CVDR/S6/22/28/1

COVID-19 Recovery Committee

28th Meeting, 2022 (Session 6), Thursday 15 December 2022

COVID-19 surveillance

Introduction

1. At this meeting, the Committee will focus on ongoing COVID-19 surveillance measures. The Committee will hold two evidence sessions, the first session, which was postponed during its pre-budget scrutiny, will focus on epidemiological wastewater sampling and the second session will consider genomic sequencing. The Committee will take evidence from the following witnesses—

Panel 1: wastewater surveillance

- Dr Rachel Helliwel, Director of Centre of Expertise for Waters (CREW) and the Hydro Nation International Centre
- George Ponton, Head of Research and Innovation, Scottish Water
- Peter Singleton, Research, Innovation and Evidence Manager, SEPA

Panel 2: genomic sequencing

- Professor Sharon Peacock CBE, Executive Director and Chair, Covid-19 Genomics UK Consortium
- Mike Gray, Service Manager for Laboratory Medicine, NHS Lothian and Dr Kate Templeton, Head Molecular Diagnostics, (Microbiology, Virology and Molecular pathology), Director STI and viral genotyping reference laboratory, Royal Infirmary Edinburgh
- Professor Rory Gunson, Consultant Clinical Scientist and Virology Clinical Lead/Laboratory Director, West of Scotland Specialist Virology Centre, Glasgow Royal Infirmary

- Professor Matthew Holden, COG-UK Principal Investigator, Public Health Scotland

2. These evidence sessions will focus what ongoing COVID-19 surveillance measures should be maintained in the current phase of the pandemic. The Committee will hear from witnesses with experience of supporting wastewater surveillance and genomic sequencing of COVID-19 variants to date. The Committee will consider any learning that has been gained from these programmes and whether this learning has been applied elsewhere.

3. The Committee will also consider what future investment may be required in surveillance measures and genomic sequencing for the ongoing COVID-19 response and future pandemic preparedness.

Background

4. The Scottish Parliament's Information Centre (SPICe) has produced a briefing paper (Paper 2) to support these sessions, which contains background information on both wastewater surveillance and genomic sequencing.

Written evidence

5. Crew have published their report SARS-CoV-2 monitoring in Scottish wastewater: Variant Detection, FAIR Data Outputs, and Lessons Learned and policy note to the report. In addition, the **Annexe** includes written evidence provided by the following—

- Dr Isabel Fletcher (submitted in response to the pre-budget scrutiny call for views)
- Scottish Water (submitted in response to the pre-budget scrutiny call for views)
- SEPA (submitted in response to the pre-budget scrutiny call for views)
- Professor Matthew Holden
- Professor Sharon Peacock, which refers to the COVID-19 Genomics UK (COG-UK) Consortium: Final Report | RAND

Next steps

6. The Committee will consider the evidence heard during the meeting.

Committee Clerks
December 2022

ANNEXE

Dr Isabel Fletcher: written submission

What should be prioritised for funding in the Scottish Government's COVID-19 Strategic Framework?

This response derives from research conducted Dr Isabel Fletcher and Prof Catherine Lyall of the University of Edinburgh into the development of the Scottish COVID wastewater testing (WWT) programme, from initial laboratory research to a routine monitoring programme. This research was funded by the Scottish Government. Forty-one key individuals from organisations including Public Health Scotland, Scottish Water, Scottish Government, the Scottish Environment Protection Agency (SEPA) and several universities were interviewed. Collaborations between researchers, industry and government were analysed to see what lessons could be learned to improve future crisis responses.

From this research we produced six recommendations, which focus on the ways in which Scottish Government and its agencies can improve their communication and co-ordination with each other and with the wider Scottish research community. This, we argue, is key for ensuring the effectiveness of future responses to emergency situations, especially in areas such as climate change and One Health, which require collaboration across policy domains.

Our report and policy brief describe our research study and findings in more detail and will be publicly available in the next couple of weeks. Please email I.Fletcher@ed.ac.uk if you would like a copy.

What should be prioritised for funding in the Scottish Government's COVID-19 Strategic Framework?

Three of our recommendations address specific funding priorities – for key research infrastructure, for knowledge brokerage within Scottish public health and for professional networks. They are listed below with a brief description of the reasoning and research evidence behind them.

A well-founded and responsive national research capacity requires an appropriate balance of public support for project and core funding to ensure the availability of key research infrastructure and capacity.

We found that small-scale and responsive funding schemes (many administered by CREW Scotland's Centre of Expertise for Waters) worked well in the case of the development of the wastewater testing programme. However, their success was contingent on standing research capacity such as category-3 laboratories, specialist equipment and the availability of appropriately trained researchers. Core funding of such key facilities should be a priority for the Scottish and UK Governments. Continuity of funding is especially important in cross-sectoral research where it takes longer to build and maintain relationships of trust.

The Scottish Government should consider adopting the good practice of the RESAS-funded knowledge brokerage units such as CREW and establish similar bodies for

the Scottish public health community that bring researchers and stakeholders together to co-create research on policy-related topics.

CREW played a crucial role in the rapid development of the COVID wastewater testing pilot programme. CREW's existing relationships with a range of key stakeholders were an important asset in the Scottish case. However, it has not been possible to identify similar knowledge-brokerage organisations within public health, and the establishment of such a network should be a second funding priority, in order to facilitate the development of new collaborations involving public health researchers and other communities.

Ensure ongoing support to enable groups such as CAMERAS to meet and maintain professional networks. These are a cost-effective way of future-proofing crisis responses and funding for such activities should be protected.

In crisis situations, people initially turn to their existing networks for assistance with unexpected and urgent tasks. Several of our interviewees referred to the value of their contacts from meetings of the Coordinated Agenda for Marine and Environmental Rural Affairs Science (CAMERAS) group – a sector-specific gathering of government agency directors. This is an example of the importance of 'weak ties' where initiating a rapid response does not always require a well-developed relationship with the individual.

Please share any other comments you have with us.

Our other three recommendations focus on the need for better communication and co-ordination between Scottish Government and its agencies, in order to improve cross-sectoral collaboration and therefore crisis responses. All our recommendations were road tested with project partners and other interested parties and comments made on our draft report suggest that they are already stimulating discussion and debate among key stakeholders.

Stronger cross-government and inter-agency links among those working in the environment and health sectors are needed to tackle future crises.

For example, the climate crisis will result in increasing threats to human health (including future pandemics) demanding responses that span public health, animal health and environment. This, in turn, will require more joined-up approaches with effective day-to-day working relationships among Scottish Government directorates and its agencies such as PHS and SEPA.

The Scottish Government could make better use of its network of Chief Scientific Advisors as a conduit for information exchange among the research and policy communities.

Researchers and other government outsiders find it difficult to identify the right person within Scottish Government to contact, partly because they find its structure hard to understand and therefore navigate. A secretariat for all the Scottish Government CSAs could act as means of connecting research and policy more effectively. This could be part of the expanded scientific advisory mechanism

recommended by the recent Scottish Scientific Advisory Council report Building on the Science Legacy of Covid-19 in Scotland.

The Scottish Government should establish a new post of Chief Scientist for Public Health to better represent the Scottish Public Health community.

Our research revealed that neither the Chief Scientist (Health) nor the Chief Medical Officer represented or provided high-profile leadership for the Scottish Public Health community during the COVID pandemic. This gap had implications for both the public standing of the sector and the possibilities for strategic co-ordination with other sectors.

Scottish Water

Briefing for the Scottish Parliament COVID-19 Recovery Committee

Monitoring for SARS COV2 (Covid-19) in Wastewater

Background

At the end of March 2020, Scottish Water was approached by researchers at Edinburgh University, Roslin Institute to explore whether the wastewater network could be used to measure the spread of Covid-19. This was based on some early research from the Netherlands that reported detection of SARS COV2 in wastewater from Schiphol Airport. As a result of these early discussions and a collective need to determine the presence and risk of SARS COV2 a project was initiated through CREW (Centre of Expertise in Waters) with Roslin Institute, Scottish Water and SEPA.

Initial Research

The initial research project was focused on developing the techniques to extract fragments of SARS COV2 from wastewater and to determine whether a repeatable method of detection would find viral material. Additionally Scottish Water was keen to understand whether there was a risk of transmission of SARS COV2 to operational teams working in the wastewater system.

The research quickly determined that the best location for sampling wastewater was the inlet for wastewater treatment works as this gave a representative loading over a 24-hour period. Extraction and detection methods were quickly developed that gave repeatable results. The research also determined that what was being detected in the wastewater was fragments of SARS COV2 virus and that transmission via this route was unlikely. The research also indicated that there was a relationship between the levels of SARS COV2 detected in wastewater and the clinical cases being reported by health boards and public health.

Developing a pilot monitoring programme

Roslin Institute and SEPA further developed the analytical methods so that SEPA could set up their lab facility to carry out analysis on a wider basis. SEPA mapped several wastewater sites against populations in each of the health board areas, to determine which wastewater works provided coverage of approximately 50% of the population in each area. Scottish Water then took this information and established a sampling programme at the wastewater treatment works identified. This pilot sampling and analysis programme was established in June 2020 taking around 40 samples per week. Initially Scottish Water utilised in-house sampling resources as operational and regulatory programmes had been scaled back due to lock-down measures. Scottish Water labs carry out ammonia analysis of samples which is used alongside flow data to normalize the SEPA analysis results for varying flows in the sewer network.

SEPA Informatics team developed a data portal that showed the levels of SARS COV2 detected for each wastewater treatment site. This information was shared with health boards facilitated by Professor Andrew Millar, Chief Scientific Advisor for Environment.

Expanding the programme

In the latter part of 2020, discussions with health boards and local authority teams showed the potential of the data that was being collected from the wastewater sampling and analysis programme. The discussions identified additional wastewater sites for sampling and the programme increased to around 120 samples per week in February 2021.

During this time, we explored whether sampling in wastewater networks was feasible and whether this could provide more granular data for managing the spread of the virus. This required a greater level of analysis of the wastewater network using Scottish Water mapping data with input from network teams. Several network sampling sites in Glasgow, West Lothian, Lanarkshire, Aberdeen and Edinburgh were identified as pilot sites for network sampling based on desk top analysis of the network. Further onsite investigation eliminated some potential sampling sites due to factors including depth of sewer, traffic management issues and network configuration issues. The first network samples were taken mid-March 2021.

By April 2021 the programme had increased to circa 190 samples per week, including circa 40 network samples.

During 2021 there was further development of the programme, through discussion with SEPA and health professionals, with the addition of further wastewater treatment sites and additional network sampling sites. This increased the overall programme to circa 200 samples per week across all parts of Scotland. To support the expansion of the programme Scottish Water recruited additional sampling resource through direct hires and utilisation of sewer network contractors. SEPA also started supplying samples to NHS Lothian and Edinburgh University Labs for sequencing to identify the dominant variant.

During COP26 additional sampling was put in place in the wastewater network to support wider SARS COV2 monitoring. During November 2021 the sampling programme was circa 280 samples per week including 55 network samples.

Post COP26 Scottish Water was taking up to circa 280 samples (mixture of works and network samples) per week to support the monitoring programme.

Stabilising the monitoring programme

Through the latter part of 2021 and early 2022 there have been discussions led by Scottish Government with health professionals as to the scale and extent of the monitoring programme and how this is built into the overall management of the pandemic. As a result, the sampling programme has been reduced to 200 samples per week which are taken only at wastewater treatment sites. This programme has been stable since May 2022.

George Ponton
Head of Research and Innovation
September 2022

COVID-19 Committee - SEPA written evidence on wastewater monitoring for Covid

Since May 2020, the Scottish Environment Protection Agency (SEPA) and Scottish Water (SW) have worked in partnership to deliver a national monitoring programme for Sars-Cov-2 RNA in wastewater.

The programme involves SEPA analysing samples collected by SW from wastewater treatment works or locations within the sewer network.

The rapid development and implementation of the programme was enabled by:

- Effective partnering with academics via research undertaken on behalf of Centre of Expertise for Water (CREW) by the Roslin Institute of Edinburgh University in March and April 2020 to identify a repeatable and practical method for detecting fragments of Sars-Cov-2 RNA in wastewater.
- The re-focusing and development of existing capabilities by SEPA and Scottish Water.

The programme's targeting is shaped by Scottish Government's public health leads and local directors of public health. The results are used for national surveillance and, during the height of the pandemic, were also targeted to help focus local test and protect effort, for instance certain communities within Glasgow were sampled to tie in with a local test centre.

The programme provides an unbiased and unintrusive means of monitoring the levels of infection. It is unbiased because it does not rely on people coming forward for tests.

The programme has the capability, and has been used, to:

- Test for Covid in wastewater from up to nearly 80 % of Scotland's population every week.
- When required, test wastewater from any population centre up to 4 times per week.

- Provide results within 48 to 72 hours, depending on the remoteness of the sampling location, with sample analysis taking under 7 hours.
- Identify infection in small areas of large conurbations or in individual facilities (e.g. prisons, schools, universities) by sampling relevant parts of the sewer network as well as wastewater treatment works.

The programme is scalable (subject to resource) and can be rapidly adjusted, for example, to increase sampling frequency at a site; increase granularity of coverage in a geographic area; or target specific sites and events (e.g. as was done during COP26 in Glasgow).

The wastewater programme and the Office for National Statistics (ONS) survey of households are the only continuing programmes providing local and national information on Sars-Cov-2 virus in the Scottish population.

The wastewater programme is currently analysing up to 200 samples to provide weekly surveillance information for nearly 80 % of the population.

The programme is funded by Scottish Government with the current programme's cost being in the region of £3m per year.

The results are publicly available on SEPA's web site.
https://informatics.sepa.org.uk/RNAmonitoring/

A more detailed dashboard, co-designed with public health experts, is available to public health staff.

Wastewater can potentially be used to test for any disease that sheds fragments of its genetic material in human excreta.

Samples collected though the programme are being used to:

- Identify Covid variants of concern (and, potentially, the proportions of those variants).

- Look for new Covid variants.
- Investigate other diseases, including Adenovirus, Polio and Monkey Pox.
- Test for antimicrobial resistance (AMR).

The biobank of samples collected previously through the programme is providing an opportunity to explore how the occurrence of above diseases has been changing over time (e.g. to understand if changes in prevalence of adenovirus in the population might be correlated with increase in hepatitis in young children).

Testing samples for influenza virus is being considered ahead of potentially the most significant flu season since before the pandemic.

Elsewhere in the world, wastewater analysis has been used to detect medical and recreational drug residues.

Scottish Environment Protection Agency
22 September 2022

Written evidence from Professor Matthew Holden

SARS-CoV-2 genome sequencing in Scotland

Pre-pandemic pathogen genome sequencing

Prior to the COVID-19 pandemic in Scotland, whole genome sequencing (WGS) had been rolled out for four groups of bacterial pathogens in the Scottish Microbiology Reference Laboratories (*Salmonella*/*Shigella* species, *Neisseria meningitides*, *Streptococcus pneumoniae*, and Shiga toxin-producing *Escherichia coli*). The funding for this was provided by NHS National Services Division (NSD) and was a relatively modest investment (£80k per year), which provided for limited sequencing for these pathogens (up to 2,500 sequences a year).

SARS-CoV-2 genome sequencing

Since the start of the pandemic in March 2020, 357,981 SARS-CoV-2 genome sequences have been generated for Scottish COVID-19 cases (as of the 6th of December 2022). Fifteen percent of these are from NHS Diagnostic and Hub laboratories (Pillar 1), with the remainder coming from Pillar 2 testing (UK Government testing laboratories).

Over the course of the pandemic, SARS-CoV-2 sequences have come from a number of sources, and seen the development of a national NHS based sequencing service for SARS-CoV-2 that is now providing the majority of sequencing for Scotland. A timeline of the developments and progress of the SARS-CoV-2 sequencing in Scotland is illustrated in Figure 1.

At the beginning of the pandemic the UKRI and Wellcome funded COVID-19 Genomics UK (COG-UK) consortium, a partnership of academic and public health agencies, generated sequences from samples that were available from NHS diagnostic labs (Pillar 1). In Scotland two COG-UK partners at the University of Edinburgh and MRC-University of Glasgow Centre for Virus Research were generating sequences for Scottish samples. As UK Government testing was established (Lighthouse lab network; Pillar 2), the Wellcome Sanger Institute started providing sequences through the COG-UK consortium. From the start, Public Health Scotland (PHS) worked with COG-UK partners to help support their activity and integration of genome data into the public health response.

Establishing SARS-CoV-2 genome sequencing in the NHS

To increase the sequencing capacity available in Scotland and support public health and clinical application of the data, PHS in partnership with the Scottish Specialist Virology Centres (SSVC) in NHS Lothian and NHS Greater Glasgow and Clyde (NHS GGC) and MRC-University of Glasgow Centre for Virus Research, obtained funding from the Scottish Government to establish an NHS SARS-CoV-2 sequencing service. This service was funded to sequence up to 200 samples a week across the two SSVCs, with bioinformatics support for the service being provided by PHS. A part of this, an Outbreak Investigation Report Service that enabled health protection teams (HPTs) and Infection Prevention Control (IPC) teams from NHS boards across Scotland to request sequencing of samples of interest and receive outbreak reports summarizing the results of the bioinformatics to help ‘rule in’ and ‘rule out’ transmission, was established.

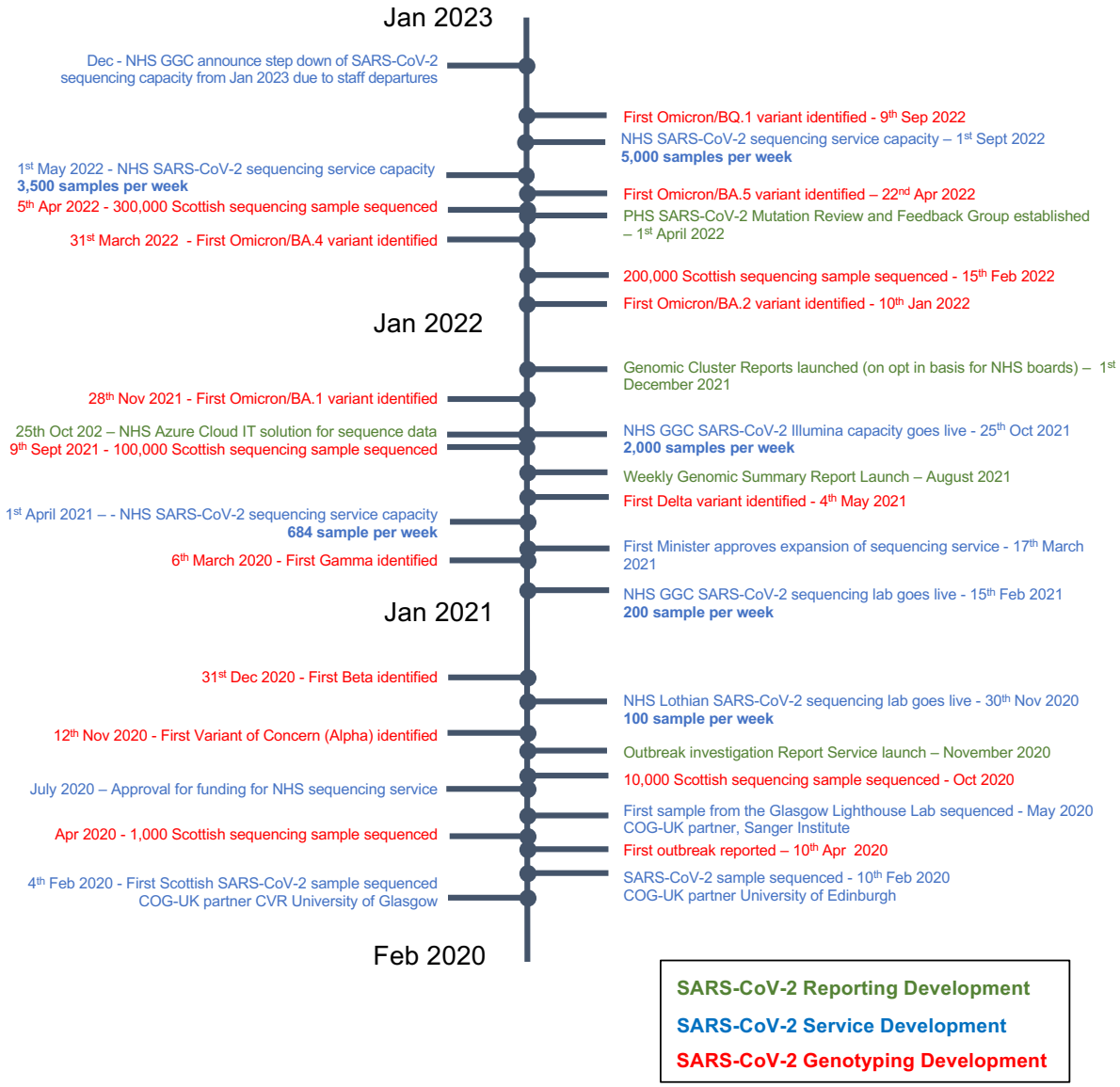
Following the establishment NHS SARS-CoV-2 sequencing service the Scottish Government made a further investment in the sequencing and bioinformatics capacity to increase the number of samples it was able to process up to 5000 samples a week. This investment helped to support the increased demand for sequencing due to the emergence and spread of Variants of Concern (VOC), and also fill the gap in coverage of the scaling down of SARS-CoV-2 sequencing by COG-UK, as it came to the end of its funding. This investment in the service not only enabled more sequences to be generated, but also permitted the development of centralized computing and bioinformatics capacity to support the analysis and dissemination of genomic data to NHS partners and stakeholders. This has included the

establishment of routine reporting to NHS boards of genotypes and genomic clusters and weekly SARS-CoV-2 mutation reports to NHS, PHS, ARHAI and Scottish Government.

Future Developments

The investment in the NHS SARS-CoV-2 sequencing service by the Scottish Government was also provided with an aim to create a legacy that could also be used to expand the repertoire of pathogens sequenced beyond SARS-CoV-2. A PHS led process and governance mechanism has been with Scottish stakeholders and partners to develop a pathogen genomic strategy for Scotland and oversee the expansion of genome sequencing. Due to current uncertainty about the future funding of SARS-CoV-2 sequencing service beyond March 2023 and the impact that this is having on staff retention, the ability to support SARS-CoV-2 sequencing in the new year is now at risk, as is the legacy of the Scottish Government investment to support the wider application and benefits of WGS for other pathogens. PHS and Scottish Government are aware of this risk and are actively discussing with their NHS partners.

Figure 1. Timeline of the development SARS-CoV-2 Sequencing in Scotland



Written evidence in advance of the Scottish Parliament COVID-19 Recovery Committee on evidence session on genomic sequencing

Author: Sharon Peacock
Director, COVID-19 Genomics UK Consortium (COG-UK)
Professor of Microbiology and Public Health, University of Cambridge

3rd December 2022

The Committee would like to hear about any learning that has been gained from the experience of using genomic sequencing in the COVID-19 pandemic and whether this has been applied elsewhere.

BACKGROUND

The ability to identify individuals infected with the SARS-CoV-2 virus – which causes COVID-19 – and to sequence and understand the viral variants circulating in the United Kingdom (UK) since the onset of the pandemic have been vital to informing public health decision making and efforts to control the virus's spread. The work of pathogen genomics experts has underpinned sequencing and research efforts.

Pathogen genomics is a scientific discipline focused on understanding the genetic code of infectious disease pathogens. The ability to do so is important for tracking transmission, identifying mutations and new variants, and informing the development of vaccines, therapies, and broader public health interventions and policies. While pathogen genomics proved valuable in tackling other infectious disease threats such as the West African Ebola outbreak from 2014 to 2016, it is the COVID-19 pandemic that really put the spotlight on the importance of pathogen genomics in public health preparedness and response globally.

The COVID-19 Genomics UK (COG-UK) Consortium was established soon after the UK went into its first lockdown of the COVID-19 pandemic in March 2020. COG-UK represents one of the largest pathogen genomic sequencing efforts set up in response to the pandemic globally. COG-UK was swiftly established to support rapid and large-scale whole genome sequencing of the SARS-CoV-2 virus to advance knowledge about the pathogen, help understand viral transmission and evolution and provide data and analytics to inform the public health response.

On 1 April 2020, COG-UK received approximately £20 million in funding from the National Institute for Health Research (NIHR), the Medical Research Council (MRC) – part of United Kingdom Research and Innovation (UKRI), – and Genome Research Limited (operating as the Wellcome Sanger Institute). £14.5M of this was allocated from the 'COVID-19 Fighting Fund' by Sir Patrick Vallance and Sir Chris Whitty. In January 2021 and April 2021, COG-UK received an additional £11.6 million from the Testing Innovation Fund and £5 million from the Department of Health and Social Care Test and Trace, respectively. The initial awards were granted to create a large-scale SARS-CoV-2 sequencing capacity within the UK and support academic research. Subsequent awards were given to help COG-UK meet the increased demand for its activities, and specifically to bolster large-scale SARS-CoV-2 sequencing capacity and equipment, and enable the transition of routine sequencing activities to the four Public Health Agencies (PHAs) of the UK.

COG-UK was a collaborative effort between 16 academic institutions, the four UK PHAs, the Wellcome Sanger Institute, and four Lighthouse Labs, as well as 14 other sequencing collaborators and 65 other collaborators from National Health Service (NHS) Foundations and Trusts and other organisations across the UK. COG-UK was rapidly established to respond to the pandemic and build on the UK's strengths in pathogen genomics, population health sciences and health informatics. The consortium was coordinated by a management team at the University of Cambridge

but operated through a decentralised model where organisations across all four nations of the UK contributed to the consortium's sequencing, research, analysis and stakeholder engagement activities.

In essence, COG-UK connected genomics with public health – with viral sequencing and analysis at the core of COG-UK's activity. More specifically, COG-UK's key aims were to:

- Provide data, analysis, tools, and research that can help guide public health decision making and policy relating to the COVID-19 pandemic.
- Advance understanding of genetic changes in the SARS-CoV-2 virus and how they relate to the spread of the virus, immune evasion and severity of COVID-19 symptoms, all of which matter for public health decision making and the development and evaluation of treatments and vaccines.
- Support national research studies, including those that can help enable future evaluations of the effectiveness of various pharmacological and non-pharmacological interventions to prevent or treat COVID-19.

The consortium was committed to sharing knowledge and promoting open science in the UK and globally so that the insights and data generated by COG-UK's activities could help support public health decision making for current and future pandemics. Given the growing realisation of the importance of pathogen genomics for public health, the scale of investment made and the commitment to sharing learning from the COG-UK experience widely, the consortium commissioned the not-for-profit Institute RAND Europe to evaluate and learn about its progress, evolution, and impacts (submitted as evidence, reference 1). Much of the text in this document is derived from this evaluation.

LEARNING GAINED

COG-UK set out to make diverse contributions to the COVID-19 pathogen genomics landscape and the pandemic response in the UK. The contents below provide a summary of COG-UK achievements in key areas of impact, provided as key learning points. More details can be found in the RAND Europe report on the Consortium (ref 1).

1. Contributions to scientific knowledge about SARS-CoV-2 and to advancing methods that support sequencing and pathogen genomics research

The sequencing of viral genomes has been essential to research and analysis seeking to understand the SARS-CoV-2 virus and its behaviour. COG-UK sequenced over a million SARS-CoV-2 genomes across the UK.

COG-UK research and analyses made substantial contributions to knowledge about the SARSCoV-2 virus, variants of concern, viral behaviour, transmissibility and spread, and to understanding the impact of diverse public health measures. The consortium also made vital contributions to advancing the methodologies used in pathogen genomic sequencing and analysis. Insights were widely disseminated through academic publications and conferences.

Efforts made by COG-UK partners to help link viral sequencing with patient metadata helped to build up a critical resource for further significant public health research. The Cloud Infrastructure for Microbial Bioinformatics (CLIMB) data and computing infrastructure (established previously through funding from the Medical Research Council) played a key role in these efforts.

2. COG-UK's sequencing data and analytics have been used to inform policies related to border control, travel, lockdown, and social distancing

COG-UK's research has contributed to government decision making since early in the pandemic. For example, work by COG-UK members at the University of Oxford in England, the University of Edinburgh, the University of Glasgow and St. Andrew's University in Scotland, alongside work by Cardiff University in Wales using COG-UK genomic sequencing data, helped enable an early understanding of the origins of SARS-CoV-2 introduction to the UK and helped to inform border control policies. Another study by COG-UK members at the University of Cambridge generated evidence on the impact of travel restrictions into the UK during summer 2020. Specific to COG-UK's impact on social distancing and mixing policies, the discovery of the B.1.1.7 variant (also known as the 'Alpha' variant) by consortium members informed a change in government policy. The discovery led to the introduction of more restrictive social mixing measures during Christmas 2020 and January 2021, as elaborated below.

> COG-UK produced the sequencing evidence and analytics that informed the UK government's decision to change the Christmas 2020 social distancing restrictions. This knowledge enabled UK policymakers to take decisive action that is believed to have saved lives. COG-UK sequencing partners and central and coordinating teams themselves cancelled Christmas plans and returned to laboratories to support demand for sequencing over Christmas 2020.
>
> The type of sequencing conducted (i.e., decisions about which samples to sequence) and communication with key UK government agencies and international agencies such as the World Health Organisation (WHO) were important for timely action. COG-UK's leadership team had argued throughout the pandemic in favour of UK-wide sequencing of randomly selected samples, although some other stakeholders advocated concentrating resources on targeted sampling. Interviewees for the RAND Europe report shared that COG-UK's decision to sequence samples from across the UK helped them identify and understand the alpha variant in a timely manner. COG-UK's communication links with WHO and others ensured the rapid dissemination of knowledge, allowing UK and international stakeholders to take prompt action. In addition, COG-UK researchers' interactions with UK PHAs facilitated analysis of the sequencing data in combination with the epidemiological information gathered by PHAs, which helped identify the B.1.1.7 as a key variant of concern.

COG-UK's sequencing data, research and work to link sequencing information with clinical metadata have informed ongoing policy decisions throughout the pandemic related to UK policy on border control, international travel and quarantine. Research has also helped increase policymaker and public understanding of the disease severity risk posed by new variants.

More specifically, COG-UK genomic data have been used to alert the UK government and policymakers to the presence of new variants in the country, including variants of concern (i.e., with greater transmissibility or severity of illness) and variants under investigation and circulating in the UK. Genomic data produced by the consortium, combined with in depth patient metadata from PHAs or research efforts, have helped to understand the spread of new variants, their location within communities, and the association between variants and disease severity.

For example, by linking genomic data to patient data, it was possible to analyse a spike protein mutation (D614G) and its association with disease severity and patient outcomes early in the pandemic. These data types have been fundamental to informing the UK's policy response to the pandemic, including outbreak management across the four PHAs in the UK (e.g. identifying outbreaks, understanding if an outbreak is due to single or multiple introductions of SARSCoV-2 and identifying opportunities to interrupt transmission chains).

According to one expert interviewed by RAND Europe, COG-UK's work also enabled the rapid detection of the Delta variant introduced by people travelling from abroad in Spring 2021, which informed the UK's subsequent travel policies. The expert also noted that it would have been difficult to distinguish the cause of viral spread without genome sequence data or determine whether it was due to a new and more transmissible SARS-CoV-2 variant rather than social behaviour. This understanding was vital in informing policy action. Knowledge about this variant of concern likely contributed to a policy decision to delay the originally planned easing of restrictions by four weeks, from 21 June to 16 July 2021.

3. COG-UK has demonstrated that pathogen sequencing data and resources can significantly impact public health interventions in specific settings, including hospitals, long-term care facilities and universities

COG-UK has contributed data, analytics and tools to support SARS-CoV-2 research and outbreak investigations in diverse settings, including hospitals, long term care facilities and universities. For an illustration of these activities, see below.

Hospital setting

COG-UK's contributions to research on implementing real-time SARS-CoV-2 genomic sequencing in a hospital setting demonstrated an impact on infection control interventions and patient safety reporting for healthcare associated COVID-19. In the HOCI (Hospital Onset COVID-19 Infection) study, COG-UK investigated the impact of integrating rapid, real-time COVID-19 genomic sequencing on infection control team decision making to prevent the spread of SARS-CoV-2 in NHS hospitals. COG-UK's sequencing capacity and software tools have also been used to investigate and understand local outbreaks of COVID19 in hospital settings. For example, very early on in the pandemic, COG-UK members developed the CIVET tool (Cluster Investigation & Virus Epidemiology Tool), which became the key software tool used for a serious incident investigation in a Northern Ireland Hospital Trust. COG-UK's capacity to conduct SARS-CoV2 genome sequencing helped identify the cause of the hospital's COVID-19 outbreak by providing information on the genetic makeup of the responsible variant.

Community-based healthcare setting

Rapid implementation of SARS-CoV-2 sequencing was used to investigate healthcare associated COVID-19 cases and transmission between hospital and community-based healthcare settings, demonstrating the utility of real-time genomics surveillance to inform infection control interventions. A COG-UK review of the role of genomics in understanding COVID-19 outbreaks identified that staff and residents in long-term care facilities were usually infected with identical SARS-CoV-2 genomes and outbreaks were primarily due to a single or few introductions rather than a series of seeding events from the community.

University setting

With funding from COG-UK, researchers from the University of Cambridge assessed transmission of SARSCoV-2 amongst students and staff to understand drivers and patterns of viral transmission. This research helped inform local infection control measures and understand their impact as well as the impact of national lockdown policies. Findings from COG-UK research and analyses were used to inform advice on diseasecontrol measures in Higher and Further Education settings.

4. COG-UK data and insights have been made freely available to the global research and innovation community to use in efforts to understand vaccine effectiveness, and to inform the development of next generation vaccines

COG-UK's sequencing data have been important as part of the vaccine response, particularly in terms of efforts to understand and evaluate how well vaccines work against specific variants. COG-UK made all SARS-CoV-2 genomic sequences publicly available and, based on the consortium's self-reported data, these sequences are regularly mined by vaccine developers. The consortium's policy of openness and widescale data sharing from the outset helped to enable groups developing and evaluating COVID-19 vaccines to understand vaccine effectiveness. There was a time during the pandemic when the genomes sequenced by COG UK constituted ~50 per cent of the total SARS-CoV-2 genome sequences in the international Global Initiative on Sharing Avian Influenza Data (GISAID) sequencing database.

Using sequencing data, vaccine developers recognised the beta variant first identified in South Africa as a variant against which they should (and did) develop a vaccine. If a vaccine does not fully prevent infection, sequencing data can also help show which variant can evade the immune system and the characteristics enabling it to do so. Thus, ongoing and future sequencing can inform future efforts to re-engineer or improve vaccines. According to a stakeholder consulted as part of the Rand Europe evaluation, it would have been challenging without such sequencing data for vaccine developers to predict where the next round of SARSCoV-2 vaccine development should be directed.

COG-UK also worked closely with the Genotype-2-Phenotype (G2P) consortium to support the virological investigation of variants of interest and concern with implications for vaccine development and collaborated with the Oxford Vaccine Group and Novavax NVX-CoV2372, providing sequencing data to their vaccine clinical trials. In addition, they engaged with Pfizer on vaccine development. The consortium also provided input into several of the UK groups working on various aspects of ongoing vaccines development, evaluation, and/or regulation, informing the next generation of

vaccines to help improve vaccine efficacy. Examples include the Medicines and Healthcare products Regulatory Agency (MHRA), the British In Vitro Diagnostic Association (BIVDA), and the Department of Health and Social Care (DHSC) Vaccine Update Expert Advisory Group (VUEAG).

5. COG-UK data have been used to understand SARS-CoV-2 susceptibility to treatments for COVID-19, with the potential to inform the development of novel therapeutics that target viral molecules

COG-UK data and methodology have been used to study SARS-CoV-2 susceptibility to COVID-19 therapeutics. For example, in a case study of an immunocompromised individual treated with convalescent plasma therapy, researchers observed a series of viral mutations that altered susceptibility to neutralisation via antibodies within the convalescent plasma. SARSCoV-2 genomic data also play a role in the development of other COVID-19 therapeutics where the drug target is a virus molecule (e.g., inhibitors of SARS-CoV-2 RNA-dependent RNA polymerase, such as Remdesivir). Such work can be facilitated by the COG-UK Mutation Explorer, an open access internet-based website that provides information on the putative biological impact of mutations on available therapeutics.

6. Changing how decision makers view and value pathogen genomics

COG-UK has substantially impacted how policymakers in the UK view and value pathogen genomics by raising awareness about its importance for public health and increasing demand for its use in decision making. COG-UK's efforts have helped raise awareness about the value of pathogen genomics and demonstrated the power and importance of pathogen genome sequencing and research in managing infectious disease pandemics and informing public health decisions.

Mutation identification and analysis can help identify many different types of viral outbreaks. However, in the early stages of the pandemic, the mutation rate of COVID-19 was thought to be relatively low. It took time and the emergence of more transmissible variants and their identification and characterisation using data generated by COG-UK and others for public health decision makers and policymakers to become aware of the value of sequencing. COGUK members also showed that pathogen genomics could be used to estimate the prevalence and spread of the virus in the population. Furthermore, the data they produced has closely reflected the public health epidemiological data from NHS Test and Trace. Below are some examples of the diverse ways that COG-UK engaged with and disseminated learning to key decision makers in the UK.

Participation in committees and working groups

COG-UK's members sat on a range of DHSC and Public Health England (PHE) groups to provide expert advice and information to help inform decisions related to the pandemic response. COG-UK also worked closely together at an organisational level with both PHE and NHS Track & Trace. As part of the PHE Variants Technical Group Meeting, COG-UK members provided scientific and operational input on variants of concern and interest. The consortium also had representatives on several Scientific Advisory Group for Emergencies (SAGE) sub-groups, including the PHE serology working group, the Social Care working group, the Ethnicity subgroup, the Hospital Onset COVID-19 working group, and the New and Emerging

Respiratory Virus Threats Advisory Group (NERVTAG). COG-UK members have also been involved in and contributed data to several reports from NERVTAG, including a joint COG-UK-NERVTAG summary statement on the evidence for genetic change in SARS-CoV-2 and effects on viral phenotypes.

Contributions to reports and briefings

COG-UK members contributed data to a series of PHE technical briefings on SARS-CoV-2 variants of concern and variants under investigation. Consortium members advised the UK government on the standards included in the legislation for commercial sequencing and data flows as part of the test-to-release programme. The consortium provided input into 36 external reports produced between 1 March 2020 and 31 July 2021 by SAGE, the Children's Task and Finish Group (TFC), NERVTAG, and PHE (see RAND Europe report for full list).

Direct reports to policymakers

During the timeframe of the Rand Europe evaluation, COG-UK submitted 18 formal reports to SAGE on the consortium's progress and preliminary and updated analyses of data at local, regional and national levels. These reports provided early insights on outbreaks in specific settings (e.g., hospitals, care homes and universities), on patterns of introduction and transmission of SARS-CoV-2 variants in the UK, and patterns of the evolution of SARS-CoV-2 mutations.

Informal feedback

Either as individuals or groups, COG-UK members provided informal feedback to requests from SAGE, GOScience and the Chief Scientific Advisor/Chief Medical Officers on numerous occasions. They fed back on topics including reinfection, genomics to estimate outbreak size, SARS-CoV-2 infections in mink, and transmission in prisons.

7. COG-UK has significantly contributed to enhancing the skills, workforce, infrastructure, networks and relationships needed to support pathogen genomic sequencing in the UK. If sustained, this capacity could significantly bolster the UK's ability to use pathogen genomics in other disease areas in the future

COG-UK's ability to rapidly bring together and focus pre-existing sequencing and research capacity and collaboration and build on it by including new collaborators who were not previously linked was widely recognised as one of the consortium's key achievements. The consortium connected many of the key individuals and institutions involved with genomics across the UK. At its inception, COG-UK was composed of 17 unique sequencing sites with a total of 134 genomic sequencing machines. COG-UK was initially set up to conduct public health virology and epidemiology research. However, given the public health system's demand for sequencing support, the consortium spent the first 18 months of the COVID-19 pandemic delivering a sequencing function as a public health service.

People worked together at speed and under considerable pressure, putting aside individual interests and professional protectionism to pursue the common mission of using pathogen genome sequencing and research to help respond to the pandemic. During the RAND Europe evaluation, some experts suggested that compared to relative agility found in the university setting, conventional structures available through PHAs would have faced greater challenges establishing equivalent research and

development provision as quickly. However, the transition of sequencing capacity to PHAs began in Spring 2021 and should help to enhance sequencing capacity within PHAs for the future.

According to some experts interviewed by RAND Europe, bringing together such diverse pathogen genomic expertise was a novel undertaking. The model of academics working and attending meetings in collaboration with PHAs was seen as particularly novel. Providing it is sustained, this type of interaction may enable a new paradigm for the future of UK public health based on collaboration across professions. COG-UK's activities have also contributed to a step change in pathogen genomics capacity across the four UK nations. Although there is further capacity building and sustaining work ahead, several people interviewed by Rand Europe emphasised the highly collaborative ways of working and knowledge and data sharing from early in the pandemic across the four nations within COG-UK. According to one interviewee, one of the devolved nations would not have been able to participate in public health genomics during the pandemic without the networks COG-UK created. Indeed, the interviewee believes that this will outlive COG-UK. Although funding is always a challenge, two other experts noted that COG-UK helped leverage funding for the devolved nations to develop their own public health genomics systems. COG-UK also developed operational, governance and management arrangements to support a highly networked and multi-stakeholder approach to public health genomics research, analysis and sequencing support for the public health system. For example, the legal frameworks, standard operating protocols and financial management protocols helped implement the networked model. They could be helpful tools for future networked public health genomics efforts that bring together diverse organisations across different UK regions.

By and large, COG-UK participants from the devolved administrations have been vocal in their support for continuing a four nation public health genomics approach in the future. They note the synergistic value of a collective approach to building sequencing capacity, securing funding and sharing expertise.

Below is an overview of different types of capacity contributions. These include building a skilled workforce, physical infrastructure (e.g., equipment and facilities), data infrastructure (e.g., cloud computing), leadership, management and governance arrangements, and strengthening networks and relationships within and between academics, the NHS and public health decision makers and policymakers.

Workforce and skills

Staff at partner organisations were retrained as needed to support sequencing efforts, and consortium funding was used to hire some new staff although the majority of people participating in COG-UK were volunteers who were employed elsewhere (for example, by universities). COG-UK newly trained numerous postgraduate staff in handling, preparing and analysing genetic material and interpreting and reporting genomic sequencing data using tools such as CIVET (Cluster Investigation & Virus Epidemiology Tool). The staff who received such training were drawn from a range of disciplines, including clinicians, biomedical scientists, nurses, health protection teams, infection control teams, diagnostic laboratory scientists/technicians and local PHA teams. More than 160 sequencing staff/volunteers and more than 650 clinicians benefited from training. This newly

trained workforce is a crucial asset of COG-UK and will be an important part of its legacy, continuing to support pathogen genomics in the future. In addition, COG-UK members shared their work at COG-UK's internal seminars, which began in September 2020. Regular seminars have been held since then and provide a format for three science presenters at each meeting drawn from across the consortium. A question-and-answer session followed presentations, enabling discussion and knowledge exchange. On average, 40 people attended each seminar.

Physical infrastructure (equipment, facilities)

There were a total of 17 sequencing sites and 134 sequencing machines across the COG-UK consortium. COG-UK's sequencing capabilities increased over time as consortium partners expanded capacity and shifted resources from research to service delivery to meet changing demand for sequencing through different stages of the pandemic. COG-UK supported the expansion of existing infrastructure by purchasing equipment for the network with COG-UK funding.

Leadership, management and governance arrangements

The consortium established a governance structure representing diverse geographies and stakeholders involved in the public health landscape and contractual arrangements, operational protocols and legal frameworks to support a four nation, multi-stakeholder approach. The ability to sustain conducive governance and management support for future networked public health efforts and align them with preexisting institutional level practices underpinned the ability to mobilise relationships, the activities needed to integrate public health genomics research in other clinical areas and the response to future threats.

Data infrastructure

Building upon the existing UK Cloud Infrastructure for Microbial Bioinformatics (CLIMB), COG-UK used its funds to rapidly develop additional computational equipment (CLIMB-COVID). CLIMB received a £1.2 million funding boost from UK Research and Innovation (UKRI) in January 2021, which helped support and expand computing capabilities (e.g., computing power, storage and analysis tools). These resources are available to microbiologists in UK academic settings for bioinformatics analysis of genomic datasets derived from next generation sequencing technologies. According to self-reported data from COG-UK, CLIMB is expected to become integral to DHSC activities, providing longer-term foundations for pathogen genomics.

Strengthened relationships between academics, NHS, PHAs, and policymakers

COG-UK was a consortium of 16 academic research partners, the Wellcome Sanger Institute and four PHAs (representing each of the devolved nations), other sequencing collaborators including Lighthouse Labs, and numerous NHS foundations and trusts. This consortium fostered unprecedented collaboration across different types of stakeholders involved in public health in the interest of advancing science and informing policy. The consortium worked with the GenOMICC team to link the virus to host genomes. It has also funded the Hospital Onset COVID Infection (HOCI) trial, which fed genomic results back to NHS sites in real-time and brought all four devolved nations together to share data. The consortium also focused heavily in strengthening relationships with policymakers (e.g., PHAs, DHSC and SAGE).

8. COG-UK helped improve the efficiency of genomic sequencing by reducing costs and turnaround times for sequence reporting

Enhancements in the genomics workforce, physical and data infrastructure and networks/relationships have helped scale genome sequencing capacity and efficiency. Between April 2020 and July 2021, the cost and turnaround time for sequencing and reporting decreased. Measuring the average time from sample collection to sequencing data upload across consortium sites, the turnaround time decreased by 70 per cent (from 20 days in April 2020 to 6 days in June 2021). Measuring the average time from sample receipt at the sequencing site to sequencing data upload across consortium sites, the turnaround time decreased by 50 per cent (from approximately 5 days in January 2021 to 2.5 days in June 2021). Regarding costs, COG-UK reported that their efforts researching and developing sequencing protocols and pipelines reduced the average cost of whole genomic sequencing by approximately 30 per cent between April 2020 and July 2021 (from £56 to £40 blended per sample).

SUPPORTING LEARNING ELSEWHERE

All COG-UK data have been uploaded as rapidly as possible to the GISAID database and the European Nucleotide Archive (ENA). These data are readily available for international scientific communities to use in virology, immunology and bioinformatics research and the design and development of vaccines, therapeutics and diagnostics.

COG-UK members adapted ARTIC methods for SARS-CoV-2 sequencing, publishing different versions suitable for a range of set ups, including a low cost environment with reduced amounts of reagents. They also reported global use of the analysis tools and websites developed by COG-UK.

The consortium was for a long time a primary contributor of SARS-CoV-2 genome sequences to GISAID, alongside contributions from other large-scale international efforts, e.g., in Canada, Denmark, South Africa, Brazil and localised initiatives in the USA. According to some individuals interviewed by RAND Europe, COG-UK sequencing data and software tools are used in various countries, with national SARS-CoV-2 genome sequencing efforts drawing on COG-UK-developed analysis pipelines and software tools. COG-UK also assisted vaccine development efforts, the results of which have implications of global relevance. In addition, the PANGO linage nomenclature developed by COG-UK members has become the standard naming criteria for SARS-CoV-2 viral lineages worldwide. Having a standard nomenclature enables researchers worldwide to better understand the patterns and determinants driving the local, regional and global spread of SARS-CoV-2 and to track new variants as they emerge.

COG-UK data, methods and protocols were readily available for the international community to use for research and pandemic preparedness efforts. Given that COG-UK research and analyses were made publicly available worldwide, anyone wishing to use COG-UK data to inform the global pandemic response could do so. For example, in Spring 2021, early data on the Delta variant was provided at speed, guiding not only the UK government's response but enabling the international community's research and preparedness. Detailed information on sequencing protocols and methods

available to the global community can be found on the COG-UK website, with multiple formats available for compatibility with different resource set ups. The website also contains a rich resource of freely available analytic tools developed by consortium members. The text below provides examples of the diverse ways COG-UK has engaged with the international community.

Sharing of resources and participation in sequencing and research collaborations

Anyone wishing to use COG-UK data to inform the global pandemic response can do so. All COG-UK data are uploaded to GISAID, and the ENA databases and academic publications are made freely available on the COG-UK website. Methodological protocols and sequencing and analysis tools are also freely available on the COG-UK website or elsewhere. COG-UK members have provided advice and expertise and have been collaborating with researchers in 28 countries (including 17 low- and middle-income countries) to support sequencing efforts.

Dissemination of learning

COG-UK has made more than six hours of video presentations freely available online, featuring consortiumwide speakers from all four nations in the UK. Presentations cover various topics, including discussions of sequencing and analysis techniques, variant introduction, tracking and analysis, and genomic informed research from hospitals, care homes and university settings. Live participation included attendees from over 50 countries, and recordings have had over 60,000 views.

Facilitation of training

In June 2021, the University of Cambridge and Wellcome Connecting Science each received just under £0.5 million for a joint project,‘ Leveraging COG-UK expertise to support the global dissemination of SARS-CoV2 genomic sequencing’. This endeavour, known as COG-Train, supports the development of a global learning community centred around online training resources in SARS-CoV-2 sequencing and analysis and share lessons learnt from the rapid establishment of a national sequencing network. This project will help support capacity building so that other nations, particularly in low- and middle-income countries, can benefit from COG-UK’s scientific, public health, operational and policy experience.

Participation in international workshops and meetings

Consortium members have participated in WHO working groups (e.g. providing advice on naming conventions of SARS-CoV-2 variants) and the Global Early Warning System Action Collaborative Advisory Council, an initiative of the Milken Institute and a collaboration between the Rockefeller Institute and FasterCures In June 2021, COG-UK members also contributed to several Rockefeller Institute workshops on standards architecture for genomic surveillance. Consortium members also participated in international collaborative meetings to exchange knowledge and ideas, e.g. a Nordic-Baltic roundtable on genome sequencing held on 8 March 2021.

Provision of informal advice

COG-UK has worked closely with the UK’s Foreign Commonwealth and Development Office, responding to requests for input and advice, including the provision of a factsheet on COGUK sequencing efforts (dated October 2020).

The Committee is also interested to consider what future investment may be required in genomic sequencing for the ongoing COVID-19 response and for future pandemic preparedness.

COG-UK has made a significant and valuable contribution to the UK's public health genomics landscape. However, what needs to be sustained is not necessarily the network as it operated during the evaluation timeframe, but the ecosystem that has been built around it.

Reflecting on the learning gained and looking to the future, COG-UK's legacy will depend on decision makers' abilities to:

1. *Deliver public health genomics capacity guided by a clear, prioritised, long-term strategic plan.* Priorities will need to reflect and reconcile the interests of the scientific community, citizens and patients, and be aligned to the long-term priorities of governments and public health decision makers across the four nations of the UK.

2. *Maintain momentum, motivation and goodwill to support a network that can bring together diverse organisations across the four nations without over-reliance on goodwill alone.* Long-term funding and sustaining committed leadership will be critical. A workforce development strategy that considers novel career pathways in PHAs and academic settings will be needed, alongside an existing or novel convening structure that can ensure a coordinated national approach as well as respond to the devolved nations' unique local needs.

3. *Ensure the involvement of all relevant actors.* COG-UK mobilised the engagement of researchers, PHAs and NHS sites across the country. As the consortium morphs into a legacy structure (closure date 31 March 2023), it may need new expertise, e.g., bringing in private sector partners to link genomics research with medical innovation, international expertise, patient and public engagement and additional involvement from the NHS to extend the role of pathogen genomics in the NHS.

4. *Stabilise and ensure adequately funded governance, management and administrative arrangements to support networked pathogen genomics capacity in the UK.* Attention should be given to where, and how far, elements of COG-UK governance that enabled rapid delivery, minimal bureaucracy and novel practices co-existing with established institutional governance and management systems, may be adaptable to future efforts. Academic researchers will require requisite independence but governance must also support synergies and ensure a shared sense of purpose across research and sequencing services informing public health.

5. *Advance data linkage in the public health landscape.* Access to linked data sets will be fundamental to understanding the relationship between infectious agent

genetics and behaviour on the one hand and disease severity and patient outcomes on the other. It will also underpin efforts to inform the development and evaluation of medical innovations. Wider collaboration between actors in the UK's public health and health data landscape will be needed.

6. *Ensure a sustainable division of labour between diverse stakeholders in the public health genomics landscape.* Attention must be paid to ensure the sustainability of the workforce required to service routine sequencing needs in PHAs and to ensure that trained research talent is not lost from academic settings. Considering what may be different in terms of workforce needs if COG-UK (or its legacy) were to tackle other infectious diseases or public health challenges will also matter.

7. *Revisit the UK's role in the global pathogen genomics landscape.* COG-UK members' expertise impacted international public health genomics efforts and there is further potential to develop COG-UK as a global training resource and expertise sharing network. At the same time, COG-UK is largely built on UK data, and a future legacy effort would benefit from an explicit focus on integrating international experiences and embeddedness in coordinated global efforts.

References

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