

Commentary

Getting Ahead of the Virus

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The world has recorded more than two million deaths from coronavirus disease 2019 (COVID-19) and is approaching one hundred million confirmed cases (1). Both numbers are underestimates of the true toll of the pandemic. Many countries in the Northern Hemisphere are in the grip of a large winter wave and have reintroduced lockdowns and intensified other nonpharmaceutical interventions to reduce stress on fragile healthcare systems. Vaccination campaigns have begun in a growing number of countries, but supplies remain scarce. And new variants of COVID-19 virus, which appear to increase its transmissibility and perhaps confer resistance to available countermeasures, have been documented in dozens of countries.

This is the state of the pandemic in late January 2021. We now have tools with the potential to bring the pandemic to an end, but the pandemic itself is slippery and continues to evolve. Just when we thought the end was in sight, we now face the prospect of new, more intense epidemics. In most countries, the response in 2020 trailed behind the pandemic. What can we do, in 2021, as a global community to get ahead of the virus?

With respect to the vaccines, our most important tool, four things can be done, principally.

First, we must ensure that the vaccines are shared globally as quickly as possible. We are fortunate in that several vaccines have already been shown to be safe and effective and we can anticipate that others will follow. Nevertheless, relative to global need, the vaccine will remain in short supply throughout 2021. If we can ensure that the vaccine is shared equitably to protect the most vulnerable, we can substantially reduce the number of deaths caused by COVID-19, limit the stress on healthcare systems, reduce the need for lockdowns, and speed global economic recovery. COVAX, the initiative led by Global Alliance for Vaccines and Immunisation (GAVI), Coalition for Epidemic Preparedness Innovations (CEPI), and World Health Organization (WHO), represents the world's best chance to ensure that all countries achieve the critical threshold of protecting their most vulnerable populations in 2021. All nations should

support it.

Second, we must do everything we can to use the vaccines we have as effectively and efficiently as possible. That means maximizing their benefit for individuals as well as populations. Manufacturers have reported efficacy rates of between 50 and 95 percent for the vaccines that have completed Phase 3 clinical trials, and all vaccines have demonstrated a reduction in the severity of disease, but the variability in efficacy rates raises questions about how best to use the vaccines we have. In a related vein, and somewhat controversially, the UK's Joint Committee on Vaccination and Immunisation has issued guidance recommending an extended dosing interval for both the Pfizer and AstraZeneca vaccines in order to increase the number of individuals receiving a first dose of vaccine (2). Other strategies, such as the sequential use of different vaccines in heterologous prime-boost regimens, might allow vaccines with different efficacy to be combined in ways that optimize the individual and population benefits they provide while allowing greater numbers of people to receive at least one dose of the most effective vaccines. All such strategies should be evaluated rapidly and prospectively to understand their benefits and tradeoffs in terms of the protection they afford.

Third, we must prepare for the eventuality of viral evolution and be prepared to implement strain changes in existing vaccines much more rapidly than we do with influenza, where 9–10 months is the norm. The emergence of new variants demonstrates the potential of COVID-19 virus to accumulate numerous adaptive and biologically significant changes that lead to increased transmission and potentially immune evasion or escape. These variants have spread globally within months of their emergence, accelerating national epidemics in the UK, South Africa, and in Manaus, Brazil, a region thought to have achieved herd immunity by virtue of a largely unmitigated outbreak (3–4). Preparing for strain changes will entail increased global viral surveillance and sequencing, immediate and transparent reporting of new variants or concerning epidemiologic and clinical patterns, a low

threshold to develop candidate vaccine seeds, and agreement with regulators on the clinical, manufacturing, and regulatory requirements — and these requirements may differ by platform. Manufacturers should aim to be able to release a revised vaccine within 100 days of the decision to develop a candidate vaccine seed.

Fourth, we should build on the vaccines we have to construct an armamentarium for the future. We do not yet know where COVID-19 will find its epidemiologic niche, but we can anticipate that it will become endemic and we must ensure that we have vaccines that can address the needs of all segments of all populations in all geographies. In the first instance, that means determining the safety and efficacy of the current vaccines in special populations, such as children, pregnant women, the immunocompromised, and the elderly. In the second, it means developing low-cost vaccines with favorable attributes, such as thermostability, that facilitate administration (and even self-administration) in a wide variety of settings. And finally, if vaccines targeting the whole spike protein or its receptor-binding domain cannot keep up with viral evolution, it may mean broadening our approach and investing in COVID-19 vaccines that present multiple structural and non-structural proteins that have the potential to elicit an immune response. Ultimately, we

should aspire to develop broadly protective coronavirus vaccines targeting epitopes preserved across many different coronaviruses.

If we are to defeat the pandemic we must get ahead of the virus and doing that will require a sustained global effort that cuts across every level of the response. The solidarity that the scientific community has demonstrated over the last year must become the governing norm. We are all in this together.

doi: [10.46234/ccdcw2021.043](https://doi.org/10.46234/ccdcw2021.043)

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Submitted: January 24, 2021; Accepted: January 29, 2021

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