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Monitoring and managing SARS-CoV-2 evolution in immunocompromised populations

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Since the start of the COVID-19 pandemic in late 2019, five SARS-CoV-2 variants of concern have emerged. The omicron (B.1.1.529) variant, first identified in November, 2021, has more than 20 vital mutations in the spike protein alone, and has rapidly spread across the world within 2 months. We hypothesise that SARS-CoV-2 infection in immunocompromised populations might propagate SARS-CoV-2 evolution and accelerate the emergence of variants (appendix).

Immunocompromised populations include a variety of subpopulations, such as organ transplant recipients receiving immunosuppressive medications, patients with cancer on chemotherapy or immunotherapy, patients with autoimmune diseases, patients with inflammatory bowel disease treated with immunosuppressive or immunomodulatory therapies, and individuals with HIV. Such populations have impaired immune system function, albeit to varying degrees, and therefore in general they are more susceptible to infections. Many viruses such as hepatitis E virus, rotavirus, and norovirus usually cause acute infection in the general population; however, such viruses frequently cause chronic infection in patients who are immunocompromised.[1]

Emerging evidence suggests that chronic infection can also occur with SARS-CoV-2.[2] In the UK, a large number of persistent SARS-CoV-2 infections have been recorded in patients who are immunocompromised, although the total number of affected individuals is expected to be much larger than that reported.[3] Prolonged infection with SARS-CoV-2 has been widely documented in individuals who are immunocompromised, including patients with HIV and liver transplant and bone marrow transplant recipients.[4,5] Patients with chronic infection seem to have worse clinical outcomes and higher mortality following hospital admission for COVID-19 than the general population.[2] Persistent infection combined with a suppressed host immune system would provide opportunities for viral evolution in this population.

For many viruses that usually only cause acute infection in the general population, prolonged infections in immunosuppressed hosts have been shown to accelerate within-host evolution and generate variants.[6] In the case of SARS-CoV-2, accelerated viral mutagenesis and changes in a number of amino acids within the spike protein have been observed in patients who are immunocompromised.[7] A prominent feature of the omicron variant is the accumulation of a larger number of mutations than any previous SARS-CoV-2 variant. It is postulated that this variant might have originated from patients who were immunocompromised, since the variant was first detected in South Africa, where there is a high prevalence of HIV. In patients with HIV who have prolonged infection with SARS-CoV-2, this extended period of infection might lead to the accumulation of many mutations.[8] Therefore, we speculate that unmonitored SARS-CoV-2 infection in people who are immunocompromised enhances the potential for viral evolution. Thus, continuous surveillance of viral evolution in patients who are immunocompromised could be important to improve preparedness for the potential emergence of new SARS-CoV-2 variants. This approach would be highly feasible since whole-genome sequencing and next-generation sequencing technologies have been widely implemented for the detection of SARS-CoV-2 mutations and monitoring phylogenetic evolution in the ongoing COVID-19 pandemic.

We propose that effective interventions are needed to actively prevent possible emergence of new variants in immunocompromised populations. However, the accumulation of excessive mutations has enabled the omicron variant to escape from the existing COVID-19 vaccines and antibody therapies.[9] Optimisation of vaccination strategies can partly, but not completely, circumvent these challenges.[10] In December, 2021, two oral direct-acting antiviral drugs were approved by the US Food and Drug Administration for the treatment of COVID-19. Molnupiravir targets the SARS-CoV-2 polymerase and nirmatrelvir (the key component of Paxlovid) inhibits the main protease of SARS-CoV-2. Both drugs are effective against wild-type SARS-CoV-2 and against variants including the omicron variant, and combined use is thought to have synergistic antiviral activity, which is likely to be attributed to their complementary mechanism of actions.[11] Treatment

with potent antiviral regimens is expected to rapidly reduce SARS-CoV-2 viral load and accelerate viral clearance in patients who are immunocompromised. Such treatment not only improves patient outcomes, but would also minimise viral evolution and the possible emergence of new variants. Combination therapy (eg, molnupiravir and nirmatrelvir) is expected to be more effective than monotherapy in this respect. Thus, we recommend monitoring of SARS-CoV-2 infections in immunocompromised populations, and implementation of effective interventions, such as treatment with direct-acting antivirals (appendix).

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