

Vaccine development needs a boost

Lessons from the rapid development, manufacture and distribution of vaccines against COVID-19 must be broadly applied to expedite vaccine development for other infectious diseases.

1 December is World AIDS Day, and the focus this year is “End inequalities. End AIDS. End pandemics.” The theme could equally be invoked for COVID-19, which shares commonalities with human immunodeficiency virus (HIV) and AIDS in terms of disproportionately affecting the most socioeconomically disadvantaged global populations, and the staggering human toll. Yet within two years of the onset of the COVID-19 pandemic, at least six different vaccines have received emergency use listing from the World Health Organization, stemming infections and deaths, whereas 40 years after the onset of the HIV epidemic, a vaccine remains elusive.

The past two years have brought further setbacks to HIV vaccine development, unrelated to the pandemic. In January 2020, the HVTN 702 efficacy study of the most clinically advanced HIV vaccine candidate — a virus-vectored first dose, followed by a protein boost — was stopped due to the absence of evidence of any protection against HIV infection in a pre-specified interim analysis. The study was a follow-up to the RV144 trial that reported in 2009 an efficacy signal of 30%, and probably puts an end to further development of this vaccine regimen.

In August 2021, results from the Imbokodo trial of a vaccine developed by Janssen and comprising an Ad26 vector (also used in COVID-19 vaccines) and protein boost showed evidence of only 25% efficacy against HIV acquisition in young women in sub-Saharan Africa, relative to placebo. The Mosaico trial of the same vaccine platform in a different study population — cis-gender men and transgender people in the Americas and in Europe — remains ongoing, but is the only large HIV vaccine trial currently underway.

This effectively dry pipeline of advanced HIV vaccine candidates should give the field serious pause. Yet there is much to be learned from the response to the COVID-19 pandemic about moving any vaccine candidate forward. Notably, the speed of the rollout of COVID-19 vaccine candidates

was facilitated by leveraging of the US National Institutes of Health-funded HIV Vaccine Trials Network (HVTN) and its trial sites and infrastructure, as well as an immediate injection of government funding. Yet the success of AstraZeneca, BioNTech and Moderna, with no prior experience in developing, manufacturing or distributing vaccines for the global market, speaks to the potential to also engage new entities and new technologies in the HIV vaccine field.

Accordingly, Moderna is launching a phase 1 trial of two vaccines against HIV using lipid-encapsulated modified mRNAs designed to stimulate a B cell response capable of generating broadly neutralizing, HIV-specific antibodies. Stabilized trimers of HIV envelope protein, mosaics of conserved regions of HIV proteins, immunogens designed to target germline precursors of B cells that produce broadly neutralizing antibodies, and new viral vectors are among current HIV vaccine strategies in early-stage clinical development that will yield results in the next few years.

But whereas HIV trials typically take years from concept to clinic, the accelerated pace of COVID-19 vaccine development — in which trials were initiated within months of their conceptualization — indicates that these delays can and should be curtailed. Harnessing mRNA for vaccine design is one way in which vaccines can be rapidly formulated — or reformulated to target viral variants — and researchers have been taking advantage of this potential for iterative vaccine design to rapidly test different constructs. However, the rapidity of the pandemic vaccine rollout was not specific to mRNA constructs, which indicates that rethinking the entire developmental process to speed the clinical translation of vaccines should extend to all novel designs for HIV and for other pathogens.

The pandemic has also exposed broadly generalizable vaccine challenges that have yet to be fully understood and surmounted. Although some scientists anticipated that the vaccines against COVID-19 would elicit sterilizing immunity against the coronavirus SARS-CoV-2, the rate of

breakthrough infections suggests that their efficacy truly lies in preventing disease, rather than preventing infection. Vaccines against COVID-19 are not alone in this context — vaccines against tetanus do not prevent infection by *Clostridium tetani*, but instead prevent disease caused by the bacterial toxin. Mosquirix, the vaccine recently recommended by the World Health Organization for protection against malaria in children in high-burden areas, reduces the frequency of clinical malaria in the first year after vaccination, but efficacy rapidly wanes thereafter. This transient protection against symptomatic disease in infants and young children, who account for 67% of malaria deaths, is nevertheless estimated to have substantial benefit.

Achieving sterilizing immunity may be a more vital target for vaccines against pathogens that establish persistent, latent infections that evade natural immunity — such as HIV, and also *Mycobacterium tuberculosis* — than for the typically short-lived, acute infection caused by SARS-CoV-2. Understanding the correlates of vaccine-mediated protection against infection versus that against disease must be an integral part of developing vaccines that impact both survival and quality of life.

The theme of this year's World AIDS Day is a call to action not solely for HIV but for all infectious diseases for which vaccines are stalled or under-resourced. These are diseases that disproportionately affect some of the most disadvantaged populations. They include tuberculosis, arguably the world's most underfunded infectious disease, which kills 1.5 million people annually and infects a quarter of the global population; and group B streptococcus, which affects the most vulnerable, killing 150,000 infants each year — to name only two. Let the COVID-19 pandemic boil down to a single message: infectious diseases infect indiscriminately. Prioritizing vaccines for all is not a zero-sum game. □

Published online: 2 December 2021
<https://doi.org/10.1038/s41591-021-01633-x>