To Prevent Future COVID Variants, We Must Protect Those Most At Risk

Protecting the immunocompromised is not only a matter of health equity, it's critical to ending the pandemic.

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As the omicron wave wanes, people across the United States are welcoming reprieve from a virus that has killed nearly 1 million Americans and hospitalized millions more.

But as recent articles in The New York Times, The Atlantic, and other outlets have pointed out, the threat of COVID-19 still looms large for millions of Americans who have compromised immune systems. As mask mandates expire and social distancing measures are curbed, cancer patients receiving chemotherapy, patients on aggressive immunosuppressive regimens, transplant recipients, and many others at high risk for severe COVID-19 continue to live in fear.

And their fear is well-founded.

Even after vaccination, severely immunocompromised people face substantial risk. For example, when researchers measured mortality of fully vaccinated solid organ transplant recipients, they found that, of those who suffered breakthrough infections, nearly one in 10 died. (Notably, this analysis predated widespread use of helpful boosters.)

But many of the pleas to protect immunocompromised patients have missed a crucial public health point: Shielding them is not only an important matter of health equity and social justice, it is a critical component in efforts to forestall the rise of new coronavirus variants. Put simply, by protecting people with weakened immune systems, we protect all of us.

Variant creation is driven by the amount of replicating virus in existence. Whether an evolutionary offshoot ultimately takes hold is a product of viral fitness, selection pressures, and host susceptibility. This equation explains why the most immunocompromised amongst us are so pivotal for preventing the rise of new mutations. When someone who is severely immunosuppressed is infected with the coronavirus, large loads of the virus can replicate for weeks or even months. And if natural immune responses and therapeutic treatments are unsuccessful, this uncontrolled viral replication can lead to the creation of mutant strains. Due to the high viral loads, the variants can easily spread to other susceptible individuals if enhanced isolation precautions are not strictly followed.

Careful case reports confirm this reality. A case study of a patient with leukemia and an acquired immune deficiency, who caught COVID-19, found that she shed the virus for as many as 70 days, and that the virus evolved significantly within her over that time. Similar reports have found evidence of within-host viral evolution of the SARS-CoV-2 virus in transplant recipients and in patients suffering from autoimmune diseases requiring aggressive immunosuppression. Patients on regimens designed to suppress B cells, the cells which produce our natural antibodies, appear to be at especially high risk for long-term infection and the accumulation of viral mutations.

If not used carefully, antiviral and antibody therapies, which many experts believe are even more critical in curing COVID-19 in immunocompromised hosts, risk worsening the problem by exerting evolutionary pressure that selects for resilient strains. Unfortunately, few, if any, high quality studies exist that doctors can use as guidance for maximizing the benefit of these therapies to immunocompromised patients while minimizing public health risk.

The reality of this concern was shown by researchers from Britain when they sequenced viral samples from a COVID-19 patient with lymphoma who had been treated with the antiviral remdesivir and convalescent plasma. Over time the researchers found evidence that the treatment was selecting for mutations resistant to the antibodies in the plasma.

This pattern has since been replicated by researchers at the University of Sydney, who published their results [March 9] in a correspondence in the New England Journal of Medicine. They identified eight patients with sustained SARS-CoV-2 infections who were treated with sotrovimab, the only recommended monoclonal antibody with retained efficacy against the omicron variant. Fifty percent of those treated with the antibody developed mutations which blocked efficacy of the drug.

These are not new principles in microbiology. Infectious disease experts have long known that tuberculosis patients who stop their treatments before the infection is cleared are at higher risk of developing drug-resistant strains. Similarly, patients with HIV who don't consistently adhere to treatment regimens are more likely to develop strains of the virus that are resistant to antiretrovirals.

Lawrence Corey, a virology and immunology expert at the Fred Hutchinson Cancer Research Center, and colleagues summarized the phenomenon in a recent commentary on Covid-19 variants: "Prolonged viral replication in the context of an inadequate immune response facilitates the emergence of immune-pressure escape mutations."

Thankfully, we have ways to protect immunocompromised groups and fight back against the emergence of new variants. In the absence of widespread masking, access to the most effective masks, namely N-95 respirators, will be increasingly important for the "one-way" protection of immune suppressed individuals. So will other non-pharmacologic interventions, such as quality indoor ventilation, rapid antigen testing of close contacts, and maintaining options to physically distance in school and work environments. Fourth doses of vaccines and increased use of long-acting antibody therapy may add additional layers of protection. And for people who do get

infected, following personalized, test-based criteria for discontinuing isolation precautions can help them avoid passing any potential new variants onto others.

However, patients with cancer, transplants, and autoimmune diseases aren't the only immunocompromised patients. Worldwide, 38 million people are estimated to be living with HIV. Although treatment efforts have made tremendous progress, only three out of four patients were on antiretroviral treatment as of 2020, according to UNAIDS, and two thirds of patients have fully suppressed the virus.

A case report published by the Centers for Disease Control and Prevention last October demonstrated that patients with uncontrolled HIV/AIDS, too, carry increased risk of variant generation. In one such patient, SARS-CoV-2 was able to replicate and mutate for weeks, ultimately acquiring mutations associated with resistance to immune neutralization.

But the case report also revealed a key to preventing the emergence of new variants in patients with HIV: After the patient started antiretroviral therapy, her HIV viral load plummeted to nearly undetectable levels and, soon after, she also cleared her SARS-CoV-2 infection. The result suggests that the public health strategy of "treatment as prevention" — treating HIV to also block transmission via viral load suppression — may be doubly important for HIV patients during the pandemic as it can reduce the harm from two viruses instead of one.

The strategies for minimizing the risk of COVID-19 variant creation among patients with uncontrolled HIV/AIDS look much different than they do for transplant recipients, cancer patients, and people with autoimmune disorders. Unlike the other groups, whose lives depend on maintaining their immunosuppression, patients with uncontrolled HIV/AIDS can reverse their immunosuppression, usually by just taking one pill once a day. The challenge for patients with uncontrolled HIV/AIDS is that many of them are disconnected from the health care system. This means public health efforts must focus not just on medical innovation but on providing social support to address the multitude of maladies that disproportionately affect people with uncontrolled HIV/AIDS — a combination of poverty, stigma, substance use, housing instability, and mental illness.

As a physician who has cared for patients with COVID-19 in the clinic, hospital, and ICU, I understand all too well the acute threat that COVID-19 poses to immunocompromised patients. And I also understand that the accumulating evidence is clear: If we care about reducing the risk of the next deadly SARS-CoV-2 variant, it is imperative that we do all we can to protect the immunocompromised. By doing what we can to save them, we just might also spare the world.

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