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LETTER TO THE EDITOR

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The significance and impact of SARS-CoV-2 variants of concern in pediatric solid organ transplantation: More unknowns than knowns

The publication by L'huillier *et al* addresses SARS-CoV-2 infection in pediatric solid organ transplant (SOT) patients and candidates, for which data remain scarce. This work highlights some of the many remaining knowledge gaps with respect to SARS-CoV-2 and pediatric SOT patients. One area of unknown relates to the emergence of new SARS-CoV-2 variants of concern (VOCs) and the potential impact of such variants on immunocompromised children. Key issues with respect to immunocompromised individuals include the genesis of VOCs, their effect on disease severity, transmissibility, and the potential impact on vaccine effectiveness.

1.1 | Genesis of VOCs

Spontaneous mutations naturally occur during SARS-CoV-2 viral replication.[1] Evidence from a small number of reports suggests that compromised immune status with subsequent prolonged viral shedding may enhance replication and through spontaneous generation of mutations, accelerate viral evolution, contributing to the emergence of new SARS-CoV-2 variants.[2,3] Mutations conferring a fitness advantage to the virus, such as increased transmissibility, replication, or immune evasion, can result in new variants that outcompete other circulating strains.[1] Selection pressure can contribute to virus evolution and the question remains whether vaccine-induced immunity and the use of antiviral therapies such as monoclonal antibodies and convalescent sera may facilitate selection of resistant variants.[4] In immunocompromised patients, where prolonged virus shedding more often triggers treatment with antiviral therapies, including convalescent sera, formation of immune escape mutants may result secondary to this additional selective pressure.[2,3] This emphasizes the unique aspects of care for immunocompromised patients with COVID-19 and the importance of preventing SARS-CoV-2 infection among this group. When infection does occur and where there is prolonged viral shedding, the use of sequencing to monitor genomic evolution and identify the emergence of concerning mutations and variants should be considered.

1.2 | Disease severity

As highlighted by L'Huillier *et al*., to date, increased severity of SARS-CoV-2 infection in pediatric SOT recipients has not been described. However, the reports of potentially increased disease severity with some VOCs in immunocompetent populations have emerged. In the United Kingdom (UK), for example, the identified B.1.1.7 lineage has been demonstrated to be associated with a higher mortality rate.[5] In addition, children may be more susceptible to this variant, although the initial reports suggest there is no signal for enhanced severity in the pediatric population.[6] The potential impact of such VOCs on disease severity in pediatric immunocompromised patients, including SOT recipients, is undetermined. Heightened surveillance of the clinical manifestations and disease severity of VOCs in these populations is therefore warranted.

1.3 | Transmissibility

Early signals suggest increased transmissibility of some VOCs, including the B.1.1.7, B.1.351, and P.1 lineages. Consistent with the data from the United States, the UK reports on the B.1.1.7 variant suggest a 43 to 90% higher reproduction number versus pre-existing variants.[7] It is hypothesized this increased transmissibility may reflect a longer infectious period and increased susceptibility in children, which is of particular concern for immunocompromised pediatric patients, who may therefore be more vulnerable to infection from VOCs.

1.4 | Re-infection/vaccine effectiveness

The risk of re-infection with divergent SARS-CoV-2 variants is a point of significant concern worldwide. In Manaus, Brazil, resurgence of COVID-19 despite high seroprevalence may, in part, be due to antigenic escape and re-infection with the P.1 variant.[8] Moreover, although rare, increased disease severity upon re-infection has been

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described.[9] For the immunocompromised population and in particular SOT recipients, the potential impact of re-infection by VOCs and subsequent severity remain unknown. Similarly, reduced neutralizing response in vaccinees' sera against some VOCs have been described, raising concern for re-infection post-SARS-CoV-2 vaccination.[10,11] Data are limited on the immunogenicity and efficacy of wild-type SARS-CoV-2 spike protein vaccines in SOT recipients; preliminary data show suboptimal responses among kidney transplant recipients after a single dose of an mRNA SARS-CoV-2 vaccine.[12] Furthermore, the emergence of VOCs may affect the speed with which SARS-CoV-2 vaccines become available for SOT recipients, as it is likely that mRNA and viral vector-based vaccines will need to be periodically updated based on circulating VOCs.[13] Moving forward, many unknowns for SOT candidates and recipients in regard to SARS-CoV-2 vaccine availability and effectiveness remain.

In conclusion, SARS-CoV-2 VOCs pose a number of unknowns for SOT recipients. The potential for the emergence of new VOCs, increased transmissibility and enhanced disease severity are all the areas of ongoing concern. The impact of VOCs on vaccine efficacy and contribution to the ongoing community transmission of SARS-CoV-2 have implications for the long-term risk to SOT recipients. Given this uncertainty, it is likely that continued strict protective measures for children who are SOT candidates or recipients will remain necessary, especially in the areas where community spread of SARS-CoV-2 remains high. We concur with L'Huillier *et al* for the inclusion of both children and SOT recipients in vaccine trials. Only by increasing our understanding of the risk posed by VOCs and the efficacy of vaccination in this population, can we formulate appropriate strategies for protecting this important and vulnerable group.

DATA AVAILABILITY STATEMENT

Not required—no data included.

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