (C19-IUC-225). For more details, see ANNEX 2.2.

Understanding the global context

The MRC/UVRI and LSHTM Research Unit Uganda has joined the research efforts by working on the full genome sequence of SARS-CoV-2 positive samples identified by UVRI, which will include analysis of sequence, and the phylogenetic placement within the global epidemic (C19-IUC-233). The work will contribute sequence data to global databases. Researchers are also investigating the psychosocial impact of COVID-19 in Uganda, to determine the coping mechanism of individuals suspected or diagnosed with COVID-19.

The MRC Unit The Gambia at LSHTM has been funded to conduct a clinical trial of potential therapeutic interventions (C19-IUC-112) and is coordinating with other research groups in the region and the WHO Solidarity trial. They are also investigating the effects of COVID-19 in pregnant women and new-born babies, based on an existing cohort study (C19-IUC-350).

CVR researchers, in partnership with Uganda Research Unit, KEMRI-Wellcome Trust Research Programme, London School of Hygiene and Tropical Medicine and University of Glasgow, have secured funding from the Wellcome Trust for a collaborative project – AFRICO19 – designed to enhance capacity to understand SARS-CoV-2 infection in Kenya, The Gambia and Uganda (C19-IUC-196).

The **MRC Epidemiology Unit** attained a Cambridge Africa Alborada COVID emergency call award to examine "sentiment and opinion analysis of public space physical activity in Lagos during lockdown" (C19-IUC-502). The research aims to contribute to public health messaging that safely encourages physical activity in the short term and health foresight interventions to reduce co-morbidity-associated vulnerability to future health emergencies long-term.

Coordinating big data

Health Data Research UK (HDR UK), the national institute for health data science, has been actively championing the use of health data to address the COVID-19 challenge and leading the world in terms of coordinating the availability and access to such a vital research resource. They are contributing to this global challenge by forging partnerships with government, NHS, industry, and academia. Teams are working on risk factors, genomics, clinical trials, care pathways and surveillance to help, for example, identifying which treatments and which clinical practices have the best outcomes for patients with COVID-19. These activities require access to – and linkage of – health data and HDR UK has built on their existing expertise and emerging capabilities to support this. In particular, HDR UK has driven forward the move from the traditional "data release" (bespoke data extractions which require significant time and resource to prepare and secure) to a model where the analysis (and analyst) accesses the data through a secure remote access service using the "Five Safes framework"[47].

Details of HDR UK's extensive pandemic-related work can be found on its dedicated COVID-19 webpages.

HDR UK has many partners in this work, working together to identify data sources and create linkages between different data repositories. These include the MRC IEU linking three datasets – Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), and COVID-19 Hospitalisation in England Surveillance System (CHESS) – to better estimate the risks of hospitalisation and mortality from COVID, according to chronic conditions and certain prescriptions (C19-IUC-051).

There are currently 120 Covid-19 datasets hosted on the HDR Innovation Gateway ranging from viral sequences (COG-UK), Covid-19 test results, Clinical information (NHS, ISARIC), Census/demographic data (ONS), clinical trials (e.g. REACT, RECOVERY, PRINCIPLE), symptoms trackers (e.g. ZOE), death registrations, and established cohorts (e.g. ALSPAC). Many of these are also MRC funded. These datasets can be accessed on request via the Innovation Gateway but are also accessible via the Trusted Research Environments for the UK nation's health services and the ONS.

If access to, and linkage between, these datasets is the 'how', HDR UK is actively involved in the 'why'; the prioritisation of research questions involving a wide range of metadata. These key activities are in part community-sourced via the HDR UK COVID-19 Activities + Skills Matchmaking Tool, an online spreadsheet. HDR UK are also implementing a prioritisation system to ensure that resources are appropriately directed to where they are needed.

HDR UK has direct access to SAGE via its Director, Prof Andrew Morris, and provides fortnightly reports to SAGE on data collation, accessibility and research results. SAGE has, in turn, endorsed the HDRUK Core Studies Programme and provided recommendations on prioritising research efforts.

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47. TREs protect – by design-are designed to protect the privacy of individuals whose health data they hold, while facilitating large scale data analysis using High Performance Computing that. Remote access, protected by multiple safeguards and cyber-security, allows researchers to access data without compromising anonymity. Thus researchers can make use of this vast quantity of data increases understanding of disease and improvements in health and care whilst keeping patient privacy and ensuring compliance with GPDR and other Data Protection legislation.

"HDR UK has created a Patient and Public Involvement (PPI) group *for members of the HDR UK community to ensure patients, carers and the public are involved throughout their work. Within the first month they shared their thoughts and ideas on our COVID-19 strategy and communication and have started helping us with our data access work. By sharing their questions and/or concerns around data access and, in particular, accelerated access to data they've been helping us determine if it's a lack of information that is available or if it's something we need to delve into deeper. A clear example of their impact was with the development of an app to estimate the possibility of death based on previous health factors. The initial feedback and input from the group has altered the future focus for this piece of work, truly showing the value of involving patients and the public from the beginning of research projects. "In my experience of working with different PPIE panels for research over the last 10 years this ranks among the most rapid, extensive and useful!"* –
Harry Hemingway, HDR UK Research Director for Human Phenome Strategic Priority".

By the end of December 2020 these efforts have resulted in 26 taskforce calls with 180 clinical/data leaders, 1,122 publications, 749 slack channel participants and 111 health data research questions identified. This strategy will ensure that the best of the UK's health data science capability will be leveraged to address the COVID-19 pandemic, accelerate access to UK-wide priority datasets, and coordinate and connect a national data science driven research effort across the UK.

In addition, HDR UK has taken a lead role in the global coordination of health data, convening the International COVID-19 Data Alliance (ICODA); an independent consortium of leading life science, philanthropic and research organisations uniting to respond to the COVID-19 global pandemic. Launched in July 2020, ICODA's mission has been to create a safe global platform for data access, use and analysis that respects confidentiality. Taking the approach spearheaded by HDR UK, ICODA aims to provide a TRE for the hundreds of global data repositories on COVID-19, which still suffer from fragmentation, mixed terminology and a need for greater coordination.

The **Cloud Infrastructure for Microbial Bioinformatics** (CLIMB) is the Big Data hub for COVID-19 Genomics UK consortium (COG-UK) and other microbial projects. This resource allows COG-UK to provide detailed track information on the transmission of COVID-19 through whole-genome virus sequencing. A further £2m in MRC support ('CLIMB-BIG-DATA, MR/T030062/1) will enable continued support for the COVID-19 research over the next five years. CLIMB has been supported by MRC since 2014 (MR/L015080/1) provides an essential national capability for microbiologists in the UK, serving more than 900 users and over 300 research groups scattered across at least 85 research institutions; from Edinburgh to Exeter, from Belfast to Norwich. dynamic bioinformatics platform to support academic research groups, government agencies and health service facing the challenges of big data in modern microbiology.

DECOVID is a highly granular, near real time clinical database and research environment from digitally mature NHS Trusts used to answer critical questions and improve patient care during the COVID-19 pandemic. Rather than basic, single day data the DECOVID database can include serial measurements (such as pulse rate, BP and O2 levels) alongside treatments prescribed and clinical outcomes, refreshed every 24hrs. The founding partners of DECOVID are University Hospitals Birmingham NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, The Alan Turing Institute (EPSRC funded), University College London and the University of Birmingham, but includes teams from the MRC Biostatistics Unit (C19-IUC-317), MRC Human Genetics Unit (C19-IUC-096), MRC Harwell Institute (C19-IUC-117), and CMAR (C19-IUC-128). See https://www.decovid.org/ for more details.

The **Lifelong Epidemiology Unit** (LEU) has supported the COVID-19 Open Research Dataset (CORD-19) an open, text-minable dataset of (primarily) publications related to Covid-19 backed by NIH and the White House (C19-IUC-053).

Refinements to diagnostic testing and vaccine delivery

The **Francis Crick Institute** was highly efficient at establishing the Crick Covid-19 Consortium in March 2020, establishing a diagnostic testing facility for the Crick and local NHS Trusts whilst publishing their SOPs for wider distribution. They have gone on to develop a novel, RT-LAMP methodology to allow easier prep (avoiding the need for expensive thermal cyclers) and shorter time to result, making it an invaluable tool for resource-poor settings (C19-IUC-353). Finally, in continuing the theme of rapid-rollout, the Crick has established a Vaccine Centre capable of vaccinating 1000 people per day and staffed by 300 Crick staff volunteers (C19-IUC-510).

The **MRC London Institute of Medical Sciences** (LIMS) are developing an early detection system for the coronavirus using Mango RNA aptamers. This emerging technology requires no RNA extraction or PCR cycling/reagents, making it suitable for sensitive, rapid (<30min) testing in the field directly from saliva samples (C19-IUC-073).

The **MRC Lifecourse Epidemiology Unit** at the University of Southampton produced some of the earliest work exploring the acceptability of a Controlled Human Infection Model (CHIM) as part of the effort to fast-track to a vaccine for Covid-19 (C19-IUC-330). The resultant paper was published in BMC Medicine July 2020 and was expanded into a larger public consultation to inform decisions about conducting a human infection studies.

Annex 5.2

Survey methodology for pandemic activities from MRC partnerships, institutes, units and centres.

Methodology for data collection

Information gathering on pandemic-related activities conducted by MRC partnerships, institutes, units, and centres (major investments) began on 01 April 2020 with a request from MRC's Chief Science Officer to the Directors responsible for MRC's major investments in the field. Initial email responses (203 activities reported, from 40/47 (85%) of the major investments) were collated by the Executive Support Team and subsequently transferred to MCMB for review. The Evaluation Team were then recruited to oversee the formalisation of reporting, with a follow-up request for additional details on 30 April 2020. By end of May 2020 the response rate was 41/47 (87%), with a revised total of 256 activities reported, of which 94 (37%) were active research projects.

Subsequent updates were partially automated; replacing email responses with a bespoke SharePoint spreadsheet for each investment to provide categorical and free text information on each project. This revised approach was used during the second round of data collection, run from August to September 2020, with a response rate of 35/47 (74%) but decent and with an increase to 328 activities reported, of which 161 (49%) were research active. The most recent request, at time of writing, was January-February 2021, with a response rates of 35/47 (74%) and 483 activities reported, of which 296 (61%) are research active or completed. The distribution of reported activities is available in the bar chart below.

While largely self-reported, at each stage of data collection the submissions have been viewed by MRC staff and supplemented – where appropriate – with additional information gleaned from investment websites, follow-up communications and news/comms sources.

Number of reported activities by MRC partnerships, institutes, units and centres
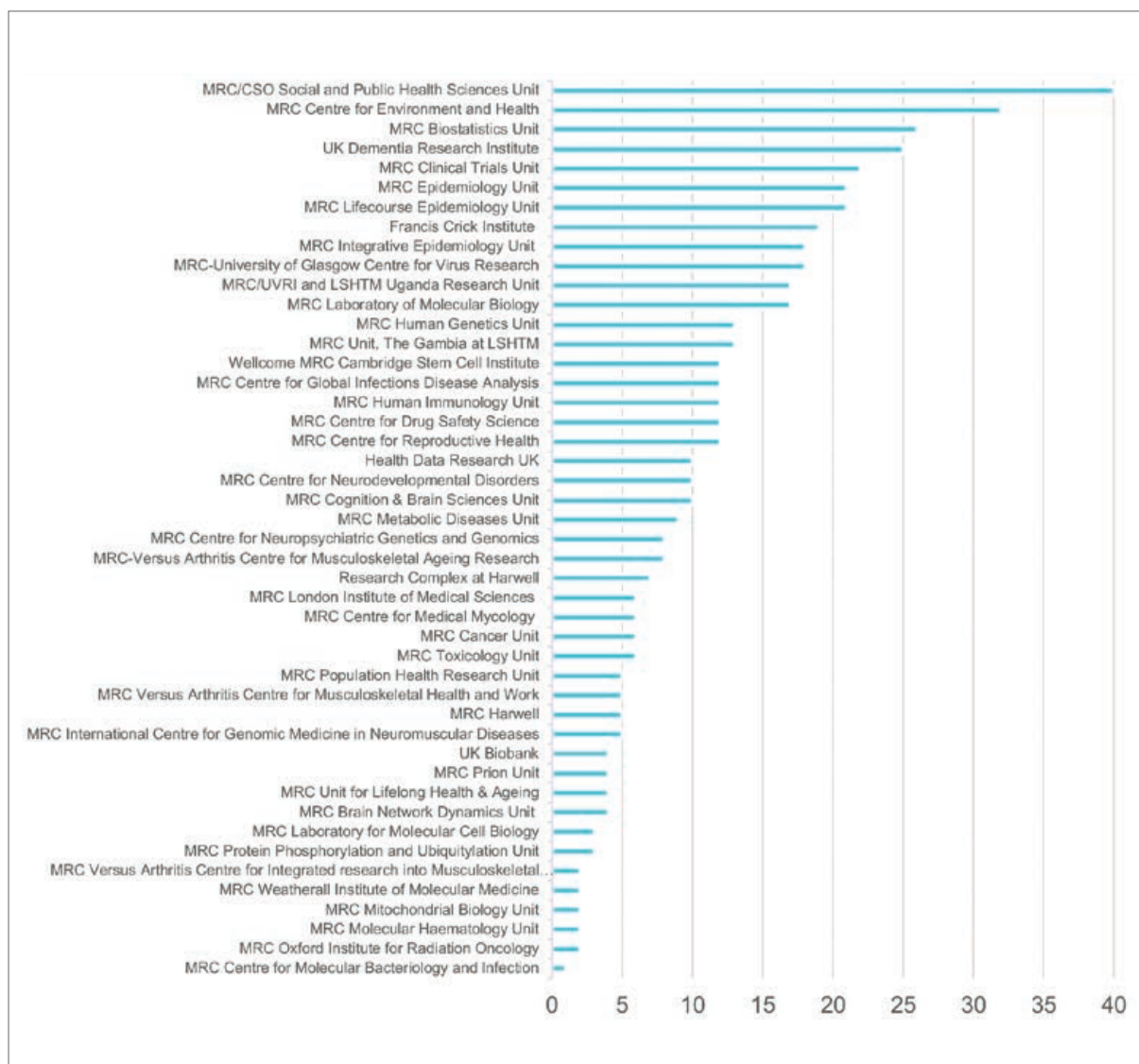
Note – This provides an overview of reported activity, and while this may be indicative of which MRC investments have been active in the pandemic the scope, scale and potential impact of individual reported activities vary considerably.

Annex 6.1

Epidemiology knowledge platform

Epidemiology is the study of the distribution of diseases or health states, and the application of this study to the control of diseases and other health problems. Population health is the study of biological and environmental influences on the physical and mental health of populations. Taken together, these two areas of medical research can offer insights into the determinants of health, wellbeing, and disease, while contributing to public health policy and changes in clinical practice.

In the context of the pandemic, epidemiology investments over the past several decades were vital for two key aspects of the UKIR's COVID-19 response. Firstly, by setting up the robust capability and expertise in disease modelling in the UK through strategic investments, scientists in this field were well positioned to inform government policy at the start of the pandemic and continue to do so as restrictions are gradually eased. Secondly, MRC-funded epidemiology projects helped establish the infrastructure provided by population cohorts, which were able to immediately respond to current needs and generate vital data on 'before' and 'after' pictures of the pandemic.

Disease modelling

Disease modelling is a multi-disciplinary subject that requires epidemiologists to work closely with clinicians, infectious disease specialists, immunologists, public health officials and others. The role of epidemiologists has been central in the COVID-19 pandemic; in particular, the mathematical models they have developed have been instrumental in understanding and predicting how the virus might behave and its impact on populations. These models have helped inform government policy around the world, at key stages of the pandemic. MRC has supported capacity building and expertise development in disease modelling over its entire history and specifically in the past decades through several strategic investments.

MRC Centre for Global Infectious Disease Analysis (MRC-GIDA): The GIDA is an internationally renowned centre of excellence for research and capacity building on the epidemiological analysis and modelling of infectious diseases. Since its establishment in 2008, GIDA has focused on making its work 'translational' – i.e. working with public health agencies and policy makers to use the research from GIDA to improve preparedness and responses to disease outbreaks. The GIDA has built long-term, sustainable partnerships with public health agencies and global health bodies such as the WHO, US-CDC, and the Bill and Melinda Gates Foundation, and works in priority areas with those organisations. These priorities have evolved to encompass delivering innovative epidemiological analysis of not only endemic diseases of major global health significance such as polio, malaria, HIV, and tuberculosis, but also of novel infectious disease outbreaks such as influenza.

In 2014, scientists at GIDA were approached by the Saudi Arabian government to assist them in risk analysis and modelling of the newly resurgent outbreak of Middle East respiratory syndrome (MERS), caused by a novel coronavirus. This was closely followed by an Ebola outbreak in West Africa, where GIDA dedicated a large team of researchers to providing real-time analytical support to WHO and country partners to analyse the case data being collected in the affected countries. The GIDA's work provided insight into the epidemiology of the Ebola outbreak, improved situational awareness of transmission trends, and assessed the effectiveness of the control measures being implemented. In 2015, the WHO declared the Zika epidemic in South America as a public health emergency of international concern and GIDA researchers were at the forefront of trying to understand the epidemiology of this previously under-studied virus, and of predicting the likely future trajectory of the epidemic. GIDA analysis published in 2016 accurately predicted an end to the Zika epidemic within three years, with the herd immunity developed within the population delaying further large-scale epidemics for decades.

All these infectious disease outbreaks have allowed researchers at GIDA to develop an increasingly rich library of analytical methods and statistical tools based on collective experience, which have been refined into a set of code libraries that can easily be deployed worldwide by public health agencies and researchers in future outbreaks. The GIDA's vital contribution to modelling the COVID-19 pandemic and informing government policy is detailed in ANNEX 2.2.

MRC Biostatistics Unit (MRC-BSU): The BSU is one of the largest groups of biostatisticians in Europe, and a major centre for research, training and knowledge transfer in biostatistics. Founded in 1913, researchers at the BSU have worked extensively to make inference from complex data accessible to the scientific community and are recognised for their strength in Bayesian inference applied to biomedicine and public health.

The BSU has expertise in working at the interface between statistics and infectious disease epidemiology, focusing on the development of statistical methods for the characterisation of epidemics, including natural history, burden and prediction of future evolution, informing the implementation and evaluation of public health policies. These methods were originally developed for monitoring and evaluating interventions in hepatitis C and influenza but were since adapted for COVID-19. The BSU's work in modelling the COVID-19 pandemic, particularly the refinement of methods for epidemic monitoring/prediction and severity estimation through nowcasting, forecasting and tracking R throughout the course of the pandemic have achieved prominence through their input into SPI-M which reports to SAGE which is helping to inform government policy.

Another key theme at the BSU is Design and Analysis of Random Trials (DART), and researchers within this theme are working on several current and future trials that are implementing novel methods. Members of the DART theme are active participants in the MRC Hubs for Trials Methodology Research Network, in particular the adaptive designs and stratified medicine working groups (ANNEX 6.4). Adaptive clinical trial expertise from BSU researchers has been invaluable for coordinating the multitude of treatment trials (ANNEX 2.1) including RECOVERY and PROTECT.

Cohort studies

MRC has funded an unparalleled collection of large-scale population cohort studies which provide a wealth of longitudinal phenotypic, biological and social data for studying health and wellbeing throughout the life course; one in 30 people (2.2m) in the UK take part in cohort studies. These cohorts have identified many important modifiable risk factors that predispose to disease and disability such as the influence of early life circumstances on health in later life, and the contribution of socio-economic position to overall health and health inequalities. In addition to providing insights into the determinants of health, wellbeing and disease, outputs from these studies have made significant contributions to public health policy and led to changes in clinical practice.

The Whitehall II Study was set up in 1985 to determine the factors that underlie the socioeconomic gradient in death and disease, and to include women in the cohort. Whitehall II findings led to the publication of the Marmot Review, 'Fair Society, Healthy Lives', in 2010 which outlined the most effective strategies for reducing health inequalities in England. The portfolio of population cohorts includes the world's longest running birth cohort (the 1946 birth cohort) and the largest longitudinal study of women's health (the Million Women study). These cohorts have had several key impacts; for example, the 1946 birth cohort provided the evidence for what is now perceived as common knowledge that early life plays a major role in many aspects of adult health such as blood pressure, obesity, respiratory health, mental health, reproductive ageing, physical and cognitive capability, and survival. As the participants enter old age, the next stage of the study will provide important insights into the ageing process.

UK Biobank

In addition to cohort studies, biobanks that store biological samples for use in research represent a valuable resource for medical research. The UK Biobank is the largest European biobank available to date and a flagship achievement for the UK. Launched in 2006 and funded jointly between the UKRI and Wellcome, it is a vast resource containing data from half a million UK individuals. It has set the standard for implementing population studies at this scale. It is more than a decade ahead of the NIH's launch of the US "All of Us" study which aims to recruit at least 1 million US citizens to find data-driven ways to improve human health. UK Biobank participants have already contributed a range of information about their lifestyles, physical characteristics and health: 100,000 are having whole body scans; 50,000 are having their whole genomes sequenced; the entire cohort will have their exomes sequenced through funding from the private sector; and the participants will be followed up for at least 25 years. Many research teams are interested in accessing the UK Biobank to examine specific associations between the genetic, physiological and lifestyle data accumulated by the programme, and long-term health and disease. UK Biobank has swiftly adapted to help tackle the COVID-19 pandemic by undertaking several major initiatives, for example with health data linkage, where data on the health of the 500,000 UK Biobank participants are being made available on a regular basis to registered researchers worldwide to undertake vital research into the genetic and lifestyle susceptibilities to COVID-19 and its long-term health consequences. Available data from health records include COVID-19 diagnostic test data, hospital inpatient data, death data and GP primary care data. To date, over 670 research groups have accessed the UK Biobank COVID-19 data, publishing over 60 papers in the public domain. Imaging data from UK Biobank participants are also a vital resource for understanding the longer term impacts of SARS-CoV-2 infection, and the UK Biobank COVID-19 repeat imaging study will help generate a unique resource to enable scientists to understand how the virus affects internal organs by collecting a second set of imaging scans from some people who have been infected with SARS-CoV-2 and from others who have not been infected.

Over the past decade, the UKRI Research councils and other major research funders have recognised the huge potential of health data research. The data collected by the resources described above as well as that being collected through surveillance of the current public health assault and the vast store of clinical health data in the UK requires continually improvements in data storage, access and analytical tools to insights they contain. Through careful and considerable investment, the funders have collectively built capacity in the sector and enabled a dramatic change in the use of large patient data and research datasets to help understand, treat, and prevent disease. MRC has prioritised strategic support to this domain of activity for more than 70 years. In 2017, MRC established the new national institute for health data science, Health Data Research UK (HDR UK) which plays a major role in the coordination of this broad portfolio of population health datasets.

Annex 6.2

Impacts of long-term historical investment by UKRI into structural biology

The structure of biologically important molecules is closely related to its function; understanding a protein's structure can therefore lead to understanding its function, which can in turn be targeted through drugs that can inhibit or enhance these functions. UKRI BBSRC, MRC and STFC have a strong and complementary history in funding ground-breaking research into the field of structural biology, spanning decades of strategic investment and support.

Key investments, major scientific breakthroughs, and impacts

Stable investment in structural biology over many years has provided a powerful springboard for research and innovation. In addition, these **key investments** in structural biology have led to **major scientific breakthroughs** and new technologies. The research councils have also nurtured an interactive community of researchers and funded specific **impactful research projects** in this field. For example:

- **First 3D structure of a protein (1958):** Myoglobin was the first protein to have its 3D structure determined, closely followed by haemoglobin, the blood's main oxygen transporter. In 1962, Dr Max Perutz and Sir John Kendrew at the MRC Laboratory of Molecular Biology were awarded a Nobel prize for their 25 years' work to determine the structures of these proteins as well as other proteins like the immunoglobulins (antibodies).

- **X-ray crystallography (1962):** MRC-funded researchers identified the potential applications of X ray crystallography in the developing field of structural biology. Early strategic investment led to the setting up of two new research units in London (the Biophysics Research Unit at Kings College) and Cambridge (Unit for Research on the Molecular Structure of Biological Systems, later renamed as the MRC Laboratory of Molecular Biology) to study the structure of biological molecules. Scientists James Watson, Francis Crick and Rosalind Franklin at these research units discovered the structure of DNA and two of them were awarded the Nobel Prize in 1962.

- **Structure of insulin (1969):** Sir Tom Blundell, the founding Chief Executive of BBSRC and a member of Dorothy Hodgkin's team in 1969 that solved the first structure of a protein hormone, insulin, and is an influential figure in the field of structural biology.

- **Flu virus structure (1981):** Sir John Skehel's studies at the MRC National Institute for Medical Research revealed the 3D structure of a key protein in the flu virus called haemagglutinin, allowing influenza to stick to cells and infect them. This opened new perspectives for the design of antiviral drugs.

- **Crystallographic electron microscopy (1982):** Sir Aaron Klug at the MRC Laboratory of Molecular Biology won a Nobel Prize in 1982 for developing a technique called crystallographic electron microscopy, which allows biological structures to be seen in 3D. Using this technique, Sir Aaron produced a detailed picture of the structure of chromatin, a large protein that holds DNA together in chromosomes.

- **Comprehensive review of UK structural biology (1995):** Led by BBSRC, this review led to the recommendation to support six Centres for Structural Biology across the UK, which were established in 1998 and enabled community-led structural biology research to develop. The review also led to the recommendation to provide the UK community (biosciences) with a new synchrotron radiation source (initially for X-ray crystallography), influencing Wellcome Trust investment too.

- **Structure-based drug design (1999):** Sir Tom Blundell, Dr Chris Abell and Dr Harren Jhoti, developed a 'structure-guided fragment-based' drug discovery approach and together founded Astex Technology in 1999 which revolutionised drug discovery research. Much of the research that led to the creation of Astex was funded by the Science and Engineering Research Council (predecessor of BBSRC and EPSRC).

- **Animal virus structural biology breakthroughs (1989 and 1998):** The determination of the structure of the foot-and-mouth disease virus (FMDV) and bluetongue virus have advanced our understanding of viral assembly, replication and infection. In turn, these insights have helped scientists at the University of Oxford to develop a FMDV vaccine, a major breakthrough in the controlling this disease.

- **Establishment of Diamond Light Source Ltd (2002):** Receiving 86% of investment from STFC and 14% from the Wellcome Trust, Diamond became operational from 2007. In the early days, much of the operational focus centred on biological materials, including protein structure. The recent strategic collaboration between the Pirbright Institute and Diamond Light Source ensures future insights and understanding of animal viruses. For example, Diamond's advanced technologies are particularly well suited to exploring the cell biology of virus-host interactions and how viruses replicate.

- **Structure of ribosomes (2009):** Sir Venki Ramakrishnan at the MRC Laboratory of Molecular Biology won a share of the 2009 Nobel Prize for Chemistry for deciphering the molecular structure and therefore function of ribosomes. Ribosomes are tiny protein-making factories inside cells. This research has shed light on how the ribosome decodes instructions from DNA and on how antibiotics work, by showing how different antibiotics bind to ribosomes. This information is critical for developing new antibiotics. Modern antibiotics work by blocking the function the bacterial ribosomes upon which bacteria depend upon for survival.

- **Cryo-electron microscopy (2017):** The development of cryo-EM is the result of nearly five decades of work by researchers who were driven to find ways to explore the structure of intact cell components at near atomic level. In 2017, Dr Richard Henderson at the MRC Laboratory of Molecular Biology was awarded the Nobel Prize in Chemistry, with Professor Jacques Dubochet and Dr Joachim Frank, for developing cryo-EM. The technique enables scientists to see the structure of biomolecules by firing a beam of electrons at proteins in a frozen solution. Compared to X-ray crystallography, where proteins are crystallised then hit with X-rays, cryo-EM can reveal the structure of a wider range of proteins, including those that cannot easily form into crystals. Commercial cryo-EM equipment is quickly becoming accessible to discovery science programmes, having been installed in many imaging research centres. The detailed information that Cryo-EM provides is already improving rational drug design. In 2007, Dr Henderson co-founded Heptares Therapeutics, a company that is applying cryo-EM and other cutting-edge structure-based design approaches to develop drugs against human disease targets that could not be attempted previously.

Understanding the structure and function of SARS-CoV-2

UKRI BBSRC, EPSRC, MRC and STFC's long term investment in structural biology facilities and knowledge advancement, along with sustained support for bioinformatics, has facilitated the underlying research contributing to the rapid response to the current pandemic. These historical investments have resulted in important COVID-19 discoveries which build on our early understanding of the structure of viruses. A selection of current projects taking advantage of these investments are summarised below:

Project 1: SARS-CoV-2 nucleocapsid protein structure

A team led by Fred Anston at the York Structural Biology Laboratory (YSBL) have purified and characterised a protein which stores and protects the genome of the SARS-CoV-2 virus, which causes COVID-19, paving the way to develop new diagnostic tests. This work builds on the legacy of the York Structural Biology Laboratory and the leadership of its pioneering structural biologists including Rod Hubbard, Tony Wilkinson and Guy Dodson. YSBL recently won a Queens Anniversary Prize for 'revolutionising our understanding of fundamental living processes' and unlocking insights 'that directly impact the development of new medicines, and industrial processes to improve sustainability and food security.'

Project 2: Engineering llama antibodies for neutralising the virus

James Naismith (Director of the Rosalind Franklin Institute) along with researchers at Oxford University, Diamond Light Source and Public Health England have shown that engineered llama antibodies neutralise the SARS-CoV-2 virus. The hope is that the antibodies (known as nanobodies due to their small size) could eventually be developed as a treatment for patients with severe COVID-19.

Project 3: Druggable target in virus protein

Professors Imre Berger and Christiane Schaffitzel from the University of Bristol have used powerful imaging (electron cryo-microscopy) to analyse the SARS-CoV-2 spike at near atomic resolution, producing a 3D structure of the spike protein and revealing the presence of a small molecule, linoleic acid (LA), in a tailor-made pocket within the spike protein. This structural study, linking LA with the spike protein sets the stage for intervention strategies that target LA binding by SARS-CoV-2.

Project 4: High resolution virus structure (C19-IUC-008)

A team led by Dr John Briggs at the MRC Laboratory of Molecular Biology is using electron tomography techniques to obtain high resolution structures of the SARS-CoV-2 virus. They are studying the S protein on virus-like particles in complex with receptors and neutralising antibodies. Some structures are already available for isolated viral proteins, but certain interactions with antibodies and the membrane fusion event that the virus triggers can only be understood when structures of these complexes and events are available at high-enough resolutions in the context of the virus. For example, the ACE2 receptor acts as the receptor for the SARS-CoV-2 virus and allows it to infect the cell. High resolution images of this virus-receptor complex will help scientists develop a deeper understanding of the molecular processes that occur during infection. The team have recently published their results.

Project 5: Inhibiting the SARS-CoV-2 polymerase (C19-IUC-009)

To replicate, the SARS-CoV-2 virus needs to transcribe and replicate its RNA into more strands of RNA. For this it uses its own RNA-dependent RNA polymerase (RdRp). Dr David Barford and collaborators at the MRC Laboratory of Molecular Biology are making this polymerase and will image it by cryo-EM in complex with a primed RNA substrate while it is being transcribed. They will then add known inhibitors such as the antiviral drugs Avigan and Remdesivir to develop a deeper understanding of how these drugs disrupt the virus by affecting its replication processes. The team have access to the one of the highest-resolution cryo-EM instrument in the world; combined with the team's expertise, the resulting atomic resolution images will help with the ongoing efforts to find drugs that are more active against SARS-CoV-2.

Project 6: Making pseudoviruses to study infection and use in functional assays (C19-IUC-257)

The SARS-CoV-2 virus is enclosed in a membrane but has several types of protein 'spikes' on the outside that can be recognised by our immune system. These spikes allow the virus to enter and infect cells by binding to a receptor called ACE2 on the surface of cells, particularly the epithelial cells lining the surface of our lungs. Dr Leo James at the MRC Laboratory of Molecular Biology and other collaborators are developing several disabled 'pseudotyped' versions of the virus that contain key structural components such as these spike proteins, so that scientists can study how the virus infects cells, and use in functional assays. Because these pseudotyped viruses contain the only the spike proteins on the outside, they are not pathogenic and can easily be studied without needing the safety precautions that a pathogenic virus would require.

Project 7: RNA structures of the virus (C19-IUC-010)

One mystery of SARS-CoV-2 is how its genes are translated. All of its genes contain a short bit of RNA on one end, and it is possible that this particular element helps the virus hijack the cell's ribosomes, to make proteins. Dr Chris Oubridge at the MRC Laboratory of Molecular Biology and collaborators are trying to understand the function of this bit of RNA, by making reporter strains (by attaching a label or a tag known as a 'reporter' to the unknown RNA, they can 'see' what it does within the cell). The team will also find proteins that bind to this unknown RNA, as it could help scientists identify inhibitors that are specific just for this virus. RNA-dependant therapeutic approaches, such as RNA interference, could also be used to halt the virus. By using chemical probes, the team have confirmed the structure of this RNA element and have now designed small molecules to target the RNA element. They are now optimising these inhibitors to reduce toxicity due to off-target effects.

Project 8: Developing inhibitors against SARS-CoV-2 protease enzymes (C19-IUC-109)

Enzymes are responsible for increasing the speed of reactions and have the ability to build up or break down other molecules. The protease enzyme found in SARS-CoV-2, named 'Covid-19 PLpro', is responsible for breaking down proteins by disrupting their chemical bonds. When the protease breaks down the viral proteins it changes their size and shape, which starts a chain of reactions that allows the virus to replicate within the cell it infects. The Covid-19 PLpro protease also interferes with the immune responses that cells mount against the virus to block viral replication and spread. Because it is essential for viral replication and host infection, Covid-19 PLpro is potentially a highly promising drug target. Dr Yogesh Kulathu and his team at the MRC Protein Phosphorylation Unit at the University of Dundee are studying the structure of this enzyme responsible for SARS-CoV-2's ability to replicate so effectively, and working in collaboration with the Dundee Drug Discovery Unit to develop inhibitors that can block it.

Project 9: Identifying genetic and structural similarities between SARS-CoV-2 and measles, mumps, and rubella (MMR) (C19-IUC-221)

By analysing genetic and epidemiological data, Professor Robin Franklin and collaborators at the Wellcome MRC Cambridge Stem Cell Institute have found structural similarities between SARS-CoV-2 and measles, mumps, and rubella (MMR). The team have found key structural similarities between the coronavirus and the rubella virus – in the Macro domain, almost a third (29%) of the amino acids were the same for both viruses. The team put forward a hypothesis in a pre-print on Medrxiv that MMR could offer some protection to vulnerable groups against poor outcomes in COVID-19 infection. Following on from the preliminary data on viral modelling, epidemiology and clinical assessment, the group are poised to embark on a series of in vivo challenge experiments that will rigorously test their hypothesis that MMR provides protection against COVID-19.

Project 10: Cause and effect in receptor binding specificity associated with transfer between host species (C19-IUC-358)

This project investigates the relationship between the spike glycoprotein from SARS-CoV-2 with the spike protein of a closely related bat virus, RaTG13. Professor Steve Gamblin at the Francis Crick Institute in London used cryo-EM to determine the structures for RaTG13 spike protein, and for both furin-cleaved and uncleaved SARS-CoV-2 spike proteins. The team compared these structures with recently reported structures for uncleaved SARS-CoV-2 spike protein, and also biochemically characterized their relative stabilities and affinities for the SARS-CoV-2 receptor ACE2. Although the overall structures of human and bat virus S proteins are similar, there are key differences in their properties, including a more stable pre-cleavage form of human S and about 1,000-fold tighter binding of SARS-CoV-2 to the human receptor. These observations suggest that cleavage at the furin-cleavage site decreases the overall stability of the SARS-CoV-2 spike protein and facilitates the adoption of the open conformation that is required for the spike protein to bind to the ACE2 receptor. The results from this project have been published.

Annex 6.3

How can we prepare for pandemics?
First step: understand their sources

The emergence of novel pandemic causing pathogens such as the SARS-CoV-2 virus can be difficult to predict. But UK academic research over the past several decades has been preparing us to face these increasingly likely global threats. The patterns in the origins and spread of new pathogens in recent years are being documented and form an essential part of surveillance strategy. These insights lead to improved disease control, shortened response times, and inform pandemic preparedness policies around the world.

Insights from zoonotic diseases

Around 60% of all human diseases are zoonotic, i.e. transmissible between animals and humans. The COVID-19 pandemic, caused by the SARS-CoV-2 virus, is thought to have emerged as a zoonotic disease; a new coronavirus initially affecting bats which then transitioned to humans, possibly via an intermediate species such as a pangolin. Considering the location of the initial outbreak at the Huanan Seafood Wholesale Market in Wuhan, it is likely that the virus made the jump to humans at a wet market where animals such as bats and pangolins are traded illegally. China has experienced several viral outbreaks in the past three decades, including the avian influenza outbreak in 1997, and severe acute respiratory syndrome (SARS) in 2003. Other zoonotic outbreaks include the Middle East Respiratory Syndrome, caused by another coronavirus, and thought to have emerged from a bat coronavirus through the intermediate of a camel. Studying the structure of the virus using high-powered imaging technologies, for example using the STFC's Diamond Light Source, can help us understand these cross-species jumps. Indeed, studying the structure of the virus responsible for the 1918 influenza pandemic showed that the virus originated from North American domestic and wild birds, a discovery made by MRC-funded scientists with the aid of Diamond Light Source in 2003.

What drives the emergence of infectious diseases?

Analysis of these previous emergence events has led to a better understanding of the causes of emergence. The increased global surveillance has shown that the frequency with which these new pathogens emerge is increasing. We now know that these infections are usually driven to emerge by ecological, behavioural, or socioeconomic changes and are strongly correlated with human population density. Specific geographical regions with interfaces between people, wildlife, livestock, and the environment have been identified as the origins of recent emerging infectious diseases, and thus are targets for intense surveillance. These advances, coupled with a better understanding of the dynamics of pathogen transmission, ecology, and evolution as they emerge and spread, promise the possibility of a rapid respond to global pandemics. UKRI BBSRC, EPSRC, MRC, NERC, and ESRC continue to fund the Ecology and Evolution of Infectious Diseases programme that supports such research with the USA and China.

The need for a multi-disciplinary approach

Given the fundamental link between human activities and the emergence of novel zoonotic diseases, the integration of social sciences, particularly focusing on human behaviour and practices, into these models is vital. For example, during the Ebola outbreak in 2014, it was vital to understand how cultural processes such as hunting methods and burial practices impacted disease transmission and curtailment. The Anthropology of Ebola project, funded by ESRC in 2015 helped set up community-based animal health committees, which can identify outbreaks early on and help form the basis of a more sustainable and locally acceptable outbreak response. The incorporation of farming and agriculture research is also vital, as changes to animal production can lead to the emergence of novel pathogens, e.g. the highly pathogenic H5N1 influenza strain is thought to have emerged due to

economic development leading to changes in animal production that subsequently led to the opening of a new niche for the pathogen. The GCRF One Health Poultry Hub, funded by UKRI in 2019 and led by BBSRC, is exploring how rapid expansion of poultry production increases risk of infectious disease and why certain processes and behaviours are risky, while also testing novel interventions for disease control. The Pirbright Institute funded by BBSRC UKRI, has a rich history of studying zoonotic diseases since its establishment in 1914, and is home to Reference Laboratories that focus on surveillance of viruses that are not endemic, but pose a threat to the UK. Pirbright Institute scientists have joined the COVID-19 research effort by collaborating with MRC funded researchers to study the effect of a promising vaccine candidate in pigs.

UKRI investment into understanding zoonoses

In 2012, the Zoonoses and Emerging Livestock Systems (ZELS) initiative was launched as a joint research approach between DFID, BBSRC, ESRC, MRC, NERC and DSTL. It aims to provide robust evidence from multi- and interdisciplinary research, to prepare for the rise of novel zoonotics and focus on those risks which impact on the livelihoods and health of poor people. Research grants with a total funding of £18.5 million, with a further £1.5 million for studentships funding was awarded to a total of 11 projects in 11 developing countries, involving 19 UK research institutions.

In 2013 the Environmental and Social Ecology of Human Infectious Diseases (ESEI) initiative was launched as an £11 million joint project between UKRI MRC, NERC, ESRC, BBSRC and the Food Standards Agency (FSA) under the umbrella of the Living with Environmental Change programme. ESEI was developed to increase our knowledge of the complex environmental and social interactions involved in the emergence and transmission of pathogens. Through ESEI, several key projects were launched that will enable us to respond proactively to the threat from novel pathogens and emerging infections, e.g. ENIGMA to study *Campylobacter* and human behaviour in a changing environment, MONKEYBAR to identify opportunities for prevention and control of *Plasmodium knowlesi*, and URBANZOO to study the epidemiology, ecology and socioeconomics of disease emergence in Nairobi.

The COVID-19 pandemic was originally a zoonosis that jumped species to rapidly infect a vast number of people, through our complex relationship with trade, travel, land use, agriculture, and food systems. Previous work supported through response mode funding by the research councils including UKRI BBSRC, EPSRC, ESRC, MRC, and NERC have informed pandemic preparedness policies and surveillance strategies for tackling infectious diseases generally and continue to provide the strong platform from which research currently targeting the COVID-19 pandemic is directed.

Annex 6.4

Trials methodology and optimizing patient recruitment knowledge platform

Clinical trials are at the heart of medical interventions that improve human health. Every vaccine, treatment, screening programme, surgical procedure, medical device, or health intervention that is available as standard of care to patients today is rigorously tested for safety and efficacy through the clinical trials process. However, clinical trials are expensive and can sometimes be inefficient; issues with patient recruitment and retention are two major bottlenecks in conducting clinical trials and contribute to many delays and associated costs. These issues are problematic, more so during a global pandemic when the urgent testing of new treatments and vaccines is a national priority. Research supported by the MRC and other medical research funders around the world have helped address some of these issues, through a) the development of adaptive trial methodology and b) the optimisation of patient recruitment into key clinical trials through centralised registers of hospitalised patients. These advances have made valuable contributions to the speed with which vaccines and treatments for COVID-19 have been available as standard of care throughout the UK and the world.

Adaptive trial design for improving clinical trial methodology

Many of the clinical trials used for identifying treatments for COVID-19 are adaptively designed, a methodology that has been embedded in the UK clinical trials landscape through MRC-funded research. Adaptive trial design allows for the rapid testing of multiple treatments at the same time, with patients being recruited to each 'arm' of the trial. In contrast to a traditional randomised clinical trial, in an adaptive trial the patient responses are observed and analysed at pre-defined interim points, and pre-determined modifications to study design can be implemented based on these observations. It allows an adaptive trial to be flexible and efficient without undermining the validity and scientific integrity of the study.

Most of the drugs used in COVID-19 treatment trials such as RECOVERY are drugs that have already been approved for human use through Phase 1 trials for other diseases. For example, the steroid dexamethasone now used to treat patients hospitalised with severe COVID-19 was approved for human use in the 1960s. While the use of repurposed drugs has removed the need for lengthy Phase 1 trials that test for safety, the adaptive trial methodology allows these drugs to be added into existing Phase 2 and 3 trials seamlessly, helping to inform subsequent clinical practice within weeks of the results being published.

MRC has a rich history of supporting clinical trials, through support for developing innovative trials methodology and the direct funding for ground-breaking new trials. The first unit to undertake clinical trials within MRC was the Tuberculosis Research Unit which was set up in 1948, following the introduction of the first drugs to treat tuberculosis. Numerous clinical trials followed, and in 1998 the Tuberculosis Research Unit evolved into the MRC Clinical Trials Unit, to bring together research programmes in HIV and cancer. Additionally, the Clinical Trials Service Unit at the University of Oxford established in 1975 is a world leader in the conduct of large-scale RCTs and combined analyses of detailed data from randomised trials, which provide reliable evidence about the safety and efficacy of treatments.

In 2008 MRC and NIHR set up the Methodology Research Programme (subsequently renamed to the Better Methods, Better Research Panel) to fund high-quality methodology research in areas including but not limited to clinical trials. The MRC Hubs for Trials Methodology Research Network (MRC HTMR), established in 2009, has an Adaptive Designs Working Group that collaborates closely with the academic community while also linking with key stakeholders such as regulatory bodies and industry. The Working Group also fund the position of an Outreach Officer whose principal task is to popularise adaptive designs among medical researchers and statisticians by visiting clinical trials units across the UK to promote the benefits of these flexible designs.

Optimising patient recruitment for clinical trials

Over the last decade, the UK and other countries, have been involved in developing a strategic approach to planning for and responding to a global pandemic. The approach is multi-faceted and includes a register of hospitalised patients (Clinical Research Network, CRN) developed through international consultation with organisations such as ISARIC. This preparedness was harnessed during the COVID-19 pandemic to facilitate rapid patient recruitment for the gamut of clinical trials that were subsequently launched.

The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) is a global federation of 55 research networks spanning 111 countries. These networks work to a) generate the evidence necessary for improving clinical care and public health responses to infectious disease epidemics and b) support the development and evaluation of new diagnostics, treatments, and vaccines.

ISARIC was formed because by 2009, infectious disease outbreaks such as the H1N1 swine flu pandemic showed that mounting clinical research in response to a rapidly emerging infectious disease is extremely challenging and often delayed. Although important pathogenesis and clinical management data were available from countries that were already undertaking related clinical studies, there was very little cross-border coordination at the time. The clinical research response was slow despite years of preparation for devastating pandemics, and although observational registries were mobilised, initiatives to launch randomised controlled trials generally missed the initial waves of the 2009 H1N1 pandemic and in many cases failed to enrol sufficient numbers of patients even during subsequent waves. This failure to have coordinated, comparable data on clinical management and pathogenesis of the 2009 H1N1 pandemic meant a missed opportunity to improve patient outcomes. MRC's Strategy Board recognised this gap in 2011 and provided an initial £160K seed funding to establish ISARIC over two years.

To address these shortcomings, ISARIC was funded in 2011 by MRC, Institut National de ma Santé et de la Recherche Médicale (INSERM), the Bill and Melinda Gates Foundation, and the Wellcome Trust. Since its inception, ISARIC has established a sustainable consortium of clinical research networks with broad geographic coverage (including low resource settings), with the capacity to conduct complementary high-quality, hospital-based pathogenesis and clinical management studies in severe acute respiratory infection patients of all ages during the inter-pandemic influenza period. ISARIC also established cross-border coordination and open-access protocols and global data registries, and with it the capacity and flexibility to respond immediately to rapidly emergent threats.

Since 2011, ISARIC has worked closely with the WHO, responding to MERS-CoV, avian influenza A/H7N9, Ebola virus, and Zika virus. ISARIC has helped standardise protocols for the rapid coordinated clinical investigation of acute respiratory pathogens of public health interest around the world, to ensure that patients with a spectrum of emerging and unknown pathogens will be enrolled in clinical trials. This infrastructure for providing open access to clinical data and samples from COVID-19 patients was instrumental in facilitating recruitment at unprecedented speed for clinical trials such as RECOVERY and hospital studies such as the ISARIC GenOMICC (Genetics of Mortality in Critical Care) study. An example of the success of these preparations is seen in the patient data for RECOVERY, with nearly 12,000 patients recruited by July 2020 (40,000 by March 2021) making it the largest COVID-19 trial in the world. In the UK, one in every six COVID-19 patients that has come into a hospital for treatment is enrolled in a clinical trial.

Annex 6.5

How are we able to develop vaccines in response to a pandemic so quickly?

Although quarantines, social distancing, and lockdown measures will help us combat the current COVID-19 pandemic, ultimately it will be a vaccine, and the ensuing protection offered by herd immunity, that will be pivotal to defeating it.

MRC has a strong foundation in vaccine development, supporting a portfolio of research relating to genetic technology and immunology. These advances from the past few decades have led to the formation of extensive networks of expertise, along with the building of a strong knowledgebase in vaccine development for infectious diseases. As a result, these COVID-19 vaccine projects have exploded off the starting block as soon as the genetic sequence of the SARS-CoV-2 virus was published.

MRC-funded COVID-19 vaccine trials

Professor Sarah Gilbert and her team at the University of Oxford spearheaded a vaccine trial for SARS-CoV-2 with the first human trials commencing in April 2020 and Phase II/III completed in November 2020. Her team used a safe version of an adenovirus (a virus that can cause a common cold-like illness) vector known as ChAdOx1. The team has engineered ChAdOx1 to make a specific coronavirus protein, known as the Spike protein, from the SARS-CoV-2 virus. Our immune system is then able to recognise the Spike protein as 'foreign' and form antibodies against it, attack the SARS-CoV-2 virus and stop it from causing an infection. By 'bluffing' the body in this way and slipping in parts of the virus that do not harm, but induce the release of antibodies, it is hoped that long lasting immunity can be provided through vaccination. The vaccine received MHRA approval in December 2020 and has since been used to vaccinate millions of people in the UK and around the world. Under normal circumstances, animal work must be completed before human trials can start, but because similar vaccines have worked safely in trials for other diseases, the work was accelerated and happened in parallel.

Professor Robin Shattock and his team from Imperial College London worked to create a viable vaccine against SARS-CoV-2, using a new technology they have developed that can potentially produce vaccines much faster than conventional methods. By using the RNA sequence of the virus, the team have developed a self-amplifying RNA vaccine that can deliver genetic instructions to muscle cells to produce the Spike protein found on the surface of the SARS-CoV-2 virus. This should then provoke an immune response against COVID-19 infection. The team advanced their vaccine candidate to Phase II trials and then paused the project to focus on developing the 2nd generation of vaccines targeting the variants of the SARS-CoV-2 virus.

The UK Vaccine Network

Between 2016 and 2021, the UK government committed to invest £120 million for the development of new vaccines in line with the advice provided by the UK Vaccine Network (UKVN), which is made up of leading experts from academia, industry and policy. For example, Professor Shattock's RNA vaccine approach for tackling COVID-19 was refined through previous UKVN funding, awarded in 2017 by EPSRC UKRI.

The Future Vaccine Manufacturing Hub launched in 2017, has been established with almost £10 millions of funding by the Department for Health and is managed by EPSRC UKRI.

Likewise, Professor Gilbert was previously funded by the UK Vaccine Network, via UKRI MRC and BBSRC, and used the ChAdOx1 vector in a Phase 1 trial against the Middle East Respiratory Syndrome (MERS) coronavirus. This work was vitally important in showing the safety and effectiveness of the ChAdOx1 platform and is why her team was subsequently able to develop a vaccine candidate for SARS-CoV-2 and launch human trials so quickly.

Vaccines Manufacturing Innovation Centre

The next stage in vaccine development after successful human trials, is the manufacturing process. To support clinical stage vaccine development, UKRI, through Innovate UK, has established the £66 million ISCF Vaccines Manufacturing Innovation Centre. Announced in 2018, the Centre will address the UK's structural gap in late-stage vaccine manufacturing process development, building on existing BBSRC and MRC funded-research. In response to the COVID-19 pandemic, this work has been fast-tracked, and it is now scheduled for completion in 2021, ahead of its originally scheduled 2022 opening.

The COVID-19 pandemic seems to have arrived at an opportune moment in genetic technology, when previous work funded by UKRI research councils including MRC, BBSRC, and EPSRC have laid the strong foundations necessary for the rapid deployment of UK scientific expertise in tackling this pandemic.

Annex 8.1:

Impediments to pandemic research progress highlighted by PIs

Access to materials, equipment or other resources

- facilitate access to equipment, including PPE, medicines and adequate staff to contribute fully to the pandemic response.

- the wild-type virus neutralising assays are very variable between different laboratories and methods used. We should establish and share reference antibodies to standardise this assay.

- We have altered the objectives slightly due to unexpected delays in procuring small molecule inhibitors to the proteases.

- the pace of experiments was slowed due to reduced occupancy in labs.
  - Substantial issues with laboratory capacity – our NHS lab has been unable to meet requirements of the study so we are now working with the CRICK who are undertaking serology and PCR assays- most important facilitator has been the close collaboration and support from the Crick Institute.

Co-ordination

- important lesson is that preparation during "peacetime" determines success in a crisis
  - Work in previous years to anticipate the need for large scale manufacture of these types of vaccines was key in allowing this consortium to deliver on its goals.

- Enablers, which should be encouraged in any national or regional initiatives, include; collaborative teamwork, pooling of staffing resources, staff flexibility, strong leadership, and a pre-existing IT infrastructure including systems to support telehealth.

- Sharing virus specific knowledge more readily:
  - Sequencing showed the virus may not be fully stable during passaging. Preparing a second edition GFP expressing virus with a GFP gene that will be codon optimised to potentially improve stability.
  - Instability of virus *in vitro*

- Attempting to partner with major care home groups.
  - The main challenge has been obtaining responses from care homes, likely due to the high demands care homes are facing during the pandemic.

- Online consent, central eligibility checking, randomisation, and central dispatch of study materials and medication or key innovations speed up the time taken for practice-changing research to emerge for improving the care of our patients.

- By putting emphasis and priority on the software that manipulates and analyses data, make epidemiology research more efficient, and higher quality, including tools to rapidly curate health records data openly, and to analyse it can create a collaborative open ecosystem for data science in healthcare.
  - allow more time for setting up stakeholder groups

- An effective national communications strategy is critical to enhancing recruitment, especially amongst minority groups initially the patient screening contained a lot of medical terminology, which may have caused confusion.
  - app less appropriate form of communication with some BAME groups

- Palliative care services must be better recognised and integrated, including into infection disease management, with improved workforce planning and management: particularly the case for charity managed services and those providing care in people's homes and in hospitals.

  - There were COVID-specific challenges with Advanced Care Planning such as:

    - Rapid, complex decision-making in the face of a new disease.
    - Sensitive and difficult conversations hard to conduct remotely, by video or phone.
    - Increased workload because of COVID-19 and staff sickness.
    - For some people, racing against their deteriorating health over a short timeframe.
    - A national context of fear and uncertainty.

Staff well-being

- current staff taking on extra work and having to manage a substantially increased workload for a long period of time -minimise the risk of employee burnout.

- Trusts are under pressure to deliver multiple competing research projects, which has led to unforeseen delays and their commitment to conduct studies (or aspects of the proposed plan).

Bureaucracy

- The main challenge encountered was access to patient data, specifically obtaining authorisation from NHSD to access the shielding patient list and authorise publication of results in briefing documents and peer-reviewed journals.

- Tension between access to NHS patient data and freedom to publish in academic journals

  - Standard consent procedures within the NHS prohibit free release of patient data to be used in research, especially if any dissemination of results is intended. Other research planning to use these data or those collected in a similar way should build these considerations in to their timeline and collaboration plan.

  - Clarity around accessing patient data under the COPI notice

  - Despite the Notice under Regulation 3(4) of the National Health Service (Control of Patient Information Regulations) 2002 (COPI) to require NHS Digital to share confidential patient information with organisations entitled to process this under COPI for COVID-19 purposes, there was still a lack of clarity accessing the shielding patient list for research purposes, leading to a delay in the study starting.

- summary care records can be used to enhance provision for safe prescribing and patient care within community based clinical trials; achieving this is a work in progress.

- We have use verbal consent which has allowed high numbers of women to participate during the pandemic and recruitment to occur by email and phone.

- A platform trial design allows a single trial infrastructure to answer several questions more rapidly in the context of rapidly evolving circumstances, and emergence of new therapeutic agents that require evaluation.

- The timeline of 6 weeks from IMP arriving on site to being released for use in the trial has been challenging.

- We have found that when we applied to MHRA to use home antibody tests for the purpose of this research they took over 2 months to tell us that they would in fact not undertake a formal approval and that we should instead conduct our own risk assessment – this led to very unnecessary delays to the introduction of this approach. We would not like others to experience these delays.

- Obtaining/signing the DSA for use of the model development (UHB) dataset took longer than anticipated.

- very appreciative of, some very quick responses to our formal application for HRA approval; this includes the initial Fast Track REC enquiry, the scheduling of formal review by North West – Preston REC, and subsequent correspondence following that review. We very much hope that our formal application to NHS Digital is similarly expedited.

- challenges in developing an agreement with Public Health England, based on study PCR assay data that was sufficient to secure funding and NHS REC approval.

Dynamics of policy development

- UK coronavirus response was delayed after the alarm was raised in January

- Politicians abdicated responsibility by their early 'follow the science' rhetoric

- Science advice to policy making needs people who bridge the two worlds

- Centralised responses wasted valuable local public health skills

- Pandemic response needs to move faster than the infectious disease

Challenges

- Industry timeframes not commensurate with need for speed

- *"Given the urgency of the COVID situation, the pathway to policy impact was much more straightforward than previously experienced."*

Medical Research Council