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Resilience to emerging infectious diseases and the importance of scientific innovation

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A B S T R A C T

This opinion piece emphasises the critical role of translational research in enhancing the UK's resilience against future pandemics. The COVID-19 pandemic demonstrated the lifesaving potential of scientific innovation, including genomic tracking of SARS-CoV-2, vaccine development, data linkage, modelling, and new treatments. These advances, achieved through collaborations between academic institutions, industry, government, public health bodies, and the NHS, occurred at an unprecedented pace. However, the UK's pandemic preparedness planning, as reflected in the 2016 Exercise Cygnus report, notably lacked provision for scientific innovation. This oversight highlights the necessity of integrating innovation and research into future preparedness strategies, not as a luxury but as a vital component of the healthcare infrastructure. The COVID-19 pandemic has underlined the importance of surge capacity for diagnostic labs, vaccine development and deployment strategies, real-time research embedded within the NHS, efficient data sharing, clear public communication, and the use of genomic tools for outbreak surveillance and monitoring pathogen response. Despite world-leading aspects of some of the UK's research response, the need to build much of the infrastructure in real-time led to avoidable delays. A proactive approach in incorporating research and innovation into the NHS's operational framework will be needed to ensure swift, evidence-based responses to future pandemics.

Introduction

To safeguard the UK population against future pandemics, translational research must be placed at the heart of the planning and operations of the National Health Service (NHS) and public health agencies. The case cannot be clearer as we emerge from the COVID-19 pandemic. Multiple innovations were central to our response against COVID-19, including mass testing[1] and genomic tracking of the SARS-CoV-2 virus,[2] the creation of vaccines,[3-5] data linkage across health systems, modelling of the impact of public health interventions,[6] and the development of new treatments.[7] These scientific advances occurred at unprecedented pace and saved millions of lives. They did not occur in isolation, but by the rapid development of interactions between academic institutions, industry, government, public health and the NHS.

Surprisingly, during pandemic preparedness planning, the impact of scientific innovation was not planned for. The Exercise Cygnus report, published in 2016, evaluated the capacity of the UK to respond to an influenza outbreak affecting 50% of the population with 'excess deaths of 200–400,000' people, before the development of an 'updated influenza vaccine'.[8] It considered the NHS, public health, social care and government response but did not mention the importance of universities, or scientific innovation in planning (Table 1). While supply chains of vaccines and treatments were considered essential, no mention was made of what to do in the event that these did not already exist. These gaps in planning highlight a need to incorporate innovation and research in any future preparedness strategy, not as a luxury which the stretched NHS cannot afford, but as an essential component of our infrastructure that can be pivoted rapidly to a pandemic response. COVID-19 highlighted the importance of having a national testing strategy and a rapid plan to enable surge capacity for diagnostic laboratories; a vaccine development and deployment strategy; an ability to answer urgent, unpredictable clinical questions with research embedded within the NHS in real time to ensure a safe, evidence-based response; the importance of efficient and transparent data sharing between agencies and a toolkit for clear communication with the public.

While aspects of the UK research response were world-leading, it was necessary to build much of the essential infrastructure in real-time, resulting in avoidable delays. In a remarkable collective effort, research networks were self-formed, emergency grants and ethical approvals were made, data linkage projects initiated, and the government injected large sums of money to catalyse a rapid 'take-off' to address critical questions that it was not possible to answer at the onset of the pandemic.

This article reflects the opinions of the author(s) and should not be taken to represent the policy of the Royal College of Physicians unless specifically stated.

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Table 1
Research interventions that were not considered in Exercise Cygnus.

Intervention	Role of academic centres/universities
Diagnostic testing	Development and testing of a new assay
	Diagnostic assurance (ensuring that PCR and LFT testing would remain sensitive while the virus evolves in the population)
	Development of Lighthouse facilities
	Use of equipment and staff from universities to help with the national response.
Vaccination	Developing an entirely new vaccine (rather than rolling out an adapted one within weeks)
	Testing a new vaccine in clinical trials at pace – Oxford vaccine trial
	Collaborations with industry – Pfizer, Moderna, Astra Zeneca, Valneva, Novavax
Tracking using genomic sequencing	COG-UK
	Modelling and prediction of vaccine escape and clinical severity of virus variants
Development of new treatments	Steroids
	Monoclonal antibodies
	Large flexible platform trials - RECOVERY
Basic science to understand mechanisms	G2P consortium
underlying severity of infection	Changes in tropism of VOCS and associated clinical severity
Data linkage and research protocols	Access to samples and data for scientists responding to the outbreak
	Standing protocols e.g. ISARIC
	Variant tracking – data linkage of genomic sequencing and clinical severity

The importance of scientific innovation during the COVID-19 pandemic

Several research initiatives were central to the UK research response to COVID-19 and included high-scale genomic sequencing, basic virology, and the development of vaccines and new treatments.

Genomic sequencing: The extensive work of the COG-UK consortium (COVID-19 Genomics UK Consortium) highlighted the critical impact of large-scale genomic surveillance on the COVID-19 pandemic. This consortium enabled the sequencing of more than two million SARS-CoV-2 genomes across the UK in real-time and contributed to major advances in our understanding of the biology and transmission of the virus. Genomic sequencing was also used to track hundreds of introductions of the virus to the UK from Central Europe via short-haul flights (and not frequently directly from China as had been widely expected).[9,10] UK researchers were the first to identify the evolution of single genome mutations that increased transmission of the virus (the D614G mutation) and facilitated immune escape (e.g. N439K, E484K) during early transmission of the virus.[11,12] These single polymorphisms in the viral genome heralded the first variant of concern (VOC) of SARS-CoV-2 (the alpha variant), also identified by the COG-UK consortium.[13] Importantly, single signature mutations that were present in the alpha variant were noted to develop in an immunosuppressed patient with chronic infection providing evidence for the leading hypothesis on how new variants are generated in another observation made by COG-UK researchers.[14] Genomic sequencing was most powerful when combined with additional data –in particular, SARS-CoV-2 sequences in those who became infected despite vaccination and clinical severity in people with different variants, accounting for differences in vaccination status, comorbidity and age. The infrastructure for such analysis was not immediately available to academic researchers and future pandemics would benefit from standing protocols to ensure availability of anonymised data (ensuring stringent data protection) to allow us to detect variants that might be associated with increased transmission, vaccine evasion, or higher clinical severity and that might require more vigorous intervention. One effective solution was to facilitate access and data protection by the provision of honorary contracts for academic scientists within the public health agencies – maintaining such arrangements, for example within the Health Protection Research Unit (HPRU) structure will provide infrastructure to enable more rapid responses in future pandemic scenarios. Another was the creation of Trusted Research Environments (TREs) and an investment in Health Data Research UK (HDR UK) that allow scientists outside public health agencies to work with secure anonymised datasets.[6]

Functional virology: Sequencing of the viral genome did not predict all phenotypic changes in the behaviour of the virus immediately. When the omicron variant emerged, it was clear from what was known about individual mutations in the spike gene that vaccine escape was highly likely, before the variant became dominant – and this was subsequently borne out both in vaccine trials and real-world vaccine roll-out studies.[15] However, a change in the phenotype of the virus, both in cell culture and *in vivo* was not predictable from the changes in the S2 segment of the spike protein that were later shown to alter the tropism of the virus to favour cell entry via endocytosis in naso-epithelial cells and away from TMPRSS2-mediated entry into lung cells. This change in cell entry and cell tropism required fundamental molecular virologists to investigate the mechanisms that lay behind this change, which coincided with a reduction in clinical severity of disease.[16,15] Specialist scientific advisory groups that provided advice to UK government and were coordinated by UK HSA, including the Scientific Advisory Group for Emergencies (SAGE), the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), and the COVID-19 Variant Technical Group (VTG), the online publications of which were used by public health agencies around the world[17] and enabled UK government to receive up to date information in a dynamic environment.

Advances in vaccine development: The landscape of vaccine development was catalysed rapidly during the COVID-19 pandemic, driven by rapid genomics and the emergence of mRNA and vector-based technologies. These innovative approaches have reshaped our ability to respond quickly and effectively to rapidly evolving viruses. The development of mRNA vaccines represented a paradigm shift in vaccinology.[4,18] Unlike traditional methods that use weakened or inactivated pathogens, mRNA vaccines employ a synthetic messenger RNA to instruct host muscle cells to produce a specific viral protein, eliciting an immune response to protein manufactured inside host cells (rather than in a factory). This technology offers remarkable advantages, including rapid development, high scalability, and the ability to rapidly tweak the mRNA sequence in response to viral mutations. The success of mRNA vaccines in the COVID-19 pandemic has not only provided a powerful tool against this virus but also set a precedent for future vaccine development against other pathogens for which the genetic sequence is available. The low-pathogenicity vector-based adenovirus vaccine (ChAdOx1) used as a delivery system to introduce genetic material into cells also resulted in a highly effective vaccine.[5] This method enables the development of vaccines with durable immunity, particularly useful in areas where maintaining cold chain logistics for mRNA vaccines is challenging.

Advances in treatment: Clinical platform trials, designed to inform practice within primary and secondary care, were critical in developing effective treatments for SARS-CoV-2 and incorporated new approaches, including online recruitment and follow-up. The success of trials like RECOVERY, the world's largest randomised controlled clinical trial for COVID-19 treatment, involving 39,000 patients, demonstrated the potential of large-scale, collaborative platform trials in rapidly identifying

effective treatments in hospitalised patients.[7] AGILE was set up as a smaller scale trial to facilitate the recruitment of participants to phase 1 and 2 substudies that aimed to identify the safe dosage for new treatments.[19] REMAP-CAP was developed to carry out phase 3 trial testing of treatments in patients with severe COVID-19 infection in critical care units[20] and PANORAMIC was a UK-wide study funded by the NIHR to evaluate community-based antiviral treatments, with 29,000 participants recruited.[21] Importantly, PANORAMIC employed online recruitment and did not require in-person visits by participants.

The development of new treatments and ways of delivering clinical trials was a strength of the UK response. The importance of addressing immune dysregulation in severe infection was a major step forward in infection research. One of the key findings of the RECOVERY trial was to quantify the effectiveness of steroids in treating severe COVID-19 after the development of pneumonitis and hypoxia in the later immune phase of the illness.[22] This discovery marked a significant advance in clinical care, offering a readily available and cost-effective treatment option for critically ill patients that was not tested in industry-sponsored clinical trials. Another important treatment advance was that IL-6 inhibitors such as toculizimab synergistically decreased mortality when administered alongside steroid treatment.[23]

Direct antiviral treatments were also developed at speed for COVID-19 and found to be most effective when administered during the early stages of infection. The repurposed drug remdesivir, an RNA-dependent RNA polymerase (RdRp) inhibitor (initially used in Ebola virus infection) was found to reduce time to recovery if administered early during infection to those most at risk.[24] Another effective antiviral treatment, used by those at high risk of severe infection is nirmatrelvir-ritonavir, which inhibits the viral protease and has retained activity despite the evolution of new viral variants.[25] An array of monoclonal antibody treatments were also developed, each with varying activity against new variants of concern (VOC) as these emerged.[26] The monoclonal antibody treatment sotrovimab manufactured by Vir Biotechnology and GSK (VIR-7831), was first isolated in 2003 from a patient infected with SARS-CoV-2 and has the advantage that it binds to a conserved area of the spike protein.[27] Nevertheless while this and other mAbs have been instrumental in treating COVID-19, particularly in the early stages of infection, they also present challenges. One significant downside is the potential for the evolution of the virus, leading to variants that may evade the antibody. This highlights the need for continuous monitoring and adaptation of treatment strategies in response to viral mutations by genomic sequencing.

Emerging technologies and future directions in pandemic preparedness

The landscape of pandemic threats continues to evolve, necessitating a dynamic and informed response that extends beyond our current knowledge base. The WHO blueprint list for pathogens with pandemic potential (revision in consultation) currently includes eight viral pathogens (COVID-19, Crimean-Congo haemorrhagic fever, Ebola virus disease and Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever, Zika and “Disease X”, representing a pathogen or pathogens that have not yet been shown to cause disease in humans.[28]).We know from genomic modelling that there are as many as 320,000 yet-to-be-characterized mammalian viruses, many of which possess zoonotic ‘Disease X’ potential.[29] This vast, unexplored virosphere represents a substantial challenge and underscores the need for continuous enhanced surveillance using for example, advanced next generation sequencing technologies.

Scientific progress will be pivotal in shaping our preparedness for future pandemics, which are likely to differ significantly from previous outbreaks. The next response to a pandemic threat should leverage the latest advances in technology, including the expanding field of artificial intelligence (AI). AI’s integration into pandemic preparedness and response strategies represents a paradigm shift in how we will approach future outbreaks, which are likely to differ significantly from those in the past. For example, the use of AI to predict protein structure and functionality from genomic data is currently being revolutionised by tools such as AlphaFold.[30] In a pandemic scenario, rapid insights into the protein structure of a novel virus could significantly shorten the timeline for developing effective therapeutics and vaccines. AI algorithms are also adept at analysing vast amounts of data to model disease spread and predict future outbreaks, incorporating international travel patterns and climate change. AI tools can be used to enhance disease surveillance systems by analysing data from multiple sources, such as social media, news reports, and healthcare databases. AI-driven diagnostic tools also have the potential to provide rapid analysis of clinical data, such as imaging and laboratory results, to assist in the early detection of infectious diseases.[31] During a pandemic, these tools could be pivotal in screening large populations quickly and efficiently.

Conclusions

Infectious diseases have been a significant health concern in the UK and around the world since the emergence of modern medical practice. The 20th century witnessed remarkable progress in combating such diseases, with the advent of antibiotics, vaccination, and improved hygiene. Today’s infectious disease threats are increasingly shaped by anthropogenic change. The rise of antimicrobial resistance, the expansion of vector habitats due to climate change and the global growth and movement of people are increasing the risk of emerging infectious diseases. Accelerated innovation with new technologies and team science will be required to monitor and control the threat.

References

1. Philippe C, Bar-Yam Y, Bilodeau S, *et al.* Mass testing to end the COVID-19 public health threat. *Lancet Reg Health Eur*. 2023;25:100574.
2. COVID-19 Genomics UK (COG-UK) An integrated national scale SARS-CoV-2 genomic surveillance network. *Lancet Microbe*. 2020;1(3):e99–e100.
3. Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615.
4. Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and safety of the mRNA-1273 SARS–CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–416.
5. Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99–111.
6. Kerr S, Bedston S, Bradley DT, *et al.* Waning of first- and second-dose ChAdOx1 and BNT162b2 COVID-19 vaccinations: a pooled target trial study of 12.9 million individuals in England, Northern Ireland, Scotland and Wales. *Int J Epidemiol*. 2023;52(1):22–31.
7. Normand ST. The RECOVERY platform. *N Engl J Med*. 2021;384(8):757–758.
8. Exercise Cygnus Report, Public Health England, 2016. Available at <www.assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/927770/exercise-cygnus-report.pdf> Accessed February 2024.
9. da Silva Filipe A, Shepherd JG, Williams T, *et al.* Genomic epidemiology reveals multiple introductions of SARS-CoV-2 from mainland Europe into Scotland. *Nat Microbiol*. 2021;6(1):112–122.
10. du Plessis L, McCrone JT, Zarebski AE, *et al.* Establishment and lineage dynamics of the SARS-CoV-2 epidemic in the UK. *Science*. 2021;371(6530):708–712.
11. Thomson EC, Rosen LE, Shepherd JG, *et al.* Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity. *Cell*. 2021;184(5)1171-87 e20.
12. Volz E, Hill V, McCrone JT, *et al.* Evaluating the effects of SARS-CoV-2 spike mutation D614G on transmissibility and pathogenicity. *Cell*. 2021;184(1) 64-75 e11.
13. Volz E, Mishra S, Chand M, *et al.* Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. *Nature*. 2021;593(7858):266–269.
14. Kemp SA, Collier DA, Datir RP, *et al.* SARS-CoV-2 evolution during treatment of chronic infection. *Nature*. 2021;592(7853):277–282.
15. Willett BJ, Grove J, MacLean OA, *et al.* SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway. *Nat Microbiol*. 2022;7(8):1161–1179.
16. Meng B, Abdullahi A, Ferreira I, *et al.* Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity. *Nature*. 2022;603(7902):706–714.
17. United Kingdom Health Security Agency Documets, UK Government Organisations. Available at <www.gov.uk/government/organisations/uk-health-security-agency>, Accessed February 2024.
18. Thomas SJ, Moreira Jr ED, Kitchin N, *et al.* Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. *N Engl J Med*. 2021;385(19):1761–1773.
19. Griffiths GO, FitzGerald R, Jaki T, *et al.* AGILE: a seamless phase I/IIa platform for the rapid evaluation of candidates for COVID-19 treatment: an update to the structured summary of a study protocol for a randomised platform trial letter. *Trials*. 2021;22(1):487.

20. Angus DC, Berry S, Lewis RJ, *et al*. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study. Rationale and design. *Ann Am Thorac Soc*. 2020;17(7):879–891.
21. Gbinigie O, Ogburn E, Allen J, *et al*. Platform adaptive trial of novel antivirals for early treatment of COVID-19 In the community (PANORAMIC): protocol for a randomised, controlled, open-label, adaptive platform trial of community novel antiviral treatment of COVID-19 in people at increased risk of more severe disease. *BMJ Open*. 2023;13(8):e069176.
22. Group RC, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693–704.
23. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637–1645.
24. Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the treatment of COVID-19 - final report. *N Engl J Med*. 2020;383(19):1813–1826.
25. Aggarwal NR, Molina KC, Beaty LE, *et al*. Real-world use of nirmatrelvir-ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study. *Lancet Infect Dis*. 2023;23(6):696–705.
26. Cox M, Peacock TP, Harvey WT. SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies. *Nat Rev Microbiol*. 2023;21(2):112–124.
27. Gupta A, Gonzalez-Rojas Y, Juarez E, *et al*. Early treatment for COVID-19 with SARS–CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941–1950.
28. Prioritizing diseases for research and development in emergency contexts, World Health Organisation, Available at <www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts>, Accessed February 2024.
29. Anthony SJ, Epstein JH, Murray KA, *et al*. A strategy to estimate unknown viral diversity in mammals. *mBio*. 2013;4(5) e00598-13.
30. Jumper J, Evans R, Pritzel A, *et al*. Highly accurate protein structure prediction with AlphaFold. *Nature*. 2021;596(7873):583–589.
31. Annarumma M, Withey SJ, Bakewell RJ. Automated triaging of adult chest radiographs with deep artificial neural networks. *Radiology*. 2019;291(1):272.