



## Letter to the Editor

## Declining COVID-19 vaccination coverage in Brazil: A global health warning



## To the Editor:

In this Journal, Antonelli and colleagues reported the positive clinical impacts of booster COVID-19 vaccine usage in vulnerable groups and posited that these observations should encourage vaccine uptake.<sup>1</sup> According to the World Health Organization (WHO), more than 13.6 billion COVID-19 vaccine doses have been administered worldwide since 2021. By the end of 2023, approximately 67% of the global population had completed the primary vaccination series, while 37% had received at least one booster dose.<sup>2</sup> Additional immunizations as part of the primary series were shown to restore or maintain an immunological status capable to provide protection against the most recent Omicron genetic variants of SARS-CoV-2, the causative agent of COVID-19. As variants of concern (VOCs) emerged and became dominant, mRNA-based vaccines were updated with modified antigens to better address the loss of Spike (S) protein epitopes originally targeted by the first-generation vaccines, which were based on the genome sequence of the wild-type (Wuhan) virus. By mid-2023, the bivalent mRNA vaccine Comirnaty Bivalent (Pfizer-BioNTech), which included antigens from both the wild-type virus and Omicron subvariants of SARS-CoV-2, demonstrated the ability to elicit significant levels of neutralizing antibodies against newer virus variants. However, the elicited immune response was markedly imbalanced, with a much stronger boost observed against the original virus.<sup>3</sup> In response, the monovalent Spikevax (Moderna) mRNA vaccine based on the XBB.1.5 Omicron subvariant, a recent form of the virus, was introduced in 2024. Unlike previous variants, Omicron and its subvariants have exhibited a pronounced ability to evade immunity through structural mutations in the S protein, enabling them to escape the neutralizing effects of antibodies generated by vaccines designed against earlier viral variants.<sup>4</sup> This immune evasion, combined with the relatively naïve immune landscape in certain populations, could increase the risk of recurrent infections and potentially severe outcomes, especially as the virus continues to evolve. Compounding this issue is the dramatic decline in immunization coverage observed globally since 2023.<sup>2</sup>

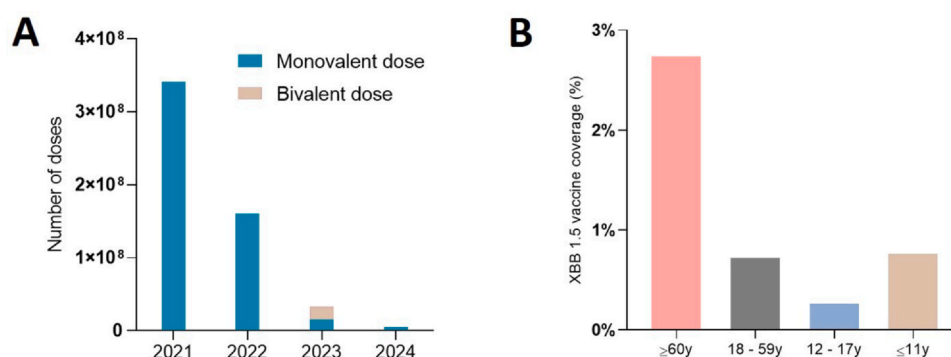
Brazil exemplifies both the progress and persistent challenges in global COVID-19 vaccination efforts. While the incidence of cases and deaths has decreased significantly since 2021, outbreaks driven by Omicron subvariants continue to cause periodic surges, mirroring trends observed worldwide. By the end of 2023, Brazil's vaccination strategy had achieved high coverage for primary series (86%) and moderate coverage for booster doses (55%), primarily utilizing monovalent vaccines targeting the ancestral strain.<sup>5</sup> However, vaccination coverage regarding updated vaccines in 2023 and 2024, remains alarmingly low (Fig. 1A). To date, except for the elderly, fewer than 1% of the Brazilian population has received a dose of the

XBB.1.5 vaccine (Fig. 1B), with adolescents exhibiting the lowest coverage rates (<0.5%).<sup>6</sup> It is important to highlight that Brazil has an estimated population of 212 million people. From this target population, only 9.3 million people received a vaccine dose in 2024, which represents less than 1% of overall vaccine coverage.

The Strategic Advisory Group of Experts on Immunization (SAGE) working group developed a framework for analyzing vaccine hesitancy, known as the 5Cs. These categories are: constraints (not perceiving diseases as high-risk or vaccination as essential), convenience (practical barriers to vaccination), confidence (distrust in the safety and effectiveness of vaccines), calculation (individuals' involvement in extensive information-seeking), and collective responsibility (a shared mindset focused on protecting others).<sup>7</sup> In Brazil, there are still few studies that effectively explore the reasons behind vaccine hesitancy among the population. However, these categories, combined with the country's vast territorial expanse, diverse political and ideological orientations, and the growing number of vaccine doses may play a significant role in shaping vaccine reluctance over the years.

Globally, similar patterns emerge and these gaps threaten the control of SARS-CoV-2 transmission and amplify the risk of severe outcomes, particularly as immune-evasive Omicron subvariants dominate.<sup>8</sup> Most high-income countries, particularly in Europe, have vaccinated more than 50% of their total populations with at least one booster dose. In contrast, most middle- and low-income countries, particularly in Africa, have achieved less than 10% coverage.<sup>2</sup> This stark disparity in vaccination coverage underscores a dramatic imbalance worldwide, with more vulnerable populations experiencing significantly lower access to COVID-19 immunization. Such inequities may promote the selection and emergence of new SARS-CoV-2 variants in populations with better vaccination access, where the virus causes mild forms of COVID-19, while the spread of these selected variants could result in severe population-level outbreaks and serious symptoms and risk of hospitalization, and eventually death, among more susceptible and less immunized groups.

The virus retains significant mutational drift capacity, particularly affecting the SARS-CoV-2 S protein. This presents a dual challenge: diminished efficacy of prior immunity and the potential emergence of variants with increased transmissibility and/or pathogenicity.<sup>3,9,10</sup> Of the more than 135 neutralizing antibody (NAb) epitopes identified in the wild-type S protein, fewer than 30 remain. Similarly, of the approximately 370 T-cell epitopes, fewer than 250 have been retained. Most of the remaining NAb epitopes are located in the receptor-binding domain (RBD) of the S protein, while the majority of the retained T-cell epitopes are found in subunit 2 (S2).<sup>9,10</sup> These data highlight the virus's ability to accumulate a significant number of mutations without compromising its capacity for replication and transmission. This is particularly notable given that the RBD plays a key role in attachment to the host cell receptor,



**Fig. 1.** COVID-19 vaccination coverage and dose distribution across age groups in Brazil, 2021–2024. (A) Total number of doses of monovalent vaccines, including first-generation vaccines based on the original virus, the current Spikevax XBB 1.5 vaccine (Moderna), and bivalent vaccines administered since the start of the National Immunization Program in 2021. (B) Vaccine coverage of the monovalent vaccine XBB.1.5, introduced in 2024, by age groups: ≥60 years, 18–59 years, 12–17 years, and ≤11 years. For vaccination coverage, we considered Brazil's target population and the number of individuals who received at least one dose of the monovalent XBB 1.5 vaccine. Data were obtained from Brazilian public vaccination monitoring dashboards.

while S2 is crucial for viral fusion and entry. Determining the limits of the virus's ability to evolve and adapt remains a challenging task.

The under-immunization of younger populations exacerbates vulnerabilities, particularly against these evolving threats. Structural mutations in Omicron subvariants, such as those affecting neutralizing antibody epitopes, have already diminished the effectiveness of earlier vaccines. Coupled with declining global immunization rates, this creates fertile ground for new variants to emerge, potentially compromising advancements in public health outcomes. To mitigate these risks, it is imperative to prioritize equitable access to updated vaccines and adopt targeted strategies for under-immunized populations. Concurrently, genomic and immunological surveillance must guide vaccine design and public health interventions, ensuring that vaccination strategies remain responsive to the virus's evolution. Without intensified efforts, the combined threats of immune escape, recurrent infections, and severe cases could compromise global health security once more.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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