
Article:
De Silva, T.I. orcid.org/0000-0002-6498-9212 and Malavige, G.N. (2021) Expansion of SARS-CoV-2 sequencing capacity globally is vital for future control of the COVID-19 pandemic. Sri Lanka Journal of Medicine, 30 (1). pp. 4-8. ISSN 2579-1990

https://doi.org/10.4038/sljm.v30i1.273

Sri Lanka Journal of Medicine **SLJM**

Editorial

Citation: de Silva TI & Malavige GN, 2021. Expansion of SARS-CoV-2 sequencing capacity globally is vital for future control of the COVID-19 pandemic. Sri Lanka Journal of Medicine, 30(1), pp 4-8
DOI: http://doi.org/10.4038/sljm.v30i1.273

Expansion of SARS-CoV-2 sequencing capacity globally is vital for future control of the COVID-19 pandemic

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Despite the worldwide devastation and suffering that the COVID-19 pandemic has undoubtedly caused, it has also shown the pace and extent to which science can respond when faced with a public health challenge of this nature. Along with the speed of highly effective SARS-CoV-2 vaccine development and large-scale pragmatic clinical trials such as RECOVERY [1], the use of rapid viral genome sequencing in tracking and monitoring the pandemic has been unprecedented. Several technological advances over the last few decades enabled this response; including significant reductions in the cost of sequencing, the availability of user-friendly bench-top sequencing devices, as well improvements in the computational capacity required to manage the increasing amounts of data generated. The use of whole genome sequencing to track hospital and community outbreaks of viruses such as influenza, norovirus and Ebolavirus in recent years had left the scientific community primed to deploy this tool rapidly to inform public health management of a pandemic for the first time in history.

Generating sequence data rapidly is of no use to a public health response unless results are shared in publicly accessible repositories in a timely way. This has also been a hallmark of the pandemic response, with many academic scientists shifting from a mindset of retaining sequence data for research and publication purposes only, to sharing their data freely and immediately on platforms such as the Global Initiative on Sharing All Influenza Data (GISAID). GISAID was originally established in 2008 in response to avian influenza outbreaks and has since been used primarily to monitor changes in seasonal influenza virus genomes. It hosts one of the largest curated repositories of SARS-CoV-2 genomes and at over 1.5 million genomes deposited to date [2], SARS-CoV-2 has now been sequenced more than any other pathogen.

Published: 2021-06-30

There are several ways in which viral sequencing has played a role in the COVID-19 pandemic. Firstly, metagenomic sequencing helped identify and characterise SARS-CoV-2 as the causative agent of COVID-19 and also allowed rapid design of the first molecular diagnostic tests. As SARS-CoV-2 spread globally, genomic data were used to understand transmission dynamics at a local, national and international level. This field of genomic epidemiology utilises mutations arising within the SARS-CoV-2 genome, which in effect are errors occurring during the viral replicative cycle, to identify patterns of transmission. This ranges from defining outbreaks on hospital wards [3], to identifying inter-continental spread and importation of SARS-CoV-2 lineages [4] into countries. What is key is that when sequencing is performed in near real-time, this information can be used to inform decisions about control measures. Sequence data are increasingly used to guide infection prevention in hospitals. They have also been used at a national level to guide implementation of non-pharmaceutical interventions, as well as assess the effectiveness of these public health measures. For example, the B.1.1.7 (alpha) variant was rapidly identified as the cause of the exponential rise in infections in the UK towards the end of 2020. Observation that a novel variant was more transmissible and potentially caused more severe disease [5] helped guide decisions for stricter national control measures. Similar considerations are relevant as the B.1.617.2 (delta) variant sweeps the UK in 2021 and appears to have a transmission advantage over B.1.1.7 [6].

Though helpful for genomic epidemiology, the majority of mutations in the SARS-CoV-2 genome have no functional relevance. During the first phase of the pandemic, only the D614G mutation in the spike protein was shown to result in a selective advantage for global spread [4, 7]. With increasing population immunity due to SARS-CoV-2 infection and vaccines, the occurrence of several spike mutations that may facilitate reduced antibody recognition have become increasingly relevant to pandemic control. Mutations demonstrated in laboratory experiments to cause reduction in neutralisation by convalescent or post-vaccine sera can be tracked as they appear in different SARS-CoV-2 lineages. The B.1.351 (beta) variant appears to result in significant reduction in neutralisation titres and some reduction in clinical vaccine efficacy against infection [8]. Such variants that represent a potential threat to SARS-CoV-2 control due to an altered phenotype (e.g. transmissibility, severity, immune escape) have been defined as 'variants of concern' (VOC). While no VOC has so far been shown to significantly negate protection from a two-dose vaccine course, especially against severe disease, the need for active prospective surveillance worldwide is very clear as we look to the future. In addition to potential immune escape, mutations may also affect the performance of molecular diagnostic tests, which could be of equal relevance to national SARS-CoV-2 control programmes.

Unfortunately, these successes in utilisation of SARS-CoV-2 genome sequencing are not universal and significant variability in scientific capacity exists between countries. The COG-UK consortium was one of the first globally to undertake large scale SARS-CoV-2 sequencing, starting in March 2020 and harnessing the collective ability of public health organisations, the Wellcome Sanger Institute and over 16 academic institutions in a de-centralised model [9]. This structure has allowed rapid feedback of sequence data not only to national public health organisations, but to local hospitals to aid control of nosocomial outbreaks. Countries such as Denmark, Germany and more recently the USA have also scaled up sequencing efforts significantly (Figure 1).

In most countries, sequencing is less systematic and patchy, with either no capacity or sequencing undertaken in one national centre. In Sri Lanka, our newly established sequencing revealed that a novel lineage emerged in country around late June 2020 (B.1.411) and was responsible for the wave of infections during October 2020 to January 2021 [11], though did not show any altered phenotype of concern. We have also detected that the dramatic increase in infections and hospitalisations that started in March 2021 is due to the B.1.1.7 (alpha) variant. Our submitted sequences still represents only 0.21% of reported cases, yet this is at present higher than India (0.07%), Nepal (0.01%), Pakistan (0.03%), and similar to Bangladesh (0.21%), demonstrating the need to scale up SARS-CoV-2 sequencing in South Asia [10]. Given the potentially more transmissible B.1.617.2 (delta) variant is currently responsible for the majority of infections in India, Nepal and The

Maldives, it is particularly important that other neighbouring countries, including Sri Lanka, remain vigilant for introduction of this variant through prospective surveillance so that adequate control measures can be implemented if necessary. Only 21 countries have deposited sequences in GISAID from over 5% of all reported cases, which are almost exclusively high-income countries (Figure 2).

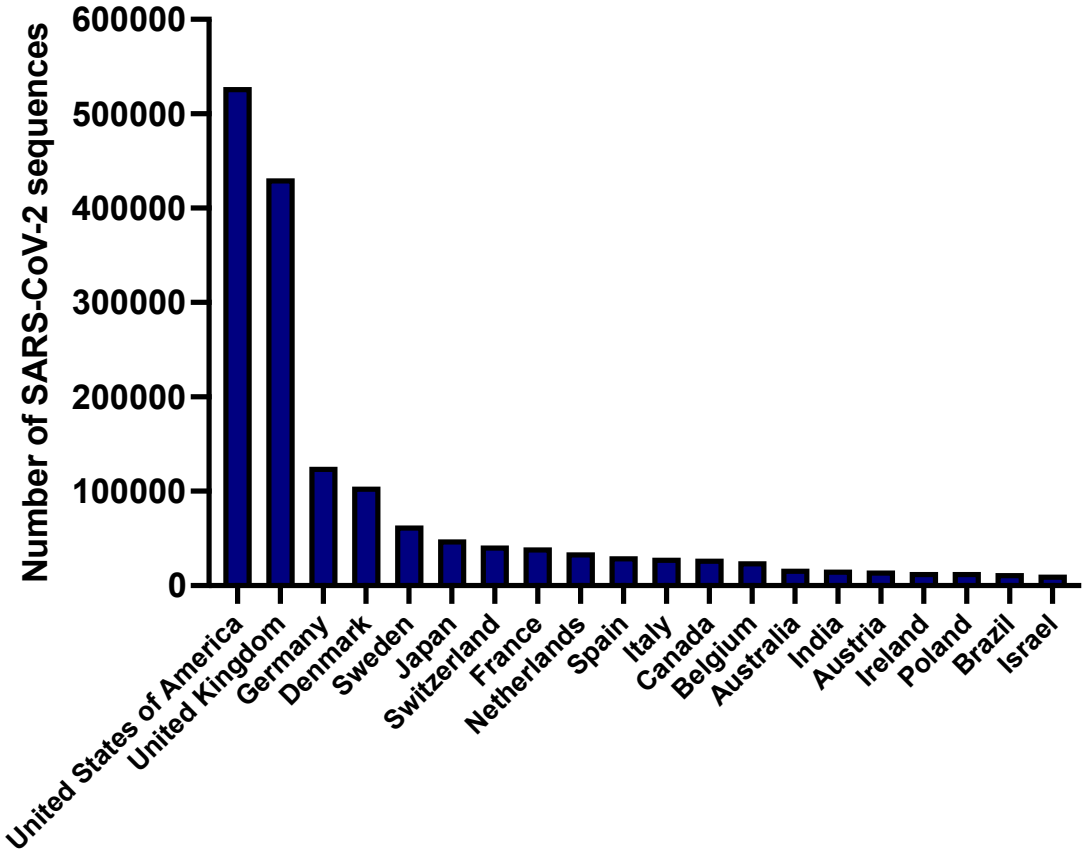

Figure 1. The number of SARS-CoV-2 genomes deposited per country.

Displayed are the 20 countries that have deposited the most SARS-CoV-2 genomes in GISAID as of the 6th of June 2021 [10].

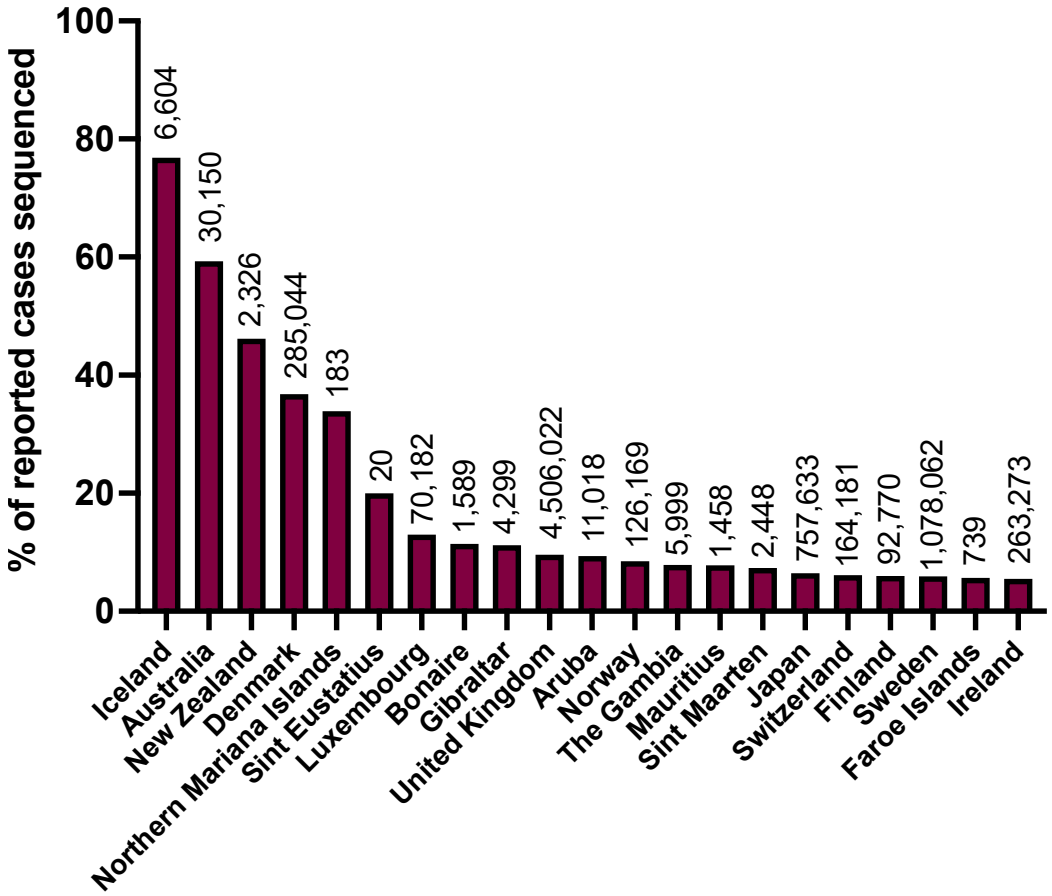

Figure 2. Percentage of total reported SARS-CoV-2 cases sequenced by each country.

Displayed are countries that have deposited sequences from >5% of all reported cases. Numbers above each column represent total reported cases. Data derived from GISAID on 6th June 2021 [10].

In addition to addressing inequity in vaccine rollout in low and middle-income countries, there is clearly a need to scale up capacity for in-country sequencing in many settings. The need to track the emergence of variants that may threaten national vaccine programmes through immune escape is vital and will continue for the foreseeable future. While this is of importance to each specific country in implementing public health measures, it is equally relevant to global SARS-CoV-2 control. If there continues to be sequencing 'blind spots' worldwide, new VOC will only be detected when they spill over into countries with high sequencing coverage, which may be too late for effective public health measures in countries where substantial spread has already occurred. Establishing and scaling up sequencing programmes in many countries will require financial investment and effective planning to overcome multiple logistical challenges. Alongside laboratory capability, bioinformatic capacity also needs scaling up. Issues such as collection of metadata, appropriate sampling strategies and how best to optimise end-to-end turnaround time from sample collection to feeding back results to public health officials requires careful consideration. To help with these processes, the WHO have produced a very helpful guide to implementation of SARS-CoV-2 sequencing for maximum impact on public health [12]. It is crucial that expanding this capacity is seen as a cornerstone of SARS-CoV-2 control in all countries as we move into the next phase of the pandemic, but also serves to build a platform to be better prepared to deal with future infectious disease threats.

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