EDITORIAL

Does the World Still Need New Covid-19 Vaccines?

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Although there was a global shortage of Covid-19 vaccines in 2021, by mid 2022, the vaccine supply will no longer be a limiting factor in efforts to provide more equitable coverage. As of April 19, 2022, approximately 11.5 billion Covid-19 vaccine doses have been administered globally.[1] Scaling up manufacturing capacity for currently available vaccines at the speed promised by vaccine producers through the COVAX (Covid-19 Vaccines Global Access) program and beyond should secure the coverage target projected by the World Health Organization (WHO) for 70% of the world population by mid 2022.[2] So why do we still need new Covid-19 vaccines?

A total of 344 Covid-19 vaccine candidates have been developed or are still in development.[3] Of these, 31 vaccine products are already in large-scale use after conditional approval by national regulatory authorities or under the WHO Emergency Use Listing. At least five different technology platforms have been used (i.e., messenger RNA [mRNA], viral-vectored, inactivated whole-virus, protein subunit, and plasmid DNA approaches). Several of the inactivated whole-virus and protein subunit vaccines need adjuvants to potentiate the immune response.

Many reasons dictate a need for the development of a range of Covid-19 vaccines available for use across the world with the aim of bringing the pandemic under control. Each vaccine product has different attributes and advantages and disadvantages, and multiple factors must be considered to guide policy decisions. Different countries and health care settings, as well as different subpopulations and age groups, may benefit from different vaccine products developed on different platforms. Efficacy and safety, as evaluated in phase 3 trials, are not the sole outcomes to be assessed in a country's decision to procure and introduce new Covid-19 vaccines. Ease of schedules, vaccine effectiveness when used in routine programs, need and frequency of boosters, cost, considerations regarding cold-chain logistics, manufacturing scalability, acceptability by communities, and scope for local or regional production are additional important factors.

To this end, we commend the development of two new vaccines, as now described in two articles in the *Journal*, one by Hager et al.[4] and one by Dai et al.[5] Both of these Covid-19 vaccines are produced on new technology platforms: Hager et al. describe a plant-based coronavirus-like particle vaccine, and Dai et al., a receptor-binding domain (RBD)–dimer–based vaccine. Both vaccines have the advantage of not requiring extreme cold-chain procedures for storage, which makes them user-friendly in primary health care settings as well as in low- and middle-income countries, and it is important that such countries were included in the phase 3 trials of these vaccines. The time period of both trials covered the circulation of several SARS-CoV-2 variants, but the trials were completed before the emergence of the B.1.1.529 (omicron) variant and subvariants.

In the phase 3 trial by Hager et al., which was conducted in Argentina, Brazil, Canada, Mexico, the United Kingdom, and the United States, the recombinant plant-based vaccine displaying the prefusion spike glycoprotein of ancestral SARS-CoV-2 combined with Adjuvant System 03 (AS03) was evaluated as a two-dose regimen. The vaccine efficacy against polymerase-chain-reaction–confirmed symptomatic infection was 69.5% (95% confidence interval [CI], 56.7 to 78.8). In a post

hoc analysis, the overall vaccine efficacy against preventing moderate-to-severe disease was 78.8% (95% CI, 55.8 to 90.8), and among participants who were seronegative at baseline, vaccine efficacy against any severity of disease was 74.0% (95% CI, 62.1 to 82.5). It is interesting to note that the median viral load among vaccinated participants with breakthrough cases was more than 100 times as low as that among the placebo recipients with incident cases of Covid-19.

In the phase 3 trial by Dai et al., which was conducted in Ecuador, Indonesia, Uzbekistan, and Pakistan (efficacy and safety assessments) and in China (safety assessment only), the RBD-dimer–based Covid-19 vaccine was evaluated as a three-dose regimen. During the 6-month follow-up period, vaccine efficacy against PCR-confirmed symptomatic disease with an onset of at least 7 days after the third dose was 75.7% (95% CI, 71.0 to 79.8), and against severe to critical Covid-19, vaccine efficacy was 87.6% (95% CI, 70.6 to 95.7). Most of the incident cases occurred during period in which B.1.617.2 (delta) was the dominant variant.

Both trials included mostly working-age adults; hence, no vaccine efficacy data are available for older persons who belong to the highest priority-use group according to the WHO Prioritization Roadmap.[6] As in the efficacy trials of the vaccines already in use, estimates of omicron-specific vaccine efficacy are lacking, as well data on durability of protection and safety in subpopulations such as older persons, pregnant women, and persons with immunosuppression. Postintroduction surveillance will be of paramount importance in the monitoring of vaccine effectiveness over time and against different virus variants and in various subpopulations and health care settings. The WHO has published guidance on how best to conduct studies of postintroduction vaccine effectiveness.[7] Findings from such studies will determine whether the two new vaccines described by Hager et al. and by Dai et al. will indeed play a bigger role in our armamentarium against Covid-19.

The first Covid-19 vaccines used during the pandemic may not be the best long-term solution. The next generation of Covid-19 vaccines will need to have broader epitope coverage to provide cross-immunity against SARS-CoV-2 variants, confer a longer duration of protection, and be easy to update in a timely manner for protection against any new variants. We should remain agile in fine-tuning the best use of Covid-19 vaccines for the greatest effect on global public health by acknowledging trade-offs. With more vaccine platforms available, we can possibly improve decision making regarding the selection of a vaccine, since different vaccine platforms may be more suitable for certain age groups, certain subpopulations (e.g., those with underlying immune-compromising or other medical conditions), and pregnant women. We may increasingly need to mix and match vaccines to leverage the benefits of each of these platforms.[8] Finally, currently available vaccines have only modest effectiveness against mild infection and transmission, which is further reduced in the context of the newly emerging omicron subvariants. Hence, to slow down the circulation of the virus and to limit the speed at which further variants emerge, new vaccines that have a substantial effect on reducing mild infection and transmission are needed, even as the world attempts to learn how to live with SARS-CoV-2.[9]

These are tall orders for vaccine developers and manufacturers, but our mandate remains to develop the best tools to prevent the emergence of new variants of concern and control the health and socioeconomic fallout from new surges. The decision by representatives of the African region to establish a network of six mRNA technology hubs[10] is a sign that countries and regions are motivated to build local and regional capacity and expand self-sufficiency not only in planning and participating in key clinical trials but also in designing and manufacturing vaccines to better meet the needs of their populations during pandemic threats. Such technology hubs will need to embrace technologies beyond the mRNA approach.

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