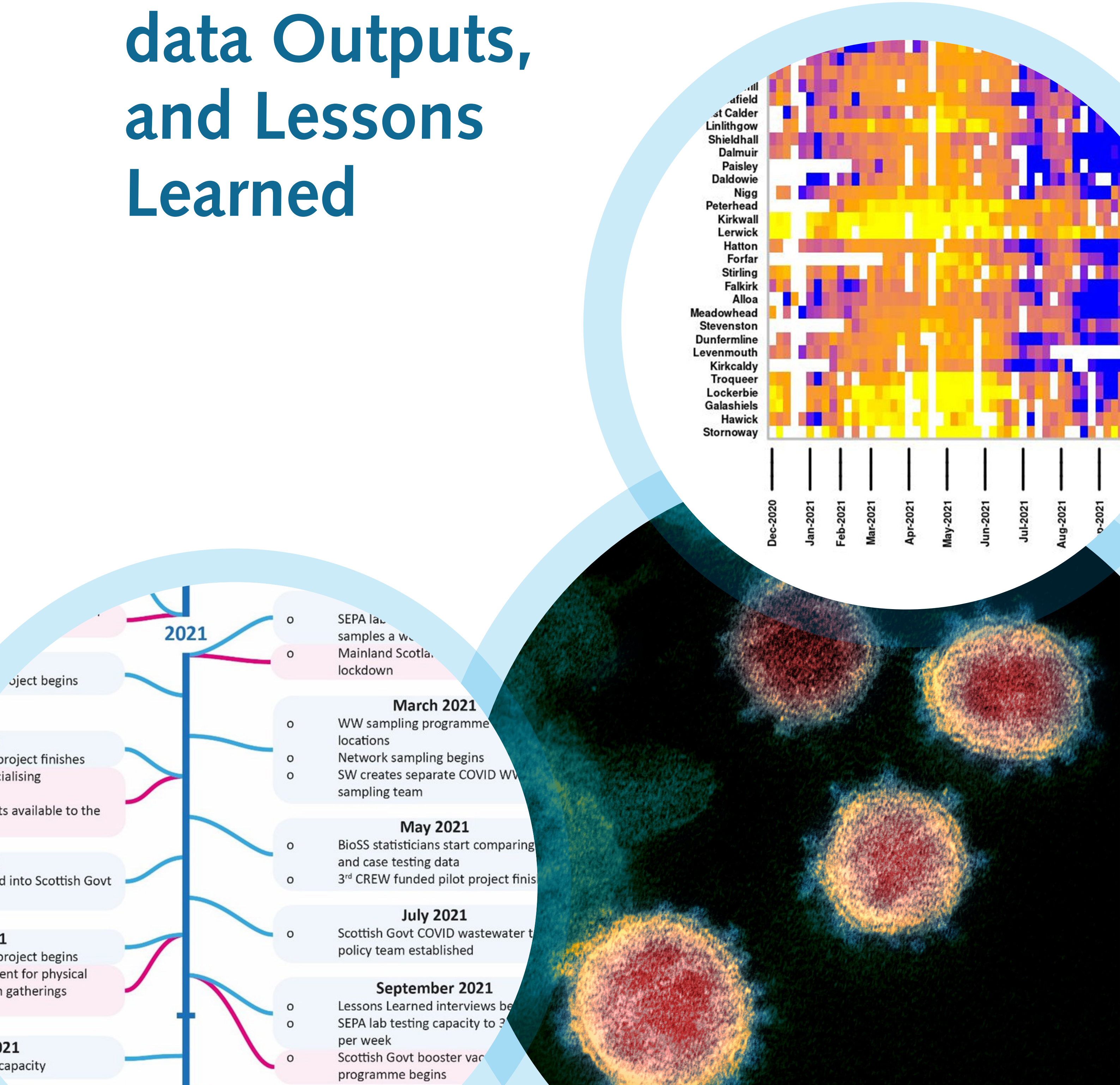
CENTRE OF EXPERTISE FOR WATERS

SARS-CoV-2 monitoring in Scottish wastewater: Variant Detection, FAIR data Outputs, and Lessons Learned



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Author biographies

Dr Isabel Fletcher is an experienced interdisciplinary social science researcher who has worked on a range of topics spanning health and environment including obesity, sustainable diets and food security. As part of this work, she has conducted many interviews with researchers, policymakers and members of the public. She has a background in the history of public health, and her research focuses on the ways in which evidence is used in the development of public policy.

Nick Gilbert is a Principal Investigator and Professor of Molecular Biology at the MRC Human Genetics Unit at The University of Edinburgh. His research group uses biochemistry and genomics to investigate how DNA is folded inside mammalian cells and to understand how this regulates cellular processes in health and disease. Much of Nick's research is interdisciplinary working closely with teams in physics and chemistry. This experience enabled his group to pivot their expertise to evaluating the prevalence of SARS-CoV-2 in patient samples and wastewater during the COVID pandemic.

Catherine Lyall has held a Personal Chair in Science and Public Policy at the University of Edinburgh since 2013. Professor Lyall is an experienced science policy researcher and evaluator of knowledge exchange and interdisciplinary research activities who consults for public bodies and universities including the UK Economic and Social Research Council (ESRC), Scottish Funding Council and the European Commission. She is regularly invited to advise on, and give international lectures about, the management and conduct of interdisciplinary research.

Dr Tomasz Zieliński manages a BioRDM team at the School of Biological Sciences at the University of Edinburgh. BioRDM main mission is to help researchers incorporate effective data management strategies into their daily research workflows. He has released various software related to biological data management and he has evaluated multiple platforms for sharing and organizing biological data. He has advocated for Open Research and adoption of FAIR principles, he created open teaching materials and delivered multiple workshops in the area of good data management practices.

Contents

Executive Summary

Background

The virus that causes Covid-19 disease, SARS-CoV-2, is excreted by infected people into the sewage system. Genetic material from the virus can be detected in wastewater (WW) samples that are collected before treatment in WW plants. The Scottish Government and its agencies have monitored SARS-CoV-2, in WW from June 2020 to the date of this report and continue to do so. This CREW research project built upon the programme of monitoring for SARS-CoV-2 in Scottish WW, which had been active for over a year when this project started.

Research objectives

1. **A method to detect variants of the SARS-CoV-2 virus in wastewater (see section 2).**

   The laboratory test used in Scotland since 2020 tested the total amount of SARS-CoV-2 viral material in WW samples, without distinguishing between the variants of the virus. This research objective aimed to test which variant(s) were present in the WW samples, which required different laboratory techniques. Trials of three alternative methods were commissioned from molecular genetics researchers at the Institute of Genetics and Cancer, led by Prof. Nick Gilbert.

   The research project was not tasked with nationwide monitoring. In response to the wave of the Omicron variant in December 2021, however, the researchers agreed to and delivered variant detection in WW across Scotland for six months.

2. **Sharing outputs from the wastewater monitoring programme by Open Research methods (see section 3).**

   The SARS-CoV-2 WW monitoring programme focused on delivering results for immediate use, reporting to Scottish Government and to the public. This research objective aimed to identify, prepare and share other technical products from the programme for different audiences, particularly researchers and other practitioners. The Biological Research Data Management team (Bio_RDM) led by Dr Tomasz Zielinski was commissioned to share the programme's outputs using the best Open Research practices of the scientific community.

3. **Lessons Learned from the development and management of the programme (see section 4).**

   Monitoring SARS-CoV-2 in WW was a new capability, developed and delivered by people and organisations working in a new partnership, under time and budget pressure. The success of the programme depended upon the ways that they worked together, as well as on the technical sampling, testing and reporting methods. This research objective aimed to identify and document the working methods, structures and interactions that contributed to this partnership in Scotland, analysing aspects of the programme that had been successful and where improvements might be made in future. The technical capabilities of the programme were not the focus here. Social scientists Dr Isabel Fletcher and Prof Catherine Lyall from Science, Technology and Innovation Studies (STIS) were commissioned by CREW to gather and analyse this information, to compare the experience in Scotland with other countries, and to infer any general lessons and recommendations for Scottish Government and its agencies in delivering future, urgent programmes.

Research undertaken

1. The 'Variant Detection' research project tested three lab methods, quantitative Reverse-Transcriptase Polymerase Chain Reaction (qRT-PCR or qPCR), digital droplet PCR (ddPCR or dPCR) and 'next generation' DNA sequencing. A sequencing-based method was implemented for nationwide monitoring in an extension to the research that also involved data scientists from Biomathematics and Statistics Scotland (BioSS).
2. The 'Open Research' team trained the laboratory researchers in Open Research methods; prepared laboratory notebooks and the protocols for laboratory and analytical methods; compiled a reference set of the monitoring data up to February 2022, along with visual displays of those data; and shared these new outputs from the programme.
3. The 'Lessons Learned' research interviewed 41 participants in the programme (see section 4.2 for study design); reviewed documents from the Scottish and international SARS-CoV-2 WW monitoring programs; and analysed the interview transcripts and documentary evidence (see appendices 2-4).

Results

1. DNA sequencing was the best method to detect SARS-CoV-2 variants in WW. The research team delivered variant detection from WW across Scotland for six months, capturing the spread of the Omicron variant from December 2021 and the BA.2 variant in the Spring of 2022, and refined detection methods in the process.

2. The Open Research team shared the programme's technical outputs in six different ways, online and in person, with a web Homepage linking to all the resources. Open Research methods for particular outputs and particular audiences promise to deliver further value from the investment in this and similar programmes. This project found that there is still a knowledge gap regarding FAIR data management practices, among both academic and non-academic partners. Training and further adoption of such practices could streamline the delivery of future projects and increase their long-term impact.

3. The Lessons Learned research found that the Scottish SARS-CoV-2 WW testing programme was an impressive achievement: a nationwide surveillance programme for a novel organism was developed collaboratively from a "standing start" in less than six months. This success was due to a combination of high-level support from key individuals within relevant organisations and the hard work and motivation of those working on the project. However, after this impressive start, the programme encountered some organisational issues that made the transition from innovative research to a routine testing programme challenging (even taking account of the accelerated timescales involved).

Recommendations

1. DNA sequencing data will likely be a valuable input to Scottish policy post-Covid-19, for example in monitoring other pathogens or Anti-Microbial Resistance genes, both in WW and in other environmental samples. Significant technical expertise is required to establish and adapt the laboratory and bioinformatic analysis methods, which are both areas of rapid innovation. This might best be delivered by a partnership of delivery agencies and molecular genetics researchers.

2. Future partnerships should establish a shared data resource early on, with support for good data management from the start, to assist both programme delivery and dissemination of outputs.

The key recommendations from the Lessons Learned review are:

3. Stronger cross-government and inter-agency links among those working in the environment and health sectors are needed to tackle future crises. Some of these recommendations address how to support those links.

4. 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.

5. 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.

6. The Scottish Government should establish a new post of Chief Scientist for Public Health to better represent the Scottish Public Health community in light of increasing need to focus on "One Health" strategies. The review findings indicate that neither the Chief Scientist (Health) nor the Chief Medical Officer currently represent or provide sufficiently high-profile leadership for the Scottish Public Health community.

7. 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.

8. 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.

1. Introduction

1.1 Background and scope

The Scottish Government and its agencies invested over £4M in monitoring of the virus that causes Covid-19, SARS-CoV-2, in WW over the interval March 2020-March 2022 (including this research project). The technical methods, outputs and working practices of this Scotland-wide programme are introduced in the subsequent sections of this report. The programme was established very rapidly in early 2020, in response to the exceptional situation arising from the novel coronavirus (SARS-CoV-2) pandemic. The creation of the SARS-CoV-2 monitoring programme was aided by the existence of a robust environmental monitoring framework operated by The Scottish Environment Protection Agency (SEPA). Together with Scottish Water, SEPA have been monitoring the levels of SARS-CoV-2, the causative agent for Covid-19, in WW across Scotland since mid-2020. The primary objective of the programme was to provide an overview of the epidemic, to inform health boards and policy makers. Timeseries data relating to SARS-CoV-2 prevalence have been disseminated to project stakeholders, mainly in the form of analytical reports prepared by BioSS (Biomathematics and Statistics Scotland) for Scottish Government, and data released publicly via the SEPA and Public Health Scotland (PHS) online dashboards. Modelling based on WW monitoring data is used by the Scottish Government to estimate the prevalence of infection, and the reproduction number (R value). WW data therefore provides estimates of these values that are independent of other data types. These estimates are combined with others to provide the best overall estimate of prevalence and R, at the Scottish and UK levels.

Funding from the Scottish Government's RESAS research programme, managed by CREW, has played a key role in establishing the programme. This project represents the next stage in these research contributions. Separate CREW projects have previously been developed (with final reporting dates and links to the project reports):

- A laboratory test for the total abundance of the virus in WW, technically a qRT-PCR assay for viral genetic material. This test formed the basis for the national monitoring programme from June 2020 to date (Tracking SARS-CoV-2 via Municipal Wastewater, Corbishley et al., 2020).
- An innovative approach to sample aerosols in sewage pipes instead of the sewage. This approach was further developed with UK Government funding (Aerosol/droplet sampling of wastewater for SARS-CoV-2, Gormley et al., 2021).
- A review of the potential applications of the WW-Based Epidemiology (WBE) approach beyond the Covid-19 pandemic, to further detect pathogens, illicit drugs and other chemicals (Review of wastewater monitoring applications for public health and novel aspects of environmental quality, Sims et al., 2021).

The epidemic has been driven by the repeated emergence and spread of viral variants. Variants of SARS-CoV-2 had been detected in WW elsewhere from mid-2020, including in England. There was no available capacity to do so routinely from Scottish WW samples. The laboratory tests for variants are different from the established test for total viral abundance, and several approaches had been reported. The development of a new laboratory testing programme was required, in order for Scotland to derive this additional benefit from the existing investment in sampling and extracting viral material from Scottish WW. The first objective of the present project was to provide a workable, testing process for variants, similar to the first CREW project's contribution to testing for viral abundance. This advance in testing was actually deployed, by the same researchers, to test for SARS-CoV-2 variants from December 2021 to May 2022.

Establishing the SARS-CoV-2 WBE programme required both technical and organisational innovation at pace, expanding and adapting the programme to the limit of the participants' capacities. There was little or no time to work on gaining the best value from the programme's technical outputs or learning from its management and organisation. Both were relevant to the many other countries that face identical challenges, and to inform the best future uses of WBE in Scotland. This opportunity informed the second and third objectives of the present project. Note that the work for these objectives focussed on the initial stages of the WW programme in Scotland, from June 2020 to February 2022, very largely before the results of objective 1 were informing the programme.

This project aimed to build on the current WW monitoring for SARS-CoV-2, to develop a process for variant monitoring, and to capture, curate and report the programme's technical outputs and organisational learning. This project was again conducted under some pressure, from the evolution of viral variants, and also because some participants who were temporarily seconded to the programme were returning to their prior work, taking their technical and management knowledge with them.

1.2 Structure of the report

The remainder of this report is organised into four further sections. Section two details the steps taken to adapt and assess laboratory genomics methods to detect SARS-CoV-2 variants in WW samples. In the third section, the actions taken to validate, store and ensure maximum access to project bioinformation data are discussed. In section four, a detailed review of the formation and operation of the SARS-CoV-2 WW testing programme and key lessons to inform future urgent responses to health and environmental crises are presented. Finally, overall project conclusions and recommendations are detailed in section five.

1.3 Project objectives

1. Variant detection: develop a laboratory test to detect previously identified variants of SARS-CoV-2 in WW. Note: the project was not tasked with delivering the nationwide monitoring but aimed to ensure that the output of the research project would best inform a national programme for variant monitoring.
2. Open Research: identify, curate and share technical products from the SARS-CoV-2 WBE programme, such as laboratory protocols, data analysis programmes and data compilations. Dissemination should be aimed at a range of users, particularly researchers and WBE practitioners.
3. Lessons Learned: capture and document the working methods, structures and interactions that contributed to the SARS-CoV-2 WBE programme in Scotland, providing analysis to infer any general lessons and suggestions on how these might contribute to future, urgent programmes.

2. SARS-CoV-2 variant detection in wastewater samples using qPCR, dPCR and next generation sequencing

Author: Nick Gilbert

2.1 Introduction

The team was tasked with developing an assay to quantify SARS-CoV-2 variants in WW samples. Gold-standard PCR assays use a TaqMan based approach. Previously, the approach was optimised for analysing SARS-CoV-2 in RNA samples extracted from VTM (viral transport medium) (Reijns et al., 2020) and saliva (Dixon, Hurd et al., in prep). Essentially, TaqMan uses a pair of PCR primers flanking a probe that is fluorescently labelled. As the PCR reaction proceeds, the fluorescence in the reaction increases, providing an accurate read-out indicative of the concentration of the DNA of interest.

Prior to the start of this project, the Gilbert team had developed and optimised TaqMan assays for the N1, N2 and E genes of SARS-CoV-2 and also developed a TaqMan assay for the S gene which, was found to have approximately 4 x less sensitivity than the N1, N2 and E gene assays. This is consistent with reports in the literature that have suggested that S-gene based assays are less successful than for other SARS-CoV-2 genes. As many of the discriminating mutations are in the S-gene, this does have an impact on designing assays that can discriminate between the variants.

Mutations that discriminate between the different SARS-CoV-2 lineages, or variants, are often found in the S-gene. Most mutations are single nucleotide changes although there are some that are small deletions. In terms of assay development, discriminating single nucleotide changes are most challenging, two nucleotide changes and then deletions are easier to discriminate. TaqMan detection probes also need to have lower melting temperatures than the flanking PCR primers, depending on the DNA sequence, this can make it difficult to design suitable probes/primers for all parts of the virus genome.

In this project, an exhaustive analysis of different primer/probes was not undertaken but instead some potential candidates were selected for proof of principal testing. Probe sequences were also sourced from Bangor University, other collaborative partners, and commercial probes from ThermoFisher.

Although qPCR is a gold-standard technique for detecting RNA/DNA, other methodologies have been developed for quantification, in particular digital PCR (dPCR). Digital PCR uses the same experimental rationale but is more quantitative because each amplification reaction is sequestered in an individual lipid droplet, and each positive droplet is counted, hence "digital". In theory, this enables better quantification of different variants or the appearance of a new variant in WW samples.

Finally, the team, with advice and support from other research groups around the UK, have investigated the use of next generation DNA sequencing (NGS) to identify and quantify coronavirus variants.

This project started in July 2021 and at that time, the predominant variant was Delta (Fig. 1 below, Hodcroft, 2021, https://covariants.org/). The team, therefore, also used 'historical' samples, collected from January 2021, to test different assays' ability to detect other variants. Optimised methodologies were then tested in real-world samples from early December 2021 when the Omicron variant rapidly spread across the UK.

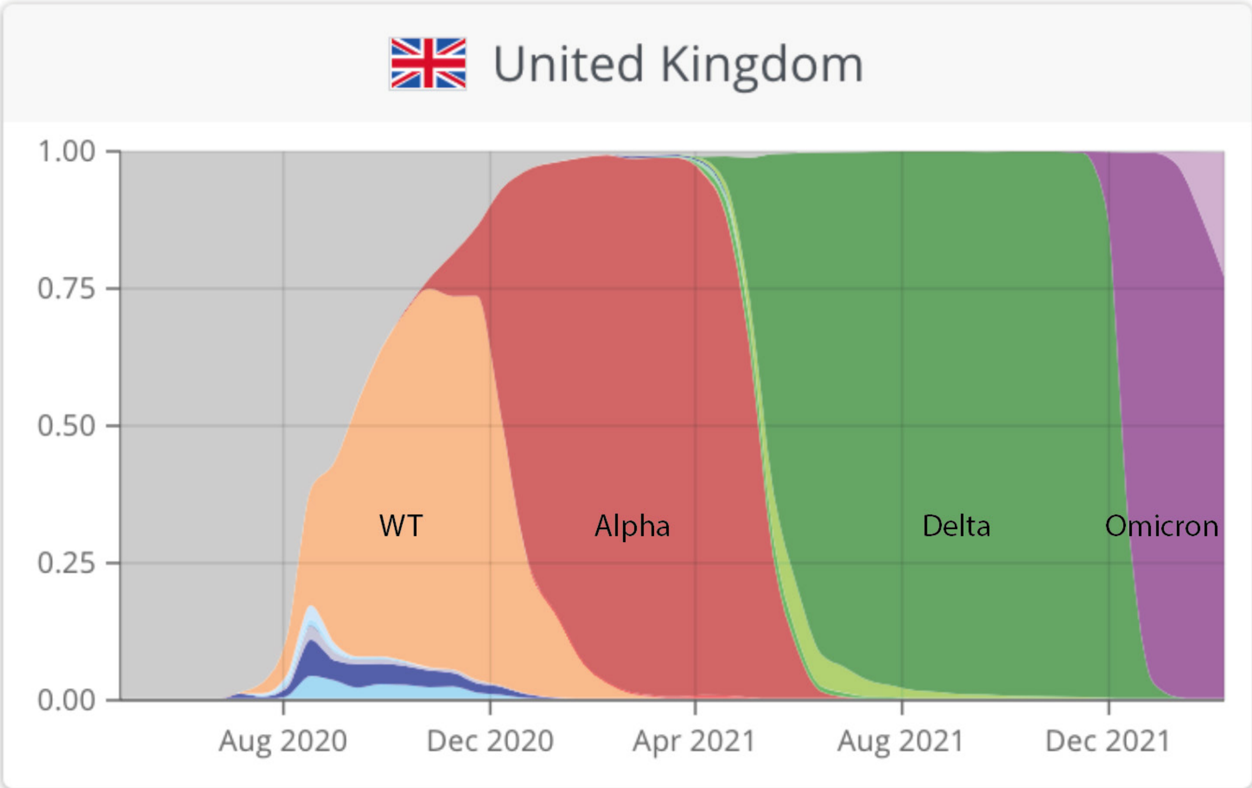

Figure 1. Appearance of SARS-CoV-2 variants in the UK as a proportion of sequences over time (image from https://covariants.org/).

2.2 Summary of laboratory methods and results

WW is a complex substrate for detecting viral RNA (vRNA) and samples were processed as follows; after WW collection by Scottish Water, the samples were concentrated, and RNA extracted by a research team at SEPA (protocols linked from https://covid-ww-scotland.github.io). RNA samples were then used to develop variant detection assays by Edinburgh University as described below. In addition, historical WW samples, with limited meta data, were provided by Exeter University for detection assay development for earlier variants. Firstly, the Edinburgh team used molecular biology approaches to estimate the integrity of SARS-CoV-2 in RNA samples provided by SEPA. There was clear RNA degradation but reassuringly there was sufficient material to potentially enable variant detection.

Based on the authors' previous studies detecting SARS-CoV-2 in saliva, experiments established a protocol for amplifying viral RNA from WW. The methodologies and enzymes used showed that, in principle, vRNA could be detected in WW samples. However, it was very challenging to estimate the absolute sensitivity of the approach as no gold-standard WW samples were available. However, by taking different RNA samples extracted by SEPA and UK Health Security Agency (UKHSA) at the height of the pandemic, most samples were positive for SARS-CoV-2 RNA, albeit towards the limit of detection for the assay (RT-qPCR).

Proof of principle studies showed that the Edinburgh team were able to identify SARS-CoV-2 RNA in WW, but the aim of this programme was to discriminate between different SARS-CoV-2 variants. To achieve this, the team examined the mutation spectrum of SARS-CoV-2 and designed primers that could discriminate between variants. Diagrams showing the mutation spectrum of different SARS-CoV-2 variants are shown on the following pages with primer and probe sequences tested for identifying variants (Fig. 2). In parallel, primers and probes were purchased from commercial sources and from collaborators at Bangor University (high level information shown for example).

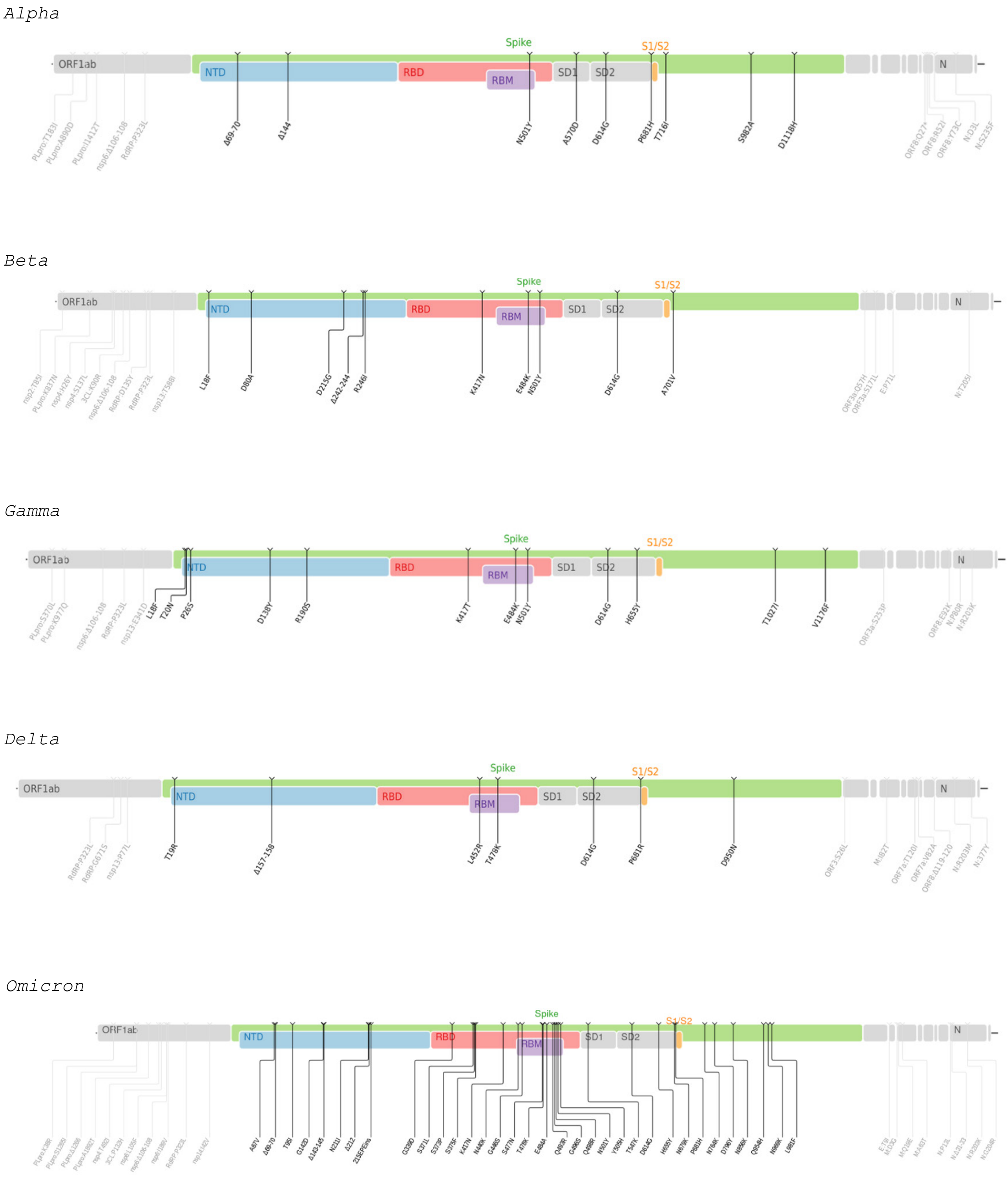

Figure 2. Schematic diagrams showing different SARS-CoV-2 variants and their spectrum of mutations.

2.2.1 Optimisation of primers for variant detection

To test the specificity of variant detection, primers and probes were optimised using synthetic RNA templates that were a mix of wild type (WT) and mutant sequences. Examples of primers for the Alpha and Beta variants are shown below.

The approach used by the Gilbert team for primer/probe design was to try a number of different primer/probe combinations and test them on synthetic samples. Some primers/probes were found to be reliable at discriminating between different variants, however this was very dependent on how dissimilar the variants were between samples. The disadvantage of this approach is that it is very time-consuming, and success is not guaranteed. It is also relatively slow (approximately 2 weeks) between designing new probes and for these to be manufactured for testing in the labs. This reduced the ability of the lab to start identifying new variants in WW in a short period of time.

Although probes were developed that could discriminate between variants in synthetic samples, the team struggled to measure the levels of different variants in WW. This experiment was undertaken by mixing together WW samples from August 2021 (containing mainly Delta) with samples from January 2021 (containing mainly Alpha) and asking if it was possible to measure different levels. From this experiment, it was concluded that assays could be developed for identifying the individual variants if they constituted more than 25% of the samples, but below this the results were extremely variable, providing little confidence in the assay. In addition to designing assays, commercial assays were tested. Some of these worked better than in-house assays which is believed to be a reflection of the many different probe/primer combinations the commercial supplier will have tested. The Gilbert team co-ordinated and shared primer/probe sequences with Bangor University. Their experiences were similar to the Gilbert team: it is possible to detect specific variants if good assays can be developed, but for some variants this can be very challenging. It should

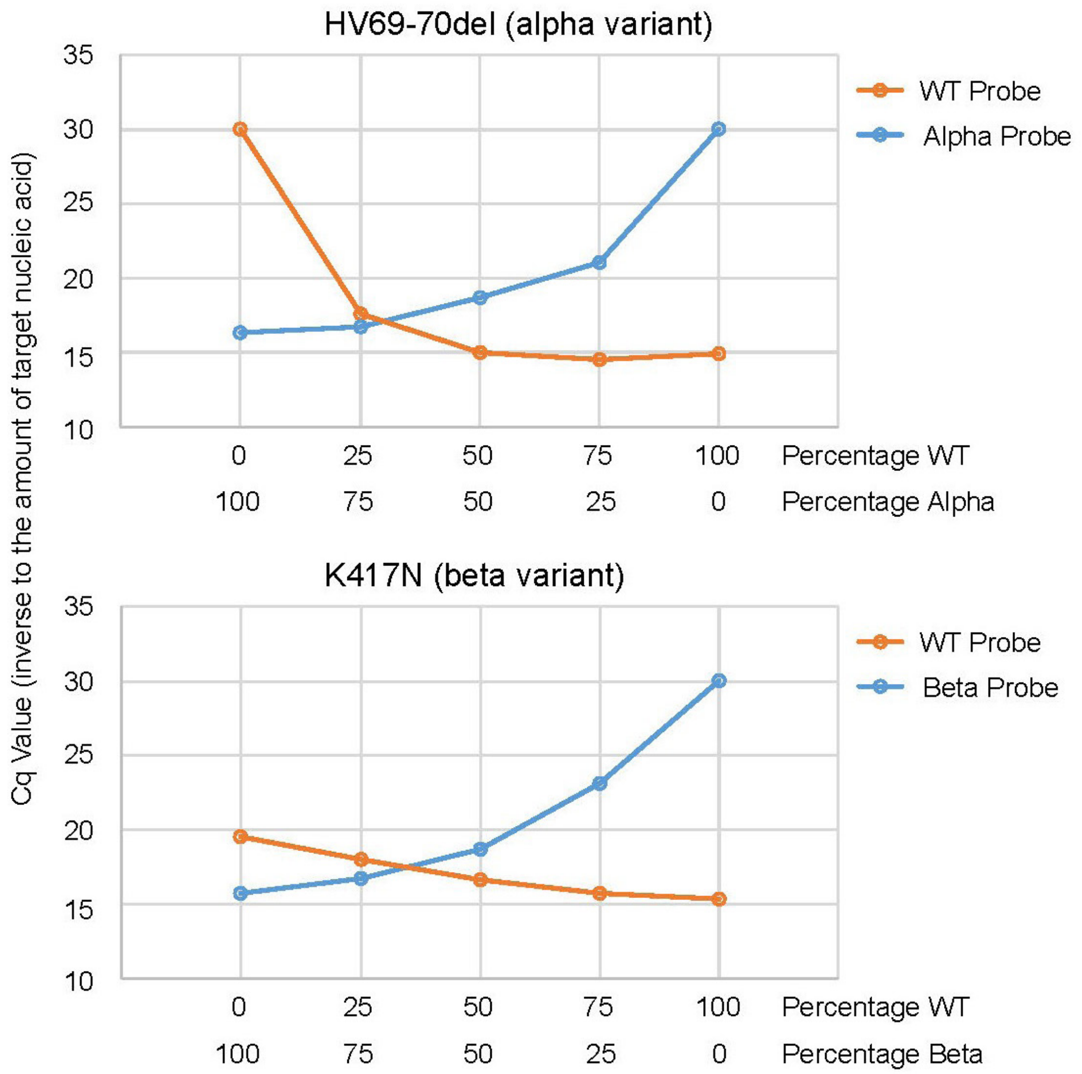

Figure 3. qRT-PCR assay to discriminate between WT and alpha (top) or beta (bottom) SARS-CoV-2 variants. Synthetic RNA templates were mixed at molar ratios of 100:0, 75:25, 50:50, 25:75, 0:100 (WT vs variant).

be mentioned that this becomes more challenging as WW samples contain a mix of variants that are all themselves mutating, and therefore different primer/probe combinations struggle to discriminate between them (see Section 2.2.4 for mutations in sub-variants).

2.2.2 Digital PCR

In parallel to using qPCR the team has tested digital PCR for quantifying WW variants. Digital PCR (dPCR) worked well for discriminating between synthetic viral variants that were present at high concentrations in samples, but the team consistently found that dPCR was less sensitive than qPCR. This is coupled with the assay taking longer to setup and that fewer samples can be analysed at once. For example, a single operator with one manual dPCR machine, can analyse only 32 samples every four hours, for a single variant. Although work is ongoing, the Gilbert team has struggled to get reliable results from dPCR on some samples that were successfully analysed by qPCR or sequencing. The team believe this is a combination of the assay being less sensitive and because detergents in these WW samples prevent the formation of oil/water emulsions that dPCR uniquely requires.

The Gilbert team (Section 2.2.3) has now analysed many WW samples by next generation sequencing (NGS). In future it would be an interesting comparison to re-test these samples using qPCR/dPCR to establish if these methods have utility for detecting variants. It does need to be highlighted though that a significant disadvantage of PCR based methodologies is that the variant has to be known in advance and for it to be possible to design an assay to detect it. An additional disadvantage is that each qPCR or dPCR assay can only discriminate between two variants at once. In theory, it is possible to multiplex PCR assays, but in the experience of the Gilbert team, this reduces sensitivity which is unacceptable for analysing already difficult samples such as WW.

2.2.3 Next generation sequencing (NGS)

In parallel to using qPCR and digital PCR, the team have developed NGS methods for analysing SARS-CoV-2 variants in WW. The advantages of this approach are that it is unnecessary to make a priori assumptions about the presence of mutations and that new variants can be identified in samples de novo. Little material is required for characterising the spectrum of variants, however, there are also disadvantages. The laboratory methods are challenging and time consuming. It takes at least 4 days for results to be generated from a WW sample, and then the information needs to be analysed by a bioinformatics

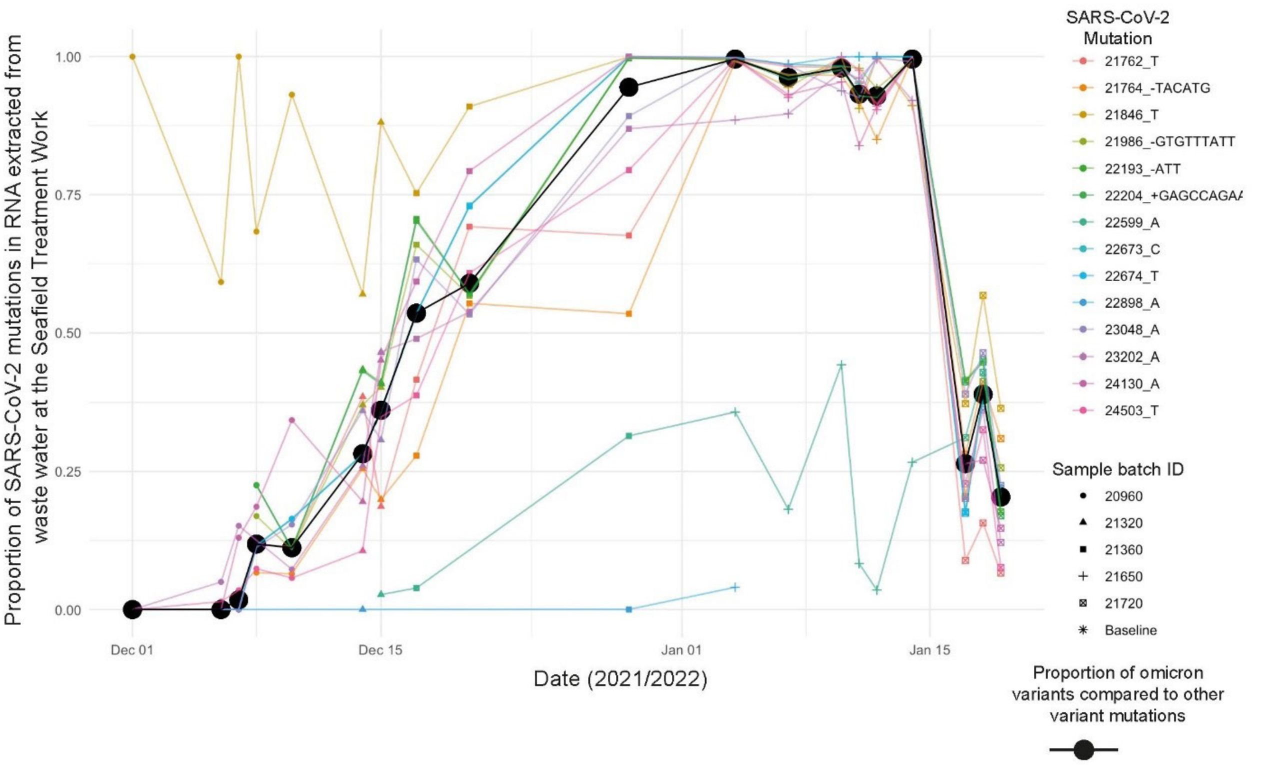

Figure 4. Time series data showing the emergence of the SARS-CoV-2 Omicron variant in WW samples from Seafield WW treatment works from 01/12/21 – 15/01/22. Coloured lines show information for different mutations, different symbols correspond to different sample batches. Black line shows the proportion of Omicron variants to other SARS-CoV-2 variants observed in all samples.

team. However, the information provided is extremely rich and can be analysed in multiple different ways.

Different strategies can be used for analysing SARS-CoV-2 in WW. The team tried several different approaches before settling on one using reagents from New England Biolabs (NEB) and a set of primers designed by Terry Burke's team in Sheffield. Initially primers were optimised for the Delta variant, but after the appearance of the Omicron variant the primers were redesigned to account for the large number of additional mutations in the Omicron spike gene. The primers designed by the Sheffield team were optimised for analysing partially degraded samples, such as WW. They are also compatible with very high throughput next generation sequencers, such as a NovaSeq™.

In the first instance, the Gilbert team optimised lab methods for analysing the coronavirus sequences taken from positive individuals, as part of the University of Edinburgh TestEd programme. This enabled the bioinformatic team, in collaboration with Biomathematics and Statistics Scotland (BioSS), to design a computational pipeline to identify individual SARS-CoV-2 variants. Since optimising the methodology, the research team has analysed over 2000 WW samples from across Scotland and used this information to monitor the spread of the Omicron variant, for example at the Edinburgh Seafield Wastewater Treatment Works (Fig. 4).

2.2.4 Next Generation Sequencing – Bioinformatics analysis

There are several different approaches for analysing next generation sequencing data. The method developed by the Gilbert team is a pragmatic one that focusses on the characterisation of amplicons that contain discriminating variants. This is most clearly seen in an example, with information taken from the GISAID data sharing initiative (www.GISAID.org). Where the sequence differences between variants have been reported (Fig. 5), the differences between the variants can be seen with the stronger the colour, the more frequent that mutation is found in that variant. Since the appearance of the Omicron variant there have now been a series of sub-variants identified (e.g., BA.1, BA.1.1, BA.2, BA.3). These have very similar sequences but there are some differences that can be discriminated by next generation sequencing (Fig. 5, lower diagram). The latest Omicron variants (BA.4 and BA.5) have fewer mutations in the spike protein making it difficult to discriminate these variants with such high confidence.

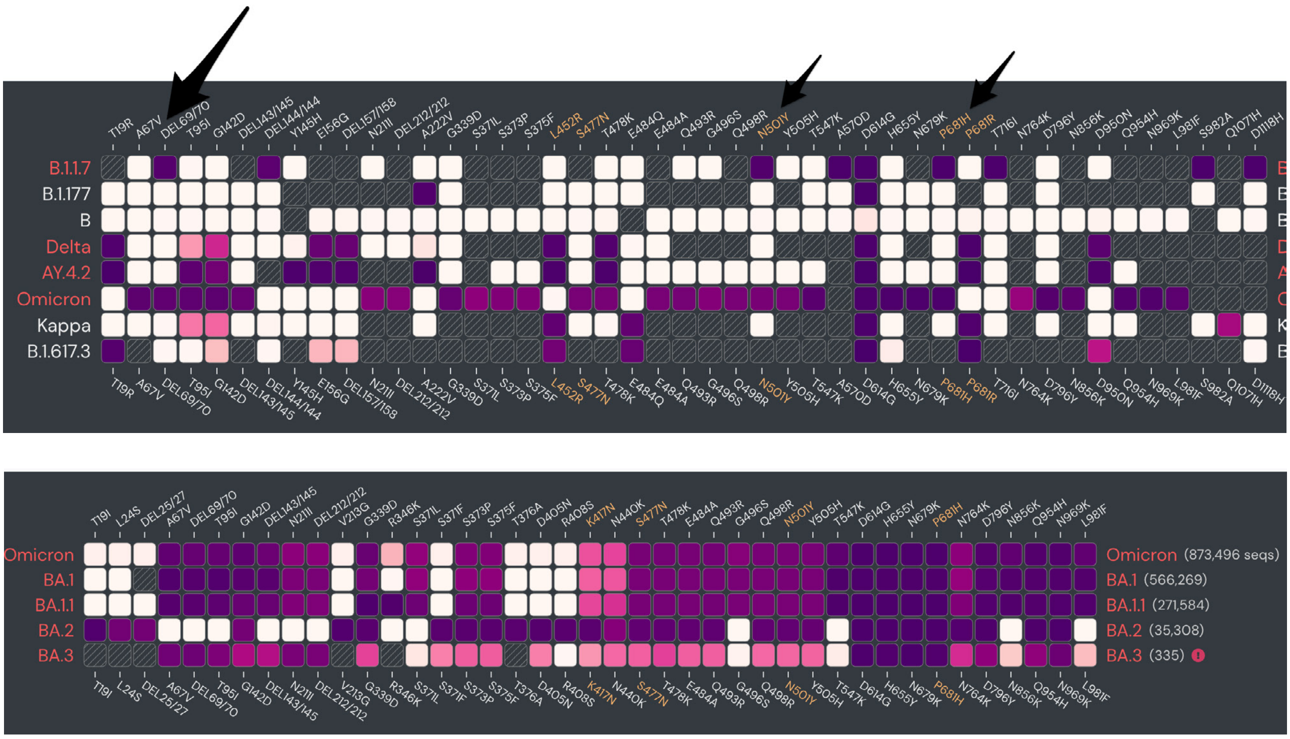

Figure 5. Heatmap diagrams showing the differences in mutations between variants as colour intensity. Lower diagram shows sub-variants of Omicron variant (images from www.GISAID.org).

2.3 Conclusions

The Gilbert team's experience of running the University of Edinburgh's TestEd programme (https://www.ed.ac.uk/tested-covid) provides expert insight into the practicalities of analysing WW samples compared to testing unique human samples isolated from saliva. In the TestEd programme, samples are analysed by qPCR, analogous to how SEPA quantifies SARS-CoV-2 RNA in WW samples. In addition, early in the pandemic some saliva samples were analysed using SARS-CoV-2-variant specific PCR, but as variants became more complex, all Covid positive samples were also analysed using sequencing to identify the exact variant. Based on that experience and the preliminary results in this project comparing genotype-specific qPCR, dPCR and targeted sequencing in WW samples, it is possible to contrast analysing pure saliva samples with complex and heterogenous virus mixtures that are found in WW samples.

In conclusion, dPCR is more quantitative than qPCR, but the sensitivity is lower than qPCR. Although methods can identify SARS-CoV-2 RNA in WW, it is difficult to quantify variants or observe low levels of different variants. This is also dependent on the mutation spectrum that discriminates between variants. In contrast, next generation sequencing is more agnostic and merely reports the information present. However, undertaking the experiments and analysing the data is not trivial and requires a highly trained laboratory and bioinformatics team.

For the TestEd programme, primer designs that were previously published by US Centres for Disease Control (CDC) were used for quantifying total SARS-CoV-2 RNA levels, similarly SEPA use pre-designed assays. A disadvantage of using PCR-based approaches for variant analysis is the need to design, test, and optimise new primer/probes for each new variant. This requires a high level of experience and time that is not typically available in routine testing facilities, but even in an academic research lab there were some variants where it was not possible to design a suitable assay to discriminate between variants. Another consideration is that every new variant will require a different test, which would be very challenging when, for example, new Omicron variants are frequently appearing.

There are cost considerations with NGS. High-capacity NovaSeq™ is currently being used that can analyse 800 samples at once which reduces the cost per sample to approximately £10 (as of March 2022). Results for sequencing this number of samples would take about 4 days to generate, whilst to analyse a similar number of samples for three variants using a dPCR based approach would take up to 10 days.

In summary, NGS provides significantly more information than qPCR or dPCR and has the potential for analysing multiple pathogens simultaneously providing valuable data for public health purposes. In preparation for this, the Gilbert team has undertaken pilot experiments to measure the level of influenza in WW.

Over the past 12 months, a close relationship between SEPA, Public Health Scotland (PHS), BioSS and an academic molecular biology research facility has been crucial for the success of the programme. This is because all partners can contribute different skills and in the case of the University of Edinburgh (UoE) there is significant critical mass to support this type of complex testing. This is exemplified by UoE having access to the Edinburgh Genomics world-class sequencing facility, bioinformatics support, and molecular biology skills. This combination of skills, expertise and facilities may be difficult to find in a routine testing lab for an ongoing SARS-CoV-2 WBE testing programme, at this present time. The strength of the sequencing methodology is the ability to test for different microorganisms at different times, but this necessitates experience in developing new assays, interpreting new data, and reporting different types of results.

3. Open Research

Authors: Livia C. T. Scorza, Sumy V. Baby and Tomasz Zieliński

3.1 Introduction

This project targets different users with different applications, compared to the outputs from the original SARS-CoV-2 WW monitoring programme, using the Bio_RDM team's expertise in data curation to gain further value from the programme's outputs. The programme's data and protocols have broad potential, for example, the methodology for SARS-CoV-2 detection developed for SEPA could be adopted by other institutions or modified to monitor different pathogens. The virus prevalence data itself could be used to develop new epidemiological models or cross-referenced with other sources of population-level data, to infer the robustness of this novel, national programme of SARS-CoV-2 WW-based epidemiology. Moreover, longitudinal, geospatial data are costly to obtain – especially taking into consideration the logistics of collecting physical samples – and thus, warrant appropriate preservation strategies.

The circumstances of the current epidemic and its management are changing continuously. National-scale SARS-CoV-2 WW monitoring ended in England in March 2022. It is therefore possible that the monitoring programme will be terminated once Covid-19 becomes an endemic infection. In such a scenario, resources can be restructured or taken offline, so the accessibility of the programme's outputs and data risks deteriorating over time.

The main objectives of the SARS-CoV-2 WW Open Research project are:

- To secure wide and ongoing, future access to the project outputs up to February 2022.
- To ensure that the outputs are ready for re-use, by adhering to FAIR data principles.
- To consider the processes of data management in the current and potential future programme.

'FAIR' stands for Findable, Accessible, Interoperable and Reusable. FAIR principles mean that research data outputs are assigned unique digital identifiers that can always be resolved to their current internet locations ('persistent identifiers'); that they can be accessed using standard web protocols; that they are stored in open, common file formats; that they are thoroughly described in line with best practices. An additional benefit of providing FAIR outputs is that they are citable so that their re-use can be properly credited, and their impact can be measured with metrics like the number of downloads or views.

The target audiences for open outputs comprise future researchers (experimentalists, modellers, statisticians), teachers (academic and non-academic), institutions that are interested in evaluating the methodology (for example, in designing future programmes), or practitioners of citizen science.

3.2 Results

The Bio_RDM team worked closely with the staff at SEPA and in the Gilbert team (University of Edinburgh), whose engagement was essential to the success of this work and provided training on data management and sharing. This report covers the stable, qPCR-based process for monitoring SARS-CoV-2 prevalence and the preliminary results from the equivalent work for the evolving, sequence-based detection of variants.

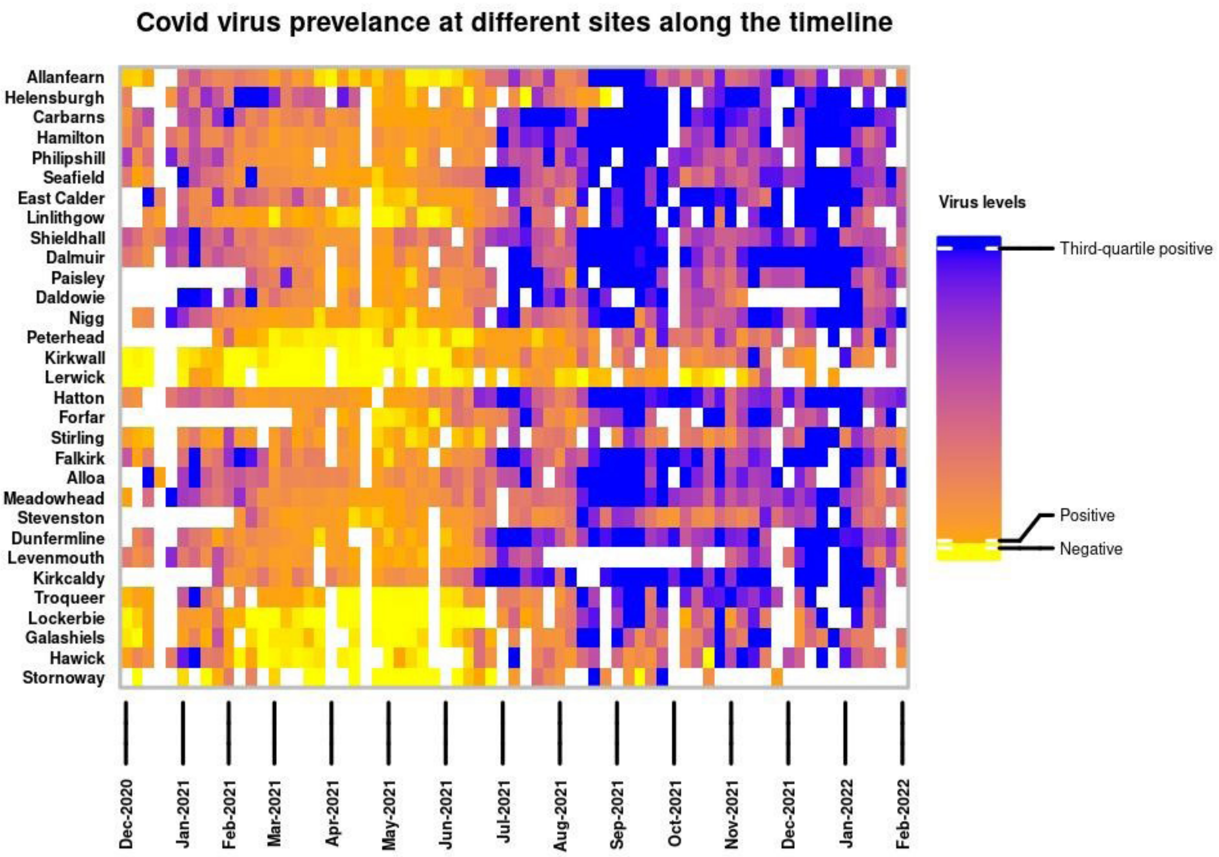

Figure 6. Heatmap showing SARS-CoV-2 RNA levels over time at selected sampling sites. This figure was generated for the data paper, to illustrate key features of the data across the Alpha, Delta and Omicron waves.

Based on input from the labs and the project leaders, suitable platforms for deposition of different outputs which maximise their visibility to the target audiences, while assuring cost-free, long term, sustainable preservation were identified, as detailed below.

(1) Multiple lab methods were published online on Protocols.io;

(2) Prevalence data, with visualisation and analysis methods were submitted to *Scientific Data* and shared online as a live resource on GitHub and a static snapshot on Zenodo;

(3) Example electronic lab notebook pages were shared on Benchling;

(4) A web Homepage was prepared, that links to all the online resources (described in points 1-3 above);

(5) The Open Research process was presented as a prize-winning conference poster.

(1) Multiple lab methods were published online on Protocols.io

The SARS-CoV-2 detection protocols have been curated, transcribed, and published in Protocols.io. Protocols.io is a secure platform for sharing research methods with an easy to use, clear user interface. The platform provides a DOI as the permanent identifier, which permits direct citation of the protocols, moreover, the system tracks re-use of information and provides impact statistics.

The same approach was taken to describe variant analysis methods. These continued to evolve as the initial research success in 2021 was redirected towards regular variant data delivery during 2022. Protocols.io links to the methods in development and are included on the Homepage (4). The final laboratory and data processing methods are described below, together with the data delivered from variant detection.

(2) Prevalence data, with visualisation and analysis methods were submitted to Scientific Data and shared online as a live resource on GitHub and a static snapshot on Zenodo.

The SARS-CoV-2 prevalence data were disseminated in multiple ways. Firstly, a snapshot of the data spanning the period from May 2020 to mid-February 2022 has been described as a "data paper", which is in publication (at the time of publishing the CREW report) for the journal *Scientific Data* which is part of the Nature group (see article preprint here, Scorza et al., 2022). Articles published in scientific journals are a traditional means of spreading knowledge for the research community. Publishing a peer-reviewed article this way provides assurance that the data paper will secure high discoverability of the datasets in scholarly search engines. Furthermore, submission to a high-impact peer-reviewed journal will ensure that the data description is of high quality, while the Nature group, a renowned publisher, guarantees long term accessibility.

Secondly, the data have been deposited in the public GitHub repository (https://bit.ly/3L8rcrn). Although typically used for computer source code, GitHub is an effective platform for sharing numerical data, especially in a text-based, interoperable FAIR format like the CSV format selected here. One of the advantages of storing data in GitHub is the ease of tracking amendments to the data or addition of new data entries, which uses the detailed 'versioning' process originally developed for code. GitHub is designed with collaboration in mind, which will make it possible to easily re-assign the responsibility for future updates of the dataset to other organisations, as required, making the GitHub version a 'living' resource. In addition to the data file containing the exact original SEPA numerical outputs, the team generated transformed data to facilitate their re-use, and shared these processed files. For example, weekly-level data were provided in a standard timeseries format, which made it easier to create

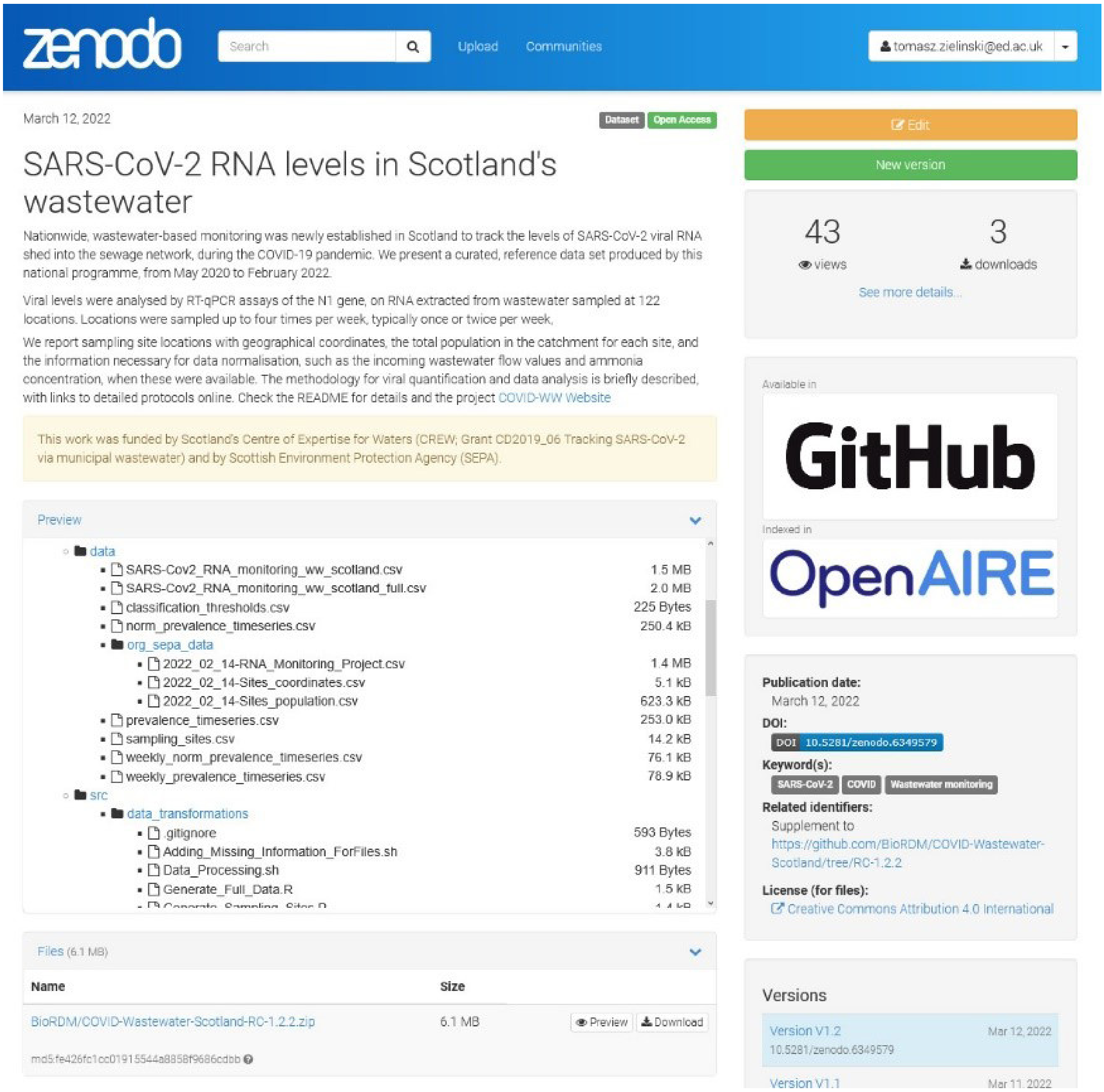

Figure 7. Screenshot showing dataset record in the Zenodo repository.

data visualizations. The code for data transformations and for generation of the graphical displays was also included.

Thirdly, both the original and the transformed data were bundled and deposited in the public Zenodo repository (Fig. 7) (https://doi.org/10.5281/zenodo.6339631). Zenodo is a reference repository, created by the multinational CERN laboratory. This will enable persistent referencing of this particular version of the dataset.

(3) Example electronic lab notebook pages were shared on Benchling

A further output is available only for the variant analysis, in the form of detailed laboratory notebooks created during the early development and evaluation of the methodology. Some Electronic Laboratory Notebooks (ELNs) used by Gilbert team researchers were shared on the Benchling platform (https://www.benchling.com), which is popular among molecular biologists. The notebooks document the research processes behind the new methodology. Their records are exemplary, with educational value, as well as constituting evidence of the professionalism and scientific rigor of Professor Nick Gilbert's team.

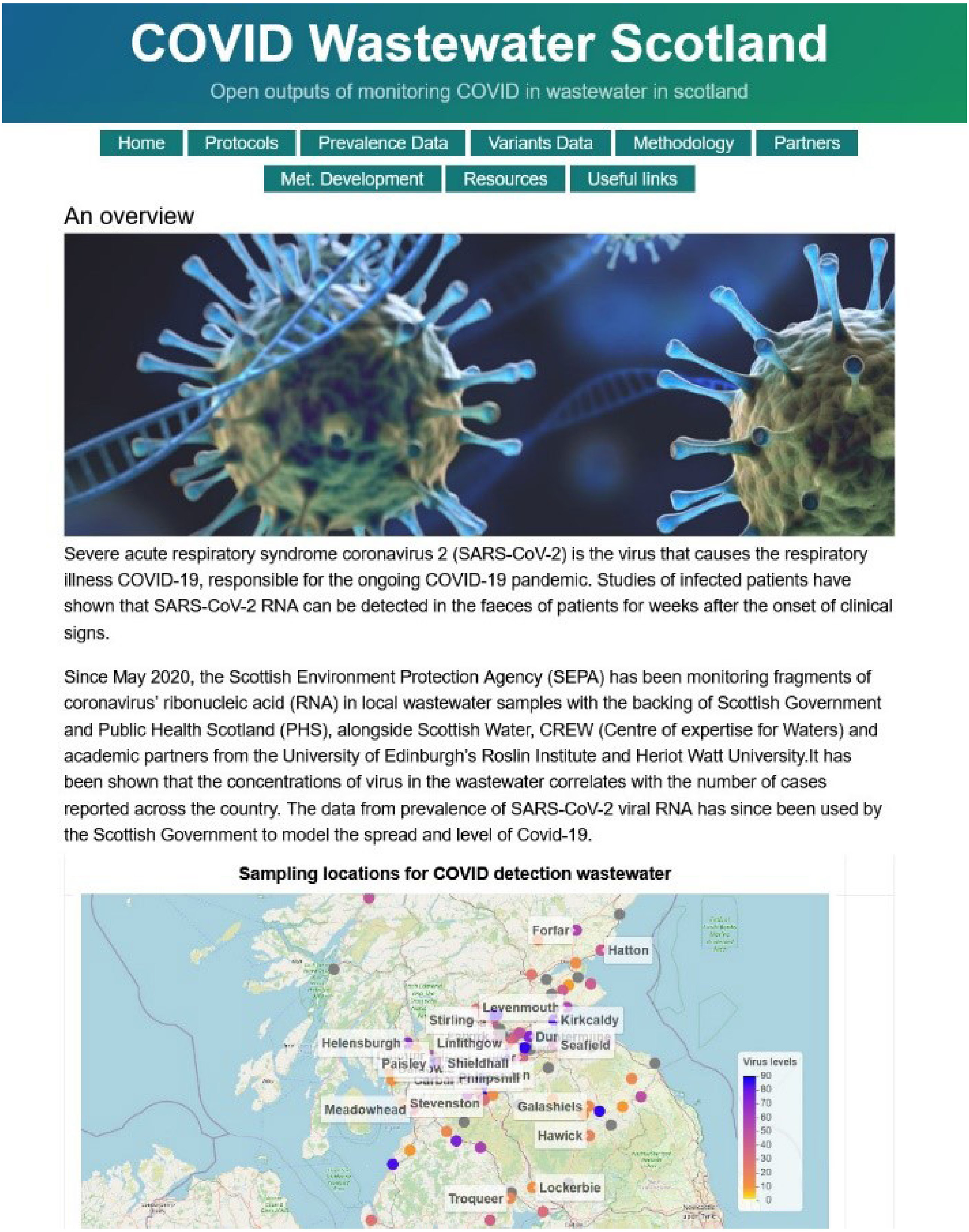

Figure 8. Edited screenshot showing landing page of the project Homepage.

(4) A web Homepage was prepared, that links to all the online resources mentioned previously.

The project background, an overview of the methodology and a catalogue of all the open outputs has been published as a user-friendly web page, or "Homepage", on the GitHub.io platform (Fig. 8). This platform offers a public facing website without any maintenance costs, where management responsibility can again be transferred as required in future. The main purposes of the Homepage are to make the outputs more accessible, to serve as a one-stop catalogue of the resources that is easy to reference, and to increase the visibility and discoverability of all the resources for any user through indexing of the web page by internet search engines.

The Homepage containing the links to published outputs is available under the link:

https://covid-ww-scotland.github.io/

(5) The Open Research process was presented as a prize-winning conference poster.

The curation process of making the outputs complete, unambiguous and available via multiple channels was presented at the Edinburgh Open Research Conference, 27 May 2022. Dr Livia Scorza won the 1st Prize for her poster presentation: "**Not going to waste - preserving Scotland's Covid-19 wastewater data**". Additionally, software notebooks in the R platform, entitled "Data wrangling with R", have been prepared as teaching tools, based on the project data and the code used for data cleaning and transformations.

3.3 The 'Open Research' process

The data curation process consists of making outputs complete, unambiguous and described with a sufficient level of detail. This turned out to be more demanding than initially assumed. It involved multiple rounds of communications with the SEPA, CREW, UoE and BioSS teams, and it was only possible thanks to the excellent engagement and support received from all the collaborators who collectively give the curated outputs the maximum clarity and hence ongoing value. However, it demonstrates the importance of timing in the curation process, as evidently people involved in development were still available to contribute and form part of the process.

The available prevalence data were curated internally in SEPA, as there were very few erroneous entries (e.g., misspelled sampling sites). The only minor issue was a small number of discrepancies in reporting some of the results as "negative" or "positive" where the viral RNA levels (gene copy numbers per ml) apparently did not match the established thresholds. This was resolved and documented during the data curation for the data publication: it reflected a period of time when a change in lab procedures required a change to the thresholds.

The use of ELN is recommended for the development of the variant detection methodology. It benefited the project by permitting experimentalists to be involved in each other's work and to provide instant feedback and assistance. Moreover, the data curator used the ELN records to draft protocols and help with comparisons of methods, with much less input required from the experimentalists. This is an early example of the benefit of using shared resources in research, in this case within the CREW project. The ELN notebooks are a perfect example of the adoption of FAIR best practices. Open Research in general aims to disseminate those practices, and to provide their benefits more widely.

3.4 Conclusions and recommendations

Both the national programme and the present CREW project involved clusters of different expertise spanning multiple institutions. They are good examples of multidisciplinary, collaborative projects. A key feature is that data produced by Scottish Water/SEPA/University of Edinburgh are re-used in organisations with different focus and expertise. Data protection is a separate consideration, not covered here because SEPA's wastewater data were already publicly accessible. Based on this experience, the following recommendations for other multi-agency projects can be formed.

For future projects, as a minimum, a collaborative platform is recommended, for example a wiki or even a shared drive for administrative information. Using this system, important documents such as meeting minutes or interim reports could be shared more effectively than via email, and more easily shared with new partners as they joined the project. The Scottish Government's Objective Connect system is one example, which allows multiple organisations to share, access and update the same document and provides a tracked record of these changes. The wastewater project lacked such a "collaboration platform".

Similarly, there is a need for a central document that captures all the decisions taken that affect the data outputs. Among the examples encountered are the thresholds for negative/positive classification and the rationale behind them, the multi-stage processes for normalising the raw WW data, and the dates when normalization parameters were recalculated.

Similar recommendations were made for the data. It is advantageous to utilize shared storage for all the outputs regardless of their origin, preferably under version control. This permits a record of which input data produced which outputs and helps to propagate best practices and allows more users to contribute to quality control, for example flagging changes to samples' identifiers. It is understood that this recommendation is more challenging, as it requires cultural changes in accessing and sharing data between organizations.

A further recommendation is that training in data management and data re-use is provided for all parties working on such projects, at the outset. Compliance with most data management practices does not create any overheads but it does avoid problems at the time of data re-use. Good practices are easy to establish at the beginning of a project, but they are much more difficult to incorporate into existing workflows as they can often cause disruptive changes. An illustrative example is the absence of units for the geographic locations of WW sampling sites. The coordinates could be misinterpreted as GPS locations, whereas they were in fact UK Grid References, but the relevant unit was not specified in the data output. Consequently, the external project W-SPHERE seems to have retrieved the coordinates afresh by using the site names: for example, the 'Seafield' WW treatment plant in Edinburgh was "relocated" to the town of the same name in West Lothian in their resource.

One approach to address these issues is to establish a data curator role from the outset of future projects, to evaluate the workflows and early outputs to flag potential issues and give recommendations.

4. Lessons learned – A review of the development of the SARS-CoV-2 wastewater screening programme in Scotland

Authors: Isabel Fletcher and Catherine Lyall

4.1 Introduction

This project reviewed the development of the Scottish programme for SARS-CoV-2 WBE to learn key lessons to inform future urgent responses to health and environmental crises. The SARS-CoV-2 WBE programme began in April 2020 with research at the University of Edinburgh's Roslin Institute and the microbiology laboratory of Scottish Environment Protection Agency (SEPA) using WW samples provided by Scottish Water. Scotland's Centre of Expertise for Waters (CREW) played a key role in bringing together these collaborators and funding the Roslin Institute research. In the summer of 2020, national WW monitoring was piloted, using samples covering approximately 40% of the Scottish population, and by September 2020 the programme had been expanded to cover 70% of the population. In December 2020, the Scottish Government identified an area of the Health Directorate that would take on responsibility for the policy aspect of this work and committed funding to support the collection and testing of WW samples for the next financial year (2021-22).

This review of the process provides a detailed understanding of the ways in which individuals and organisations, from the research and policy communities, collaborated in developing the Scottish WW testing programme. Qualitative methods were used (interviews supplemented by desk research) to derive a series of "Lessons Learned" for future collaborations that demand rapid research and policy responses. These in turn led to a set of six actionable recommendations for improving emergency preparedness (Section 4.8).

There are similar SARS-CoV-2 WBE testing programmes in many countries, but Scotland was one of the earliest to get underway. Given the recent establishment of a further programme of research to recently develop an assay for SARS-CoV-2 variants, it is timely to analyse how this first programme was established and learn lessons from these first-hand accounts. This needed to be done before many of the participants return to their routine "day jobs" and this valuable knowledge is lost. This research addressed the whole process of developing the SARS-CoV-2 WBE testing programme, from the first "test development" phase of the research to the routine operation of the national SARS-CoV-2 WBE testing programme and the current "variant testing" phase of the research.

Social scientists, experienced in analysing research collaborations across different disciplines and sectors conducted the research in a project commissioned from CREW (Scotland's Centre of Expertise for Waters. A qualitative social science study[1] analysing the challenges and enablers of interdisciplinary and cross-sectoral rapid responses to emerging situations was undertaken using expertise in inter- and transdisciplinary research collaborations to provide best practice recommendations ("lessons learned") to improve future responses.

A major component of this research involved interviewing individuals working on WW research and the testing programme from organisations such as the Roslin Institute, the Scottish Environment Protection Agency (SEPA), the Scottish Government and Scottish Water.

The following questions were reviewed:

- Which individuals and organisations have taken part in this research and subsequently in the development of the Scottish WW testing programme?
- When did they participate, what did they contribute and how did they do this?
- What was their experience of collaborating in this research – what helped them take part and what made it harder?

1 For those readers less familiar with the qualitative research method, we include a short introduction to the underlying processes of data collection and analysis in Appendix 4.

- What role did Scottish Government funding play in the successful development of this testing programme?
- What lessons can be learned to improve future collaborative responses to health and other emergencies?

This research was part of a larger project, funded by the Scottish Government, *Methodology for the Detection of new variants of SARS-CoV-2 in Wastewater* led by Professor Nick Gilbert of the University of Edinburgh Institute of Genetics and Cancer and managed by CREW. The social science element of this research was led by Dr Isabel Fletcher in collaboration with Professor Catherine Lyall, both of the University of Edinburgh School of Social and Political Science. The empirical phase of the qualitative study focused largely on the qPCR detection of total prevalence of Covid-19 in WW which occurred prior to the variant detection but Fletcher and Lyall remained part of the project group throughout.

Finally, it is worth emphasising that CREW commissioned a "lessons learned" review from the authors. This was in recognition that the SARS-CoV-2 WBE programme could provide a stimulating case study, illustrative of future research collaborations which might potentially be conducted across the health and environment policy sectors (in light of global issues such as climate change) and under less-than-ideal conditions (in the case of Covid, restrictions due to the national lockdown, etc).

This type of study has different goals from a programme evaluation in that it does not set out to assess performance against a pre-agreed set of metrics or indicators. So, it is not evaluative or judgemental in the sense of criticising "good" or "poor" performance. The purpose of a learning review is to enable participants in the activity – and wider stakeholders – to reflect on processes, outcomes, research and policy contexts, etc. as well as on their role in such activities. A learning review will also draw on the knowledge and expertise of the research team which, in this case, comprised senior academic social researchers experienced in this type of review methodology and familiar with the challenges of transdisciplinary collaborative research, working in conjunction with the broader project steering group[2].

2 Given the rapidly changing set of circumstances under which the wastewater testing project took place, the learning review provides a snapshot seen through the eyes of those informants who were willing and able to participate in the learning review study. Following the completion of our study, we have been asked to re-state (see p.45) that Public Health Scotland (PHS) had completed a significant organisational change prior to the pandemic, and whilst the learning review interviews covered the period May 2020-December 2021, many PHS staff were new in post.

4.2 Study design

This research used qualitative methods – interviews supplemented by desk research – to provide a detailed understanding of the ways in which individuals and organisations collaborated in developing the Scottish WW testing programme. Interviews took the form of partially structured conversations which allowed the interviewer to respond to the interviewee by asking for more information or checking that they had fully understood key points. This form of data collection can, therefore, provide a more nuanced and complex account of a specific case than alternative methods, such as surveys and questionnaires (Ritchie et al., 2013).

Data collection began by developing a map (Fig. 9) of the key institutions and individuals involved in all stages of the development of the programme from the initial research through to its current day to day management. This initial mapping was made possible in such a short timeframe by information from CREW, the research funder and project manager. CREW is Scotland's Centre of Expertise for Waters[3]. It aims to support the development and implementation of water policy and has existed for 11 years. In that time, CREW has established an extensive network of academic contacts in all areas of Scottish water research. CREW funded and managed three previous projects related to Covid WW testing in Scotland.

The initial process began by talking to those involved in the first CREW-funded research project (Corbishley et al., 2020) to develop a test for SARS-CoV-2 in WW, and then contacting other researchers who had, or were currently, working on related CREW-funded projects (Gormley et al., 2021; Sims et al., 2021)[4]. After this, key collaborators in organisations such as the Scottish Environment Protection Agency (SEPA), Scottish Water, and the Scottish Government were approached. In this manner, the experiences of those who were involved early in the process but were now no longer working on SARS-CoV-2 WBE testing, were captured and the ways in which the initial research was taken up and used to develop the Scottish national testing programme was examined.

Interviews were semi-structured, making use of a topic guide but also allowing interviewees to raise any additional issues that they considered important. The resulting conversations lasted between 30 and 70 minutes. Topics covered included: the interviewees' involvement

3 https://www.crew.ac.uk/

4 This research was funded as part of a larger project that included two other work packages focusing on assay development (Variants of Concern) and data sharing (Open Science). These three work packages ran in parallel and interviews with researchers from the other work packages were part of this research.

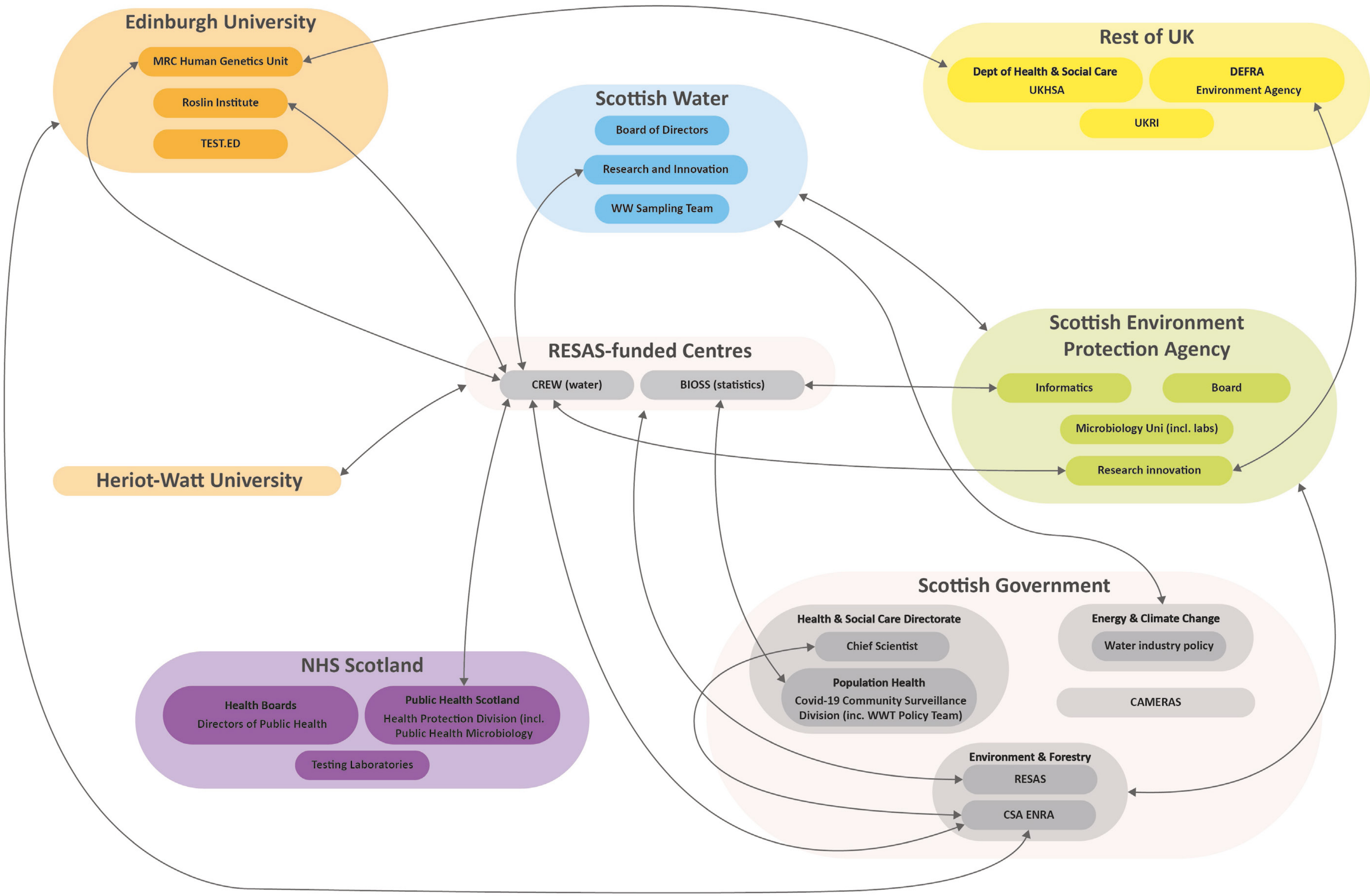

Figure 9. Mapping of main stakeholders in the Scottish SARS-CoV-2 WBE Testing Programme and their relationships (only includes those raised in the interviews).

in the WW research and testing programme; which individuals and organisations they collaborated with as part of this work; their experience of those collaborations and their motivations for doing this work; and the effects of lockdown and other pandemic restrictions. Interviewees were also asked to contribute key lessons learned that this report should highlight. As is often the case with qualitative interviewing, informants found it helpful to reflect on their experiences, with several interviewees saying that they had enjoyed these conversations or even found them to be "therapeutic".

Forty-one interviews were conducted between September 2021 and April 2022 (see Table 1). All, except one, of these interviews were conducted online by the lead author. All interviews were recorded and transcribed by a professional transcription service. Ethics review was provided by the University of Edinburgh School of Social and Political Science.

Table 1: Interviewees and their institutional affiliations.

Institutional affiliation of interviewee	No of interviews
NHS (inc. Public Health Scotland)	3
Scottish Environment Protection Agency	6
Scottish Government	9
Scottish Research Centres/Universities	17
Scottish Water	4
Beyond Scotland	7

Note that these numbers add up to more than 41 because several interviewees had more than one institutional affiliation.[5] These institutional categories are deliberately broad in order to preserve interviewee anonymity as much as is possible in such a small sample. For full details of how interviews were anonymised, and research data stored, see the Participant Information Sheet, included as Appendix 3.

Being part of a CREW-funded research project and making use of their network of contacts in research practice and policy, made the task of approaching potential interviewees initially seem relatively unproblematic. It was reasonably straightforward to establish contact with research scientists and arrange interviews. CREW's established relationship with Scottish Water and SEPA also made it fairly easy to identify relevant individuals to interview within these organisations, contact them and arrange interviews. Partly because their organisational websites do not provide details that allow individuals or groups responsible for particular areas of work to be contacted, it was much harder to identify who should be interviewed within Scottish Government and Public Health Scotland (PHS), to the extent that this caused delays in the data collection. While nine interviewees were affiliated with the Scottish Government (Table 1), the only individuals, contacted directly, who declined to be interviewed were from Scottish Government.

The resulting interview transcripts were initially analysed to identify common themes present across several interviews and then thematically analysed using NVivo™ qualitative coding software[6] and a further reiteration of these themes. This is a standard method for analysing the data resulting from in-depth qualitative interviews (Ritchie et al., 2013; chap 10).

In parallel with the interviews, two pieces of desk research to inform these findings were undertaken. The first of these was an extensive literature review of existing research on collaborative research in crisis situations and how to ensure the rapid uptake of evidence, a summary of which is included in the following section of this report. The second search explored recent scientific literature and organisations' website to identify potential international case studies to compare with the development of the Scottish programme[7].

4.3 Locating this review within existing scholarship

Within the social sciences, a traditional "narrative literature review" more usually combines both summary and synthesis, often within specific conceptual categories. Unlike the "systematic review" more common in the medical sciences, this type of literature review is less structured, may cover a broader set of topics, and does not have the core focus on comprehensive coverage and evaluation. The synthesis presents information in a way that demonstrates to readers how the research fits within a larger field of scholarship and indicates how the researcher plans to investigate and analyse the research problem. As such, the literature review is an essential contribution to the subsequent analytical framework, as discussed in Appendix 4. Only the key elements (of a much more detailed literature review) most pertinent to the findings and subsequent discussion are presented here.

Initial discussions with various inter-and transdisciplinary scholars in an international network identified prior research that might help provide an understanding of rapid response research that spans both discipline and organisational boundaries. More accurately termed "transdisciplinary" research (TDR) (rather than "interdisciplinary"), there is a substantial literature about the barriers and enablers of such collaborations which

5 Interviewees were speaking as individuals and not on behalf of their organisations.

6 https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

7 We acknowledge Nathalie Dupin's work on these literature searches.

are typified by a "co-production" process between academic researchers and other external partners[8]. This type of research is most often reported in the context of sustainability science and, to a lesser extent, in healthcare settings. While UK research policy advocates for "interdisciplinary" research and research that has societal "impact", the term TDR is less prevalent in the UK but there is much to learn from this literature (see Lyall et al., 2015).

A related term with which UK researchers may be more familiar is "team science". Typically defined as any collaboration between a group of scientists to address a particular scientific challenge, the team may be chosen from a broad range of disciplines, bringing together their individual skills and knowledge to solve a particular problem. In contrast to TDR, the "Science of Team Science" (SciTS) literature speaks rather less to the issue of bringing academic and clinical researchers together with societal partners. Both the TDR and SciTS literature are relatively silent on the issue of how best to convene newly emergent collaborations in response to a crisis, so this literature review also encompasses emerging interest in "rapid approaches to research" in healthcare and draws on the concept of "swift trust", developed in the context of emergency humanitarian responses.

4.3.1 Forms of collaboration: transdisciplinary research and team science

The view prevails that "boundary spanning teams have better outcomes" (in terms of productivity and impact) when compared with less diverse teams or solo scientists (Hall et al., 2018). Success in team-based research depends on; good coordination and communication, building trust and dealing with team conflict, having shared goals, and the availability of resources. Hall et al.'s (2018) review emphasises the extended time and effort needed to develop shared knowledge of different disciplinary contributions to a project as well as the work involved to bridge institutional cultures, policies, and procedures across organisational boundaries. There is a substantial literature on how to overcome these challenges (e.g., Gilligan, 2021; Bozeman & Youtie, 2017; Syme, 2008; NRC, 2015; Bracken & Oughton, 2006; O'Connor et al., 2003; Ganapati & Mostafavi, 2018; Hardy, 2018).

In the context of team building in response to Covid-19, Fry et al. (2020) report that articles in the Covid-19 period are less likely to be internationally co-authored than pre-Covid-19, indicating that scientists rapidly reorganised to narrow their research focus and maximise efficiency. This led to smaller team sizes which reduce transaction costs of communicating among the group with the expectation that this would speed up research and writing processes. This raises questions related to team formation, such as: the "speed-skill trade-off"; a favouring of existing elite structures; increasing inequities in the science system; reductions in knowledge diffusion and novelty; and fewer opportunities for validation. Fry et al. (ibid.) conclude that the consequences of narrowing and focusing of research and associated reduction in team size and international scope may mean that results arrive more quickly, but results and capacities may be diffused more slowly.

Transdisciplinary research (TDR) further extends the research "team" to include both a variety of disciplines and actors from public agencies, civil society and the private sector, typically with the aim of "developing knowledge and practices that promote what is perceived to be the common good" (Pohl and Hadorn, 2007). TDR amplifies both the benefits and challenges of collaborative team science by adding several dimensions, most notably the introduction of different types of knowledge producers to the team. The hallmarks of TDR identified by Cannon (2020) – namely its problem-solving focus in response to an identified issue or threat; time- and resource-intensiveness; reliance on trust-based relationships; and barriers created by university structures and norms – are widespread throughout the literature. Among the common barriers to successful TDR are:

- "Professional cultures" (Harris & Lyon, 2013).
- Cognitive cultural differences (Klein, 1996).
- Lack of "collaboration readiness" factors (Hall et al., 2008).
- Role ambiguity among team members (Huning et al., 2021) and difficulties in assigning roles for team members across levels of expertise and rank.
- Lack of information sharing between agencies (Daher et al., 2020).

4.3.2 Forming teams and building "swift trust" in emergency situations

Reviews of the literature on the co-ordination of teams (e.g., Mayo, 2020) confirm that teamwork is best in stable conditions, where people have learned over time to work together (Hackman, 2011). So, what happens in situations where time is limited? Work from the "sociology of disaster" (Drabek and McEntire, 2003) indicates that individuals and groups typically become more cohesive and unified during situations of collective stress. The concept of "swift trust" (Meyerson et al., 1996) describes the trust developed in temporary teams within or between organisations, particularly when there is time pressure or

8 See, for example Vienni-Baptista et al. (2022) and the SHAPE-ID toolkit, for a detailed discussion of the literature on ID/TD and the multiple uses of these terms.

achieving project goals is of great importance (Mishra, 1996). In temporary organisational settings where people do not have any prior relationship, individuals have to initially assume trust, interact as if trust were present and then later verify and adjust their trust beliefs in response to accumulating experience of the collaboration (Meyerson et al., ibid.). Building trust is not an end in itself: trust increases commitment (Morgan and Hunt, 1994; Miettila and Moller, 1990) and both trust and commitment are seen as prerequisites for building effective coordination among actors (Conway and Swift, 2000).

Behavioural uncertainty happens due to lack of complete information about one's partners in a network (Williamson, 1985), hence information sharing among partners creates transparency and the quicker the team can build trust and operate effectively (Lu et al., 2018). Trust is also built through prior experience of working together, building trust through progression of projects, norms of cooperation, and sanctions exerted on those who might transgress norms of behaviour (Pohl et al., 2010; Yusuf, 2008). Intermediaries are found to play a key role in bringing new teams together and building trust across professional cultures. When discussing the use of trust, respondents in the Harris and Lyon (2013) study referred to the importance of having information on other collaborators (bios, websites, pictures, CVs, etc.) but that information alone is not sufficient: norms of cooperation also shape how trust is used, such as reciprocity (helping each other on specific problems and sharing knowledge) and keeping to agreements (for example not publishing material without others' permission) (Harris and Lyon, 2013).

In their discussion on the "return on relationships" in the context of emerging infectious diseases, Fair et al. (2016) develop these themes further with examples of how transdisciplinary research collaborations established prior to crises can transform responses to outbreaks and in some cases could even prevent one from occurring, concluding that "established relationships may be paramount in preventing the next pandemic". Fair et al. (ibid.) criticise current – quantitative – return on investment (ROI) metrics for not taking into consideration the importance of relationships and networking. They argue that few studies consider the dynamics of building informal networks across disciplines (see also Stephens and Stephens, 2020) and institutions that result in existing infrastructures of relationships that can be called upon when pathogens emerge, and questions need to be answered quickly and collaboratively. Fair et al. (ibid.) confirm that diversity and breadth of a multidisciplinary team can present challenges to communication and teamwork, particularly in the midst of crisis, when it may be too late to build trust and establish communication mechanisms.

4.3.3 Rapid response research and getting evidence into policy in crisis situations

"Rapid response" research is not a new phenomenon in the social sciences: Manderson and Aaby (1992) attribute it to the growing involvement of social scientists in practical disease management in the 1980s; Fitch et al. (2000) trace the first formal rapid methodologies to the late 1970s, and the production of the first formal guidelines on conducting rapid assessment during the mid-1980s. Rapid research is characterised by: short timeframes; team-based research; a range of data sources (including secondary data) and data collection techniques; and a strong link to timely interventions or recommendations (Vindrola-Padros, 2019). In discussing "rapid research" partnerships, Vindrola-Padros (2021) highlights misalignments between healthcare organisations and academic partners[9] if the research approach is seen as unhelpful or irrelevant to decision-making or if academic researchers are unable to work in the fast-paced healthcare environment or if there are barriers to research use caused by organisational stress and restructuring. Richardson et al. (2021) offer practical recommendations for conducting applied research in a "nimble" way, including:

- Data requests to respondents should not conflict with professionals carrying out their jobs or conflict with other requests for similar data (McNall and Foster-Fishman, 2007; Vindrola-Padros et al., 2020).
- Identify aspects of the research to be explored simultaneously rather than sequentially by designating tasks within the team (Vindrola-Padros et al., 2020).
- Share "actionable findings" in almost real time - straightforward recommendations that can be easily understood and translated into changes in policy and/or practice (Vindrola-Padros et al., 2020).
- Practices and systems must be co-ordinated ("This is something which cannot be taken for granted").
- Host universities asked to allow researchers to begin research in advance of any official award letter (not all university accounting systems were able to facilitate this in the Richardson study).
- The personal and health costs to researchers if allocation of research time is inadequate.

9 Note that Vindrola-Padros (2021) writes from the perspective of a qualitative social researcher working within a healthcare context. Nevertheless, there may be parallels to be drawn with the SARS-CoV-2 WBE programme in building relationships of trust within public health.

- High degree of trust between gatekeepers and research team based on relationships developed through past contact and the applicants' academic track-record.
- Direction of rapid research somewhat shaped by the availability, seniority, and depth of existing relationships between participants and gatekeepers.

Many of these themes are discussed in greater detail in sections 4.5 (Results: key themes from interview data) and 4.6 (Discussion).

4.4 Timeline of Scottish wastewater testing programme

At the end of March 2020, researchers from the KWR Water Research Institute in the Netherlands published a pre-print article describing the first ever detection of SARS-CoV-2 (COVID-19) in sewage from a series of WW treatment plants, including Schiphol Airport (Medema et al., 2020). Importantly, this research detected the presence of SARS-CoV-2 RNA fragments in WW before any cases were reported in the Dutch population.

Previously, researchers at the Roslin Institute – a publicly funded animal sciences research institute and part of the University of Edinburgh – and at the Scottish Environment Protection Agency (SEPA) had already realised that they might be able to use their expertise to develop such a test, and these Dutch results confirmed the possibility.

The Roslin researchers contacted Scottish Water and through them were put in touch with CREW, the Scottish Government funded Centre of Expertise for Waters. An important part of CREW's role is commissioning research to address urgent water policy issues via their draw-down funding mechanism. This does not normally involve commissioning new scientific research, but this was in the context of a national crisis and Scottish Water's urgent need to know whether workers in its water treatment plants were at increased risk of contracting Covid-19 from WW.

By early April 2020, the Roslin research group had acquired initial funding from CREW for a pilot project to develop a PCR-based test [10] for SARS-CoV-2 in WW and the first samples were delivered by Scottish Water to the Institute's laboratories. At the same time, the microbiology team at the SEPA laboratory in Edinburgh were also working on this problem. The first CREW-funded project ran from April to August 2020 and culminated in the successful development of a protocol for testing for SARS-CoV-2 in WW, the results of which were then handed over to the SEPA microbiology team. Independently, in June 2020, the SEPA team also successfully developed a "proof of concept" testing method.

Following this initial funding from CREW, a larger group of Roslin researchers, which also included colleagues specialising in epidemic modelling, successfully obtained Natural Environment Research Council (NERC) funding as part of one of two UK-wide consortia (N-WESP)[11]. One N-WESP project investigated the infectivity of SARS-CoV-2 in sewage sludge and the second modelled the spread of Covid-19, relating this epidemiological analysis to the WW data created by the first CREW-funded pilot project.

In the period May to November 2020, the second stage of the Scottish testing programme implemented national SARS-CoV-2 WW monitoring across 28 locations, without additional funding. This used Scottish Water's existing sampling capacity – including the auto-sampling processes that ran in many treatment centres – to test samples covering approximately 40% of the Scottish population. The output data were used in Scottish Government's central epidemic modelling Hub (later Division). In July and early August 2020, Covid outbreaks in Aberdeen, Dunfermline and Kirkwall show up in the WW testing data in parallel with or even in advance of cases being diagnosed, demonstrating the surveillance value of this data.

By September, the Scottish Water sampling programme now covered approximately 70% of the population. Meanwhile, a second CREW-funded pilot project, running September 2020 to April 2021 began a review of SEPA and Scottish Water's joint working response to the pandemic restrictions, not including the monitoring programme. The findings of this research were reported in a confidential, internal report that provided helpful background and context to the current study.

By December 2020, the accumulated data demonstrated the utility of SARS-CoV-2 WW testing. Scottish Government's Health Directorate funded programme expansion, and then committed for the 2021-22 financial year; in the process, lead policy responsibility for the programme within Scottish Government passed from RESAS to the Population Health Directorate. CSA ENRA continued to provide scientific advice (see section 4.6.1).

By March 2021, Health Boards were encouraged to request local sampling at over 100 locations – a process labelled "network sampling" by interviewees – leading

10 Polymerase chain reaction (PCR) is a laboratory technique used to amplify DNA and RNA sequences. A PCR-based test is using this method to amplify and therefore detect fragments of SARS-CoV-2 RNA excreted by infected individuals in wastewater (i.e., sewage).

11 https://nwesp.ceh.ac.uk/

to another increase in the number of samples tested. WW testing data began to be used locally, as Health Boards sent mobile testing units to specific locations, following up unexpected WW signals with surge testing (Fitzgerald et al., 2021). In this period, RESAS funded data integration of WW testing data with individual case data. This was done by Biomathematics and Statistics Scotland (BioSS), a Scottish Government funded research centre, and managed by the Scottish Government central Covid Hub in order to create a direct line into central planning. By June 2021, Scottish Government pandemic models incorporated WW data, and the Scottish Government Covid WW testing policy team was also established at this time. The third CREW-funded pilot project, running from February to May 2021 reviewed post-Covid applications of WW monitoring, such as detecting other viruses, antibiotic-resistant organisms, and pharmaceuticals.

In August 2021, CREW funded a fourth pilot project to develop an assay to detect the different variants of SARS-CoV-2 – "variants of concern". This work was done by the MRC Human Genetics Laboratory at the Western General Hospital (also part of the University of Edinburgh). At the time of writing, this project is due to run until the end of June 2022 and this Lessons Learned Review is the main output of one of its work packages.

From September 2021 until when this report was being drafted (February 2022), the national sampling and testing programme has continued to process up to 300 samples per week. Increasing levels of infection, driven by the arrival of the Omicron variant in late November 2021, have initially reduced the surveillance value of WW testing for prevalence, but reductions in numbers of PCR tests conducted and the possibility of variant testing add value to its use for public health surveillance. SEPA has automated parts of the testing process and re-organised its laboratory work force (e.g., creating a lab manager post), with the aim of reducing pressure on staff and now has the capacity to undertake variant testing. Against the backdrop of Scottish and UK-wide uncertainties in government budgets, interviewees reported that discussions are taking place about which organisation should provide variant testing services in the future. A schematic diagram of the timeline for the actions noted above is shown in Fig. 10.

Overall, this narrative demonstrates an impressively agile response to a crisis situation. In less than six months, the results of the first CREW-funded pilot project (combined with the work of the SEPA laboratory staff) were used to develop a national SARS-CoV-2 WW testing programme. This was a bottom-up response to a national health emergency; a research, sampling and testing programme developed collaboratively by a network of highly motivated individuals from the different organisations who saw an opportunity to use their skills for the public good. It involved some of them taking on increased workloads for extended periods, as well as negotiating the difficulties of conducting research and testing during the lockdown and ongoing pandemic restrictions and those involved deserve recognition and gratitude.

However, despite this immediate term success, the uptake of this complex bottom-up initiative by Scottish Government has not always progressed smoothly. As outlined below, structural constraints have impeded progress, despite efforts of individuals "on the ground" and high-level support from the Scottish Government, Scottish politicians, Universities and the Board of Directors of Scottish Water and SEPA. As well as problems with service planning and implementation, there have been issues around which organisation "owns" this initiative, and who the ultimate "customer" is for the data produced by WW testing that, to date, have proved challenging and are likely to continue to do so. Issues of programme ownership and final use of wastewater data influence decisions about where the data is collected and how it is analysed.

4.5 Results: key themes from interview data

In this section four key themes identified from the interviews are discussed: participants' experiences of collaboration; the ways in which these collaborations relied on existing networks within research, practice and policy; the new relationships that developed from the work on SARS-CoV-2 WW testing; and the problems many participants experienced in securing inter-agency participation and buy-in to the WW testing programme.

4.5.1 Experiences of collaboration

Participants' experiences of collaboration were largely very positive: "at that point when we needed to collaborate, it was absolutely brilliant because it was just one of those, sort of, 'can do' moments" (Interview 19, SEPA employee). This was often attributed to a shared desire to contribute, in the context of a national crisis: "everyone had a pandemic head on" and "it was like, we will do anything we can to help and assist the general national effort" (Interview 22, Scottish Government employee[12]). Many interviewees described how they "just wanted to be useful" (Interview 4, Researcher) and early on, individuals

12 In order to preserve anonymity, very broad terms are used here: university researchers are described as "researchers" and all other interviewees as "employees". Listing institutions or job titles would be too revealing and no difference in status or rank is implied by this nomenclature.

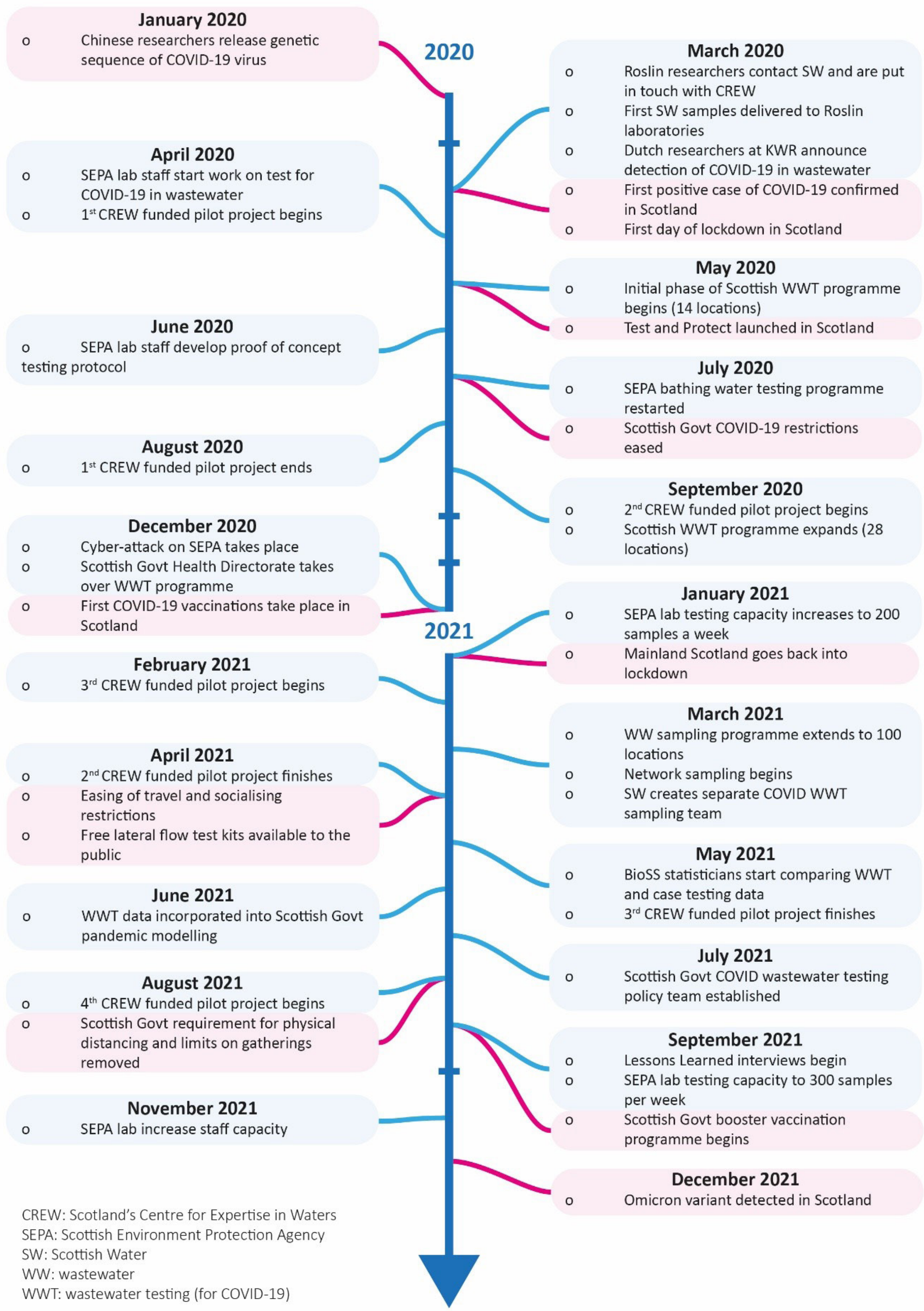

Figure 10. Timeline of key events in the Scottish SARS-CoV-2 wastewater testing programme (selected external events in pink).

and organisations identified relevant skills and resources that they could contribute and set about identifying the best way to use them.

The success of these collaborations relied heavily on the ways in which individuals used their existing networks, for example to identify potential collaborators (and verify their expertise), secure funding or other resources or sometimes deal with problems arising from their joint work. This is a well-recognised phenomenon of small countries such as Scotland, exemplified by the use made by some interviewees of contacts gained from attending meetings of the Coordinated Agenda for Marine and Environmental Rural Affairs Science (CAMERAS) group, for example. This group had a reputation as "slightly dysfunctional", but, in interviews, members describe using these pre-existing contacts to keep the WW testing work going e.g., by borrowing key pieces of laboratory equipment.

The most important of these networks was the one established by CREW in its previous work commissioning and managing research to inform Scottish Government water policy. CREW played a very important role in bringing the initial stakeholders – the Roslin research team, Scottish Water and SEPA – together. It also funded and project managed all four of the SARS-CoV-2 WWT pilot projects, extending its normal activities beyond the synthesis of existing research to the oversight of basic research. The total funding for the first three projects was just under £100,000, showing the impact that small amounts of well-targeted "pump-priming" funding can achieve when a well-founded national research capacity already exists. Without CREW's support, it is not clear that the Scottish WW testing programme would have got off the ground so speedily. CREW is one of five RESAS-funded centres which aim to improve links between research and policy, and to date, it has not been possible to identify a similar network of research, policy and brokerage organisations within Scottish public health.

Scottish water and SEPA are used to collaborating and appear to, consistently, maintain good working relationships in this area. The Roslin Institute was a new partner in WW research but has significant expertise in the nature and transmission of infectious diseases. The first two CREW-funded pilot projects drew on Roslin's existing pool of expertise to recruit researchers and members of the project advisory boards. The University of Edinburgh has also developed TEST.ED[13], its own testing programme for members of the University, and this network became important when setting up the fourth CREW-funded pilot project investigating the possibility of testing WW for different variants of SARS-CoV-2. New collaborative relationships have also emerged as part of the WW testing work. Some of these were research relationships spanning medicine and veterinary medicine, others were policy relationships that spanned specific topics crossing environment and health sectors.

13 https://www.ed.ac.uk/tested-covid

However, many interviewees experienced difficulties in trying to get members of the public health community to engage with the WW testing research: this situation was labelled "the elephant in the room" by more than one interviewee when asked about their experiences of collaboration in this project[14]. A few individuals from the Scottish public health community were very engaged – including the current Chief Scientist for Health and Social Care – furthermore, many staff at Public Health Scotland (PHS) were new in post following organisational change. This may explain why those developing and running the WW testing programme found it hard at the time to develop good working relationships with this community[15].

Two key reasons for this situation were suggested. Firstly, PHS and their colleagues in Population Health were leading the Scottish response to the pandemic and simply did not have the capacity to respond to something they saw as experimental in nature[16]. This attitude shifted somewhat when bio-informaticians from SEPA and Bios began to plot WW testing data against case data, revealing an apparent relationship between the two. This and the prediction of localised outbreaks in the summer of 2021 highlighted the potential of WW testing as a non-invasive means of population surveillance when prevalence is low.

The public health value of WW testing data has increased, as this report is written (June 2022), due to the steep reduction in PCR testing numbers. This began in early January 2022 when the Scottish Government advised that it was no longer necessary to confirm a positive lateral flow test (LFT) with a PCR test and that fully vaccinated visitors to Scotland did not need to take pre-departure Covid tests.

Secondly, the re-organisation that created PHS took place in the spring of 2020, just as Covid-19 cases began to occur in Scotland, and this resulted in internal and external communication problems which reduced their capacity to respond to enquiries about new collaborations.

14 As described above, this was echoed by difficulties in trying to obtain interviews from those working in the Scottish Government Population Health Directorate and for PHS in this review.

15 Experience from Canada strongly echoes this finding where: "much of the initial work and advancements that were viewed and promoted with optimism by the research community and locally engaged public health partners have been met with varying degrees of scepticism and even indifference among public health decision-makers" (Hrudey and Conant, 2022).

16 Subsequently, as the evidence of apparent relationships between WW data and clinical case data developed, the value of WW data has become recognised and wider interest in the research has grown.

Interviews revealed more fundamental concerns regarding privacy and sharing health data. PHS were seen as unwilling to share to their data below the neighbourhood level due to concerns about potentially identifying individuals and stigmatising communities[17], even with bio-informatics colleagues who are used to working with confidential data and have the facilities to do so securely. The system governing Scottish health data was also described by one interviewee as "deeply flawed" and "fragmented" to the point where "nobody controls [health data] in its entirety" (Interview 17, Researcher).

4.5.2 Exploiting existing capacities

The initial WW testing research relied heavily on the facilities of the Roslin Institute, notably its category-3 microbiology labs and trained personnel that could handle a newly identified pathogen causing serious illness in humans, as well as their ultra-low temperature freezers required for storing some of the WW samples. These capabilities exist because of Roslin's core funding from the Biotechnology and Biological Sciences Research Council (BBSRC).

Both Roslin and SEPA laboratory staff were able to work on the WW testing programme because many of their routine activities were cancelled during the "Lockdown" period. Research funders, such as the Wellcome Trust and UKRI, allowed university researchers the flexibility (and later funding) to undertake Covid-related work in this early period. However, the reduction in routine testing was particularly important for SEPA staff as their laboratory was running at full capacity before the pandemic: they would not have been able to take on a new piece of work had the bathing water testing programme (which is one of their regulatory responsibilities) not been significantly curtailed due to the Government's instructions for people not to travel out of their immediate neighbourhood, meaning that bathing areas were relatively empty.

Initial problems with capacity involved shortages of laboratory consumables and lack of specific pieces of equipment. Some of these issues were resolved by informal borrowing between institutions e.g., when, making use of contacts from CAMERAS meetings, SEPA was able to borrow a refrigerated centrifuge from the Scottish Agricultural Science Agency. Problems with SEPA's lab capacity occurred later in the summer when the bathing water testing programme resumed whilst simultaneously the WW testing programme began to increase from 35 to 200 samples a week (it subsequently increased to 300 samples a week after the summer of 2021). As described below, this was partially solved by deploying staff from other parts of the organisation and then taking on temporary staff.

Initially, Scottish Water used their existing sampling capacity to provide WW samples to the Roslin researchers and later to the SEPA laboratory. This remained the case through the pilot stage of the testing programme and the initial phase, covering 40% of the population. In March 2021, the network sampling programme was established. This was a highly responsive system where health boards could request samples from specific locations. By this time, Scottish Water had created a separate Covid WW monitoring team and employed a project manager who streamlined and automated some of the systems, increasing the capacity of the organisation to respond effectively.

As several interviewees outlined, by the end of 2021, when most interviews took place, these three institutions (Roslin Institute, SEPA, Scottish Water) had essentially embarked on a bottom-up process to develop a WW testing programme. It was an initiative developed to the limits of Scottish Water and SEPA's existing sampling and testing capacities, and the challenge was now for Scottish Government to take over management of this new programme and absorb it into its routine activities. Moreover, this had to happen at an accelerated pace, in a matter of months, rather than the normal one or two years that might have been required previously to plan and implement such a programme. The capacity of the Scottish Government to take up this initiative and further develop it was hindered by the lack of capacity of the Scottish public health community outlined above.

4.5.3 Limits to ad-hoc responses

As argued above, the Scottish WW testing programme was a successful response to a crisis situation. Individuals across the key organisations – the Roslin Institute, SEPA and Scottish Water– were able to co-opt existing capacities and capabilities and create a nation-wide testing and sampling programme in less than six months. Moreover, this programme continued to expand significantly in the following 18 months and is still running.

Despite this impressive achievement, there were important negative effects of this ad-hoc way of working. The most important was the increased workloads taken on by some staff in these organisations (and elsewhere). Some interviewees could set aside or re-allocate elements of their usual work, particularly during lockdown, but others could not or were so centrally involved in the development of the WW testing programme that it appears to have significantly increased their working hours (and decreased their time off work) until more formal arrangements were

17 We understand that due to their legal responsibility to protect personal data, PHS might not have been able to share certain kinds of data, but the perception of our interviewees was that they were unwilling to do so.

made within both organisations, a process that took about 12 months in both Scottish Water and SEPA.

Both Scottish Water and SEPA deployed existing staff during the pandemic period and took on agency and temporary staff to carry out aspects of the WW testing programme, particularly once the programme started to expand. Scottish Water employed more samplers and SEPA re-deployed staff from other laboratories and then took on agency staff. However, this was often done as a short-term response and longer-term planning would have reduced both expense to the organisation and uncertainty for staff, some of whom were on very short-term rolling contracts.

Staffing appears to have caused particular problems for the SEPA laboratory where redeployed staff ended up stuck doing long periods of routine and very repetitive tasks without an end date, leading to significant dissatisfaction among deployed employees and other laboratory staff. One interviewee described "the monotony, the day in, day out" of this very routine, yet crucial, laboratory work, which was carried out "as the sample numbers started to ramp and ramp and ramp… and there sort of being no sign of the end" concluding, "the Delta wave just nearly broke the team" (Interview 14, SEPA employee). These very human responses to the experience may point to the need for additional public investment in instrumentation in anticipation of future crises requiring routine surveillance testing.

The Roslin Institute and the University of Edinburgh also made use of short-term (less than 6 months) contracts to hire laboratory researchers for several of the CREW-funded pilot projects, especially the current work on identifying variants of concern. In this case, criticisms focused on the slowness of the University's HR processes which did not take into account the short-time timescales necessary when conducting research that responds to a public health emergency.

Improvised use of existing systems sometimes resulted in awkward or less efficient processes, requiring for example, manual, rather than automatic, data entry or significantly increasing the time taken to complete specific tasks. One interviewee linked this problem to a lack of communication between the different agencies involved: "if we'd had more involvement in the development of a sampling programme in terms of being able to give feedback in the beginning, I think we might have come up with a more streamlined approach" (Interview 18, Scottish Water employee).

Difficulties were also experienced in aligning processes across the different agencies – a simple but very frustrating example was that SEPA laboratory staff did not initially understand the Scottish Water system for labelling samples and had to puzzle it out on their own with no input from the Scottish Water sampling team. This is a small example of a larger problem of communication within and between organisations that made the collaboration harder than it needed to be. One interviewee described how requests for information were relayed several levels up her organisation to be communicated to a partner organisation and then the answer relayed back to her the same way, when it would have been much easier if she could have emailed her counterpart directly to sort out everyday problems. Communication problems within organisations also meant that several interviewees (including quite senior individuals) felt that they did not fully understand aspects of the WW testing programme and how their work fitted into it: "I don't really have a very good feeling as to what the long-term vision is… if I don't know the information then I can't really make a, a bigger contribution (Interview 11, Researcher).

The interviews revealed a broader problem with ad-hoc, on the hoof, response as shown by the way in which the constant expansion of the testing programme – combined with the short time scales involved and the necessary urgency of responding to a national public health crisis – has meant that, until very recently, there was little or no time for many of those involved to take a step outside the day to day development and then running of the programme to think about it strategically[18]: "I would like to get a little bit more strategic, but yes, it's very much day to day stuff, keeping it going, running around going how do I clarify…what my budget is, how do I keep the stakeholders on board now while still going, things are still uncertain, but can you continue to do it please?" (Interview 23, Scottish Government employee).

Questions such as what data would be most useful and/or meaningful for public health colleagues; were the existing arrangements the best use of resources; and who in Scottish Government should take responsibility for the programme were not addressed in a co-ordinated fashion. This highlights the broader problem of the lack of collaboration across environment and health research and policy that appears to exist within Scottish Government: "people from RESAS don't really understand what goes on in Public Health, and people from health don't really understand what goes on in RESAS" (Interview 23, Scottish Government employee). Such policy "siloes" persist and will be increasingly problematic due to the stated need of One Health approaches to tackle other priority issues, such as anti-microbial resistance. Interviewees attributed the lack of co-ordination of WW

18 An exception was the report on future applications of wastewater based epidemiology published in May 2021: https://www.crew.ac.uk/publication/review-wastewater-monitoring-applications-public-health-and-novel-aspects-environmental

research and testing at the Scottish level to poor policy co-ordination both within Scotland and between the Scottish and UK levels of governance.

Interviewees stated that such discussions about the future of the sampling and testing programme, are now starting to take place, stimulated in part by the potential future applications of WW monitoring to a wider range of viruses (such as influenza and Norovirus) and broader health issues (such as anti-microbial resistance). However, this is a very recent development, and despite this, some interviewees still described it as being difficult to plan for the future of the programme, even if it was part of their role.

4.5.4 UK-wide differences in wastewater testing programmes and wider Covid-19 responses

One of the key differences between Scotland and England highlighted by many interviewees was the benefit of Scotland having one national water authority, with an explicit mandate to act in the public interest. To its credit, very early on in the pandemic the board of Scottish Water seems to have taken a decision to support the WW testing programme and provided internal resources to back up that decision. They were not the only organisation to behave in this manner – the SEPA board of directors seems to have adopted the same approach – and the sharing of resources outlined in the previous section was probably facilitated by the fact that all the organisations are part of the public sector. However, in the case of Scottish Water, interviewees contrasted this approach with the fragmented situation in England, where, initially, it was difficult to get similar commitments from the privately owned water companies, partly due to difficulties in communication and companies' concerns about the costs involved. Later on, the sheer size of the English water industry meant that greater resources could be used in developing their testing programme but getting to this point was a slow process that one interviewee likened to "manoeuvring an oil tanker" (Interview 23, Scottish Government employee).

This is one facet of a wider set of contrasts between the smaller and often more informal world of Scottish research and policymaking leads and compared to much larger English (or UK-wide) organisations. The smaller, relatively well-connected nature of Scottish research and policy seems to have been a key factor in the fast development of the WW testing research and the early establishment of the WW testing programme. Existing networks and capacities – such as those developed by CREW – made possible an agile and effective response to a national emergency. However small size and relatively informal approaches, whilst responsive and flexible, may also indicate a lack of capacity which ultimately led to some of the issues around strategic planning outlined above.

The greater size of the English research and policy organisations meant that, once the water companies were engaged, much greater resources were available to develop their WW testing programme, including a very successful communication strategy targeted at regional Directors of Public Health. One interviewee argued that the different levels of funding available in the two countries led to very different approaches to developing the testing programme. In Scotland, the testing programme was developed to make use of the existing resources, increasing sample numbers in line with the capacity of the SEPA laboratory. Whereas in England, the more expensive approach of outsourcing testing whilst a new laboratory was built was adopted. This removed existing constraints on testing capacity because numbers of tests could be specified in advance and also the new laboratory could conform to social distancing requirements.

A final comparison between Scotland and England highlighted by many interviewees was different approaches to data sharing in the two countries[19]. The underlying narrative was one of Scottish willingness to share the WW testing data (which has been in the public domain since October 2020) compared to the unwillingness of the equivalent English institutions to release their data to the extent that more than one interviewee described the UK government as "secretive" and unwilling to share data. However, differences between different sectors and organisations – often in environment and public health – mean that the situation is more complex that this account allows. For example, as outlined above, several interviewees highlighted Public Health Scotland's inability to share data below a certain geographic level, one stating that patient confidentiality was being used as an excuse not to share data.

4.5.5 International comparisons

In the final stages of this learning review, international data on WW testing (WWT) programmes in countries outside the UK specifically were gathered to see if the issues highlighted above, of limited involvement of public health in WWT initiatives, had been experienced in other countries.

This involved preliminary scoping research in this area, a desk-based study and a small number of interviews for three case studies – Switzerland, Australia (Canberra) and the Netherlands. These cases were selected in order to explore three contrasting scenarios where organisations from different sectors led the development of the testing

19 UKHSA released their wastewater testing data 10 months after the Scottish data was made available online.

programme. In Switzerland it was led by a water research institute with expertise in environmental monitoring, in Australia by a university public health department, and in the Netherlands, it was a joint venture between a water research institute and public health institute. Of the three, the Swiss situation is most similar to the Scottish one, where SEPA was the lead government agency and PHS was less involved. In making this selection, the findings from the Scottish programme were compared to test whether the initial lead organisation in each collaboration came from environment or from public health, might have an important influence on the resulting links established between the two sectors.

This is a small subset of the many countries that have made use of WWT research to establish Covid-19 monitoring programmes – respondents referred to activities in Finland, Hungary, Italy, Luxembourg, South Africa, Spain, and several states of the USA. The Rockefeller Pandemic Prevention Institute[20] runs a regular roundtable on WW-based epidemiology that includes participants from more than 40 countries; the Covid Poops dashboard[21] – a summary of global SARS-CoV-2 WW monitoring efforts by University of California Merced researchers – lists 142 dashboards from 66 different countries.

Switzerland

In Switzerland, research to develop a test for SARS-CoV-2 in WW was conducted by researchers from Eawag, the Swiss Federal Institute of Aquatic Science and Technology which is part of a wider network including the two universities of ETH Zurich and ETH Lausanne (EPFL)[22]. The work was initially funded by Eawag – interviewees highlighted the importance of the flexibility of their funding and overall support – and data collection began in February 2020, the start of the outbreak in Switzerland. A year later in February 2021, a further collaboration, funded by the Swiss National Science Foundation, between Eawag, EPFL and the Swiss Federal Office of Public Health (FOPH) began collecting and testing daily samples from six WW treatment plants across Switzerland. In collaboration with bioinformatics colleagues, the project began producing estimates of the prevalence of different variants of SARS-CoV-2 in May 2021. At the time of writing (May 2022), the project had funding until the end of July 2022.

In contrast to the Scottish case, Swiss WW testing research was conducted by the laboratories of experienced and well-established microbiological researchers who specialise in the analysis of WW and the environmental transmission of pathogens. Moreover, these researchers are based in a publicly funded institute for water research (Eawag) which has good links to both Swiss universities (e.g., EPFL) and the Federal Office for the Environment (FOEN). Before the WWT project, Eawag had some links to the national public health body (FOPH) but according to one interviewee these links have been strengthened by the Covid-19 work: "I think it just took time to build those relationships and so…that's something I'm thinking about in the context of our work is how can we continue and maintain these relationships for the next event" (interview 41, Researcher). This project remained as research, rather than becoming a national surveillance programme as water management in Switzerland is the responsibility of individual cantons rather than the federal government, and only a few cantons decided to develop such a programme.

Australia (Canberra)

In the Australian Capital Territory (ACT), WW testing research was undertaken by a collaboration centred on the Australian National University (ANU) National Centre for Population Health and Epidemiology[23]. The lead researcher was an epidemiologist and this collaboration also involved researchers from ANU departments – including the Research School of Biology and the School of Medical Research – as well as Canberra Hospital, the local privately-owned water company, ICON Water, and the Health Directorate of ACT. The research began in March 2020, and the sampling programme started in April 2020[24]. Having taken samples daily for 18 months it is now one of the longest running WW sampling programmes in Australia. The laboratory research and initial sampling programme was funded solely by ANU. As in Scotland, researchers also made use of existing facilities, especially ANU laboratories. However, after the sampling programme was awarded to a private contractor, a follow-up research project at ANU, sampling from a quarantine hotel, was funded by the ACT Health Protection Service.

Unlike Switzerland and Scotland, in Canberra WW testing was developed by a public health-led collaboration – the research was devised by an epidemiologist based in a university centre for population health who recruited laboratory colleagues from medicine and biological sciences. This may have been one reason why the research was readily taken up by the state health department: "they were really interested… they were always really positive and engaged" (interview 36, Researcher). Another reason could be that ACT Health Protection Service has a water microbiology division that undertakes seasonal microbial monitoring of major bathing sites[25].

20 https://www.rockefellerfoundation.org/pandemicpreventioninstitute/

21 https://ucmerced.maps.arcgis.com/apps/dashboards/c778145ea5bb4daeb58d31afee389082

22 https://www.eawag.ch/en/department/sww/projects/sars-cov2-in-wastewater/

23 https://nceph.anu.edu.au/

24 https://www.anu.edu.au/news/all-news/tracking-covid-19-transmission-through-our-sewage

25 https://www.health.act.gov.au/about-our-health-system/population-health/environmental-monitoring/recreational-water-quality

This means that there is in-house expertise on water testing, including an understanding of the data produced by such research, whereas in Scotland, bathing water quality monitoring is undertaken by SEPA. Further interviews would be needed to establish if this institutional arrangement means that good links exist between the Health Protection Service and ICON Water.

Netherlands

The Dutch research on WW testing was some of the earliest in the world to be conducted. It drew on the expertise of researchers in the KWR Water Research Institute[26] in PCR testing and their involvement in a WHO investigation of the 2003 SARS-1 outbreak in Hong Kong: "it was a quick assembly of what we learned from the clinical virology, the PCR assay, and the WW virus concentration assay we already had" (Interview 37, Researcher). The group put a pre-print of their protocol online at the end of January 2020 which was widely consulted by other researchers – many of the UK interviewees for this review referred to this pre-print as a source of information and inspiration to develop their own protocols. Prior to the pandemic, the National Institute of Public Health and Environment (RIVM)[27], had been conducting WW testing for antimicrobial resistance, and this infrastructure was rapidly re-purposed to test for Covid-19, so the two organisations worked in parallel to develop a WW testing programme. When a nationwide surveillance programme was developed, RIVM expanded its surveillance to cover all 313 water treatment centres and KWR developed a programme of high-resolution sampling in specific locations to better predict trends in the WW data and understand precisely how they related to case testing data. Perhaps, because the RIVM is part of the Ministry of Health, Dutch water researchers do not seem to have the same issues as their Scottish colleagues in accessing health service case testing data.

The timeliness of this research, combined with the experience of the researchers involved and the reputation of KWR means that the Dutch research was an important international milestone in WW testing for SARS-CoV-2. However, its adoption by the Dutch government may have been helped by the fact that this work was developed jointly by KWR and RIVM[28]. Like the ACT Health Protection Services, RIVM also has a water virology laboratory and again the existing expertise and working relationships may have facilitated the uptake of this new surveillance programme.

The overall conclusion from these comparative cases is that the organisation who leads the initial research and piloting projects matters – research from public health departments and led by public health researchers may gain traction more readily with government ministries of health. Existing institutional structures also seem to matter – the fact that the relevant public health bodies in Canberra and the Netherlands both have water virology departments may be one factor in explaining the success of their WW testing programmes. In contrast, in the Scottish experience, it appears that an environment-led project was trying to engage a public health agency with no previous history of water virology work. This limited public health involvement in WWT was not, however, unique to Scotland: one interviewee who had knowledge of more than 40 WW testing programmes argued that "only one or two other nations have managed to get [WWT] really integrated into public health response, and they've been the ones where it's come out of health organisations, rather than environmental spaces" (Interview 35, UK Government employee).

4.6 Discussion

To summarise the findings described above, the Scottish SARS-CoV-2 WW testing programme was developed collaboratively from a "standing start" in less than six months. This success was due to a combination of high-level support from key individuals within relevant organisations and the hard work and motivation of those working on the project. However, after this impressive start the programme encountered a series of structural issues – operating at the middle tier between the ministerial/directorial level and board of directors and those conducting the research and implementing the work of the project. It is arguable that these issues have made the SARS-CoV-2 WW testing programme's transition from innovative research to a routine testing programme more difficult than it should be (even taking account of the accelerated timescales involved) and may even impede the future development of WW epidemiology as a tool of Scottish public health surveillance.

The successful elements of the development of the SARS-CoV-2 WW testing programme include:

- The important role played by CREW in establishing and funding the pilot research projects.
- The flexibility of initial institutional responses.
- The sharing of specialist knowledge and research data among collaborators.
- The use of existing capacities and internal resources to develop the testing protocol, share it between collaborating organisations and set up the initial sampling and testing programme.

26 KWR is a private research institute largely owned by Dutch water companies: https://www.kwrwater.nl/en/

27 https://www.rivm.nl/en

28 https://www.kwrwater.nl/en/actueel/update-covid-19-sewage-research/

- The public availability of project data and its accessibility via the SEPA dashboard.
- The further collaborative work undertaken to link the SARS-CoV-2 WW testing data to the individual case data.

The less successful elements of the programme include:

- Its apparently hesitant take up by Scottish Government leading to a lack policy "ownership".
- The limited involvement of Public Health Scotland, and therefore weak public health rationale behind the development of the sampling programme.
- Ongoing use of ad-hoc approaches to organising the programme, some of which relied on extended periods of heavy workloads for some individuals.
- The lack of strategic leadership as both research and testing programmes expanded well beyond the scope of the initial pilot projects.

Detailed reflections on these strengths and weaknesses follows below, with reference to the initial analysis and with further links to the existing literature outlined above.

These successes point to the importance of brokerage functions in creating collaborative conditions and, specifically, the work of organisations like CREW: "the existence of the concept of CREW and the fact that we all had this common meeting place was absolutely key" (Interview 19, SEPA employee). This is one area where the Scottish environmental research sector is performing well, and their good practice should be emulated in other sectors, such as public health research. These findings also highlight the need for Scottish government to fund basic science capabilities – as noted above, core-funded facilities were crucial to the success of the initial research, as were the internal capacities of SEPA and Scottish Water. A key example of such capacities is the design of the well-regarded SEPA WW testing dashboard by one of their data scientists. Finally, these successes also highlight the benefits of open-source science and the tensions between those benefits and the need for patient confidentiality, especially with respect to health data.

The case of the development of the Scottish SARS-CoV-2 WW testing programme illustrates some well-known, and recurring, issues in science policy, namely how governments allocate research funding and what are the best ways of maintaining standing research capacity. One interviewee argued "you can't chuck people fifty grand here and there and expect that to maintain any kind of medium term, not even long term, but medium-term capacity in an area… the core funding required to maintain what Government was looking for just hasn't been there" (Interview 2, Researcher). The evidence outlined above demonstrates not only that the Scottish Government relied on "borrowed" expertise from universities and research institutes in its pandemic response, but also that it continues to rely heavily on cross-funding from the UKRI (and to a lesser extent the Scottish Funding Council) to support and maintain research laboratories and ensure a supply of trained staff to work in them[29]. In the authors' opinion, this means that is necessary to re-consider the increasing reliance on short-term project-based funding models in science and improve levels of core funding for key institutions, in order to maintain capacities and capabilities as research increasingly requires a longer-term, transdisciplinary approach. Resilience requires maintaining a healthy and diverse research ecosystem.

In the spring of 2020, SARS-CoV-2 was a novel organism, but the science involved in the research to develop an initial test for RNA fragments in WW, and later on to develop a test for variants of concern, was not novel science. Moreover, the research was conducted at a speed that made "excellent" science an impossible goal: "having done something quick and dirty, is quick and dirty good enough or do you have to optimise it?" (Interview 2, Researcher).

It is arguable that the SARS-CoV-2 WW testing programme was an example not of "excellent science" but of "good enough" and timely science[30]. This means that it's necessary to recognise the negative impacts of the contemporary preoccupation with funding "excellent science" above all else, (e.g., Lyall, 2022) and reflect more broadly about the range of research skills and capacities that are developed from public funding of science. SARS-CoV-2 WW testing relied on established techniques – the novelty came from applying those techniques to a newly discovered virus – what will happen if the next pandemic response requires novel science and therefore training researchers in new techniques?

Lockdown, and other pandemic restrictions, had complex effects on the initial research and development of the sampling and testing programmes. Paradoxically, lockdown had the important positive effect of enabling the early work to take place by freeing up staff and resources in the Roslin Institute, Scottish Water and SEPA: "probably timing was beneficial because obviously, you know, other work had stopped due to lockdown… the team was sitting there with a lot less to do so they could, in the short term, pick this up" (Interview 18, Scottish Water employee).

However, the restrictions imposed during the first lockdown, in particular, also made this work much more

29 Division of responsibilities for science policy and funding between national and regional levels of governance has, of course, long been a feature of Scottish devolution (see, for example, Lyall, 2007).

30 Science in this context refers to both university laboratory research and the routine monitoring and testing activities carried out by organisations such as SEPA and Scottish Water.

difficult. These difficulties included negotiating access to laboratories and water treatment facilities, persistent shortages of PPE and laboratory supplies, problems in successfully arranging deliveries to closed buildings, and reductions in laboratory staff numbers due social distancing requirements. Shortages of laboratory supplies and consumables lasted for several months, and the logistical problems were so bad during lockdown that one interviewee argued that the lockdown regulations "hobbled our ability to actually do the science needed to better understand what was happening in the pandemic" (Interview 2, Researcher).

4.6.1 Scotland-specific issues

A final key factor in the successful establishment of the WW testing programme was the important role played by Professor Andrew Millar, the former Chief Scientific Advisor for Environment, Natural Resources and Agriculture (CSA ENRA). The CSA was not involved in assessing the research proposal for the first CREW-funded pilot project. Since May 2020 he used his technical expertise in molecular biology to underpin a much wider role advocating for the value of WW testing within Scottish Government and beyond – facilitating contact between the public sector bodies involved in the project, briefing senior politicians about its results, trying to develop links with colleagues in the Scottish public health community and representing the Scottish SARS-CoV-2 WW testing programme at UK-wide meetings. In this way, the former CSA was initially making up for the lack of a WW testing policy team within Scottish Government by developing and/or maintaining relationships with key internal and external stakeholders. To re-state this point in the language of the previous Timeline section, he was filling the "gap in the middle" and he continued to provide scientific input and act as a champion for the programme. He has also stated his intention to continue some of these activities beyond the end of his term as CSA ENRA in December 2021, to conclude the current CREW project and contribute to Scottish Government's future planning. However, many of these activities are beyond the normal scope of a CSA's role – which again highlights the improvised nature of organisations' responses to the pandemic.

From the foregoing discussion of the findings presented here, in the context of existing scholarship outlined in section 4.3, it can be inferred that, at minimum, success in this type of rapid response research requires "collaboration readiness". It necessitates the availability of suitably trained personnel, facilities (including, in this case, access to specialist category 3 labs) and access to adequate resources and supply chains[31]. Significantly, collaboration readiness also hinges on less tangible requirements. Rapid response collaborative research requires that functional, working relationships between partners are already in place or can be rapidly brokered. This in turn, obliges a level of trust between partners and agencies, or at minimum, an attitude of "assumed" trust (Meyerson, 1996). This was evidenced between some, but not all, potential partners within the SARS-CoV-2 WW testing programme. Comparative international interviews (Section 4.5.5) suggest that the lack of trusted working relationships between certain actors may explain the difficulties in achieving rapid take up of the WWT surveillance data within the Scottish health sector.

Successful transdisciplinary research is built on an ethos of openness (Pohl and Hadorn, 2007). Such collaborative relationships take time to operate effectively. As contemporary and future research problems require increasing collaboration across disciplines and sectors, it is essential to question how research is funded in order to sustain the complex multi-partner projects required to address pressing global social challenges such as novel zoonotic infections, increasing rates of anti-microbial resistance, and increasing health risks associated with climate change. In such situations, it is no longer sustainable to focus on short-term project funding – these "wicked" problems require greater core funding and the consequent continuity of expertise that such funding develops. In light of the findings above, it is arguable that it is vital that such funding also includes adequate resources for networking, co-ordination, integration and brokerage and that these functions are accorded appropriate status within the collaboration.

4.7 Lessons learned

The findings of this review apply to the development and operation of the SARS-CoV-2 WW testing programme at a range of scales, from the micro to the macro level. This is reflected in the following list of key lessons learned which will form the basis of the recommendations in the conclusion of this report. Please note, they are listed thematically and not in any order of priority.

4.7.1 Preparing for future emergencies

- Effective emergency responses to health crises such as pandemics require stronger links between academic research laboratories and both government-funded testing laboratories (SEPA and SW) and private sector contract testing laboratories.
- Laboratory researchers should be considered key workers and contingency plans put in place to acquire key research consumables (pipettes, reagents, PPE, etc) in case of another pandemic.

31 Including routine laboratory supplies.

- Some of the collaborating organisations appear to need to develop (or make better use of existing) crisis preparedness planning (task prioritisation, minimum standards, streamlined redeployment & hiring processes, low tech communication practices) and rely less on ad-hoc responses.
- In crisis situations, people turn to their existing professional network first. Initiatives that develop and extend such networks without requiring large investments of time can potentially improve organisations' resilience.
- Re-organising public bodies (notably PHS and UKHSA) during a pandemic should be avoided.

4.7.2 Funding research and infrastructure

- Core funding of research institutes and universities was important in allowing this research to be conducted (especially as it required using Cat3 labs and ULT freezers), it is critical that such national capacity is be maintained.
- Expanded laboratory facilities and staffing would ensure more sustainable responses to future emergency situations by public agencies such as SEPA.

4.7.3 Communicating within and across agencies

- Communication needs to be improved within Scottish Government and its agencies – it is evident that there is already loss of institutional knowledge about the WW testing due to the way responsibility for programme has moved around Scottish Government, demonstrating the importance of continuity.
- Improved horizontal communication between some organisations would ensure that people working on the same material/problem can talk to each other directly rather than information travelling up several levels in one organisation, and back down another parallel set of levels before being acted on.
- In order to improve organisational transparency for outsiders, the Scottish Government and PHS websites should have easily identifiable contact points and provide more details about their organisational structures.

4.7.4 Co-ordinating across policy sectors

- Within the Scottish Government, this review highlighted an apparent lack of communication between the directorates responsible for environment and those responsible for health, and these policy "siloes" are hindering the Governments responses to key issues like Covid and may impact future challenges such as AMR.
- High-level co-ordination of the WW testing programme was lacking in Scotland and future crisis responses need to develop faster policy responses in order to co-ordinate new programmes of work developed across the different Scottish agencies and their external collaborators.
- Ideally new initiatives, such as the SARS-CoV-2 WW programme, should be led by the most relevant agency (in this case Public Health Scotland). If that is not possible then tailored communication and co-ordination strategies should be developed to encourage update of the result by key practitioners.

4.7.5 Sharing knowledge and data

- Approaches to data sharing could be much more consistent especially across the devolved administrations but also within the Scottish Government, and among its agencies; there also needs to be greater clarity about who owns this data (perhaps with a duty of openness for public bodies whilst maintaining necessary procedures for privacy).
- 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.
- Where Scottish Government commissions/funds learning reviews, public sector employees should be encouraged to participate and provided with appropriate guidelines on how to do so.

4.8 Conclusions and recommendations

The Scottish SARS-CoV-2 WW testing programme was an impressive achievement. In approximately 6 months, and working under pandemic restrictions, collaborators from the Roslin Institute, Scottish Water, the Scottish Environment Protection Agency (SEPA) and the Scottish

Government – supported by Scotland's Centre of Expertise for Waters (CREW) – developed a new test protocol for SARS-CoV-2 in WW and established a nation-wide sampling and testing programme covering approximately 80% of the Scottish population.

This review of these activities demonstrates the existing strengths of the Scottish science ecosystem, illustrates the effective ways this system can respond to large-scale crises, and recommends refinements to improve this preparedness. This review further demonstrates that, in future, the Scottish Government should be able to fully adopt validated 'One Health' approaches that many have argued will be necessary to manage the future impacts of the climate crisis. However, this study also reveals some weaknesses in cross-sectoral working across health and environment, and in the take up of research by Scottish Government, and the recommendations target these areas.

These recommendations, based on empirical evidence, have been piloted with a group of key stakeholders[32] and draw directly on the Lessons Learned established in the previous section. These recommendations – aimed at the Scottish Government and its agencies – represent actionable improvements to key processes.

Many of these recommendations address ways in which these public organisations can improve their communication with each other and with the wider Scottish research community, and so better co-ordinate their activities to achieve optimal outcomes in emergency situations.

Recognising that the specific topic of pandemic preparedness will be considered in greater detail by the Scottish Government's Standing Committee on Pandemic Preparedness (SCoPP)[33] – due to report in the next 18 months – these recommendations largely focus on the key ways in which the effectiveness of crisis responses can be improved across the broad 'One Health' science policy landscape.

1. **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.

2. **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.**

   Small-scale and responsive funding schemes worked well in this case, but their success was contingent on standing research capacity such as cat-3 laboratories, specialist equipment and the availability of appropriately trained researchers. Continuity of funding is especially important in transdisciplinary research where it takes longer to build and maintain relationships of trust across organisational boundaries

3. **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. This could be part of the expanded scientific advisory mechanism recommended by the recent Scottish Science Advisory Council (SSAC) report *Building on the Science Legacy of Covid-19 in Scotland.*

4. **The Scottish Government should establish a new post of Chief Scientist for Public Health to better represent the Scottish Public Health community in light of increasing need to focus on "One Health" strategies.**

   The review findings indicate that neither the Chief Scientist (Health) nor the Chief Medical Officer currently represent or provide sufficiently high-profile leadership for the Scottish Public Health community. This gap has implications for both the public standing of the sector and the possibilities for strategic co-ordination with other sectors and with the Chief Scientific Advisors (Recommendation 3).

5. **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 SARS-CoV-2 WW testing pilot programme. CREW's existing relationships with a range of key stakeholders were an important asset in the Scottish

32 They were discussed at a webinar attended by roughly 35 individuals many from the collaborating institutions and including representatives from Scottish Government and its agencies: https://www.crew.ac.uk/news/webinar-lessons-be-learned-development-scottish-sars-cov-2-wastewater-screening-programme

33 https://www.gov.scot/news/preparing-for-future-pandemics/

case. However, it has not been possible to identify similar knowledge-brokerage organisations within public health.

6. **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.**

   In crisis situations, people initially turn to their existing networks for assistance with unexpected and urgent tasks. 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.

5. Overall conclusions and recommendations

The SARS-CoV-2 WW monitoring programme returned independent estimates of key metrics of the Covid-19 epidemic and here, also tracked the progress of two successive variants. The advantages of WBE have been its cost-effectiveness and independence from testing behaviour. Non-invasive wastewater sampling avoids the bias due to the individual testing behaviour in the population at any point in time. The wastewater monitoring process has also remained comparable over the course of the pandemic, whereas the regimes for individual testing have changed very significantly. There remain uncertainties in interpreting wastewater data relating to the persistence and shedding rate of the virus (Li et al., 2021). Wastewater monitoring in Scotland has proved scalable, to focus on specific locations of interest on demand. It has the potential to provide earlier detection than other data sources (Medema et al., 2020), though the timing in practice depends upon many factors in both the wastewater monitoring and the comparator data. In principle, wastewater monitoring is also adaptable to multiple pathogens and to chemical signatures (Sims et al., 2021).

All three elements of this ambitious project sought to provide better evidence of the SARS-CoV-2 epidemic. They each depended upon collaboration between researchers at the University of Edinburgh and partners (Scottish Water, SEPA, BioSS and Scottish Government) with CREW facilitating communication between these partners.

After testing but rejecting PCR-based methods (qPCR, dPCR) to detect viral variants, the laboratory team optimised a method based on DNA sequencing. Over 2000 WW samples from across Scotland were analysed to monitor the spread of first Omicron and then BA.2 variants between November 2021 and March 2022. This method also has future potential for analysing multiple pathogens simultaneously. An important outcome of the project is the pilot experiments which have commenced to measure the level of influenza virus, as well as SARS-CoV-2, in WW.

Making the data and methods generated by the Scottish programme most widely available safeguards the public investment, contributing to build resilience for future pandemics or crises. This has been achieved by providing training on data management and sharing to the lab researchers, and by depositing project outputs on suitable platforms to maximize visibility to the target audiences (published lab protocols, a publication in the journal *Scientific Data*, and an externally hosted 'front page' website), while assuring cost-free, long term, sustainable preservation.

Similarly, valuable lessons may be learned from the operational processes that have developed across government, utilities, regulators and scientists to enable the monitoring of SARS-CoV-2 in WWs in Scotland. The 'Lessons Learned' phase synthesised these lessons, from a qualitative social science study. Four themes characterised the rapid, cross-sectoral responses to the emerging Covid-19 situation: participants' positive experiences of collaboration; the ways in which these collaborations relied on existing networks within research, practice and policy, notably mediated by CREW; the new relationships that developed from the work on WW testing; and the problems many participants experienced in securing inter-agency participation and buy-in to the SARS-CoV-2 WW testing programme. The programme had pushed the limits of Scottish Water and SEPA's existing sampling and testing capacities, using agile, ad hoc approaches that were not ideal in the medium-term. The challenge is now for Scottish Government to take over management of this new programme and absorb it into its routine activities.

Qualitative assessment of the difference between the equivalent programmes in the 4 UK nations is continuing.

5.1 Recommendations

The laboratory tests demonstrate that a sequencing-based method is the most robust and reliable for variant detection (and possibly for several pathogens) in WW. The technical demands of this approach would currently require the participation of expert researchers at least for data analysis in the face of a changing mix of variants, and possibly also for the laboratory sample preparation [the former CSA notes: These skills are relevant to other analyses within SEPA's remit and likewise for NatureScot, SASA, Marine Scotland, Scottish Forestry and possibly other agencies. This need was recognised before Covid-19. RESAS funded a pilot study in this area in 2019, which was arranged by a sub-group of CAMERAS that comprised these agencies and researchers from RBGE, the University of Edinburgh and elsewhere. The experience of this variant detection project reinforces the need for Scottish Government agencies to gain routine access to modern DNA sequencing methods and data analysis.

Any cross-sectoral project of this type should establish a collaborative data platform. A shared drive for administrative information is the minimal step (such as the Scottish Government's Objective Connect), a wiki for research information is an intermediate level, and shared storage for all the programme data and other outputs is more challenging but more valuable. Training and technical capability would be required, which might for example be provided by CREW. One approach would be to fund a data curator role routinely in future projects, to test the workflows, flag potential issues in data management and give recommendations that facilitate reporting and sustainable data dissemination.

The Scottish research ecosystem responded to the Covid-19 pandemic with flexibility, creativity and commitment. In the SARS-CoV-2 WW monitoring programme, research was rapidly translated into a national programme by equally agile and committed responses from Scottish Government agencies, from SG RESAS as a research funder, and the CSA ENRA and CS (Health) as senior champions. The existing connections of trust among the partners critically underpinned their responses. That social infrastructure merits explicit Scottish Government attention, recognition and continued investment, for example through the RESAS Centre of Expertise model, as exemplified here by CREW. In future challenges that require a response across Environment and Health policy areas, this Learning Review indicates that the Scottish Government also needs enhanced capacity to use, and if necessary to adopt and manage, the outputs from its researchers and agencies. That absorptive capacity appeared to be at or beyond its limits in this case, particularly as the response crossed from Environment to Health policy areas.

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