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SARS-CoV-2 vaccination strategies: Should the extended dosing interval strategy be implemented in future pandemics?

The World Health Organization (WHO) considered COVID-19 for more than three years a public health emergency of international concern (PHEIC) at a pandemic level. After a cumulate of 770,875,433 confirmed cases, including 6,959,316 deaths (up to September 19, 2023), fortunately, the COVID-19 mortality burden has significantly decreased in the last year (2022–2023) primarily due to effective vaccination (a total of 13,505,262,477 doses have been administered globally) (https://covid19.who.int/), despite Omicron and its sub-lineage variants' emergence [1,2]. However, the vaccine allocation was not as smooth as everyone would have liked, considering shortages or difficulties in promptly obtaining the vaccines for several countries, especially low- and middle-income countries (LMIC). In some cases, that led to the necessity of applying different strategies, such as extending the time interval in which the second dose was administered. Here, we present a perspective on implementing this vaccination strategy, particularly in low-income (LIC) and LMIC countries facing future pandemics.

Worldwide, there has been inequity when distributing COVID-19 vaccines (Fig. 1) [1]. Only 26.4 % of LICs have received at least one dose, increasing cases and mortality (Fig. 2) [2]. For example, there is an estimation that waiting one day for vaccination increased 1.9 % the number of cumulative cases in LIC compared to high-income countries (HIC) [3]. Moreover, by June 2022, under 40 % of healthcare workers in LIC have a complete vaccination scheme [4]. Therefore, a globally focused strategy of extended vaccination dosing intervals could reduce gaps in vaccination access [26].

In January 2021, Canada and the United Kingdom (UK) decided to extend the second dose administration as a public health approach. The delayed strategy was initially based on the efficacy of a single dose in third-phase clinical trials of messenger RNA-based (mRNA) vaccines. The aim was to obtain partial protection for as many individuals at higher risk, providing temporary immunity and decreasing morbidity and mortality [5,6].

Evidence from the real world and the analysis of published clinical trials further support this decision. A pooled analysis of four randomised clinical trials of the AstraZeneca ® (ChAdOX) vaccine evaluated the effectiveness of the dosing strategy against symptomatic SARS-CoV-2 infection. The study found high effectiveness with an interval between the two doses greater than or equal to 12 weeks compared to an interval between doses of less than six weeks: 81.3 % (95 % CI: 60.3–91.2 %) vs. 55.1 % (95 % CI: 33.0%–69.9 %) [7]. An English observational study conducted between December 2020 and February 2021 showed a reduction in symptomatic infection, hospitalisation, and death of 70 %, 85 %, and 80 % after the administration of a single dose of the Pfizer-BioNTech vaccine and 75 %, 80 % and 80 % after the administration of a single dose of the AstraZeneca vaccine, respectively, between 21 and 42 days after application [8].

Recently, an analytical Canadian population-based study carried out between May and November 2021 reported a 5–10 % higher vaccination efficacy regarding symptomatic infection when comparing the extended dosing interval of 7–8 weeks for mRNA vaccines to the standard dosing interval (3–4 weeks) after the second dose. Also, vaccine effectiveness against hospitalisation exceeded 90 % regardless of the dosing interval. This effect was observed even during this country's delta variant predominance period [9,27]. These findings and the potentially lower risk of myocarditis/pericarditis secondary to vaccination led to WHO recommendation on Pfizer/BioNTech ® vaccine dosing intervals for the ideal eight-week difference between the two doses in 2022 [10].

Regarding immunogenicity, an extended dosing interval shows a better antibody response. With AstraZeneca vaccine in adults between 18 and 55 years of age at a dosing interval of 12 weeks, a two to threefold neutralising antibody response is found against alpha, beta and gamma variants over a dosing interval of less than six weeks [7]. Similarly, the Pfizer/BioNTech vaccine increases anti-receptor-binding domain (RBD) antibody titers that enhance humoral immunity and plaque reduction neutralisation test titers to 50 % and 90 % against wild-type SARS-CoV-2 and Alpha, Beta and Delta variants [11].

A concern of many detractors of this strategy has been the theoretical risk of selecting variants with a greater capacity for dissemination of SARS-CoV-2 with the extended dosing interval strategy, as it relates to lower production of neutralising antibodies before the application of the second dose [12]. However, SARS-CoV-2 has eluded the immune response induced by any vaccination strategy, and new variants have emerged [25]. These variants, such as Omicron and its sublineages, have greater transmissibility [13]. Nevertheless, this global phenomenon seems unrelated to the extended dosing interval strategy. Furthermore, despite known lower vaccine effectiveness for infection in such variants, prevention for both hospitalisation and mortality remains high [14]. Moreover, a study evaluating the extended dosing interval strategy showed increased activity in neutralising antibody production against Omicron lineages BA.1, BA.2, BA.4 and BA.5 when compared to a shorter 3–4 week dosing interval and a similar antibody production after a booster dose indistinctly of the interval vaccination strategy [15].

It is essential to highlight that some populations in which this strategy should not be applied due to the precautionary principle, given their higher mortality. The first is the population with cancer and immunosuppression. Lower immunogenicity has been described after a dose of the vaccine, which could be related to lower effectiveness and a

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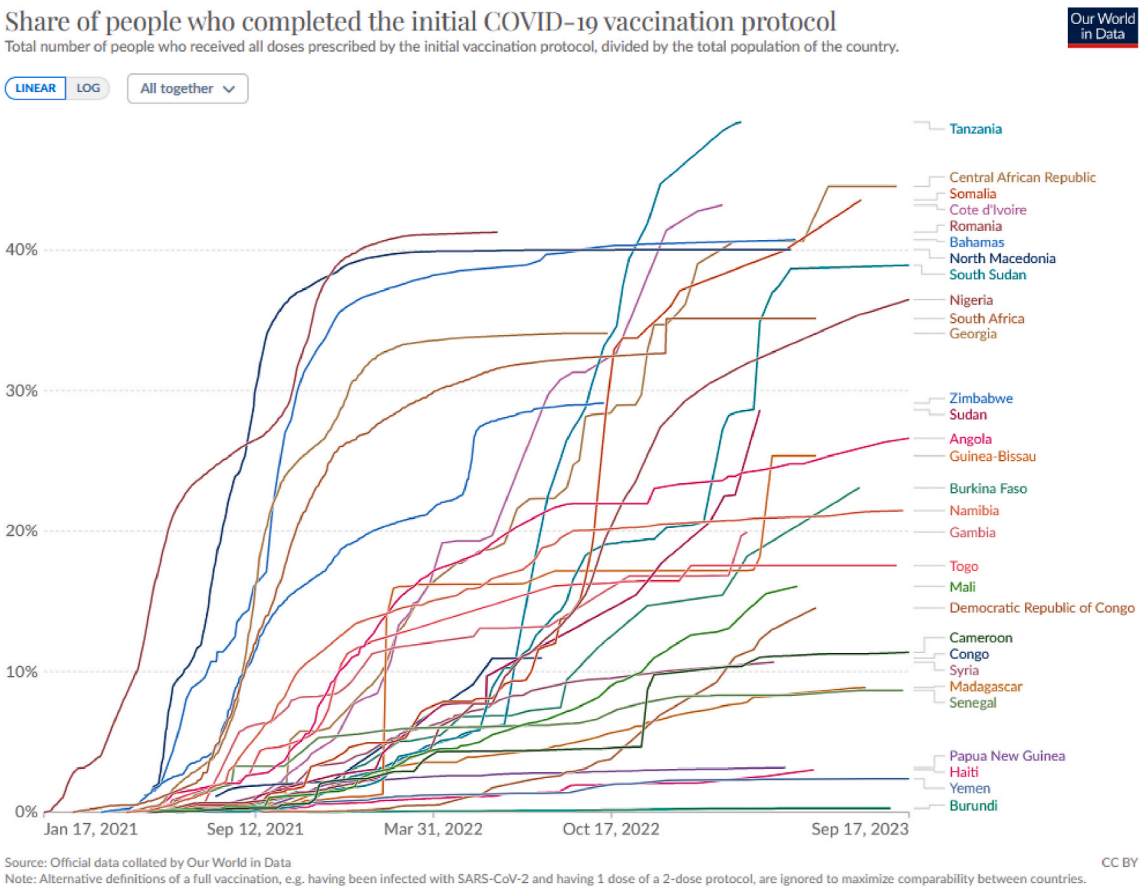

Fig. 1. Share of people who completed the initial COVID-19 vaccination protocol in selected countries of Africa, Middle East, Americas, Europe and Asia-Pacific (with less than 50 %).

higher risk of hospitalisation and death from COVID-19 [16].

The other population comprises people over or equal to 60 years, with a mortality risk ten times higher than the general population [17]. However, these findings are worth contrasting with the real-life effectiveness data of deferral in older adults from the UK, very similar to the effectiveness in healthcare workers, conferring benefits for this population [8]. Furthermore, the benefit of extending the dosing interval could be lost when periods of high epidemic waves with increased transmissibility concur with introducing new variants for which vaccines tend to have less effectiveness [18]. It is also essential to consider that the extended dosing interval strategy has not been evaluated with the inactivated virus vaccines (e.g. Sinopharm or CoronaVac/Sinovac ®); therefore, the rescheduling of the second dose would not be recommended with these vaccines according to current evidence [19].

Currently, taking into account the importance of integrating COVID-19 vaccination into the national immunisation programs and understanding the importance of learning from the situations faced in this pandemic, the application of an extended dose interval is a strategy that can be useful and effective for the administration of the COVID-19 vaccine to future generations and to face future pandemics [10,20]. In this sense, in the application of vaccines for other microorganisms, there is evidence supporting extending the dosing intervals, as in the case of human papillomavirus or hepatitis B, delays of six months to one year in the vaccination scheme are related to an effective immune response [21–23].

Finally, it is relevant to assess that this deferral approach complies with ethical principles in the distribution of vaccines. Using the EEFA approach (ethics, equity, feasibility, and acceptability) [24] from the ethical point of view, the evidence informs this recommendation. It complies with the principle of beneficence, achieving an impact at the population level by reducing infections, hospitalisations, and premature deaths compared to the conventional strategy. Furthermore, regarding equitable distribution, this principle is met by offering the first dose of the vaccine in a shorter time to a more significant number of people with a similar risk of acquisition and complications from COVID-19 or other diseases and by taking into consideration not applying the strategy deferral in populations at high risk of mortality.

The strategy is feasible since it does not require infrastructure or human resources, unlike the one organised for broad immunisation coverage in the countries. Regarding the acceptance of the strategy by the population, by allowing faster access to the vaccine, it is very likely that it will be accepted by society; however, it must be accompanied by clear and transparent communication in which the evidence is presented.

It is convenient to consider three critical aspects in implementing this strategy: 1. The strategy is to delay, not to eliminate, the additional doses required, for which the complete resource of the vaccines must be available within an established period. 2. The additional doses required should be scheduled when applying the first because many people could forget it or have a false conviction of complete protection with a single application. 3. The need to continue after the first dose with effective non-pharmacological prevention measures that reduce the risk of contagion. Maintaining these measures will improve the impact of this strategy; suspending them will put its success at risk.

We call for delaying the second dose of the vaccine in future pandemic scenarios, considering the most vulnerable populations [28]. Although guaranteeing enough vaccines for all countries would be ideal, it is unrealistic; therefore, this strategy could improve access to vaccination, achieving better immunogenicity and appropriate clinical results [29–31]. We strongly believe that increasing the vaccination dose

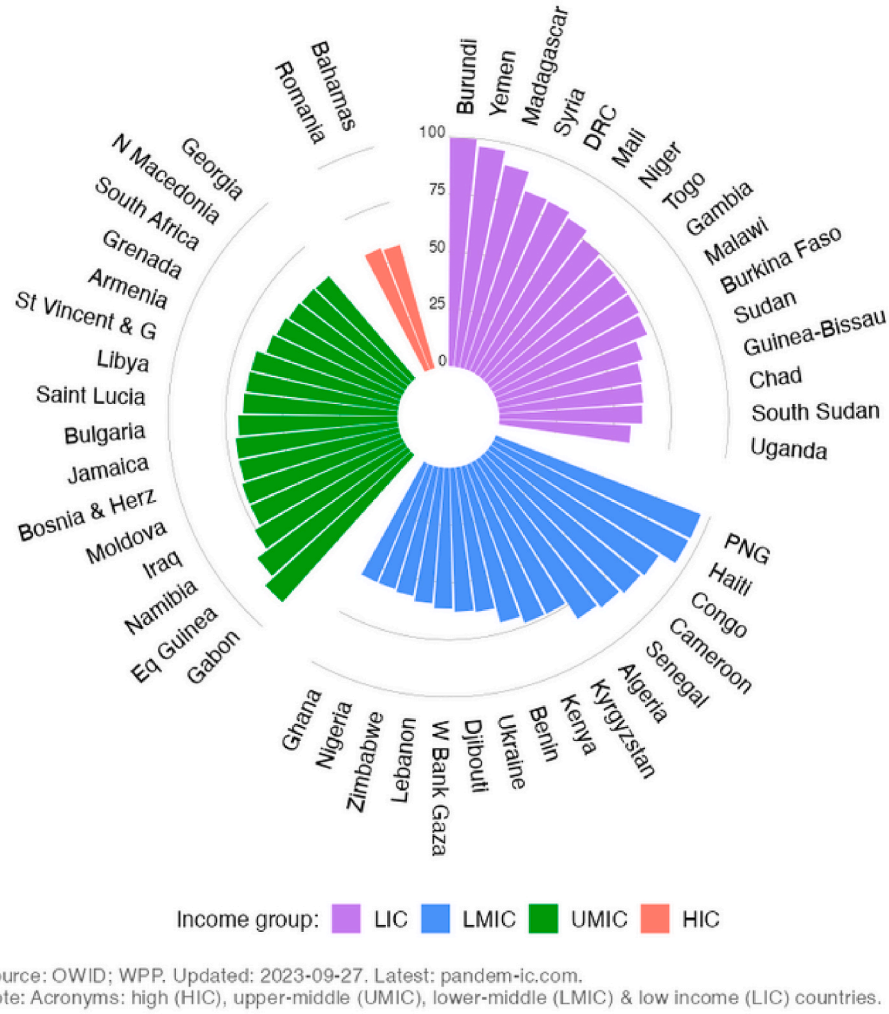

Fig. 2. Top 50, by income group, of countries with highest share of unvaccinated population (%).
Source: https://pandem-ic.com/the-50-least-vaccinated-countries-in-the-world/, access October 1, 2023.

interval could be a valid approach.

Conflict of interest

Authors have no direct conflict of interest.

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