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EDITORIAL COMMENTARY

Editorial Commentary on "Severity of Illness Caused by Severe Acute Respiratory Syndrome Coronavirus 2 Variants of Concern in Children: A Single-Center Retrospective Cohort Study"

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The Coronavirus Disease 2019 (COVID-19) pandemic has seen terms such as genome sequencing, Delta, Omicron, and variant of concern (VOC) become household words, used ubiquitously by the media, political leaders, and healthcare professionals. Nearly half a century since the publication of the first genome, Bacteriophage phi X174, a viral genome with just over 5000 base pairs [1] and 25 years since the publication of the whole genome of *Hemophilus influenzae* [2], sequencing of pathogen genomes now shapes every aspect of the COVID-19 pandemic. For those working in clinical infectious disease practice, it raises the question about the role of pathogen genomics in routine pediatric care.

In this edition of *Journal of the Pediatric Infectious Diseases Society*, Edwards et al compare clinical outcomes in 714 children diagnosed (October 2020 to February 2022) with COVID-19, by VOC [3]. Illumina sequencing was undertaken on randomly selected samples from SARS-CoV-2-positive children. Clinical outcomes were collected retrospectively. After adjustment for key demographic covariates, comorbidities, and community SARS-CoV-2 incidence, the alpha and delta SARS-CoV-2 variants were not associated, when compared with non-VOC, with more severe outcomes. Children infected with the gamma VOC had more severe outcomes: a 5-to-11-fold increase in the odds of hospitalization, intensive care unit (ICU) admission, requirement for respiratory support, or being diagnosed with severe disease as per the World Health Organization (WHO) Clinical Progression Scale. In those without either prior infection or receipt of COVID-19 vaccination, children with the Omicron variant, when compared with children with non-VOC infection, were more likely to be admitted to ICU or be diagnosed with severe disease.

These results are in contrast to data published from multiple countries demonstrating that, compared with earlier VOCs, infection with the Delta VOC was associated with more severe disease with greater risk of hospitalization, intensive care admission, and death [4–6]. Compared with the Delta VOC, the prevailing evidence suggests that infection with the Omicron variant is associated with milder disease, with less frequent hospitalization, severe disease, and death [7–11]. Of note, these studies exploring the severity of the Omicron variant have been performed in predominantly vaccinated populations, incorporating vaccination or past infection status as a potential confounder. When the severity of the Omicron variant has been assessed by vaccination status, studies have demonstrated consistent results in both vaccinated and unvaccinated individuals [7–9]. Two and a half years into this pandemic, the higher odds of severe outcomes in children with the Omicron variant, when restricted to non-immune children, should cause us to pause and reassess. As pediatricians, we must continue to advocate an approach that balances the risks and potential harms of SARS-CoV-2 infection, against any potential risks and harms of interventions introduced earlier in the pandemic to protect the community. Despite evidence of waning immunity [12], vaccination remains a key element in our COVID-19 strategies as do additional non-pharmaceutical interventions, particularly for our highest-risk children.

These compelling data would not be available to us without the capacity to link pathogen genomic data with patient outcomes. COVID-19 has demonstrated the unpredictability of the pandemic and the importance of real-time genomic data to detect, track, and evaluate the impact of emerging variants. Prior to 2020, genomic surveillance was largely restricted to the arena of outbreak investigations, monitoring influenza strains, and small

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studies of antibiotic-resistant bacteria. COVID-19 has demonstrated the potential benefit, both for patient care and for public policy.

To realize these benefits, sufficient samples must be sequenced to ensure the early detection of new variants. Although recent funding commitments are welcomed [13], they do not completely solve 2 ongoing challenges. As COVID-19 has demonstrated, new variants can arise unexpectedly, and in unexpected places. Global sequencing capacity requires investment, particularly in lower-middle-income countries. More than two-thirds of countries have sequencing capability, but as highlighted in the WHO Global Genomic Surveillance Strategy for Pathogens with Pandemic and Epidemic Potential (2022-2023) [14], stabilizing and sustaining this global sequencing capacity will be critical, both during the current and ahead of future pandemics. With greater capacity, the global genomic sequencing network has the potential to be used in the investigation and acute management of disease that could constitute public health emergencies, including cholera, influenza, Ebola virus disease, bacterial meningitis, and polio.

As demonstrated by Edwards et al, the true benefit of genomic sequencing will remain limited unless it can be combined with critical metadata. When used with clinical, epidemiological, and other multi-source data, genomic data for pathogens with pandemic and epidemic potential inform risk assessments, the development of vaccines, therapeutics, diagnostic assays, and decisions on public health and social measures [14]. Without associated demographic and geographic data, identifying the source and transmission of new variants will be lost. Without associated outcome, vaccination, and treatment data, the severity of emerging variants and potential for immune or drug escape will be missed as will the potential to develop tools that can predict these outcomes from genomic data alone. Speed is essential to ensure rapid utilization of genomic data, for the individual patient, the community, and global health.

As we transition to the new era of pathogen genomics, utilized by researchers, public health practitioners, and clinicians alike, we must continue to advocate for global equity and safe and appropriate use of metadata to ensure that we receive the full return on investment.

Note

Potential conflicts of interest. The author certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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