

Boosting COVID-19 protection: insights from a Brazilian population-based cohort

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The development of effective and safe COVID-19 vaccines has been crucial in mitigating the health and economic impacts of the SARS-CoV-2 pandemic.¹ However, the rapid surge in COVID-19 cases due to the Omicron variant has raised concerns due to its heightened transmissibility and increased ability to evade neutralizing antibodies,² leading to waning vaccine effectiveness over time.^{3,4} Consequently, the World Health Organization indicated the adoption of booster doses to restore protection against adverse COVID-19 outcomes. Although real-world evidence studies have shown increased protection against severe COVID-19 with the use of a second booster dose (for both monovalent and bivalent vaccines),⁵⁻⁷ data on its effectiveness in preventing serious outcomes such as hospitalization and death among middle-aged people and in low and middle-income contexts are still scarce.

With the preceding description as a backdrop, Neto and colleagues present in this issue of *The Lancet Regional Health Americas* a target-emulated trial using a population-based cohort of over 46 million individuals aged 40 years or older in Brazil.⁸ These individuals received a homologous primary series of CoronaVac, ChAdOx1, or BNT162b2, and any third dose product available, and were eligible for the fourth dose. The study showed that, in a population whose two-dose scheme was predominantly with ChAdOx1 and CoronaVac, a fourth dose of COVID-19 vaccine, compared to only three doses, provided meaningful (relative vaccine effectiveness of 44.1%) and sustained (≥ 120 days) protection against the composite outcome of hospitalization or death. This finding was consistent among individuals from the general population aged 40–59 years. Moreover, the study revealed that while a fourth dose of mRNA-based vaccine conferred reduced risks of hospitalization or death immediately post-vaccination compared to an adenovirus-based booster, this distinction diminished after 120 days.

From both clinical and health policy standpoints, the findings of the study of Neto and colleagues have significant implications. The evidence supporting the effectiveness of a fourth dose in bolstering protection against severe COVID-19 outcomes among adults aged

40 years and older underscores the importance of ongoing vaccination campaigns for the general population, particularly in regions experiencing high transmission rates. This is especially relevant to low and middle-income countries (LMICs) where population vaccination coverage is still suboptimal. Consequently, strategies to increase access to COVID-19 vaccines are imperative, given that inadequate access to vaccines in low-income countries, for example, has limited the impact of COVID-19 vaccination on preventing deaths,¹ highlighting the need for global vaccine equity. In this context, the findings of the study of Neto and colleagues suggest that opting for an adenovirus-based booster could be a pragmatic choice, especially in regions where mRNA vaccines are not accessible. Health policymakers must consider these findings when formulating vaccination strategies and allocating resources to maximize the impact of booster campaigns and ultimately mitigate the burden of the ongoing waves of SARS-CoV-2 activity. Moreover, the study results could be used to combat the current scenario of vaccine hesitancy,⁹ also a relevant problem in high-income contexts, through targeted and culturally sensitive health communication strategies using evidence-based data.

Unanswered questions persist from both clinical and public health perspectives. The long-term durability of protection conferred by these booster doses, for example, is uncertain and will demand additional real-world studies. From a public health standpoint, the optimal timing and frequency of booster doses to maintain protection against emerging variants need to be elucidated. Additionally, strategies to address disparities in vaccine access and uptake, particularly in marginalized communities, require ongoing attention and innovation. There is also a critical need for research focusing on the equitable distribution and accessibility of booster doses in LMICs. Factors such as vaccine supply chain constraints, logistical challenges, and vaccine hesitancy can impede the efficient rollout of booster campaigns in these settings. Understanding the socio-cultural, economic, and infrastructural barriers to booster uptake is essential for devising targeted interventions to ensure equitable access to booster doses across diverse populations within LMICs. Moreover, assessing the cost-effectiveness of booster strategies in resource-limited settings is imperative for informing public health policies and allocation of limited resources to maximize population-level benefits. Addressing these research gaps is paramount for optimizing the



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effectiveness of booster dose strategies and mitigating the impact of COVID-19.

Contributors

Regis Goulart Rosa has conceptualized and wrote the comment.

Declaration of interests

Regis Goulart Rosa reports honoraria fee related to lectures from Pfizer research grants from Pfizer, MSD, and Brazilian Ministry of Health.

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