Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Time to redefine a primary vaccination series?

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In the third year of the COVID-19 pandemic, it is getting harder to define what a full-dose COVID-19 vaccination series is, especially in the era of emerging variants such as omicron (B.1.1.529). The definition might differ depending on the dominant variant in circulation, the availability of vaccines, the risk factors of vaccine recipients, and the availability of surveillance and COVID-19 vaccine safety and effectiveness data. Inequitable vaccine availability adds to the problem as on one hand, in many high-income countries, a fourth dose of an mRNA vaccine is offered and gives well tolerated boosting of cellular and humoral immunity,[1] and on the other hand, only 19·7% of people in low-income countries have received at least one dose of any COVID-19 vaccine.[2] These facts all make it difficult to comment on what a primary COVID-19 vaccination series should consist of and how we should boost protective immunity in the face of emerging variants in a world with marked inequalities.

In *The Lancet Infectious Diseases*, Karin Hardt and colleagues[3] report on the efficacy, safety, and immunogenicity of a second dose of Ad26.COV2.S vaccine against COVID-19 given as part of the ENSEMBLE2 trial, wherein participants were randomly assigned from the first visit either to get two doses of the vaccine or two doses of placebo 2 months apart. The two-dose regimen provided 75·2% (adjusted 95% CI 54·6–87·3) efficacy against moderate to severe–critical COVID-19 and 100% (32·6–100·0) efficacy against severe–critical COVID-19. Meanwhile, the final analysis of the double-blind phase of the ENSEMBLE vaccine trial showed that primary vaccination with a single dose of Ad26.COV2.S had 56·3% (95% CI 51·3–60·8) efficacy against moderate to severe–critical COVID-19, 74·6% (64·7–82·1) efficacy against severe–critical COVID-19, and 82·8% (40·5–96·8) efficacy against COVID-19 related death.[4] The data collection for the primary analyses of one-dose and two-dose regimens was completed before the global dominance of delta (B.1.617.2) and the emergence of omicron.

The follow-on, single-arm, open-label, phase 3b, Sisonke study in health-care workers in South Africa showed that after two doses of Ad26.COV2.S vaccine, effectiveness against severe disease during the omicron surge was equal to that of two doses of BNT162b2.[5] Moreover, a longer interval (4 months) between the two doses of Ad26.COV2.S led to lesser omicron immune escape than other two-dose vaccine regimens (given 3–4 weeks apart).[6] However, vaccinees receiving two doses of Ad26.COV2.S had greater omicron immune escape than vaccinees receiving three doses of mRNA vaccines or three doses of different heterologous regimens. These findings suggest that a third dose of either Ad26.COV2.S or another vaccine might act as a booster dose for a two-dose regimen of Ad26.COV2.S.

Thus, we consider that two doses should be regarded as the primary vaccination series for Ad26.COV2.S in the era of omicron. WHO's updated recommendations also echo this point of view and advise that all efforts should be taken to provide a second dose 2–6 months after the first dose, particularly to the highest-priority and high-priority groups.[7] When a second dose is to be given, WHO supports a flexible approach either to use two doses of Ad26.COV2.S vaccine or a heterologous vaccination schedule. A single-dose regimen is still an acceptable option for countries challenged with supply constraints and vaccine deployment issues.

It is clear that there is a constant need to review the available data on vaccine efficacy and generate effectiveness data for the COVID-19 vaccines in the context of emerging variants. The ultimate goal should be to provide the best protection from severe disease, hospitalisation, and death with the lowest number of doses of available COVID-19 vaccines. The best chance to stop this pandemic is to make vaccines available for everyone, everywhere. The efforts to provide booster doses should be balanced with the efforts to attain vaccine equity.

We declare no competing interests.

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