Part of the conference series
Breakthrough science and technologies
Transforming our future

The science of COVID-19

Held on 30 – 31 March 2022

Conference report

THE ROYAL SOCIETY

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Contents

Introduction

On 30 – 31 March 2022 the Royal Society hosted a conference on the science of COVID-19. This meeting, supported by AstraZeneca, forms part of the Royal Society's Transforming our future series.

The Transforming our future meetings are unique, high-level events that address scientific and technical challenges of the next decade and bring together leading experts from the wider scientific community, including academia, industry, government, and charities. The meetings are organised with the support of the Royal Society Science, Industry and Translation Committee.

The conference series is organised through the Royal Society's Science and Industry programme which demonstrates the Society's commitment to integrate science and industry across its activities, promote science and its value, build relationships and foster translation.

The programme was organised by Professor Dame Linda Partridge FMedSci FRS, Royal Society Biological Secretary, Dr Steve Rees OBE, AstraZeneca, Steve Bates OBE FMedSci, UK Bioindustry Association, and Professor Charles Bangham FMedSci FRS, Imperial College London. The conference celebrated the exceptional endeavours of the scientific community over the last two years.

Speakers highlighted successful collaborations between industry, government, the NHS, academia and regulatory authorities and reflected upon advances in cutting-edge science and technology that have benefitted the UK life sciences base and which demonstrate the importance of sustained investment in this sector.

This report is not a verbatim record, but a summary of the discussions that took place during the two days and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society.

Image: Delegates during the conference.

"The huge success of vaccines, the development of new treatments, devices and tools, and the ability to understand how the virus transmits were often viewed by members of the general public as miraculous quick wins. In fact, these achievements were standing tall on the shoulders of scientific work that had taken place over decades in many different research areas, and in many cases without an obvious application at the time. There can be no clearer case for stable, long-term investment in the scientific endeavour."

Dame Linda Partridge FMedSci FRS, Royal Society Biological Secretary

Executive summary

The past two years have been marked by unprecedented levels of collaboration and innovation across academia, industry, the NHS and government.

This meeting offered an opportunity to consider how these developments are likely to influence preparedness efforts for future public health emergencies and benefit the life sciences sector more broadly. Key themes include:

The COVID-19 response

- The rapid design and deployment of safe, effective vaccines was enabled by several decades of basic and clinical research. It is essential that investment in the life sciences is sustained to develop vaccine technologies which offer a durable immune response against COVID-19 and which may also prove effective against other novel pathogens.
- Novel therapeutics, including monoclonal antibodies and antiviral drugs, exhibit significant potential to attenuate severe COVID-19 disease in high-risk patient populations.
- Mechanisms of variable immune responses to COVID-19 and predictors of severe infection have been established. Much, however, remains poorly understood, in particular the propensity for and pathogenesis of long COVID, which will lead to devastating impacts upon quality of life and the national economy for years to come.
- The UK demonstrated the potential of large-scale genomic sequencing to track the spread and evolution of SARS-CoV-2 and contribute to vaccine design and development.
- The SARS-CoV-2 virus will continue to evolve. Future variants may be more transmissible and may cause more virulent disease. Sustained research and monitoring activity will be essential to predict the properties of such variants and to identify and contain localised surges in infection.

"This conference has distilled learnings from the pandemic which will help us succeed in future, not just to address future pandemics but to improve and transform healthcare for all of us. That has always been the key challenge, both before the pandemic and today."

Dr Steve Rees OBE, AstraZeneca

Image: Delegates networking during the conference.

Ways of working

- Public behaviour, trust, and engagement with science were essential to all areas of the pandemic response and should remain integral to policy-making in future public health emergencies. Thousands of individuals participated in NHS clinical trials and in mass testing through the network of Lighthouse Laboratories. Self-testing is now widely accepted and has the potential to revolutionise diagnosis and management of other infectious and non-communicable diseases.
- Regulatory authorities adopted a flexible, collaborative approach to assessment, evaluation, and authorisation. Research funders accelerated their review processes for critical initiatives. These changes may inspire new operational norms.
- Platform trials, participant registries and other innovations in clinical trial design are likely to facilitate the testing and approval of future vaccines and therapeutics. Clinical research is most effective when firmly embedded within NHS infrastructure.
- Agile, adaptive manufacturing systems enabled unprecedented efficiency gains for the production of vaccine batches, emergency ventilators and novel diagnostic tools.
- International collaboration between scientists and policy-makers from the earliest days of the pandemic was critical in characterising the genetic make-up of SARS-CoV-2 and in swiftly identifying the emergence of new variants of concern over time.
- The Oxford-AstraZeneca vaccine in particular has prevented many deaths in lower-income countries. Nonetheless, there remain significant inequalities and inequities in data-sharing and in access to vaccines and therapeutics.
- Interdisciplinary collaboration has been a powerful tool in all areas of the pandemic response. It will remain critically important for future public health challenges such as antimicrobial resistance and aging-associated diseases.

"Scientific capability and skillsets can be flexible. Post-pandemic we will need the ability to continue to innovate, in particular within the manufacturing sector. Similarly, building upon recent regulatory innovations and sharing those with other regulators will help us next time around."

Steve Bates OBE, UK Bioindustry Association

"COVID-19 has demonstrated that it is essential to build the response to infections on a strong foundation of basic science, to drive collaboration between disciplines, and to strengthen the national and international systems of surveillance so that we can respond faster to the next epidemic."

Professor Charles Bangham FMedSci FRS

KEYNOTE

Overview of the pandemic and the science

Sir John Bell GBE FMedSci FRS, Regius Professor of Medicine at Oxford University and Life Sciences Champion for the UK government, reflected on the successes and failures of the UK's response to COVID-19, and highlighted some of the key priorities for future pandemic preparedness.

Image: Sir John Bell, Oxford University

"There is no question that the UK scientific community did get the country out of a lot of trouble. Scientific contributions by a lot of people were also really instrumental in containing the pandemic globally."

Sir John Bell GBE FMedSci FRS, Oxford University

The emergence of a novel pathogen that precipitated a major global pandemic should not have taken the UK by surprise. There were important shortcomings in preparation and planning, due in part to complacency around the risks of infectious diseases and to chronic under-resourcing of public health services.

While the 2009 H1N1 flu pandemic and the 2013 flu epidemic abated relatively rapidly in the UK and before many clinical trials could conclude, the COVID-19 pandemic has offered a unique opportunity to study a new disease in real time. It is imperative that successes and failures in the UK's management of SARS-CoV-2 are scrutinised to increase the resilience of public health systems and ensure a swifter, more effective response to further outbreaks and future pandemics.

Successes

The UK benefits from a robust life sciences base across many disciplines including virology, structural biology, and diagnostics. This facilitated effective coordination of scientific expertise, exemplified by the pace and quality of UK-led vaccine development.

Novel programmable platform technologies and regulatory innovations enabled vaccines to be produced in record time. These advances have enormous potential to accelerate the design of vaccines to target a range of diseases.

Safety and efficacy data from studies of the Oxford-AstraZeneca vaccine demonstrate dramatic reductions in severe illness, hospitalisation, and mortality, including in high-risk populations, where ChAdOx1 has been widely deployed. To date almost 3 billion doses have been administered globally.

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial incorporated insights from studies conducted during the 2013 flu epidemic. Investigators demonstrated the safety and efficacy of repurposed therapeutics, informed by well-powered sample sizes and high-quality data. UK-led epidemiological surveys provided up-to-date spatial information on infection rates. The Lighthouse laboratories processed hundreds of thousands of swabs per day and the introduction of self-testing in late 2020 proved a powerful tool in reducing transmission.

The COVID-19 Genomics UK Consortium and Genomics England (GeL) engaged in international collaborations to identify new variants as they emerged. The UK Coronavirus Immunology Consortium delivered vital studies funded by the NIHR and UKRI that enhanced scientists' understanding of immune responses to SARS-CoV-2.

Failures

Sustained pressures on public health resources left the NHS with little resilience to innovate or to meet additional demands in early 2020. Testing capacity was limited. Government policies did not adequately reflect lessons learned from past public health crises and the initial response was slow. Some UK politicians did not demonstrate sufficient understanding of relevant scientific concepts such as uncertainty.

Inconsistencies in official scientific advice amongst politicians and scientific experts worldwide was inevitable but unfortunate. These were compounded by insufficiently rigorous evaluation of non-pharmaceutical interventions such as mask-wearing and social distancing.

Many advanced economies – the UK included – took a nationalistic approach to public health messaging and to the procurement of vaccines and therapeutics. This has exacerbated global inequalities, undermined economic development policies, and stymied the recovery of lower-income countries. Multilateral funding institutions did not always offer well-targeted financial support.

Looking to the future

SARS-CoV-2 will remain endemic for some time. New variants may result in further outbreaks. Future pandemics caused by as yet unknown pathogens are inevitable. Most national economies have suffered immensely. It is critical that the UK and the rest of the world exploit opportunities from the COVID-19 pandemic and incorporate learnings into robust preparedness policies:

- The NHS must be adequately resourced to maintain a base level of resilience.
- Bolstering investment in the UK's outstanding infectious disease research ecosystem is vital.
- Further work is needed to devise more efficient ways of processing and deploying genomics data.
- The collaborative and interdisciplinary approach to scientific endeavour must be sustained, especially within vaccine development.
- Alternatives to mRNA and viral vector technologies should be explored to identify solutions which provide a more durable immune response.
- Anti-profiteering measures will be essential.
- Consideration for global inequities must underpin every aspect of preparedness efforts and policy development.

KEYNOTE

Sensing pandemics: pathogens, people, places and possibilities

Professor David Nabarro CBE, Special Envoy on COVID-19 for the World Health Organisation, reflected on the principles that should guide national and international responses to future public health emergencies.

Effective responses to public health emergencies must be underpinned by inclusive narratives which acknowledge contextual complexities. National and international responses to the COVID-19 pandemic have led to tensions and conflict between government, scientific advisers, and wider society. The past two years have thrown the social gradient into stark relief, with individuals in lower socioeconomic groups experiencing significantly worse outcomes for health, financial stability, and quality of life.

"In the long term, dealing with all infectious diseases is about human behaviour and changes in behaviour."

Professor David Nabarro CBE, World Health Organisation

Four key principles should guide the response to future pandemics:

1 **People must remain at the heart of a pandemic response.** The 2014 – 2016 Ebola epidemic was contained in large part due to the willingness of individuals and communities to work together to establish and enforce behavioural change. When public health measures are perceived to have been imposed top-down, hostility and mistrust are inevitable. Interventions by governments, scientists and employers must be grounded in a common understanding that people are active partners in a pandemic response.

2 **Prevention of transmission must be a priority.** Although it is possible that the virus will attenuate over time, SARS-CoV-2 will remain endemic. Societies have a range of tools at their disposal, including mask-wearing, social distancing, and ventilation. In periods of high prevalence, political leaders and employers should not vilify those who wish to exercise caution to protect themselves or others. This is especially important now that the UK and other Western countries have begun to ease restrictions.

Image: Professor David Nabarro, World Health Organisation

3 **Protection of the most vulnerable individuals is paramount.**

Many aspects of the pathogenesis of COVID-19 remain unclear, particularly around the later-life implications of post-COVID syndrome. Even though the Omicron sub-lineages appear to be associated with milder symptoms, the disease should still be treated seriously. Vaccination remains a critically important intervention to reduce severe illness, mortality, and possibly the likelihood of developing post-COVID syndrome. Governments must continue to prioritise at-risk individuals in vaccine and booster rollouts.

4 **Detecting and preventing major outbreaks is critically important.**

The past two years have indicated that as new variants and sub-lineages emerge, major outbreaks or 'waves' of infection occur at approximately four-monthly intervals. It is essential that scientists and public health professionals remain equipped to recognise the early signs of surges in infection rates. Public services, local authorities and employers must be prepared, resilient and adaptable. It is especially important to help the public understand the need to contain localised outbreaks.

These principles must be embedded into international practice, underpinned by robust, adaptable and well-resourced public health systems. Pandemics require unprecedented co-operation between individuals, communities, authorities and governments. Failure to place equity concerns at the heart of collaborative emergency responses carries a high price. There have been some extraordinary innovations and success stories over the past two years. The challenge now is to maintain this momentum for the benefit of society.

KEYNOTE

mRNA vaccine technology: How a novel approach has helped combat the COVID-19 pandemic

Professor Özlem Türeci MD, Co-Founder and Chief Medical Officer of BioNTech SE and Professor of Personalised Immunotherapy at the University Medical Center Mainz and the Helmholtz Institute for Translational Oncology in Mainz, Germany, described how three decades of research into mRNA vaccine technology enabled the Pfizer-BioNTech mRNA vaccine against COVID-19 to be developed, trialled and approved within just ten months.

With over six million deaths recorded to date, the COVID-19 pandemic has been one of the deadliest disasters in human history. When the SARS-CoV-2 virus was recognised in early 2020 as a destructive force with the potential to spread rapidly worldwide, the vaccine race began immediately. This was a formidable challenge given that SARS-CoV-2 was a new and – at the time – poorly-understood pathogen.

Shortly after Chinese researchers released the SARS-CoV-2 genetic sequence in mid-January 2020 the German biotechnology company BioNTech SE launched 'Project Lightspeed'. The aim was to deliver a safe and effective vaccine in less than one year without taking shortcuts, using a novel technology based on messenger ribonucleic acid (mRNA).

mRNA is a single-stranded RNA molecule encoding the amino acid sequence of a particular gene. It plays an important role in protein production and is straightforward to produce synthetically. mRNA vaccines deliver a blueprint of the vaccine antigen into cells. They can be packaged in lipid formulations to enhance specificity. These cells then reproduce the antigen, which triggers the immune system to generate antibodies and T cells. mRNA vaccines are most effective when they target dendritic cells, which have the capacity to induce potent and multifaceted immune responses.

> "A global health crisis should not be the primary impetus to leverage innovations with the potential to transform human health. Major breakthroughs in science and research take time, vision, and the appropriate financial resources. Boosting innovation should therefore be a priority."
>
> Professor Özlem Türeci MD, BioNTech SE, University Medical Center Mainz and the Helmholtz Institute for Translational Oncology

The Pfizer-BioNTech vaccine BNT162b2 is based on this technology, encoding the mRNA sequence of the spike protein. Phase III trial findings were published in November 2020 and the vaccine was granted conditional marketing authorisation in the UK and the EU in December. To date, over 2.6 billion doses have been delivered to more than 165 countries and territories. BNT162b2 demonstrates 95% efficacy against the wild type strain of the virus, including in elderly and vulnerable populations.

This was made possible by extensive and collaborative research by Özlem Türeci and her husband, Professor Ügur Şahin, MD, over the past 30 years. They founded BioNTech in 2008, originally to devise personalised vaccines for cancer patients. Based on the belief that every cancer patient's tumour is unique, their team combined decades of ground-breaking research in immunology, cutting-edge therapeutic platforms including mRNA, cell therapies, antibodies and small molecules to activate a patient's immune system against their tumour and to develop individualized immunotherapies for cancer as well as other diseases.

The earliest mRNA technologies, developed during the late 1990s and early 2000s, elicited insufficient immunogenicity to achieve material tumour shrinkage. Modifications to the mRNA backbone led to progressive advances in stability and translation within dendritic cells, and a greater than 1,000-fold improvement in the ability of mRNA vaccines to trigger an immune response.

Parallel studies led by colleagues at Stanford University[1] offered a way to reduce the immune system's endogenous defence response against synthetic mRNA and thereby increase the immunogenicity of mRNA vaccines. Studies undertaken during 2012–2015 revealed that when mRNA vaccines are delivered within a lipid nanoparticle formulation into dendritic cells in lymph nodes, the immune response can eradicate large tumours in mice and shrink metastatic tumours in humans.

BioNTech has now produced hundreds of personalised cancer vaccine doses for use in clinical trials. The use of computer algorithms along with refinements to manufacturing and quality control processes have reduced the delivery lead time to 3 – 5 weeks per patient.

In early 2020 the team drew upon their experience of studying a new genetic sequence – that of SARS-CoV-2 –, developing a bespoke antigen and producing a vaccine at pace. Discussions with pharmaceutical companies and with regulators began at an early stage to accelerate the review process and large-scale manufacture.

It is likely that a vaccine able to resist multiple variants of SARS-CoV-2 will be needed in the future to address waning immunity after administration of the vaccine over time as well as to address potential immune-escape variants. It is critical that science and technology receive substantial investment and that policymakers, investors and the biotechnology industry prioritise innovation across all disciplines.

1. Karikó et al. Incorporation of pseudouridine into mRNA yields superior non-immunogenic vector with increased translational capacity and biological stability. Molecular Therapy. 2008;16(11): 1833 – 40. https://pubmed.ncbi.nlm.nih.gov/18797453/ (Accessed 15 April 2022)

The origin of COVID-19

Professor Edward Holmes FRS, University of Sydney, presented evidence that suggests a zoonotic emergence of the SARS-CoV-2 virus in the Huanan Seafood Market in Wuhan at the end of 2019, and briefly considered strategies to minimise the risk of catastrophic pandemics in the future.

The origin of SARS-CoV-2 and the mechanisms behind its transmission to humans have been subject to considerable scrutiny. The viral genome exhibits approximately 80% sequence similarity with SARS-CoV-1, which emerged in China's Guangdong Province in 2002/3. It is also related to other betacoronaviruses such as MERS-CoV and Human coronavirus HKU1. It is most closely related to BANAL-20-52, a coronavirus found in *Rhinolophus* (horseshoe) bats from Laos, with which it shares 96.8% sequence similarity. Many other viruses with high levels of sequence similarity to both SARS-CoV-1 and SARS-CoV-2 have been observed in areas of south-eastern China and south-east Asia inhabited by *Rhinolophus* bats.

The Huanan Seafood Market

The market is located in north of the Yangtze River in central Wuhan. An examination of the earliest cases of COVID-19, dating to December 2019, shows that this was the viral epicentre, even controlling for sampling and reporting bias. Approximately half of the first 164 documented cases were identified in individuals who had attended the market. All cases seemed to have been derived from an epidemic wave that started at the market.

Following the market's closure on 1 January 2020 public health authorities swabbed surfaces within the market as well as some frozen animal specimens. Strikingly, positive swabs for SARS-CoV-2 were clustered in environmental samples from the southwestern corner of the market, where the majority of stalls selling these animals were situated. Swabs also revealed that two distinct lineages of the virus (denoted A and B) were present in the market. This suggests that SARS-CoV-2 is likely to have originated in bats and then infected an intermediate host such as a racoon dog before transmitting to humans in the market. There may even have been two independent jumps from animals to humans within the market.

The likely market-associated emergence of SARS-CoV-2 exhibits strong similarity to SARS-CoV-1, which is believed to have emerged in live animal markets in Guangdong province.

Image: Professor Edward Holmes, University of Sydney

"Clearly we need better surveillance on this human / animal interface – this is where the risks lie and where zoonotic disease outbreaks will occur in the future."

Professor Edward Holmes FRS, University of Sydney

Debunking the laboratory leak theory

There has been some speculation that the virus appeared following a laboratory leak from the Wuhan Institute of Virology (WIV). However, spatial mapping shows that the epicentre of the virus outbreak was located in a different part of Wuhan than the WIV. In addition, laboratory staff consistently returned negative PCR and antibody tests. SARS-CoV-2's furin cleavage site – a component of the viral spike protein which helps enable SARS-CoV-2 to infect human cells – is considered suboptimal. If researchers had been conducting experiments using a man-made virus they would have been likely to have engineered an optimal cleavage site.

Most of all, there is no evidence that WIV staff were working on SARS-CoV-2 prior to the pandemic.

In sum, there is no evidence that SARS-CoV-2 emerged following a laboratory leak.

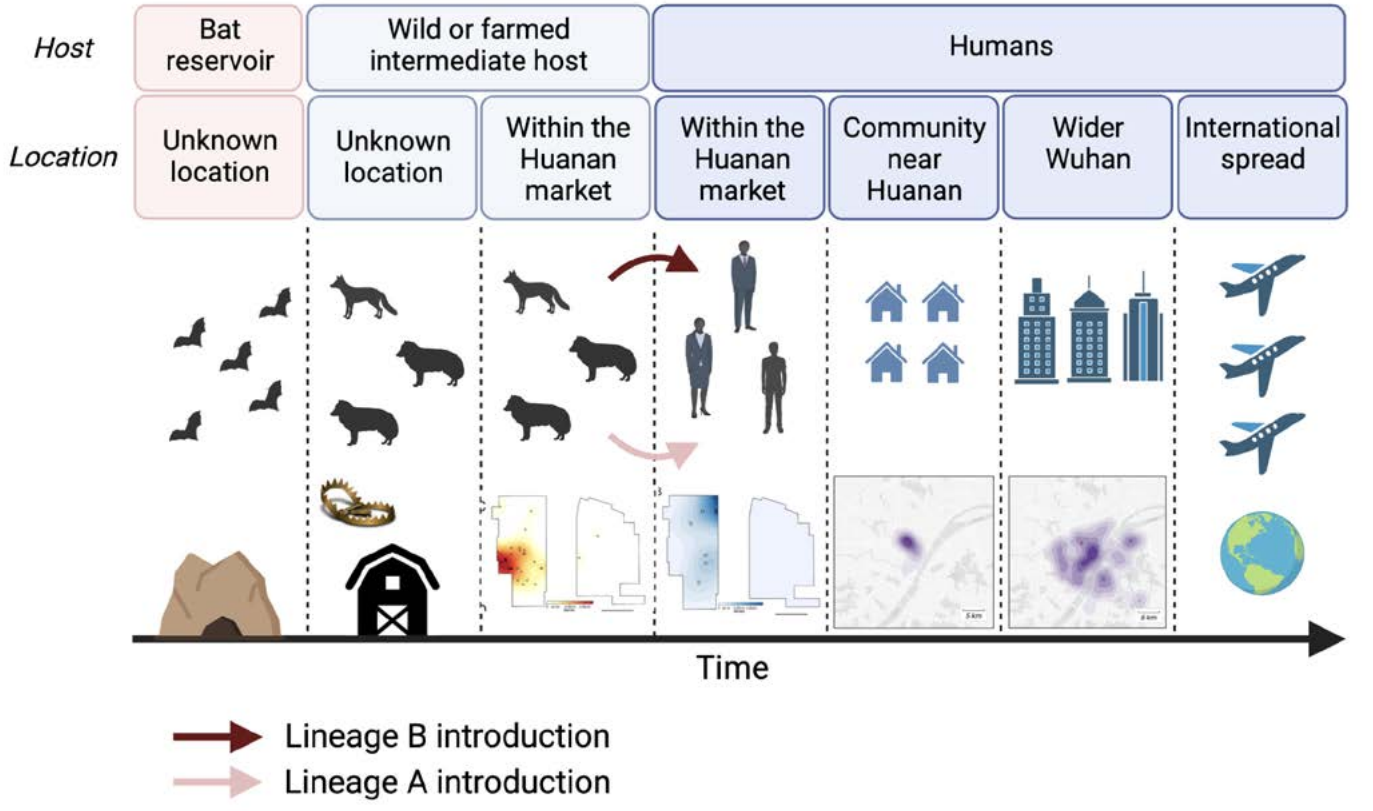
Preventing future zoonotic outbreaks

The species sold in live animal markets are a ready source of future zoonotic outbreaks. During 2020 Professor Holmes and colleagues at Nanjing Agricultural University sampled almost 2,000 game animals – including racoon dogs, porcupines, and badgers – at the feeding facilities that supply live food markets. They identified 102 mammalian viruses, 20% of which posed serious risk to humans through potential spillover infections.

Climate change may further increase the risk of zoonotic transmission as global surface temperatures warm, and as the ongoing destruction of habitats brings humans and animals into greater proximity. There is an urgent need for active surveillance of people working at the animal / human interface including in markets, fur farms and animal rescue centres. Advanced technology such as metagenomic surveillance and the VirScan platform – that undertakes human serological profiling and identifies infection history – will be essential in helping to prevent future pandemics.

FIGURE 1

A schematic diagram of key milestones in the emergence of SARS-CoV-2



Credit: Worobey et al. The Huanan market was the epicenter of SARS-CoV-2 emergence. *Zenodo* [Preprint]. 2022. https://zenodo.org/record/6299116#.YoUX0ajMKUk (Accessed 15 April 2022)

SARS-CoV-2 Variants: evolution in real time

Professor Wendy Barclay CBE FMedSci, Imperial College London, outlined the molecular virology that appears to explain the Omicron variant's higher transmissibility and reduced severity, and reflected on how SARS-CoV-2 may evolve in the future.

Image: Professor Wendy Barclay, Imperial College London.

Viruses that jump from animals into humans may evolve in the short term to become more transmissible and in the medium term to be more capable of evading antibodies induced by prior infection or vaccination. This pattern is demonstrated in the SARS-CoV-2 variants of concern that have emerged since the Alpha variant began spreading in December 2020.

The Delta variant has now been almost entirely superseded by the Omicron variant. In the UK, the Omicron BA.1 sub-lineage predominated in early 2022 but was then displaced by the BA.2 sub-lineage. Although Omicron variants are generally associated with milder outcomes, they are more resistant to antibodies generated by the existing suite of COVID-19 vaccines. This is because the sequence of the spike protein of these variants differs from that of the ancestral spike of the virus that first emerged in 2019 and that is used to manufacture the vaccines.

Further variants, recombinants (which arise when a cell is infected with two variants simultaneously) and sub-lineages will evolve as COVID-19 becomes an endemic disease. To predict the likely transmissibility and severity of future variants scientists must examine how these variables have been shaped by the molecular virology of the Omicron variant. The UK 'Genotype to Phenotype' consortium has attempted to do this using reverse genetic analysis to create viruses with defined sequences in the laboratory, and through a suite of in vivo and in vitro studies to map the sequences that determine outcomes.

"With a lot of recombinants being reported around the world at the moment, and the propensity of coronaviruses to undergo recombination, it is quite possible that we will see a future variant that is both severe and antigenically distant from the wild-type."

Professor Wendy Barclay CBE FMedSci,
Imperial College London

The mechanisms of SARS-CoV-2 infection

- Each SARS-CoV-2 particle contains surface spike proteins. These bind to ACE2 receptors in host cells. Each spike also contains a furin cleavage site, composed of four amino acids. Cleavage activates the spike and enables the virus to fuse with and enter host cells.
- The spikes of wild-type (original) SARS-CoV-2 virus particles contained a weak furin cleavage site. As the virus circulated in humans, it mutated to evolve a more efficient cleavage site. The Delta variant displayed the strongest cleavage site and was therefore able to fuse very efficiently with target cells, become more virulent and thus cause more severe disease.
- Furin cleavage divides each spike into two domains, S1 and S2. The S1 domain encodes the part of the protein that allows virus particles to bind to the ACE2 receptors, which is predominantly the part that human antibodies see. The S2 domain drives fusion with host cells.

The Omicron variant

The Omicron spike contains more than 35 largely novel mutations. Analysis of the sequence alone would predict a strong cleavage site similar to Delta. However, Omicron infection is not associated with strong fusogenic activity. It seems that whilst Omicron's S1 domain increases receptor binding, enhancing transmissibility, mutations on the S2 domain appear to slow fusion to host cells, leading to less severe disease.

To access host cells Omicron virus particles can pass directly into the cell cytoplasm or enter more slowly through endosomes. The ability to use both of these two entry routes may help explain why Omicron is more contagious than previous variants. There is some evidence to suggest that Omicron favours the endosomal route. However, endosomes contain proteins that serve as restriction factors and prevent some virus particles from entering cells in this way. It appears that these restriction factors are particularly active in the lungs where they attenuate the virus, resulting in milder overall symptoms. Omicron can thus replicate fast in the nose, spreading quickly from one person to another, but results in less severe disease because it is restricted in the deeper lung.

Anticipating future variants

The most concerning future variants or recombinants would show a marked difference in genetic composition compared to the vaccine antigens and also a phenotype that intensifies both receptor binding and fusion, leading to increased transmissibility of infection and greater virulence of disease. Since coronaviruses are generally susceptible to recombination as well as to accumulation of multiple mutations, this is a reasonably plausible scenario which should caution against assumptions that all future SARS-CoV-2 variants will be mild.

Immune responses in COVID-19 and other coronavirus infections

Professor Stanley Perlman, University of Iowa, discussed how the timing of interferon expression in response to infection can influence innate and adaptive immune responses and contribute to the progression of severe COVID-19 disease.

Immune responses to viral infection can be grouped into two categories:

1 Innate responses, including interferons (signalling proteins which induce cells to activate antiviral defences), pro-inflammatory cytokines (proteins released in response to a virus and which stimulate the production of immune cells), and innate cells (neutrophils, macrophages, and NK cells); and

2 Adaptive responses, including T cells and antibodies which develop over time.

Human challenge studies for common coronaviruses demonstrate that the adaptive immune response induced by natural infection or by vaccination – although powerful – typically wanes over time. Many coronaviruses are eventually able to evade or inhibit immune responses by secreting specific proteins.

Numerous studies have attempted to understand why certain COVID-19 patients develop severe or persistent infection. A dysregulated host immune response to SARS-CoV-2 may play a critical role in these variable outcomes.

In murine studies, SARS-CoV-2 has been shown to replicate rapidly in the lungs, and the concentration of virus particles typically peaks within 16 – 24 hours of infection. Murine and clinical studies of COVID-19 and other coronaviruses suggest that the timing of interferon release is particularly influential:

- If no or minimal interferon is secreted, mice typically experience mild symptoms.
- If interferon is secreted before peak virus concentration is attained, interferon is highly protective against inflammation and severe outcomes, even if virus particles remain in circulation within the body for some time.
- Delayed or suppressed interferon secretion can lead to excess production of pro-inflammatory cytokines, lymphopenia (reduced levels of lymphocytes and thereby reduced protection against severe illness), and a poor virus-specific T-cell response. Lymphopenia may also impair the antibody response. These dynamics aggravate viral infection and can cause severe disease, including lethal pneumonia.

Image: Professor Stanley Perlman, University of Iowa

These findings are significant given that interferon is a core component of the innate immune response. They have important implications for clinical trial design. Identifying a way to stratify future trials across different patient subsets based on propensity for early or delayed interferon secretion may help understand the variable efficacy of therapeutic interventions. It may also enable clinicians to recognise which individuals might benefit from targeted interferon treatment. An improved understanding of innate immune response variability may also provide tentative clues concerning the pathogenesis of long COVID.

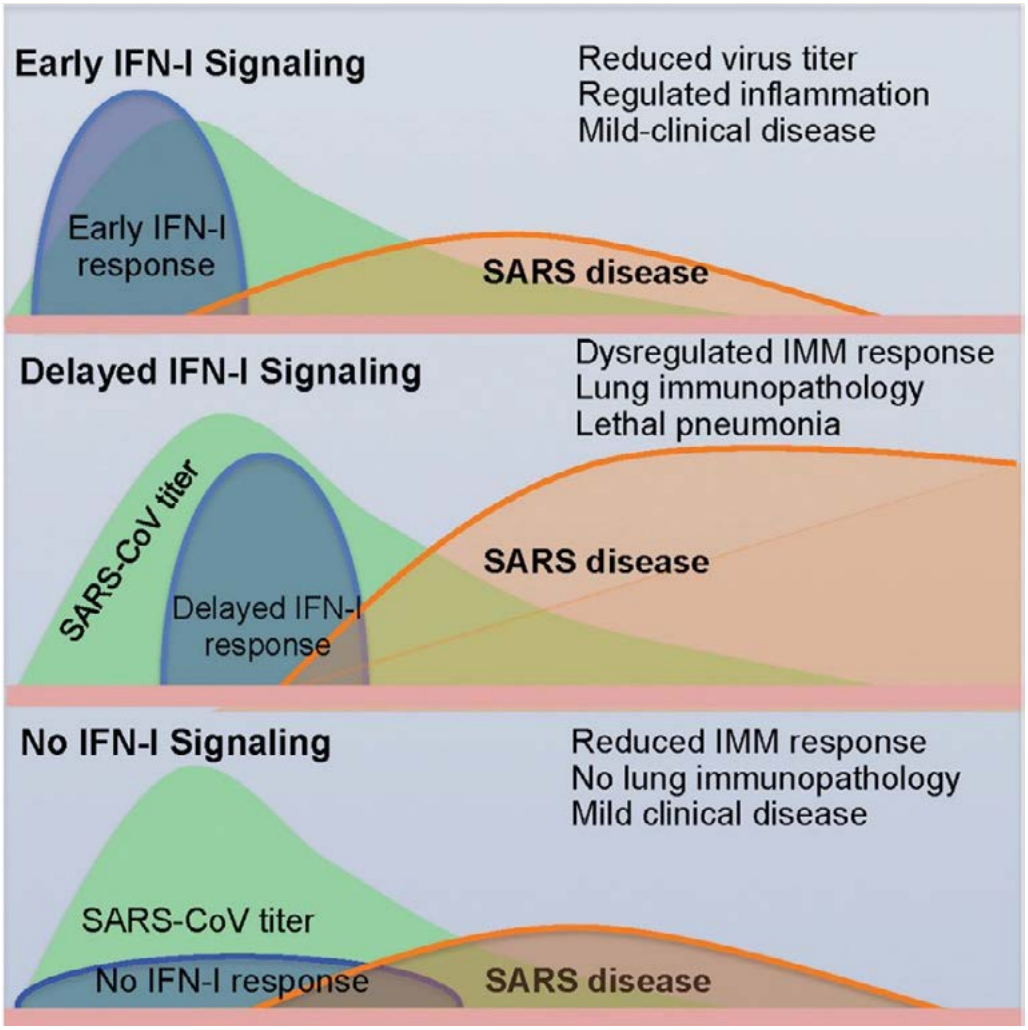
"In patients who do poorly there is an imbalance in innate and adaptive immune response."

"The timing of interferon response relative to the kinetics of virus replication plays a critical role in good versus severe outcomes in SARS-CoV-2 infection."

Professor Stanley Perlman, University of Iowa

FIGURE 2

The relationship between IFN-I signalling, inflammatory monocyte-macrophage response and clinical outcomes in SARS-CoV-infected mice.



Credit: Channappanavar et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host & Microbe*. 2016;19(2): 181-193. https://doi.org/10.1016/j.chom.2016.01.007 (Accessed 15 May 2022)

Lessons learnt from the Vaccine Taskforce

Dame Kate Bingham, Managing Partner at SV Health Investors and Chair of the UK Vaccine Taskforce from May to December 2020, reflected on how the UK should leverage learnings and opportunities from the vaccine race to strengthen preparedness for future pandemics.

Image: Dame Kate Bingham, Managing Partner at SV Health Investors

The UK Vaccine Taskforce (VTF) was established in April 2020. It assembled stakeholders from industry, academia and government to procure safe and effective COVID-19 vaccines for the UK population as swiftly as possible and to bolster domestic capacities in development, manufacturing and deployment.

In December 2021 the G7 Chief Scientific Advisers released the 100 Days Mission First Implementation Report[2]. This set out a roadmap to deliver diagnostics, therapeutics and vaccines within 100 days of detecting future pandemic threats. This ambitious goal will be achievable only by capitalising upon lessons and opportunities from the COVID-19 vaccine race.

Effective partnerships

The UK has long benefited from a highly collaborative scientific ecosystem. In early 2020 a range of commercial, academic, not-for-profit and government entities joined forces with the University of Oxford and AstraZeneca.

Together these parties established large-scale manufacturing infrastructure for a range of different vaccines around the world even before formal contracts or financial commitments had been fully negotiated and agreed. The VTF employed a venture-capital-style partnership approach rather than an adversarial style of working with vaccine companies. This venture capital mindset could in theory revolutionise national and international approaches to major healthcare challenges.

Alignment and speed

A particularly bold and innovative decision was to develop large-scale drug substance and drug product manufacturing capacity nationwide before safety and efficacy data on candidate vaccines became available. Scenarios for a range of vaccines were modelled and nine manufacturing sites across the UK received major investment. Design and development teams were prepared for production and release to begin as soon as trials were complete and the MHRA had issued regulatory approvals.

2. UK Cabinet Office. 100 Days Mission to Respond to Future Pandemic Threats. 2021. https://www.gov.uk/government/publications/100-days-mission-to-respond-to-future-pandemic-threats. (Accessed 10 April 2022)

To recruit large numbers of clinical trial participants rapidly, particularly older individuals and those with underlying health conditions who were most at risk, the NHS COVID-19 Vaccine Research Registry was launched in July 2020. Over half a million volunteers signed up, of whom one-third were aged 60 or over. More than 50,000 participated in UK COVID vaccine trials which successfully generated registration-quality data. Such registries are likely to be instrumental tools for future therapeutic and vaccination studies in both emergency and non-emergency settings.

Handling uncertainty and risk

The levels of uncertainty and financial risk associated with vaccine procurement were unprecedented for the UK government and public sector. The VTF nonetheless invested $900 million in 2020 to invest in manufacturing and procurement before it was confirmed whether any vaccine was safe, effective and could be manufactured at scale. A total of $3.7bn was committed for seven different vaccines. Risks were managed carefully:

- Detailed due diligence was performed by the expert external VTF team to prioritise the most promising vaccines from over 190 possible candidates being developed around the world.
- An 'investment committee', comprising ministers from the Department for Business, Energy & Industrial Strategy (BEIS), the Department for Health and Social Care (DHSC), the Cabinet Office and the Treasury, that was modelled on the venture capital industry enabled rapid review of proposals by relevant stakeholders and swift decision-making. Civil servants safeguarded public procurement processes
- Contract schedules tied payments to milestones and deliverables and the VTF prioritised transparency when planning and justifying activities.

Future pandemics

- Despite the remarkable efficacy of the existing suite of COVID-19 vaccines, further research and development (R&D) will be needed to reduce transmissibility, improve durability of the immune response, and increase the use of adjuvants to enhance potency.
- The UK financial outlay for deployment of two or more doses of injectable vaccines was considerable. Research into alternative cost-effective products such as pills, patches and sprays will be required, especially for distribution to low-income countries.
- The UK manufacturing ecosystem is more mature and resilient than in 2019. Whilst bioprocessing production and fill finish facilities have been up-scaled it will be imperative to maintain sufficient capacity and flexibility to permit a rapid surge manufacturing of vaccines when required.

"About 40 institutions came together, setting aside their commercial work in order to scale up vaccine development and manufacturing. This was an astonishingly altruistic and effective approach."

Dame Kate Bingham, SV Health Investors and Chair of the UK Vaccine Taskforce

Development and testing of the Oxford-AstraZeneca vaccine

Sir Andrew Pollard FMedSci, Director of the Oxford Vaccine Group, discussed the successes of the Oxford-AstraZeneca vaccine partnership and highlighted the scientific, industrial and policy priorities for future pandemic preparedness efforts.

"Vaccine development required a huge multidisciplinary team with a shared vision working in earnest haste."

Sir Andrew Pollard FMedSci, Oxford Vaccine Group

The Oxford-AstraZeneca vaccine (ChAdOx1-S) is a recombinant, replication-deficient, chimpanzee adenoviral vector vaccine. It is manufactured using a modified chimpanzee adenovirus to be non-infectious to humans and unable to reproduce within the body, but capable of generating neutralising antibodies against COVID-19.

Phase I single-dose clinical trials were initiated in Oxford in April 2020 but switched to a two-dose strategy in view of enhanced immune responses with a second dose. Phase III studies launched in the UK, South Africa, Kenya and Brazil in late June 2020. Initial Phase III results were published in December 2020 and ChAdOx1-S received regulatory approval in the UK on 30 December. WHO granted emergency listing in mid-February 2021 and the first doses for global supply were released shortly thereafter. Both trial and real-world data demonstrates that ChAdOx1-S is highly effective in geographically, ethnically and socially diverse populations, including in older and more vulnerable individuals. Even as levels of neutralising antibodies fall naturally over time a good level of immunity is maintained. So far, ChAdOx1-S has offered effective protection against new variants.

The Oxford-AstraZeneca team has received considerable acclaim for condensing the testing and licensing process into just eight months. This was made possible by extensive research into viral vector vaccine platform technologies over the past 40 years. When Chinese researchers released the genetic sequence of SARS-CoV-2 in mid-January 2020 the team were able to swiftly slot the sequence into their existing framework for coronavirus vaccines and undertake animal studies to generate initial safety and efficacy data.

Image: Sir Andrew Pollard, Oxford Vaccine Group.

A number of other factors contributed to the success:

- The partnership between Oxford and AstraZeneca was initiated at an early stage, and manufacturing commenced whilst trials were ongoing. AstraZeneca helped set up over 20 manufacturing sites worldwide, including in lower- and middle-income countries.
- AstraZeneca provided critical manpower to navigate the international regulatory landscape and secure the necessary global approvals by early 2021.
- Thousands of individuals volunteered to participate in the Phase I, II and Phase III trials, enabling recruitment to proceed at an unprecedented rate. Phase III trial sites were set up with exceptional efficiency.
- Academic, Government and industry partners shouldered large financial risks by investing in development and manufacturing before trials had concluded.
- Science journalists worked closely with the Oxford-AstraZeneca team to manage the flows of misinformation and speculation around the safety profile of ChAdOx1-S.

Planning for the future

Stakeholders worldwide must begin planning now for the next global pandemic. More investment in research and development will enable vaccines to be designed on novel platforms against a range of infectious threats. To facilitate swift and reliable supplies of vaccines to low and middle-income countries it will be essential to maintain ChAdOx1-S supply chains and manufacturing sites. Future pandemics will require vaccine distribution to be better targeted to the people and the regions in greatest need.

> "There has been some talk about how everything went incredibly quickly when making vaccines, and that really isn't true: many of the platforms and technologies started being developed years ago."
>
> Sir Andrew Pollard, Oxford Vaccine Group

Navigating a global response to the pandemic to develop a vaccine made for the world

Dr Tonya Villafana, Global Franchise Head, Vaccines & Immune Therapies, AstraZeneca, detailed AstraZeneca's role in the development, manufacture and supply of the Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1-S). Dr Villafana reflected on the challenges that lie ahead and emphasised AstraZeneca's commitment to offering vaccines at cost to low-income countries.

Image: Dr Tonya Villafana, AstraZeneca.

"We have an exciting future. The opportunities to participate as an important player and collaborator in the COVID-19 response has set us up for more work in vaccines and immune therapies."

Dr Tonya Villafana, AstraZeneca

Industry has played a vital role in the global response to the COVID-19 pandemic. As cases surged around the world in early 2020 AstraZeneca initially provided practical support, donating PPE to lower-income countries, partnering with the UK government to deliver testing and screening services, and developing monoclonal antibodies with the potential to prevent and treat infection.

It was clear that vaccination offered the only viable route out of the crisis. In April 2020 AstraZeneca partnered with the University of Oxford to develop and deliver a recombinant adenoviral vector vaccine. The collaboration quickly gathered momentum, fuelled by a shared belief in the moral responsibility to make a safe and effective vaccine affordable and accessible worldwide.

The vaccine development programme enrolled over 65,000 participants to 20 clinical trials in over 15 countries. Real-world effectiveness data amassed since the start of vaccine rollout is impressive. ChAdOx1-S provides a 96% reduction in the risk of severe disease following two doses in adults aged 75 or above, and offers substantial protection against hospitalisation in elderly individuals living with co-morbidities. The vaccine has an acceptable reactogenicity profile, meaning that the initial inflammatory response generates only minor and conventional adverse events.

To date ChAdOx1-S has obtained over 120 regulatory authorisations worldwide. Almost 3 billion doses have been manufactured for use in over 180 countries. Two-thirds of these have been supplied to lower-income nations. AstraZeneca was the first manufacturer to partner with the Coalition for Epidemic Preparedness Innovations (CEPI) and with Gavi, the Vaccine Alliance. The organisation is the first and one of the largest contributors to the COVID-19 Vaccines Global Access (COVAX) scheme and it is estimated that the vaccine has prevented five million hospitalisations. AstraZeneca has initiated technology transfer agreements with emerging economies, largely in Asia and Latin America. It has strengthened regional supply chains and bolstered manufacturing capacity in middle-income countries including Thailand and Brazil.

The past two years have brought numerous challenges. A typical batch of vaccine requires up to four months to progress from initiation to release. As countries scrambled to sign procurement agreements in early 2021 it was difficult to manage expectations for manufacture and supply. AstraZeneca and the University of Oxford had to navigate a steady flow of speculation in the international media regarding the vaccine's safety profile.

As many countries prepare to manage COVID-19 as an endemic disease, questions and challenges persist:

- Future clinical trials will require innovations in digital infrastructure and data governance.
- Further regulatory innovation and harmonisation on an international scale is required.
- The recommended frequency of booster doses must be further explored.
- Mechanisms to modify vaccines when faced with variants of concern will be needed.
- Vaccines must remain affordable to lower-income countries. This will also minimise the emergence of vaccine-resistant variants.

The past two years have offered valuable lessons. Public-private partnerships are an essential element of the research and development ecosystem. Investment in future-focussed R&D and regional manufacturing is critical. A successful response to a public health crisis requires both private and public sector organisations to exploit novel digital tools, adapt quickly, and embrace new ways of working.

From watchdog to enabler – regulation in COVID-19 and after

Dame June Raine, Chief Executive of the UK Medicines and Healthcare products Regulatory Agency (MHRA), reflected on how the systems and processes governing the regulation of clinical research have evolved over the past two years, and explained that the COVID-19 pandemic will mark a turning point in regulatory policies and methodologies.

Image: Dame June Raine, UK Medicines and Healthcare products Regulatory Agency (MHRA)

As the national regulatory body for healthcare interventions, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has been a critical player in the COVID-19 response both in the UK and internationally.

The MHRA has traditionally acted as a watchdog, conducting assessments once pre-clinical testing and clinical trials are complete. However, the COVID-19 pandemic compelled it – and other regulators – to embrace a more proactive, flexible and collaborative approach. It seems likely that COVID-19 will serve as a watershed in operational standards.

In January 2021 the UK government launched the MHRA Innovative Licensing and Access Pathway.

This collaborative initiative seeks to capitalise upon recent changes to accelerate the delivery of novel healthcare interventions to the NHS. Alongside this, the G7 Therapeutics and Vaccines Clinical Trials Charter[3] is expected to be incorporated into UK law in the coming months. It seeks to improve international collaboration in clinical trials, develop opportunities to repurpose therapeutics, and increase the diversity of trial participants. The MHRA will continue to participate in the International Coalition of Medicines Regulatory Authorities COVID-19 Working Group's efforts to improve alignment of regulations governing healthcare research.

3. UK Department of Health and Social Care. G7 Therapeutics and Vaccines Clinical Trials Charter. 2021. https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-therapeutics-and-vaccines-clinical-trials-charter (Accessed 15 April 2022)

The G7 100 Days Mission[4] will likewise rely on regulators to maintain and cultivate the innovations of the past two years, including:

- **Testing**
  The MHRA adopted the World Health Organisation's concept of Target Product Profiles to establish minimum and optimum characteristics and performance thresholds when assessing point-of-care testing technologies.

- **Clinical infrastructure and trials**
  The MHRA supported Nightingale hospitals to access locally manufactured equipment and infrastructure, minimising operational delays. Underpinned by preparatory work from the UK National Institute for Biological Standards and Control (NIBSC), the MHRA offered real-time guidance during pre-clinical studies and clinical vaccine trials. Safety assessments were undertaken frequently and data were reviewed on a rolling basis. Continuous dialogue was maintained with vaccine development teams. When Oxford-AstraZeneca vaccine trials concluded in November 2020 the MHRA had already reviewed substantial quantities of robust data which enabled regulatory approval to be issued within a few weeks.
  The RECOVERY trial's platform structure (testing multiple interventions in parallel) provided high-quality and actionable data in record time. It is likely that this trial design will become prevalent in future.

- **New collaborations**
  Many novel diagnostics and devices were submitted for approval by multidisciplinary consortia such as University College London, University College London Hospital and Mercedes-AMG High Performance Powertrains, who developed the UCL-Ventura CPAP (Continuous Positive Airway Pressure device). Approval was granted within ten days and the device was subsequently made available off-patent worldwide, including to lower- and middle-income countries.

- **Interactions with the public**
  The Chair of the Commission on Human Medicines made regular appearances at press conferences and public briefings to enhance transparency around the use of evidence in decision-making.

"COVID-19 has catalysed a change from a watchdog to an enabler and a facilitator and I'm enormously proud that the MHRA has had a part to play."

Dame June Raine, UK Medicines and Healthcare products Regulatory Agency (MHRA)

4. UK Cabinet Office. 100 Days Mission to Respond to Future Pandemic Threats. 2021. https://www.gov.uk/government/publications/100-days-mission-to-respond-to-future-pandemic-threats. (Accessed 10 April 2022]

Mass testing capacity: people, production, productivity

Professor Chris Molloy, Chief Executive Officer of Medicines Discovery Catapult, highlighted the remarkable achievements of the Lighthouse Laboratories Network in mass PCR testing and reflected on future priorities.

Diagnostic testing plays a critical role in infection surveillance and if accompanied by appropriate public health restrictions can significantly slow the spread of disease. In March 2020, COVID-19 cases were rising exponentially, but UK capacity (via the NHS) was able to process just 8,000 tests per day. This catalysed the UK's largest ever diagnostic initiative.

Building the largest diagnostic network in British history

The first three Lighthouse Laboratories were established in March 2020 in Cheshire, Milton Keynes, and Glasgow, as national sample processing hubs under the NHS Test and Trace scheme. From a standing start, these laboratories were clinically active within four weeks and together realised the highest per capita testing capacity of any large country. By May 2020, they were operational 24/7 and had processed over a million tests. They would eventually be able to increase the volume to over 0.5 million per day, as the Lighthouse Laboratory Network expanded. Whilst working at scale their robust quality control and analytics enabled the Alpha variant to be swiftly identified and tracked as it spread across the UK in late 2020.

The industrial scale development was facilitated by specialists from industry, academia and the charity sector who united to offer expertise and capital equipment. Clinical experts and health and safety professionals from the NHS and Public Health England embedded NHS quality standards alongside the industry rigour within the Lighthouse Laboratory systems.

The Lighthouse Laboratory Network innovated to maintain long-term testing capacity:

- Established updated and high-quality testing standards for implementation across the NHS.
- Explored miniaturisation and automation technologies to reduce processing lead times.
- Set up additional supply chain agreements to safeguard stocks of critical reagent materials such as ethanol, plastics and primers, and identified alternative reagents for more efficient sample analysis.

Image: Professor Chris Molloy, Medicines Discovery Catapult.

"So many people just said: 'use us', 'what do you want?', and 'what do you need?'. That attitude must be retained because that is how we go to war with a disease, and that is what we can do now."

Professor Chris Molloy, Medicines Discovery Catapult

These activities were complemented by the National Industry Consortium for COVID-19 mass testing diagnostics, a group of 40 companies who set aside sector competition and joined forces to boost domestic capacity in design and manufacturing of novel diagnostics. Between September 2020 and May 2021, the UK achieved a 500-fold increase in lateral flow test production. Automated processes that reduced factory workforce requirements by 90% received clinical validation. In addition, Consortium members explored alternative bio-degradable materials to reduce environmental impact.

Beyond the laboratory

To help the public understand the rationale for testing and associated behavioural changes the Lighthouse Laboratory at Alderley Park supported the development of an educational video resource 'The Journey of a PCR swab'. A Living History collection was organised at the London Science Museum and showcases the role of PCR testing in the UK's pandemic response and highlights the contributions of individual scientists and technicians.

The Network also provided training for thousands of young scientists who are now equipped to enter a vibrant job market with lifelong skills.

Moving forward

Having processed over 150 million COVID-19 samples, the network of Lighthouse Laboratories officially ended in late March 2022, in line with the Government's evolving response to the pandemic. In mid-2021 the UK Health Security Agency established a large-scale 24/7 PCR testing laboratory at the Rosalind Franklin Institute in Leamington Spa. This facility will lead and scale up mass testing initiatives as required.

Additional priorities for the future include:

- Encouraging individuals to consent to share biological data to facilitate industry validation of novel testing technologies.
- Strengthening domestic capacity in antibody research, development and manufacturing.
- Developing digital adjuncts to improve the effectiveness of diagnostic tools, and exploring remote delivery technologies for mass testing.
- Capitalising on increased public understanding of self-testing and of personal health responsibility.

> "This was a shining example of the power of purposeful people, unified by a common goal, working together to shine a beacon of light through the darkness of the pandemic. The lights may be off on the network, but the safety light remains on."
>
> Professor Chris Molloy, Medicines Discovery Catapult

Image: Staff working as part of the Lighthouse Laboratory Network.

Deriving actionable information from SARS-CoV-2 genomes

Professor Sharon Peacock CBE FMedSci, University of Cambridge and Executive Director and Chair of the COVID-19 Genomics UK Consortium (COG-UK), outlined how COG-UK spearheaded scalable genomic sequencing of SARS-CoV-2 for public health benefit.

Image: Professor Sharon Peacock, University of Cambridge

"The past two years have shown beyond doubt that sequencing generates actionable information that supports an effective public health response."

Professor Sharon Peacock CBE FMedSci, University of Cambridge

Viral genomic sequencing involves laboratory analysis to ascertain a virus's genetic composition and identify mutations or new variants. The UK benefits from a well-funded genomics research base, and UK teams have previously conducted sequencing on the Ebola and Zika viruses, HIV, TB, and foodborne pathogens.

The COVID-19 Genomics UK consortium (COG-UK) was established in March 2020. The consortium was composed of teams from 16 UK universities plus the four national public health agencies and the Wellcome Sanger Institute. It marked the first time that these agencies had executed substantial data-sharing agreements.

In early March COG-UK began sequencing SARS-CoV-2, supported by an initial £14.5 million grant from the UK Department of Health COVID-19 Fighting Fund, and an in-kind contribution of £5.5 million from the Sanger.

Although the UK was not the first country to release a genetic sequence of SARS-CoV-2 it was one of the first to rapidly scale up sequencing to provide a vital contribution to vaccine development and variant tracking.

By mid-March 800 genomes had been sequenced, with data stored and analysed on the MRC-funded Cloud Infrastructure for Microbial Bioinformatics (CLIMB) platform. The consortium navigated logistical and methodological challenges to ensure that virus samples reached regional sequencing sites promptly and that genomic information could be appropriately linked to patient metadata. The innovative tools developed by Consortium members during this period are now deployed worldwide, including the Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) software which facilitates classification of genetic lineages.

By November 2020, 50,000 genomes had been sequenced, which provided actionable data to illustrate the virus's international and national spread and inform regional restrictions. By June 2021 the total had risen to 500,000, which is around ten times more than Public Health England's annual output in 2019. COG-UK began to innovate to enhance the efficiency and cost-effectiveness of genomic services and reduced sequencing costs by 40%. By the peak of the Delta wave one million genomes had been sequenced.

In the autumn of 2021 COG-UK transferred responsibility for long-term pathogen genomics sequencing to the four UK Public Health Agencies, with ongoing support from the Wellcome Sanger Institute.

Future activities are likely to include:

- Combining two million virus genomes with host genetics and electronic health records data to help investigate genetic determinants of susceptibility to severe infection.
- Improving UK capabilities in metagenomics (the full genetic analysis of genomes within environmental samples) to study reservoirs of novel viruses, improve detection of emerging viruses, and use whole-genome sequencing to inform surveillance of anti-microbial resistance.
- Enhancing technologies to enable place-based sequencing, helping develop targeted responses for localised outbreaks.
- Working closely with Public Health Agencies to help shape priorities.
- Advocating for improved global data-sharing, and strengthening sequencing and bioinformatics capacity worldwide. Supported by funding from the Wellcome Trust and the UK Foreign, Commonwealth and Development Office COG-UK has launched COG-Train, an international programme offering massive online open-access courses, virtual classrooms and training workshops to scientists based in Africa, Asia and Latin America.

Learning from the pandemic on diagnostic testing for asymptomatic and early disease

Dr Ruth March, Senior Vice-President and Head of AstraZeneca Precision Medicine and Biosamples, described AstraZeneca's COVID-19 staff testing initiative and reflected on the potential of self-testing to boost early detection of disease.

In mid-March 2020 AstraZeneca pioneered a diagnostic testing system for employees in its offices, laboratories and manufacturing facilities across the world. AstraZeneca's lean operating model meant that a small increase in staff absence – whether due to genuine or suspected infection – would directly impact the supply of essential medicines for patients, healthcare facilities and clinical trials. At the time, public testing resources were allocated largely to symptomatic cases, to healthcare professionals and to others working on the frontline.

"As a diagnostics industry we have seen at least 5 – 10 years of progress sandwiched into that initial surge of diagnostics development in the first nine months of the pandemic."

Dr Ruth March, AstraZeneca

Ordinarily it would take around 18 months to establish such a testing network. In early 2020, systems were operational within 18 days, facilitated by access to AstraZeneca's laboratories and diagnostics expertise. Challenges included:

- The need to employ healthcare professionals to swab employees and ensure that positive cases were notified promptly at a time when national health systems were experiencing acute pressure.
- The need to select suppliers carefully to avoid compromising the supply of essential goods and equipment to the frontline.
- Initial uncertainties around temperature requirements for transportation and storage.

Initial uptake was only 30%. Surveys and interviews with staff led to various adjustments:

- Many individuals were averse to nasopharyngeal swabs. Laboratory scientists adapted the testing technologies to accept saliva samples.

Image: Dr Ruth March, AstraZeneca.

- Many encountered difficulties with the mobile phone application and found it difficult to commit to a testing slot. AstraZeneca's IT team simplified the application, trained staff how to use it and introduced self-service slots.
- Rapid antigen (lateral flow) tests were introduced for visitors, employees returning from leave and staff not based near laboratories.
- AstraZeneca introduced family pool testing. If an employee was unable to attend work due to suspected COVID-19 infection in their family, all household members were invited to send a batch saliva sample. Laboratories would confirm whether or not their household contained a positive case.
- Later batches of testing kits and packaging minimised single-use plastic. This condensed the laboratory time required to process each sample and reduced the environmental footprint of each test.

These measures resulted in a five-fold increase in employee uptake of testing. To date, AstraZeneca has never had to close a manufacturing line or research laboratory due to COVID-19 infection.

"Self-testing has become public and accepted by the population. It's not something you do in hospital; you do it for yourself."

Dr Ruth March, AstraZeneca

Looking to the future

Continuous self-testing is now widely accepted across the globe. In many countries testing kits are available off-the-shelf.

There is significant potential to extend these innovations to other diseases, notably to cancers. Too many patients receive a diagnosis when their disease is already at an advanced stage. Early diagnosis is crucial for long-term survival. When combined with continuous testing to monitor levels of circulating tumour DNA (a biomarker which indicates the presence of cancerous cells), the chance of a cure is increased because treatment can commence before symptoms appear. If immediate intervention was not necessary, diagnostic testing would enable early-stage cancers to be monitored and managed as a chronic disease.

CLOSING KEYNOTE DAY 1

Science into policy and practice for COVID-19

Sir Chris Whitty KCB FMedSci, Chief Medical Officer for England and Chief Medical Adviser to the UK government, reflected on the intersection between science and public policy during the past two years, and discussed priorities for the next phase of the pandemic response.

Image: Sir Chris Whitty, Chief Medical Officer for England and Chief Medical Adviser to the UK government

> "Because we were dealing with a new and potentially catastrophic problem, we as scientists had to recommend to government and the public very substantial measures with big social and economic implications."
>
> Sir Chris Whitty KCB FMedSci, Chief Medical Officer for England and Chief Medical Adviser to the UK government

The UK stands at an inflection point in its response to SARS-CoV-2. In the initial months of the pandemic, policies were developed from first principles. They were influenced largely by information from countries experiencing early waves of infection such as China and Italy and by modelling based on piecemeal clinical and epidemiological data.

Later in 2020, widespread testing and surveillance combined with the swift launch of observational studies enabled interventions to be better targeted to individuals. The UK was in a strong position to generate robust scientific data:

- Investment in vaccinology had increased in the wake of the 2014 – 2016 West African Ebola epidemic.
- Lessons from shadow (retrospective) clinical trials undertaken following the flu epidemics and an outstanding network of expertise at UK research centres facilitated the swift inception of trials for therapeutic and vaccine candidates.
- Funding was fast-tracked and NHS leaders were committed to testing drugs in trial settings prior to deployment.

As a result, data from UK observational and interventional research endeavours influenced policies and outcomes in many countries.

These advances helped the UK move from social interventions such as lockdowns and quarantine to medical interventions based on testing, drugs and vaccines. The vaccine rollout has led to a remarkable reduction in death rates. Although research into new vaccines and therapeutics continues apace the surge in cases of Omicron sub-lineage BA.2 in the UK demonstrates that the pandemic is not over. Much remains to be understood about SARS-CoV-2, and vaccine-resistant variants may well emerge in the coming years.

At the height of the pandemic UK policymakers faced significant challenges. The government had to make swift choices based on incomplete evidence and evolving science. In normal times, public health policymakers seek to balance the difficulty of an intervention – including cost, enforceability and public support – against the magnitude of potential benefits and the strength of underlying evidence. In this case, the Scientific Advisory Group for Emergencies (SAGE) had to provide policymakers, and ultimately the general public, with a coherent scientific assessment to inform decision-making whilst remaining transparent about significant evidence gaps, uncertainty, and the likelihood that regulations would change.

Measures were implemented with substantial impacts on the job security, education and mental and physical health of the UK population. The government had to act decisively on issues that would ordinarily undergo review within specialist divisions. Scientists and policy officials faced legitimate challenge from scientists and organisations who deemed measures either too restrictive or not stringent enough.

Interdisciplinary science, including synthesis of science from many disciplines, is often undervalued yet has rarely been more important. Whilst government policy is frequently informed by science, few – if any – issues of this magnitude have definitive scientific solutions from a single discipline. The scale, scope and complexity of the problems necessitated synthesis both within and between basic, applied and behavioural scientific disciplines.

As the UK adjusts to life with fewer restrictions scientists and policymakers must contemplate the successes and failures of the past two years and consider strategies for managing future outbreaks:

- A vigilant and responsive approach will be essential as variants emerge and cases ebb and flow.
- Non-COVID research activities put on hold during the pandemic must be revived whilst maintaining investment in pandemic preparedness efforts.
- The UK and other countries have benefitted enormously from international collaboration including the willingness of Chinese investigators to release the genetic sequence of SARS-CoV-2 in early 2020 and of South African researchers to share findings from Omicron studies in late 2021. Ongoing international collaboration will be critical.

Long COVID: A long-lasting legacy of the pandemic?

Dr Nathalie MacDermott, NIHR Academic Clinical Lecturer in Paediatrics (Infectious Diseases), King's College London, drew upon her personal experience to highlight the disease burden of long COVID and emphasised the importance of incorporating the risks and long-term implications of this condition into public health decision-making.

Image: Dr Nathalie MacDermott, King's College London.

"We talk about hospitalisations and deaths, but I don't hear people acknowledging that long COVID is an issue which we need to consider when adjusting our public health measures. Economically, this is going to be to our downfall in the coming years."

Dr Nathalie MacDermott, King's College London

The UK Office for National Statistics (ONS) estimates that as of 31 January 2022 approximately 1.5 million people, or 2.4% of the UK population, were experiencing symptoms associated with long COVID. 45% of these individuals had been living with symptoms for more than one year.

There is currently no specific or universally-accepted definition of long COVID. The UK National Institute for Health and Care Excellence (NICE) published the first definition[5] in October 2020, stating that:

- Symptoms lasting up to four weeks typically represent 'acute' COVID.
- Those that persist for four to eight weeks are described as 'post-acute' COVID.
- Patients with symptoms that linger or return more than 12 weeks after infection are generally diagnosed with long COVID, or 'post-COVID syndrome'.

5. UK National Institute for Health and Care Excellence. COVID-19 guideline scope: management of the long-term effects of COVID-19. 2020. https://www.nice.org.uk/guidance/ng188/documents/final-scope (Accessed 20 April 2022)

A WHO study, published in October 2021[6], describes broad clusters of symptoms including fatigue and cognitive dysfunction which begin or persist within three months of infection, last for at least two months, and cannot be explained by alternative diagnoses. Self-report studies indicate over 200 symptoms.

Long COVID in adults

The UK Department for Work and Pensions revealed that applications for Personal Independence Payment (PIP) – which offers support to individuals living with a long-term health condition or disability – have risen by 20% over the past 12 months.

This represents the highest year-on-year increase since PIP was established and seems likely to have been influenced by long COVID. The long-term economic effects will be substantial and will include:

- Reductions to labour force productivity;
- Reductions in earning potential and tax revenue;
- An increased unemployment benefit bill;
- Financial implications for employers who make adjustments for employees.

Long COVID in children

Many secondary and primary school pupils have been infected with the Delta and Omicron variants. Approximately 2% of young people who contract COVID-19 develop persistent symptoms following COVID-19 which are consistent with long COVID. It is not clear how long these symptoms may persist, and most paediatric long COVID clinics have been established only in the last six months.

The decision to offer COVID-19 vaccines to children and teenagers was hotly debated. Despite initial speculation that mRNA vaccines might increase the risk of paediatric myocarditis (inflammation of the heart muscles) this was shown to be 400 times lower than the risk of developing long COVID.

The impacts on children and families are significant. Prolonged disruption to education will affect eventual earning power. Parents and carers also suffer loss of income if they give up work to care for their child.

Priorities for the future

The pathogenesis of long COVID remains poorly understood. The NIHR has dedicated significant research funding to diagnostics and therapeutics, but more investment is needed. It is likely that there are several phenotypes which will require differentiated treatments. Research findings may also benefit patients living with myalgic encephalomyelitis/chronic fatigue syndrome, who typically share some symptoms with long COVID patients.

Although long COVID has recently received more coverage in the UK media, public health decision-making still appears to be driven largely by numbers of infections and deaths from acute COVID. Reliable diagnostic tools, data and clinical trials are urgently needed to reduce reliance on self-reported information and to distinguish long COVID patients from those with other illnesses.

Scientists and politicians have a moral duty to ensure that the enduring impact of long COVID upon quality of life, livelihoods, healthcare services and the national economy is directly acknowledged and placed at the heart of decisions to tighten or ease public health restrictions in the future.

6. World Health Organisation. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (Accessed 20 April 2022)

Immune pathogenesis and therapeutics for COVID-19

Professor Ling-Pei Ho, University of Oxford, and Chair of the UK NIHR Respiratory Translational Research Collaboration, discussed the unique features of lung disease in COVID-19 and the results of two high-profile immunology studies that she was part of.

Computerised tomography (CT) images of lung disease in COVID-19 patients highlight unique features of this infection. Lung CT changes reveal damage to airspaces and predominantly peripheral lung consolidation, reflecting alveolar damage and attempts at reparation. The predilection for alveolar lining is likely caused by the high concentration of ACE receptors on the alveolar epithelium, providing the virus with an entry point for propagation whilst simultaneously damaging these cells. It is now known that the elderly, males, diabetics and those with high body mass index are at higher risk of developing severe COVID-19 disease. When admitted to hospital, patients with persistent fever and with high levels of C-reactive protein and neutrophils have often fared worse. Two studies led by UK investigators have offered a particular contribution to global efforts to understand the underlying reasons for these trends.

Image: Professor Ling-Pei Ho, University of Oxford

Coronavirus Immune Response and Clinical Outcomes Study (CIRCO)[7]

CIRCO was a prospective longitudinal immune profiling study in corticosteroid and therapeutics-naive patients performed during the first wave of the pandemic. It was the first UK study to investigate underlying mechanisms in severe COVID-19 disease and was led by Professor Tracy Hussell in Manchester, supported by the NIHR Respiratory Translational Research Collaboration. COVID-19 patients provided fresh blood samples shortly after hospital admission and at regular intervals throughout their stay. Patients were then classified as having mild, moderate or severe disease according to the highest disease severity during their stay, and the highest form of ventilatory support required.

The study demonstrated the importance of treating patients early following admission, as maximal abnormalities appeared early during hospitalisation.

Patients who developed severe disease during hospitalisation showed an abnormal immune response as follows:

- Low levels of CD3 T lymphocytes (white blood cells involved in the antigen response), B-lymphocytes (white blood cells involved in the antibody response) and neutrophils upon admission. These were most marked in patients who went on to develop severe disease.
- Presence of abnormal monocyte cells with features of immaturity (young blood cells). These were also most marked in patients who developed severe disease.
- Levels of T lymphocytes and neutrophils that did not normalise over time.
- Increased blood levels of the IL6, IL10, MCP-1 and IP10 cytokines.

7. Mann et al. Longitudinal immune profiling reveals key myeloid signatures associated with COVID-19. *Science immunology*. 2020;5(51). https://pubmed.ncbi.nlm.nih.gov/32943497/ (Accessed 17 April 2022]

COVID-19 Multi-omic Blood Atlas (COMBAT)[8]

COMBAT was a large multimodality phenotyping study led by Professor Julian Knight at the University of Oxford. It integrated clinical, immunobiology, machine learning and advanced data science technologies to examine blood immune signatures and cellular drivers of severe disease, explore causes for heterogeneity in clinical disease and to identify biomarkers for severe COVID-19.

Results identified higher prevalence of immature neutrophils, neutrophil progenitors, immature platelets and immature monocytes as correlates of severe COVID-19 disease. A protein signature of 11 proteins was able to differentiate patients with higher mortality and disease severity from those who fared better. These proteins included the cytokines GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-6, CCL-2, CXCL-20, CCL19 and CCL20. IL-6 and GM-CSF antagonists were subsequently shown to improve disease outcomes in clinical trials, and anti-IL-6 biologics (such as Tociluzimab) are now used as standard of care NHS treatment for patients with severe COVID-19 disease.

Both CIRCO and COMBAT showed that emergency myelopoiesis – an immune process where the bone marrow produces greater numbers of myeloid cells in response to high inflammatory signals – was a major correlate of severe COVID-19 disease. COMBAT also identified a signature biomarker which may allow clinicians to distinguish those at greater risk of severe disease.

Future priorities include understanding how emergency myelopoiesis contributes to severe disease, investing in interventions that minimise or inhibit the binding capacity of SARS-CoV-2, and integrating Phase II and Phase III therapeutic trials to accelerate the path to licensing of new drugs.

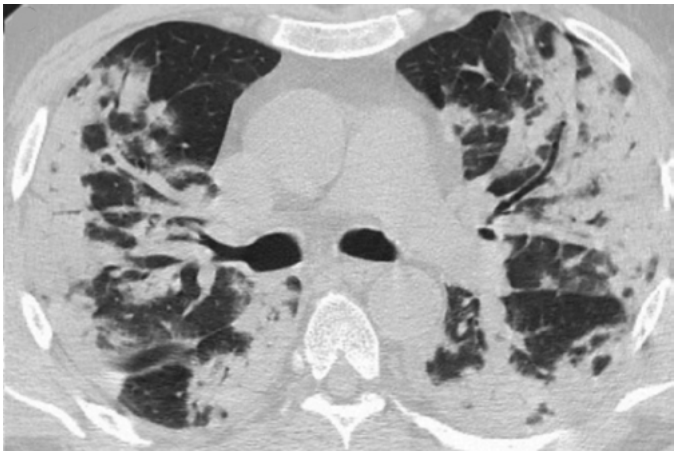


Image: Lung CT scan from a patient with severe COVID-19 disease, and data from the COMBAT study

"Rapid and in-depth scientific studies of immune mechanisms of severe COVID have worked hand in glove with clinical trials of new therapeutics."

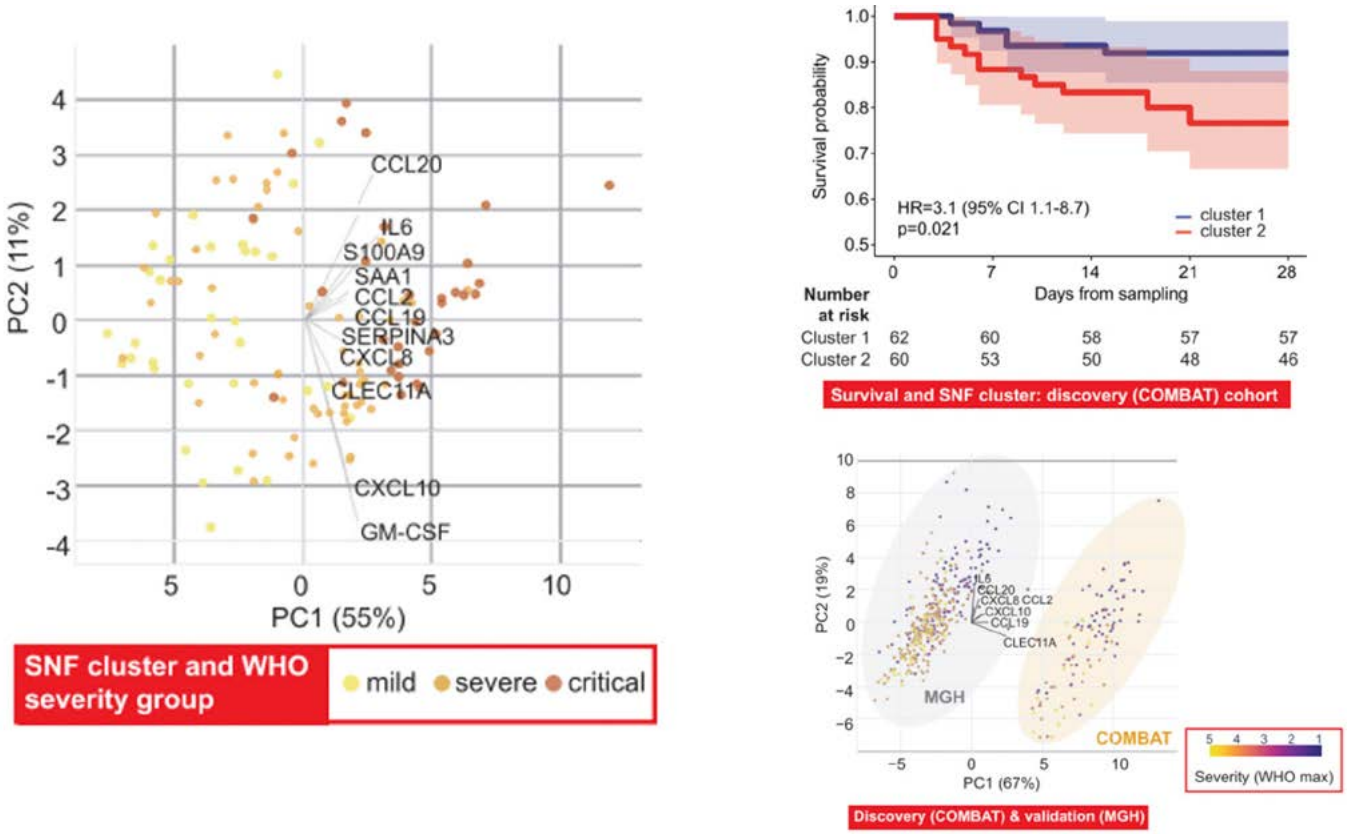
Professor Ling-Pei Ho, University of Oxford

8. COMBAT Consortium. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. *Cell*. 2022;185(5): 916-938. https://www.sciencedirect.com/science/article/pii/S0092867422000708?via%3Dihub (Accessed 17 April 2022)

FIGURE 3

Data from the COMBAT study

COMBAT identified 11 proteins that were associated with severe and critical disease and with higher mortality. The COMBAT data were replicated in an independent group of patients from Massachusetts General Hospital in the US.



Credit: COMBAT Consortium. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. *Cell*. 2022;185(5): 916-938. https://www.sciencedirect.com/science/article/pii/S0092867422000708?via%3Dihub (Accessed 17 April 2022)

Molnupiravir for the treatment of COVID-19

Dr Jay Grobler, Associate Vice President, Infectious Diseases and Vaccines, Merck, explained how the oral antiviral prodrug molnupiravir can reduce the risk of hospitalisation or death due to COVID-19 in high-risk patients.

Molnupiravir is an oral antiviral licensed for use in COVID-19 patients with mild to moderate disease who are at high risk of hospitalisation. It is a prodrug of the small molecule N-hydroxycytidine (NHC), first described in the 1960s. N-hydroxycytidine 5'-triphosphate (NHC-TP), the active metabolite of NHC, is incorporated by viral polymerases and introduces errors into RNA viral genomes, impairing the ability of the virus to replicate and infect. Cell culture analyses and animal studies have demonstrated that NHC is active against multiple viruses such as influenza and coronaviruses including SARS-CoV-2 and associated variants of concern.

"With the lessons learned from COVID-19, perhaps molnupiravir will find a place in the armamentarium to address the next pandemic as well."

Dr Jay Grobler, Merck

In humans, however, NHC exhibits poor oral bioavailability. To overcome this obstacle, molnupiravir was developed in 2019. As a prodrug of NHC, molnupiravir becomes pharmacologically active once metabolised within the body and thus has significant therapeutic potential to target important human pathogens.

In early 2020, scientists at Merck joined forces with Ridgeback Biotherapeutics to trial molnupiravir in patients with COVID-19. Pre-clinical in vitro and in vivo studies showed promising results:

- Molnupiravir exhibited robust antiviral activity, reducing both the production of viral particles as well as their infectivity in cell cultures and in animal models including mice, ferrets, and hamsters infected with SARS-CoV-2.
- NHC reduces viral infectivity through the introduction of errors in the viral RNA. In cell cultures, a six-fold increase in error rate generated a 26,000-fold decrease in the production of infectious viral particles. Similar results were observed in animal models.

Image: Dr Jay Grobler, Merck

- Ferrets infected with SARS-CoV-2 easily transmitted the virus to other ferrets within the same living space. When the animals were treated with molnupiravir no transmission to uninfected ferrets was observed.

The MOVe-OUT Phase II trial enrolled adult participants with mild to moderate COVID-19. It evaluated the safety and efficacy of molnupiravir at 200mg, 400mg and 800mg doses administered twice daily for five days. Results indicated that:

- Nucleoside substitution – which signifies inhibited viral reproduction – increased at all dose levels. The highest increases were observed in the 800mg arm.
- Errors were randomly distributed across the SARS-CoV-2 viral genome.
- Five days after starting treatment no infectious virus was detected in participants who had received 400mg or 800mg of molnupiravir (Ridgeback Protocol 006). In contrast, infectious virus was identified in 11% of participants in the placebo arm.

The subsequent Phase III study recruited 1,550 unvaccinated outpatients aged 18 or older with a risk factor for severe disease (such as diabetes mellitus or obesity) and who were within five days of symptom onset. Patients randomised to the molnupiravir arm received 800mg twice daily for five days. Interim analyses revealed that twice as many patients were hospitalised or died in the placebo arm compared to the molnupiravir arm. 90% of deaths and a larger number of serious adverse events occurred in the placebo arm. Patients in the molnupiravir arm showed greater sustained improvement and less progression in self-reported symptoms including shortness of breath, loss of taste, and loss of smell. No safety concerns were identified.

A study into molnupiravir's potential to attenuate household transmission is ongoing. It is likely that this prodrug will remain an important tool in the targeted response to future pandemics.

Fighting COVID-19 with broadly neutralising antibodies

Dr Davide Corti, Senior Vice President, Antibody Research, Vir Biotechnology, discussed the rapid development of the monoclonal antibody sotrovimab to target patients at risk of severe COVID-19 infection, and explored the wider prophylactic and therapeutic potential of broadly neutralising antibodies.

Image: Dr Davide Corti, Vir Biotechnology

"We have evidence that antibodies with very broad ability to recognise different viral species can offer a real opportunity for off-the-shelf therapies. They can counter antigenic drift and potentially also antigenic shift."

Dr Davide Corti, Vir Biotechnology

Monoclonal antibodies (mABs) are proteins secreted by clones of plasma cells or memory B cells. They bind to their targets, epitopes of surface antigens (the component recognised by the immune system) such as viruses, infected cells or cancer cells. mABs have revolutionised the treatment of several human diseases, especially cancers and autoimmune disorders. Over 100 have been licensed since 1986, of which 10% treat infectious diseases (IDs). The development of ID mABs has accelerated in recent years, facilitated by new methods and techniques which enable mABs to confer protective immunity upon individuals at risk of developing severe disease.

In January 2020 Vir Biotechnology had already commenced work to develop mABs against coronaviruses. Given the genomic similarities between SARS-CoV-1 and SARS-CoV-2, blood samples from a SARS-CoV-1 donor provided several antibodies able to recognise the SARS-CoV-2 spike protein.

Of these, antibody S309 displayed potent in vitro neutralising activity against SARS-CoV-2, and high binding affinity to the spike protein. S309 exhibited a different epitope-targeting strategy from existing mABs and resulted in killing and phagocytosis (cell ingestion) of killer cells.

S309 was isolated in February 2020 and developed in collaboration with GlaxoSmithKline. Following the introduction of mutations to prolong its half-life it was manufactured at scale in less than five months, almost four times faster than the typical lead time.

Sotrovimab and the Omicron variant

In vitro studies to investigate the efficacy of sotrovimab against the Omicron sub-lineages BA.1, BA.1.1, and BA.2 showed:

- A minor loss of potency against BA.1 and BA.1.1.
- A 15-30-fold reduction in neutralisation potency against BA.2. This led the US Food an d Drug Administration (FDA) to suspend its recommendation to prescribe sotrovimab to patients living in states with high prevalence of BA.2.
- S309 retained activity against BA.2 in promoting killing and phagocytosis of target cells expressing the BA.2 spike protein on the surface. In vivo, S309 protected mice from infection with BA.2. This in vivo efficacy was shown to rely on Fc-mediated effector function.

Other more broadly neutralising mABs have the potential to overcome the antigenic shift and drift associated with the Omicron variant. New delivery technologies may enhance efficacy. Further improvements to mABs' half-life and the introduction of mutations to induce T cell responses may improve their prophylactic potential and accelerate the development of antibody-driven vaccines.

COVID-19 therapeutics: Revelations and revolutions

Sir Peter Horby FMedSci, University of Oxford, examined recent innovations in clinical trial design and drug discovery that are likely to transform the UK's approach to researching and treating disease.

"We've seen quite a shift in the way we are treating infections: we are looking both at the patient and at the virus, and targeting the therapy based on both of those dimensions."

Sir Peter Horby FMedSci, University of Oxford

The race to identify safe and effective therapeutics against COVID-19 revolutionised clinical trial frameworks and catalysed the drug development process. This led to unexpected successes and promising innovations which must now be sustained through targeted investment.

During the 2009 H1N1 flu pandemic the processes governing regulatory approval of clinical trials and patient recruitment were lengthy and cumbersome. No new therapeutics for severe flu were identified before cases dwindled in early 2010. To circumvent these difficulties a bold and innovative approach was adopted.

- Many COVID-19 patients admitted to hospital in the UK were enrolled into major platform trials such as RECOVERY or REMAP-CAP. This enabled frontline NHS staff to integrate research into routine care and offer alternative treatments. The RECOVERY trial has randomised over 47,000 participants aged between 0 and 103, including pregnant women.
- This unusually large patient population generated robust data on clinical outcomes, including around drug interactions, and facilitated sub-group analysis. Factorial design – where two or more interventions are compared simultaneously – further increased the number of data points.
- The RECOVERY trial assembled all study documentation on an electronic platform. This allowed patients to be enrolled and randomised within just eight minutes, dramatically increasing the enrolment capacity of clinical teams.

Image: Sir Peter Horby, University of Oxford.

- Investigators embraced data linkage and triangulation methodologies to record and identify clinical outcomes. Further collaboration with regulators will be required to optimise these tools.

Prior to March 2020, immunomodulation – using specific drugs to alter the immune system response – was rarely sanctioned for patients with acute viral infection. However, studies demonstrated that a combination of three immunomodulators – dexamethasone, tocilizumab, and baricitinib – reduced mortality rates in patients with late-stage COVID-19. This opens the pathway to evaluate immunomodulation in cases of pneumonia or seasonal flu.

Another revelation was that administering monoclonal antibodies appeared to reduce the mortality risk in hospitalised patients. Although many monoclonal antibody trials closed early due to insufficient sample sizes, a larger trial of Casivirimab/imdevimab showed significant improvements.

Such advances have facilitated a shift to targeted therapies based upon both patient biomarkers, such as serostatus, and the virus genotype.

Choosing drugs for UK COVID-19 treatment trials

Professor Patrick Chinnery FMedSci, University of Cambridge and Clinical Director of the UK Medical Research Council, described UKRI's role in funding a portfolio of platform trials to accelerate new treatments for COVID-19, and explored how this approach might serve therapeutic studies for non-communicable diseases.

Image: Professor Patrick Chinnery, University of Cambridge and Clinical Director of the UK Medical Research Council.

"If we embed the research in the NHS – which is the NIHR's vision – we will not only enhance delivery of clinical trials but will also promote the ability to transfer those new insights into clinical practice."

Professor Patrick Chinnery FMedSci, University of Cambridge and Clinical Director of the UK Medical Research Council

In early 2020 the UK was faced with an escalating public health crisis precipitated by a novel pathogen with undefined disease mechanisms, no identifiable biomarkers, and no approved treatments. Working closely with the NIHR, UKRI swiftly launched an unprecedented funding response with three main elements:

- Redirecting and boosting funding invested in long-term strategic partnerships such as the MRC Units and Centres in virology, immunology, and outbreak modelling.
- Allocating over £200 million to the UKRI Rapid Project Response, a suite of rolling funding calls with a two-and-a-half-week review timeline. These were aimed at the broader UK scientific community and addressed urgent priorities as they evolved over time. A portion was co-funded by the UK Department of Health and Social Care.
- Participating in the COVID-19 National Core Studies Programme, designed to amplify UK research and infrastructure to address urgent scientific and policy questions including epidemiology and surveillance, immunity, and clinical trials infrastructure.

Initially, publicly funded therapeutic research evolved from the grassroots upwards, relying largely on repurposed drugs. Reconfiguration and integration of the landscape evolved from Easter 2020 onwards. UKRI established the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) to objectively identify and trial potential therapeutics, remaining adaptable as scientists' understanding of the pathogenesis of COVID-19 evolved.

Submissions were reviewed by expert working groups and formally recommended by UK-CTAP to the UK Chief Medical Officer and trial investigators if appropriate.

Recommendations informed Phase I, Phase II, and Phase III platform studies funded by UKRI and NIHR during 2020 and 2021. UK-CTAP united experts from all four devolved UK administrations and also collaborated with the WHO, the EU and the US National Institutes of Health to avoid duplication. In parallel, UK investigators could apply for the NIHR's Urgent Public Health Research Prioritisation status, enabling expedited trial set-up and targeted delivery support.

Lessons from COVID-19 platform trials:

Some of these tools and strategies could be implemented when designing therapeutic trials for non-communicable diseases. Key learnings include:

- Bold, visionary leadership and clear coordination are essential to reorient and focus scientific efforts, guide the drug development process, and build public confidence.
- Effective partnerships must be nurtured between research teams, industry, and regulators, leading to platform-wide agreements on how trials should progress from Phase I to Phase IV.
- Independent, transparent and agile scientific guidance is required to safeguard objectivity when assessing therapeutic candidates for trials.
- Sharing published and unpublished data on an international scale helps assess priorities and guide decision-making.
- Embedding trials within NHS infrastructure and other research facilities enables studies to progress at pace and leads to the rapid adoption of trial recommendations in clinical practice, delivered by experienced teams. Further investment in research capability within the NHS will be needed.

"We can do [platform trials] on a UK-wide scale, make real progress and get real answers, improving the health of the nation and reducing NHS costs in the process."

Professor Patrick Chinnery, University of Cambridge and Clinical Director of the UK Medical Research Council

Leadership, technology and agile thinking in response to COVID-19

Brian Holliday, Managing Director for Siemens Digital Industries, highlighted the role of innovation in emergencies and outlined how the VentilatorChallenge UK Consortium produced thousands of ESO 2 Emergency Ventilators during the first wave of COVID-19 infection.

In mid-March 2020 media reports revealed that Italian COVID-19 patients were dying in hospital carparks due to a lack of ventilation equipment on intensive care wards. It was estimated that by the end of March the number of severe COVID-19 cases in the UK could place comparable pressures on NHS resources.

At the time there were fewer than 9,000 mechanical ventilators in the UK. Domestic production capacity stood at 50 units per week. International procurement options were limited. On 17 March the Prime Minister challenged UK manufacturing industries to produce several thousand ventilators within weeks.

The VentilatorChallenge UK Consortium (VCUK) was established two days later. It comprised representatives from British manufacturers and suppliers including Siemens, Siemens Healthineers, McLaren, Airbus, Ford and Surface Technology International Ltd. From March – July 2020 VCUK supported medical device company Penlon Ltd. to optimise the manufacturing product lifecycle of their ESO 2 Emergency Ventilator, which received MHRA approval in mid-April. Each unit required around 700 parts sourced from 88 suppliers and involved a rigorous inspection and certification process.

By mid-June 2020 more than 11,000 ESO 2 devices had been produced at peak pace - 200 times faster than Penlon's previous record. This was enabled by:

Agile remote working

Microsoft Teams proved a vital tool for team-building and remote communications. Cloud-based Manufacturing Resource Planning software made data fully available to all parties at all times. Microsoft HoloLens virtual reality headsets facilitated 'site visits' to manufacturing locations across the UK, minimising the risk of infection spread.

Image: Brian Holliday, Siemens Digital Industries.

Digital twinning

A team of Siemens engineers used 3D CAD software to create a digital twin (accurate virtual model) of the sub-assembly process for ESO 2's absorber breather component. They then optimised the sequence of assembly steps, resulting in a 50% reduction to the number of manufacturing workstations. Ergonomic modelling reduced the per-operator workspace to two metres. Running operator training and assembly in parallel – building in resilience to absorb staff rotation or absence – generated a time saving of 85%.

Hackathon

A major manufacturing bottleneck was the 45 minutes initially required to accurately calibrate the ESO 2 flow valve. Siemens initiated a four-day hackathon, convening early career professionals and VCUK consortium members. The teams used CAD software to design a precision calibration device which enabled an in-situ test and eliminated numerous iterative steps. They then fully automated the process using a programmable logic controller (industrial computer) to reduce the calibration time to just 45 seconds.

"When confronted with a challenge of this scale, a compelling purpose is essential; one which appeals to intrinsic human motivation."

Brian Holliday, Siemens Digital Industries

Essential drivers of success included:

- Fostering a 'will-do' culture by assembling resilient, adaptable and lean teams around a clear and compelling purpose.
- Use of Digital Tools to simulate and verify products and production methods rapidly.
- Leveraging iterative and highly innovative approaches based on the minimum viable product approach, allocating full resources to swiftly overcome constraints.
- Prioritising flexibility in budgets and business cases.
- Eliminating unnecessary hierarchy and encouraging innovation from early career professionals with growth mindsets.

Image: The Penlon ESO2 Ventilator.

Machine learning for pandemic response and societal resilience

Dr Kenji Takeda, Director of Academic Health and AI Partnerships at Microsoft Research, showcased innovative collaborations that highlight the potential of machine learning to inform pandemic response efforts and preparedness activities.

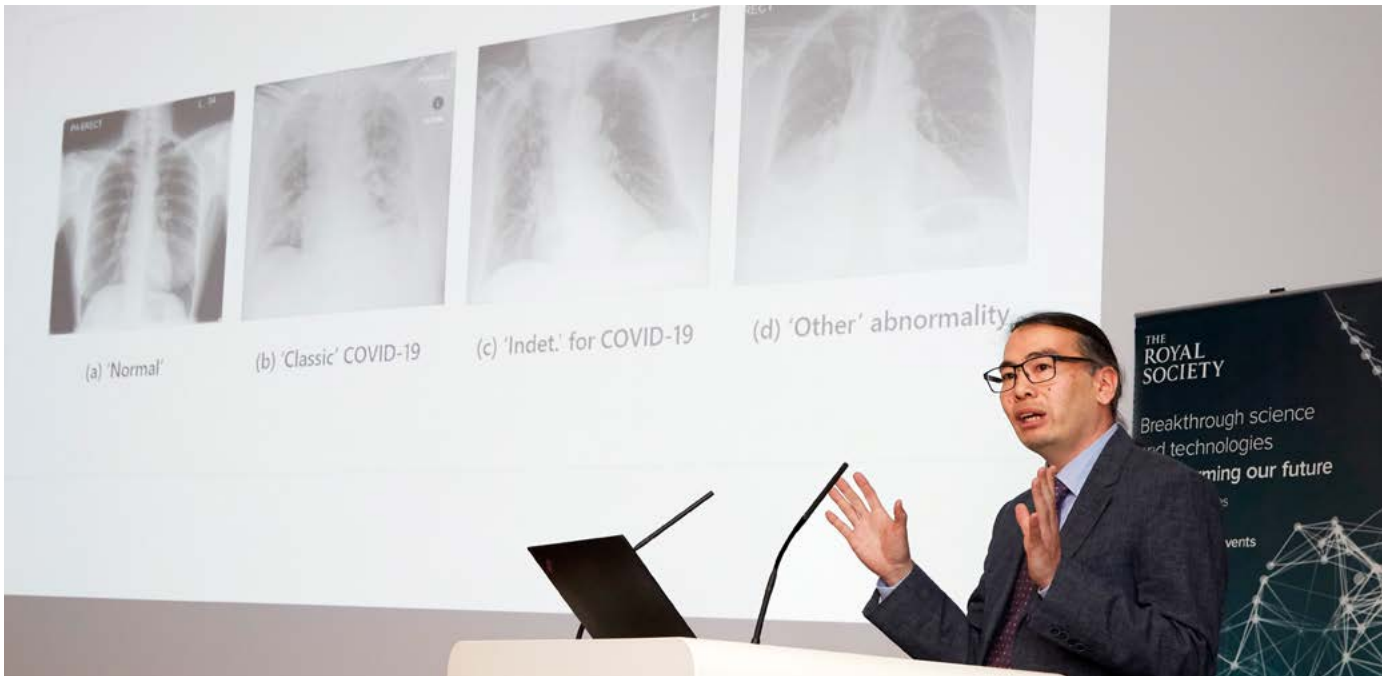


Image: Dr Kenji Takeda, Microsoft Research

In recent years a growing number of collaborative initiatives have demonstrated the potential of machine learning to enhance societal wellbeing and resilience. As SARS-CoV-2 spread around the world scientists and researchers across the Microsoft community sought to leverage their expertise for public benefit.

One of their most significant contributions was Microsoft Research's *Studies in Pandemic Preparedness*[9]. This programme comprises multiple projects with two core objectives: to support the ongoing COVID-19 response, and to explore how machine learning might influence preparedness efforts for future pandemics and public health crises.

Machine learning for treatment and diagnostics

- **Deep learning for COVID-19 triage using chest X-rays** University Hospitals Birmingham (UHB) NHS Foundation Trust had an existing collaboration with the medical imaging team at Microsoft Research in Cambridge, using Project InnerEye[10] open-source software (OSS) to help accelerate radiotherapy planning workflows. In early 2020 the UHB clinicians suggested using a chest X-ray machine learning model to determine whether an individual was likely to have COVID-19 and potentially helping triage hospital admissions. They worked with Microsoft to train their model on a large public X-ray dataset, then refined it using a UHB COVID-19 dataset. The model performs at least as accurately as clinicians and will be further developed through collaboration with clinical experts.

9. Microsoft (2022). Studies in Pandemic Preparedness. https://www.microsoft.com/en-us/research/collaboration/studies-in-pandemic-preparedness/ Studies in Pandemic Preparedness - Microsoft Research (Accessed 8 June 2022)
10. Microsoft (2022). Project Inner Eye. https://www.microsoft.com/en-us/research/project/medical-image-analysis/ (Accessed 8 June 2022)

- **Using observational data to inform clinical trials**
  A team of biomedical engineers and economists from Johns Hopkins and Stanford Universities used machine learning to investigate causal inference in federated (distinct) patient-level datasets, where it can be important to adjust for patient co-morbidities. They recommended methodologies to analyse data from multiple sources without combining them, improving the precision and reliability of estimates to inform whether clinical trials for a given therapeutic would be beneficial. This work could help repurpose and accelerate access to effective interventions in public health emergencies.

Machine learning for infection prevention and control

- **Understanding patterns of infection**
  Computational DNA specialists in the joint Microsoft Research and University of Washington Molecular Informatics System Lab conducted a proof-of-concept study on Seattle's bus networks. By placing fabric sensors on bus air filters they were able to detect the presence of COVID-19 along different bus routes. This suggests the potential to inexpensively modify existing infrastructure to enable 'passive sensing' on transportation systems or in buildings.

- **Supporting epidemiological modelling**
  In March 2020 Professor Michael Cates FRS and colleagues at the Royal Society, including Microsoft Research Cambridge Lab Director Professor Chris Bishop FRS, established the Rapid Assistance in Modelling the Pandemic (RAMP) initiative that invited individuals with computational modelling expertise to contribute to epidemiological modelling of SARS-CoV-2. Microsoft supported RAMP's efforts to enhance open-source machine learning and modelling tools, including enabling a team from the Alan Turing Institute to generate a 36,000-fold increase in the efficiency of a particular epidemiological model. The work is continuing with a new collaborative effort towards quantifying and explaining epidemiological model uncertainty between the Universities of Edinburgh, Exeter, Oxford, Johns Hopkins, Washington, the Wilson Centre, and Microsoft.

- **Using end-to-end monitoring of the biological environment to predict vector-borne disease**
  Microsoft Premonition is a network of robotic field biologists which use machine learning and cloud-scale metagenomic analysis to collect information on pathogen species and disease vectors. These tools have the potential to provide situational awareness through mapping the distribution of vectors and pathogens in near real-time, facilitating timely and targeted interventions.

Machine learning for mental wellbeing

Researchers at Rice University, Texas, are contributing to initiatives that use machine learning to help healthcare workers and caregivers at particular risk of burnout and to recommend targeted interventions.

Machine learning has played a significant and multifaceted role in the pandemic response and has demonstrated how multi-disciplinary teams are key to successful projects. A final example is the collaboration between Adaptive Biotechnologies and Microsoft, which has resulted in ImmuneCODETM[11], mapping the T-cell response to SARS-CoV-2, and T-Detect™, the first T-cell based diagnostic authorized by the US FDA.

These efforts demonstrate how ongoing collaboration between artificial intelligence specialists, domain experts and machines is critical to maximise the public health potential of machine learning technologies.

"Machine learning and collaboration between experts in different fields, and between people and machines, are critical to help us build a more resilient society together."

Dr Kenji Takeda, Microsoft Research

11. Adaptive Biotechnologies. ImmuneCODETM. HYPERLINK "https://immunerace.adaptivebiotech.com/data/" Data - immuneRACE (adaptivebiotech.com) (Accessed 8 June 2022)

Sharing data and information on COVID-19 and other emergencies

Professor Christopher Dye FMedSci FRS, University of Oxford and former Director of Strategy at the WHO Office of the Director General, discussed some of the key priorities, challenges, and opportunities in data and information sharing during international public health emergencies.

"The call for data-sharing is persistent and becomes more intense during epidemics…we need to build data-sharing laws, regulations, and conventions around the incentives for getting towards a shared goal. That is critically important."

Professor Christopher Dye FMedSci FRS, University of Oxford

Sharing data and information on an international scale is vital to ensure an effective response to global public health emergencies. During the 2021 G7 summit in Cornwall, UK, the seven national science academies proposed ways that G7 leaders could improve data sharing during emergencies.

The need to improve access to data becomes more intense during epidemics and pandemics. Although it can be relatively straightforward to identify and agree data governance protocols, embedding these into standard practice is challenging, given ethical, legal and privacy concerns. Principles to guide this process include:

- Being intentionally selective about which data are converted into useful information to inform policymaking. A vast array of increasingly complex and diverse personal, environmental and spatial data is now available. The most valuable information is obtained from well-contextualised data and metadata, and careful consideration should be given to the process of inference – how raw data can be turned into actionable information.

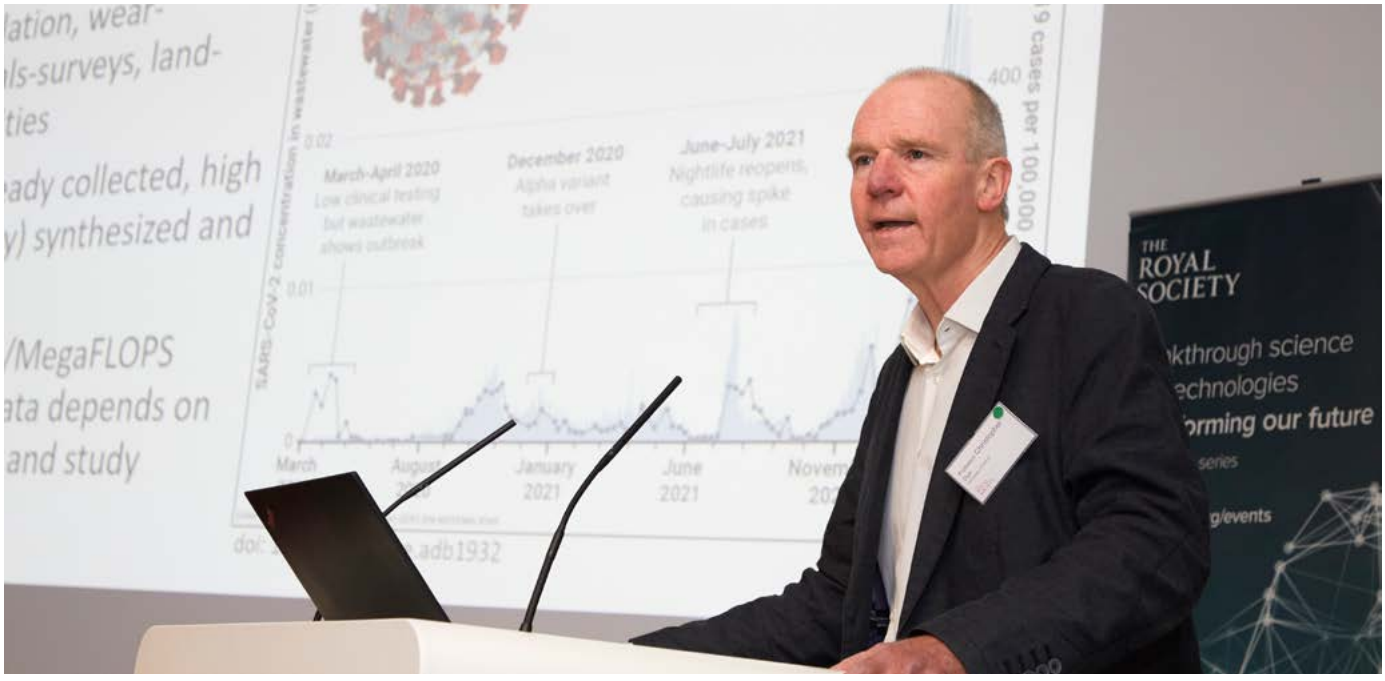


Image: Professor Christopher Dye, University of Oxford.

- Developing international data-sharing treaties and regulations that are informed by shortcomings in previous legislation. The International Health Regulations (2005) have been poorly enforced and have failed to account for national concerns, related for example to the economic impact of declaring an emergency.
- Cultivating shared goals and incentives around data sharing. International tensions have previously arisen when biosamples from specific populations have been used to manufacture diagnostics and therapeutics for broader deployment. Negotiations must proceed sensitively, informed by prior experience, for example with sharing influenza data.
- Establishing comprehensive international data architecture. In May 2021 the WHO launched a Hub for Pandemic and Epidemic Intelligence in Berlin, a collaborative platform to share multi-sectoral data and assemble expert networks to predict, detect and prepare for global public health emergencies. It is essential that such infrastructure navigates intercultural differences underpinned by mutual trust.
- Modernising national data systems. Even in many wealthy countries public health data infrastructure is not fit for purpose. Robust domestic systems are a precondition for successful international collaboration. Recent research suggests that outbreak responses prove most effective when guided by well-established mechanisms and entities such as national and local public health laboratories and agencies.
- Balancing data sharing and protection. Although these are often framed as trade-offs, good data protection policies build confidence to share appropriate data for clear and compelling purposes rather than precluding access by default. The circumstances which foster and inhibit mutual trust around data-sharing should be further explored.
- Strengthening data literacy amongst the general public, civil servants and government ministers. The COVID-19 pandemic has offered opportunities to advance data literacy through discussion and visualisation of statistics such as the R (reproduction) number, epidemic curves, case numbers and risk analysis.

PANEL DISCUSSION

Translational research and data-sharing, pandemic preparedness efforts, and priorities for the UK life sciences sector

Professor Patrick Chinnery, Professor Chris Dye, Dr Brian Holliday, Dr Kenji Takeda and Dr Melanie Lee drew together some of the key themes around translational research and data-sharing. Sir Andrew Pollard, Dame Kate Bingham, Dr Tonya Villafana, Dr June Raine, and Steve Bates reflected on recent scientific, technological, and regulatory innovations and discussed how these will influence priorities for pandemic preparedness and for the life sciences sector more broadly.

Image: (Left to right) Professor Patrick Chinnery, Professor Chris Dye, Dr Brian Holliday, Dr Kenji Takeda and Dr Melanie Lee

"Ultimately, research is part of good clinical practice, and the two have to go hand in hand to advance knowledge and directly benefit patients. COVID-19 reminded us of this approach, and of the need to embed it more thoroughly in the NHS."

Professor Patrick Chinnery, University of Cambridge

Translational research and data-sharing

- In principle international public health regulations may be legally binding, but in practice they are often treated as a starting point for international discussion. Less formal societal and cultural changes are typically more influential in the relative success or failure of emergency public health measures. Policy must be based upon ongoing dialogue with the general public, who may interpret data and health messaging in diverse ways.

- The successes of the UK Vaccine Taskforce and the VentilatorChallengeUK Consortium – as well as numerous other initiatives – have demonstrated the potential to innovate at scale and at pace when activities are underpinned by a common goal and shared values. Vaccine equity and international data-sharing efforts must be addressed through intensified co-operation and with comparable urgency. Progress will be impossible without innovative, diverse, and interdisciplinary teams.
- Machine learning offers enormous opportunities for societal benefit in the broadest sense to addresses – amongst others – challenges around healthcare, sustainability and accessibility.

"I saw the benefits of bringing together diverse people, skills, insights and capabilities, and trying to tackle problems differently. I'd like to see this approach much more widely exploited."

Brian Holliday, Siemens Digital Industries

COVID-19

- COVID-19 will continue to evolve and is likely to become a seasonal endemic disease. Ongoing virological research will be needed to try to predict the properties and behaviours of future variants and to facilitate the development of multivalent vaccines to offer protection against multiple variants and sub-lineages.
- The early release of the full SARS-CoV-2 genomic sequence and pre-clinical data by research teams in China was critically important for vaccine development in the UK and worldwide. Chinese researchers also shared their Phase I clinical data, which allowed UK investigators to open informed discussions with the MHRA at an early stage. International scientific co-operation and consortium-building must underpin ongoing refinements to COVID-19 vaccines, clinical trials, and future preparedness efforts.
- Unequal access to vaccines and therapeutics will mar collaborative efforts. A sustained commitment to WHO's global vaccine equity targets and to the development of relevant infrastructure in resource-limited settings must remain a priority for the UK and for other Western countries.
- It is unlikely that regular booster vaccines will be a sustainable long-term solution. Research and development into alternative mechanisms to stimulate and maintain a durable immune response to COVID-19 will be required.
- There is high potential for immunobridging and human challenge studies to complement data acquired from clinical trials and to accelerate the testing and scale-up of novel interventions. The MHRA and other regulators must develop standards and risk frameworks to support research teams in their acquisition and evaluation of high-quality data.

Image: (Left to right) Kate Bingham, Dr Tonya Villafana, Dame June Raine, Sir Andrew Pollard and Steve Bates.

Future considerations

- Scientific, technological and methodological learnings from the COVID-19 response must be leveraged to advance the development of vaccines and therapeutics for other diseases with a high mortality burden. This is especially important since basic research and clinical trials for many of these diseases have been deprioritised. In particular, the dynamic and collaborative working relationship between investigators and regulators must be maintained. There is an appetite for more innovative and risk-proportionate regulatory frameworks.
- Digital technologies have significant potential to enhance the effectiveness of clinical trials by reducing costs, alleviating time constraints and helping to identify pharmacovigilance signals. On the other hand, many countries have faced enormous difficulties in accessing sufficient and reliable health data to inform their pandemic response.
- Innovations in UK vaccine manufacturing capacity must be sustained. Whilst certain facilities might be leased to the commercial sector, the government should retain authority to commission a rapid shift to large-scale manufacture of vaccines and therapeutics during public health emergencies.
- It is critical that the substantial investment committed by the UK government to science and innovation since early 2020 is maintained to reflect the gravity of future pandemic threats and the need to remain one step ahead. The national response to COVID-19 has demonstrated the vital role of both industry and academia in innovating for a collaborative, resilient, and adaptable scientific ecosystem.

"Our partnership with regulators – in particular the MHRA – and the ability to work closely together for the common good whilst not cutting any corners was incredibly important".

Sir Andrew Pollard FMedSci, Oxford Vaccine Group

"We need to have multivalent vaccines that can be manufactured quickly and at scale. We must continue to develop the infrastructure to manufacture and deliver these vaccines, including to low-population and low-income countries."

Dr Tonya Villafana, AstraZeneca

"Industry will be an important partner in building a robust ecosystem and should continue to work with other stakeholders in the UK, the US and worldwide so that we can move in lockstep together to achieve solutions quickly."

Dame Kate Bingham, SV Health Investors and Chair of the UK Vaccine Taskforce

Early career scientists

Four early career scientists discussed the competencies developed during their time working on the frontline of the COVID-19 pandemic response.

Each of them highlighted an appreciation for the unique opportunity to contribute to innovations of critical importance to the nation and to the world. The scientists reflected on how their experiences have equipped them with the skills and resilience to influence future advances within the UK life sciences landscape.

A student's role in delivering the UK's mass testing COVID-19 response

Olivia Crossley, University of Sheffield

"I developed a number of softer skills which have prepared me for a professional working environment such as collaboration, time management and organisation."

Olivia Crossley, University of Sheffield

In March 2020 Olivia Crossley was in the second year of her BSc in Biochemistry at the University of Birmingham (UoB). Having observed the dedication of NHS staff and of laboratory scientists in her department she worked as a Processing Operative and Testing Assistant for the university's on-campus COVID-19 asymptomatic testing site. This was established in November 2020 as a partnership between UoB and NHS Test and Trace and fuelled by the UK government's drive to expand mass testing.

Olivia developed her practical skills including handling biological samples and implementing sterile techniques. She is now studying for an MSc in Advanced Cell and Gene Therapies at the University of Sheffield, which will host one of three Gene Therapy Innovation Hubs funded by LifeArc, the MRC and the BBSRC.

Olivia's MSc research project focusses upon modulating DNA damage and toxic protein aggregation in C9orf72-related ALS/FTD dementia pathology. Olivia is committed to science communication, and in her spare time she volunteers for medical innovation platform Personalize My Medicine, writing articles on cancer and rare diseases for medical professionals and the general public.

Early career experiences

Becca Goodwin, IT Customer Engagement Analyst, AstraZeneca

"If the pandemic hadn't happened, I don't think I would have learned so fast to perform under pressure to tight deadlines and to work so independently."

Becca Goodwin, AstraZeneca

After completing her A2 Levels in 2016 Becca Goodwin was keen to combine study with practical experience. She began an IT apprenticeship at AstraZeneca's Macclesfield premises. The scheme allowed her to undertake rotational placements across different areas of IT and in the wider organisation. At the end of her second year Becca chose to specialise in data analytics. Following a placement working with global supply chain teams she commenced her final rotation, providing IT support to AZ's science functions.

The first lockdown was announced two weeks later, and many staff began to work from home. Becca played a critical role in automating the full end-to-end matrix data collection process to enable data to be accessed remotely.

She also fostered collaborative relationships between the IT function and scientific colleagues, helping to streamline the technical language used by both teams.

These experiences have enabled Becca to appreciate the unique priorities and pressures facing each team and the need to provide a positive experience for colleagues who have less confidence with digital technologies. She works independently to tight deadlines, and is currently planning her master's dissertation for her degree in Digital and Technology Solutions from Manchester Metropolitan University. Becca emphasises that apprentices are highly valued team members, and she regularly attends careers fairs to promote degree apprenticeships as an alternative to full-time university study.

My role as an Apprentice during the manufacture of the Oxford COVID-19 vaccine

Emilia Reyes Pabon, University of Oxford Clinical BioManufacturing Facility

"It felt amazing to be part of such a great team and to be able to support them with the skills that I had developed during my time at the CBF."

Emilia Reyes Pabon, University of Oxford Clinical

Emilia Reyes Pabon was part-way through her Level 3 BTEC Apprenticeship in Applied Science at the University of Oxford's Clinical BioManufacturing Facility (CBF) when the SARS-CoV-2 virus began to spread worldwide. In February 2020 CBF staff were notified that they would begin work immediately to develop and manufacture an adenoviral vector vaccine against COVID-19.

Having already received training in Good Manufacturing Practice and gained hands-on laboratory experience within the CBF, Emilia worked as an Operations Technician within the vaccine manufacturing team.

She was responsible for the maintenance of clean rooms, the sterilisation of equipment, and for the preparation of 500 vials used in Phase I vaccine trials in Oxford during April 2020.

After completing her Level 3 BTEC with Distinction in September 2020 Emilia was named Oxfordshire Apprentice of the Year 2021. She is now in the second year of a Foundation Degree in Applied Bioscience at the University of Kent, following which she aspires to undertake an MSc and develop her career in the development and manufacturing of Advanced Therapy Medicinal Products (ATMPs). Emilia believes that the opportunity to gain practical laboratory or industry experience alongside theoretical study is a valuable alternative to a conventional university degree, and she is an active advocate for apprenticeships both locally and nationally. Host employers can also benefit from the insights of younger colleagues to improve established systems and processes.

The role of a laboratory scientist apprentice in AstraZeneca's COVID-19 response

Adam Powell, Level 6 Laboratory Scientist Apprentice in Biopharmaceutical Development, AstraZeneca

"Being based in a research and development lab meant that I would be supported throughout the whole of my apprenticeship by experts with years and years of experience."

Adam Powell, AstraZeneca

Adam works at AstraZeneca's headquarters in Cambridge whilst studying part-time for a BSc in Applied Bioscience through the University of Kent. He was attracted to the degree apprenticeship scheme because it offered the opportunity to gain laboratory experience from the start and to contribute to biopharmaceutical research with real-world impact.

Adam's role involves using chromatography-based separations to purify biological molecules, such as antibodies, which are then provided directly to research teams. It typically takes 3 – 4 weeks to express and purify one of these molecules. In 2020, Adam and his colleagues were challenged to halve this lead time. By marshalling his knowledge from the first year of his apprenticeship Adam reduced the duration of the purification process to four days. This experience has enhanced his independence, his confidence, and his understanding of analytical techniques and quality control.

The network of apprentices across AZ can be leveraged to help disparate teams to work together more closely. Adam is a strong advocate for apprenticeships and engages with his community to encourage students to consider these schemes.

Lessons learned from the COVID-19 pandemic for science communications in an emergency

Fiona Lethbridge, Senior Press Officer at the Science Media Centre, outlined key learnings that arose from the intersection of science and the media during the COVID-19 pandemic.

"The size, scale, and nature of the pandemic meant that public understanding has arguably never been more important."

Fiona Lethbridge, Science Media Centre

The Science Media Centre (SMC) was founded in 2002 in the wake of high-profile scientific controversies including the discredited association between autism and the MMR (Measles, Mumps and Rubella) vaccine, and the public enquiry into BSE (Bovine Spongiform Encephalopathy) and new-variant CJD (Creutzfeld-Jakob Disease). It is an independent body that helps journalists to enhance the accuracy of and use of evidence in scientific reporting. Since early 2020 the SMC has run approximately 250 press conferences on COVID-19 research and policy and has sent out around 1,800 'rapid reactions' from scientists.

Key learnings from the past two years include:

- The general public was able to access cutting-edge science explained by expert scientists in the media. This was essential to maintain understanding of scientific developments, to explain where the weight of evidence lay, and where uncertainties existed. Many scientists regarded media work as an integral part of their role.
- It is important for research institutions to maintain capacity to engage with the national media alongside their own institutional communications priorities and channels. Some institutions were unable to adequately support their scientists to address time-sensitive media requests.
- Media outlets must invest in their specialist journalists covering science, health and the environment. These individuals prioritise relevant content and are adept at reflecting evidence and uncertainties. In many cases, news coverage from science journalists was more measured than reporting by political journalists.

Image: Fiona Lethbridge, Science Media Centre.

- Scientists should talk about evidence rather than offering personal opinions on policy issues. Public interest is best served by scientists who comment on the areas where they are most knowledgeable. Scientists specialise for good reason. What distinguishes science from opinion and ideology is that scientists speak with reference to their own research or other research.
- Scientists appointed to SAGE should be encouraged and supported to speak to the media individually to build public trust and understanding in the science. SAGE was more open than during previous emergencies, and independent scientists participating in SAGE often engaged with the media. Public access to the Chief Medical Officer and Chief Scientific Adviser was also notably greater during COVID-19 compared to previous emergencies.

- Multiple voices and open scientific disagreement are integral to 'good science'. Politicians frequently stated that they were 'following the science', but during the early months of 2020 there was little established scientific consensus. Glossing over uncertainty and conflicting views to create a simple 'message' is unscientific, and risks undermining public trust in science. The public interest is best served by allowing a wide range of good scientists to have a voice and to thrash out disagreements and uncertainties in the public arena.
- New scientific data should be presented by the scientists who have done the research, supported by scientific press officers from their research institutions, even if the data was commissioned by government. The communication of this science should not be controlled by government departmental communications teams directed by Number 10 or by the Cabinet Office. Science should not need a 'grid' slot. For example, national statistics have been communicated to the public independently of government since 2007.

Public understanding of and engagement with science was essential to all elements of the pandemic response. Many learnings are not specific to COVID-19 and will be highly applicable to the next scientific emergency.

"Specialist science, health, and environment journalists are our best allies in the fight against misinformation."

Fiona Lethbridge, Science Media Centre

KEYNOTE

Investment in the UK Life sciences

Sir Patrick Vallance FMedSci FRS, Chief Scientific Adviser to the UK Government, emphasised the importance of maintaining investment across the life sciences to ensure that the UK is equipped for further SARS-CoV-2 outbreaks and future pandemics.

"COVID-19 highlighted the strength of Life Sciences in the UK, but also opportunities for improvement. Investment, biosecurity and global surveillance need to be prioritised going forward to improve our resilience and security and to generate benefits for the whole of the UK and the world."

Sir Patrick Vallance FMedSci FRS, Chief Scientific Adviser to the UK Government

The COVID-19 pandemic has showcased the UK's outstanding life sciences base. This is exemplified by academic and discovery output, university rankings, publication capacity, citation impact, and the number of major pharmaceutical and biotechnology companies with a UK hub.

The past two years have also demonstrated the importance of safeguarding and increasing investment in this sector to ensure adequate preparation for the next public health crisis. As the initial pandemic response gathered momentum in early 2020 it became clear that certain areas were underfunded and under-resourced.

These included large-scale vaccine manufacturing capability, industrial mass testing capacity, and the capability to scale life sciences start-ups into sustainable enterprises.

The UK's October 2021 spending review pledged a £5 billion research and development package for the life sciences industry over the next three years. Investment priorities will not be limited to biomedical research but will include data science, engineering, manufacturing and supply chains, plant and animal health, and skills development.

Image: Sir Patrick Vallance, Chief Scientific Adviser to the UK Government

Novel ways of working

The COVID-19 pandemic obliged key stakeholders to operate in innovative ways:

- The UK government and funding agencies, including UKRI, NIHR and the Wellcome Trust, committed large tranches of money to genomics research and technologies. As a result, the UK rapidly established itself as a world leader in SARS-CoV-2 viral sequencing.
- The Office for National Statistics (ONS) delivered nationwide surveillance studies, overseeing a network of clinical research organisations who employed specialist staff. The weekly ONS COVID-19 Infection Survey generated valuable data on infection rates which was widely utilised on an international scale.
- The complexity of the issues at stake necessitated unprecedented interdisciplinary collaboration. Specialists across industry, academia and government united to address questions with direct implications for operations and public policy. These included maximising access to data, identifying mechanisms to reduce transmission risk, and establishing longitudinal studies.

- The UK Vaccine Taskforce marshalled financial and human resources with exceptional efficiency to establish domestic manufacturing sites within months.
- The MHRA and other regulatory bodies demonstrated a highly flexible and pragmatic approach to enable assessment of vaccines and therapeutics in record time.

Priorities for the future

Although restrictions in the UK have eased, the COVID-19 pandemic is not over. Future public health crises are inevitable. Priorities for the coming years will include:

- Attracting private sector investment to complement the government's commitment to life sciences research and development.
- Strengthening the UK's biosecurity strategy.
- Improving global surveillance mechanisms and connecting these to genotyping activities to help understand the impact of variants on immunogenicity.
- Implementing the 100 Days Mission roadmap[12]. This will include preparing contracts and infrastructure so that no time is wasted on high-level planning or on protracted negotiations at critical moments. The Mission is committed to strengthening global manufacturing capacity and prioritising equitable access to vaccines and therapeutics.

12. UK Cabinet Office. 100 Days Mission to Respond to Future Pandemic Threats. 2021. https://www.gov.uk/government/publications/100-days-mission-to-respond-to-future-pandemic-threats (Accessed 10 April 2022]

The Royal Society is a self-governing Fellowship of many of the world's most distinguished scientists drawn from all areas of science, engineering, and medicine. The Society's fundamental purpose, as it has been since its foundation in 1660, is to recognise, promote, and support excellence in science and to encourage the development and use of science for the benefit of humanity.

The Society's strategic priorities emphasise its commitment to the highest quality science, to curiosity-driven research, and to the development and use of science for the benefit of society. These priorities are:

- Promoting excellence in science
- Supporting international collaboration
- Demonstrating the importance of science to everyone

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