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Genomic surveillance to combat COVID-19: challenges and opportunities

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Although the development and increasingly widespread availability of effective and safe vaccines provides the greatest hope for the future recovery from the increasingly devastating COVID-19 pandemic, there are other preventive efforts that offer an immediate route to decreasing morbidity and mortality. Genomic surveillance is emerging as a vital necessity to achieve effective mitigation and containment. Since SARS-CoV-2 variants have already been detected, it is crucial to obtain reliable evidence about whether they are more contagious, virulent, or more resistant to the available COVID-19 vaccines well before they spread throughout the world. Genomic surveillance leverages applications of next-generation sequencing, creates the availability of whole genome data, and advances phylogenetic methods. These methods offer novel means to detect variants that are phenotypically or antigenically different. Genomic surveillance will facilitate greater early anticipation as well as initiation of effective strategies to mitigate and contain outbreaks of SARS-CoV-2 variants and other novel viruses.

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Introduction

Few responsible health authorities would disagree that, worldwide, the more than 190 million cases and more than 4 million deaths from COVID-19 caused by SARS-CoV-2 constitute the largest global public health emergency since the 1918 influenza pandemic.[1,2] Although the development and increasingly widespread availability of effective and safe vaccines provides the greatest hope for the future recovery from the increasingly devastating pandemic of COVID-19, there are other preventive efforts that provide an immediate way to decrease morbidity and mortality. Epidemiological surveillance of communicable diseases, or watchfulness over the distribution and trends of incidence through the systematic collection, consolidation, and dissemination of data, has been the gold standard for disease control for more than a century. The use of these vital components of widely available and accepted public health strategies of mitigation and containment contributed to smallpox becoming the first and only human infectious disease ever eradicated from the world.[1]

While epidemiological surveillance is essential for the control of COVID-19, it is our personal view that genomic surveillance is equally crucial. Specifically, genomic surveillance leverages applications of next-generation sequencing, creates the availability of whole genome data, and advances phylogenetic methods. These methods offer novel means to detect variants that are phenotypically or antigenically different well before they spread throughout the world.

Rapid evolution of RNA viruses

Similar to other RNA viruses, which include influenza, SARS-CoV-2 continually accumulates polymorphisms in its genome. As the viral genome acquires these nucleotide changes, researchers can combine innovative genomic analytics with more traditional epidemiological tools to permit early phenotypic and immunological characterisation of new variants that might be as important as containment in understanding the potential infectious and pathological significance.

RNA viruses are more prone to replication errors than DNA viruses. SARS-CoV-2 has some proofreading functions, which means variants typically accrue more slowly than in other RNA viruses such as influenza or norovirus.[3,4] In fact, SARS-CoV-2 has a predicted rate of evolution, accumulating on average two polymorphisms per month.[5] In addition to leveraging these changes to identify different lineages of virus that might be spreading in a population, the availability of this sequence information allows researchers to identify variants that might alter the detection, infectivity, or severity of the disease. Particular interest has been focused on changes in the spike protein responsible for host cell binding and entry that could result in false negatives in existing diagnostic tests. Additionally, such variation could affect transmission rates, health outcomes, therapeutic responses, and vaccine effectiveness.

Geographical spread of COVID-19

After the pandemic began over a full year ago and began to propagate, especially in the USA, more than 300 000 cases of COVID-19 emanated from a single international business conference in Boston, Massachussets, in February, 2020. By performing large-scale sequencing and phylogenomic analyses of patient samples between March and May, 2020, researchers identified a unique genomic signature of the SARS-CoV-2 virus circulating at this conference that was used to trace downstream spread. By November, 2020, patients carrying virus with this unique genomic signature had been detected from 29 different US states. This finding, in turn, led to the recognition that super spreader events rather than individual transmission are responsible for most cases of COVID-19. By understanding the central role for overdispersion of SARS-CoV-2, public health strategies using localised lockdowns could substantially reduce the impact of the current pandemic in comparison to the 1918 influenza pandemic.[6,7]

Genomic surveillance of COVID-19

With respect to genomic surveillance of COVID-19, the vast majority of the most reliable data derive from the COVID-19 Genomics UK (COG-UK) collaborations between academicians and public health authorities.[8,9] Among their extraordinary accomplishments already, COG-UK has repetitively sequenced entire SARS-CoV-2 genomes as the virus spreads across the country. As one example of this application, genomic analysis of a rapidly expanding cluster of COVID-19 in southeastern England revealed that a new variant of concern, called alpha (B.1.1.7), was responsible for more than 50% of the cases in this locality between September and early December, 2020. Another variant, delta (B.1.617.2), arose in India, but accounted for more than 90% of all cases in the UK by June, 2021. Infection rates were five-fold higher among children (aged 5–12 years) and youths (aged 18–24 years) than older people (aged ≥65 years), and most cases were among unvaccinated people.[10] There is also suggestion that some vaccines are less able to neutralise the delta variant.[11] The shifting of predominant variants raised awareness for conducting large-scale sequencing in contexts where there are immunocompromised individuals or patients treated with antiviral agents that might increase the mutation rate and give rise to new viral lineages. These considerations can be combined with other data sources, such as geographical information from smartphones, impending signs of infection from wearables, and viral concentrations in sewage, to strategically deploy public health measures to a specific population, a term coined precision public health. As soon as the initial person is diagnosed with a highly transmissible form, contact tracing and strict isolation should be enforced. These countermeasures should constrain its spread, as long as this variant is rare. In 2020, only non-pharmaceutical interventions (regional restrictions, targeted testing) could follow identification of new variants, whereas now, it might be possible to intensify vaccination campaigns (eg, ring vaccination or high localised coverage) in response to findings. Just as important as identifying which regions are changing, this type of genomic analysis can also identify those viral regions that are most resistant to change that can then be exploited for drug design and vaccine development.

As this virus continues to evolve, the basic and clinical research communities have come together in a remarkable spirit of collaboration to permit the timely sharing of multidimensional genomic and epidemiological data (eg, GISAID) on a global scale that can be leveraged for further diagnostic and vaccine development.[12] The current vaccines induce an immune response to several regions around the spike protein and lead to 90–95% efficacy against the original viral form. By contrast, however, basic research is emerging that shows that some variants of concern (eg, beta [B.1.351] and gamma [P.1]) are not completely neutralised by vaccine-induced antibodies.[13] Although the possible clinical relevance remains unclear, these findings highlight the urgent need for genomic surveillance and the continued timely sharing of this information with the worldwide research community. This is crucial not only for the initial design of vaccines but also their refinement in real time in response to emerging genetic variability of the virus.

For **GISAID** see https://www.gisaid.org

WHO has endorsed genomic surveillance as a worldwide priority and cites the previous successes achieved in Ebola virus disease and influenza.[14] Within the Americas, the Pan American Health Organization has created the COVID-19 Genomic Surveillance Regional Network of its member nations to help achieve these goals through increasing sequencing capacity.[15] Of the currently classified variants of concern (ie, alpha, beta, gamma, and delta), the best-characterised SARS-CoV-2 variants, alpha and beta, were first reported in countries with active surveillance and genomic mapping. In countries forgoing this tool, there is strong likelihood of similarly novel variants of concern emerging and spreading without detection. The USA accounts for 4·5% of the global population, but as of July, 2021, leads the world with 18% of reported COVID-19 cases (more than 34 million).[2] By contrast, the USA ranks 43rd in the world in surveillance and genomic sequencing of viral variants.[16] Thus, there is an urgent case for making a substantial investment in the USA's public health infrastructure. Although first proposed in July, 2020, the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) project has been slow to get off the ground.[17] In February, 2021, the US President announced the investment of nearly US$200 million in the Centers for Disease Control and Prevention to "identify, track, and mitigate" emerging SARS-CoV-2 variants, with an additional appropriation from the American Rescue Plan Act.[18] Given the current continued high levels of transmission in the USA, establishing a systematic, widespread surveillance system will be crucial in monitoring the evolution of domestic variants of concern, along with those from other countries. Indeed, with such efforts gearing up, it is now known that several variants of concern are circulating in the USA.[19] For example, the alpha variant became the dominant form among new cases reported in the USA as of March, 2021,[20] but as of July, 2021, the delta variant accounts for 83% of cases.[21]

A needed change to foster communication that does not refer to SARS-CoV-2 variants by geographical location was brought about by the nomenclature put forward by WHO in May, 2021.[22,23] Along with genomic detection, there is a similar need for worldwide initiatives to track the evolution of viral infections by building global capacity, providing scientific and technical expertise, and supporting underdeveloped countries and vulnerable populations. Further increasing the capacity for surveillance and genomic sequencing at the global level will contribute to a more effective response against the current pandemic by capturing undetected novel variants not only in the spike

region affecting viral entry but also other portions of the viral genome influencing viral replication, proofreading, and transcription.[24,25] This new knowledge will lay the groundwork for more effective public health and medical strategies related to the current pandemic and future viral outbreaks.

As suggested by studies completed this year,[26,27] the current evidence raises concerns about both decreased monoclonal antibody responses and reduced vaccine effectiveness in SARS-CoV-2 variants. In one in-vitro investigation, the data suggest that vaccines might need to be updated and immunity monitored to compensate for viral evolution, as plasma from mRNA-vaccinated patients was less effective against SARS-CoV-2 variants than the original strain.[26] In another in-vitro study, the beta variant, first detected in South Africa, exhibited complete escape from therapeutically relevant monoclonal antibodies as well as neutralising antibodies in COVID-19 convalescent plasma.[27] Most recently, a phase 3 clinical trial of more than 15 000 patients in the UK for a protein-based vaccine reported an efficacy of 89·7% (95% CI 80·2–94·6). Furthermore, the alpha variant was detected in more than 60% of confirmed cases, suggesting good vaccine effectiveness.[28] By contrast, in 4400 patients in a South African phase 2b trial of the same vaccine, the efficacy was only 49·4% (95% CI 6·1–72·8). Further sequencing data revealed that 92·7% of cases were the beta variant.[29] In these studies, sequencing has been useful in identifying mutations, including mutations that are associated with reduced vaccine efficacy or increased virus transmissibility. Additional variants that have shared mutations are probably similar regarding their response to treatment, and further demonstrate the need for genomic surveillance.

Conclusion

In summary, it is our personal view that genomic surveillance to combat COVID-19 is essential and needs to be implemented worldwide in a comprehensive and collaborative manner. It can provide the actionable information on which to implement a more targeted public health strategy that addresses local priorities through stakeholder engagement and mitigation efforts, while awaiting the future recovery made possible by achieving herd immunity through vaccination. Increased international collaborative efforts offer unique opportunities to achieve rapid genomic surveillance and leverage the experiences of high-income countries, especially the UK, and deploy them to low-income and middle-income countries throughout the world. Genomic surveillance will facilitate greater early anticipation as well as initiation of effective strategies to mitigate and contain outbreaks of SARS-CoV-2 variants and other novel viruses.

Contributors

All authors contributed equally with the exception that JDR and CHH conceived the idea and wrote the first draft.

Declaration of interests

DLD reports that he is a consultant to the US National Institutes of Health, the US Food and Drug Administration, and the pharmaceutical and medical device industry on the design, monitoring, and analysis of clinical trials. He receives compensation for serving on several industry sponsored data and safety monitoring committees including AstraZeneca, Amgen, Actelion, Bristol Myers Squibb, DalCor, GlaxoSmithKline, Merck, Sanofi, Boston Scientific, Medtronic, Mesoblast, Intercept, Duke Clinical Research Institute, and Population Health Research Institute of Hamilton. He holds no stock in any pharmaceutical or device company. CHH reports that he serves as an independent scientist in an advisory role to investigators and sponsors as chair of data monitoring committees for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, DalCor, and Regeneron; serves as an independent scientist in an advisory role to the Collaborative Institutional Training Initiative; serves as legal counsel for Pfizer, the US Food and Drug Administration, and UpToDate; receives royalties for authorship or editorship of three textbooks and as co-inventor on patents for inflammatory markers and cardiovascular disease that are held by Brigham and Women's Hospital; has an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority; and does not own any common or preferred stock in any pharmaceutical or medical device company. All other authors declare no competing interests.

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