Retrospective cohort study of COVID-19 in patients of the Brazilian public health system with SARS-COV-2 Omicron variant infection

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Abstract

Several vaccines against COVID-19 are now available, based on different techniques and made by different laboratories spread around the world. With the roll out of the vaccination process in an advanced stage in many countries, and the reduced hospitalization risk by the Omicron relative to Delta variant infection, despite the higher transmission risk of Omicron, may lead to a misinterpretation of the results, as infection by Omicron is associated with a significant reduction of severe outcomes and shorter hospitalization time than the Delta variant. We compared the in-hospital mortality due to the Omicron (Jan-Mar 2022) with Gamma (Jan 2021) and Delta (Oct-Dec 2021) variants of patients in the Brazilian public health system. This study also discusses the decrease of booster vaccine effectiveness in hospitalized patients due to the Omicron compared with the Delta variant. Without a remodeling of vaccines for new variants, booster doses may be necessary with a shorter time interval

Main

With the emergence of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, the World witnesses an unprecedented and rapid effort for the rational design, development and emergency approval of vaccines against the disease. While several already available vaccines are based on well-known methodologies, such as the inactivated virus vaccine CoronaVaC (Sinovac Biotech) [1], others use relatively new approaches: non-human adenovirus AZD1222 (AstraZeneca) [2], mRNA BNT162b2 (Pfizer) [3] and RNA Ad26.COV2.S (Janssen) [4] vaccines.

Despite the more than 10 billion vaccine doses administered around the world by 10 March 2022 [5], and the proven disease control measures including mask wearing and adaptation in businesses and schools, new SARS-CoV-2 Variants of Concern (VOC) are still emerging. The latest examples are Delta variant (B.1.617.2) designated VOC on May 11, 2021, and Omicron variant (B.1.1.529) designated VOC on 26 November 2021 [6].

The Delta variant was classified as VOC due to its increased transmissibility, with an increased viral load in infected individual one thousand times higher relative to the original SARS-CoV-2 virus [7]. The Omicron variant is also spreading faster than any previous variant, surpassing Delta in early 2022. Its transmission risk is twice as high as Delta's in non-household settings, particularly observed in transmission between unvaccinated individuals. This may indicate that briefer contact events may be sufficient for transmission. The Omicron variant has also an increased capacity of evading vaccine-triggered immunity [8].

Despite the higher transmissibility of Omicron [9], mitigation policies as social distancing and mask mandates have been shown to effectively reduce the impacts of outbreaks, as clearly shown by the measures adopted in European countries, and in US and Brazilian states [10], and can be implemented easily and rapidly to reduce the impact of the Omicron variant.

Infections by the Omicron variant result in a smaller Hospitalization risk than the Delta variant [11,12], despite the higher transmission risk. This may lead to a misinterpretation of results as infection by Omicron is associated with less severe outcomes and shorter hospitalization than the Delta variant. The present study compares in-hospital mortality by the Omicron variant during January through March 2022 with Gamma during Jan 2021 and Delta during October through December 2021, for patients in the Brazilian public health system.

We discuss the decrease in booster Vaccine Effectiveness (VE) of hospitalized patients for infections by Omicron, compared with the Delta variant. Feikin et al. published a systematic review of the VE considering the period from 17 June 2021 to 2 December 2021, but without data for the Omicron variant [13]. We stress the fact that a rational design of vaccination considering all variants and the respective VE is important to an effective mitigation of the current pandemic [14], with the side effect of lowering the probability of emergence of yet new variant, that tend to emerge in countries with low vaccination coverage.

Results

Figure 1 shows the number of hospitalized individuals per million inhabitants for the period from 01 January to 23 March 2022, according to vaccination status. This finding clearly shows the vaccine effectiveness, even without considering immunosenescence. In summary, unvaccinated are about twice the number of vaccinated for all hospitalized individuals per million.

Figure 1. Hospitalizations and in-hospital deaths per million inhabitants between 1st January 2022 and 23 March 2022, according to vaccination status and age group. Unvaccinated include partially vaccinated individuals.

Hospitalization is significantly higher in unvaccinated or only partially vaccinated individuals. The number of hospitalized individuals increases and the number of recovered people significantly reduces with aging. The amount of people who died is practically the same as those who recovered after hospitalization for the age group over 80. There are no vaccinated children aged 0-9 years old in our analysis as vaccination for 5-10 years old only started in Brazil by 14 January 2022.

Unvaccinated individuals are the majority of hospitalization and deaths from COVID-19 during October to December 2021 (with dominance of Delta variant) and January to March 2022 (with Omicron variant dominant). The number of hospitalization and deaths for the second period is 3.6 and 4.2 times higher when compared to the early period (Tables S2-S3).

Compared to late 2021, booster VE against severe outcomes for infections by the Omicron Variant decreased 16.7% on average. CoronaVac VE decreased 15.32%, from 96.93% (95% confidence interval (CI: 96.35 - 97.51)) to 81.62% (95% CI: 80.99 - 82.23) when compared with late 2021. AZD1222 decreased 23.77%, from 96.56% (95% CI: 96.13 - 97.12) to 72.79% (95% CI: 72.20 - 73.37), and Ad26.COV2.S decreased 29.28% from 87.73% (95% CI: 83.65 - 91.80) to 58.44% (95% CI: 53.43 - 63.46). BNT162b2 VE

decreased 7.52% with Omicron variant, from 98.35% (95% CI: 97.52 - 99.18) to 90.84% (95% CI: 89.92 - 91.75), presenting the highest VE when compared to the other vaccines (Table 1).

Table 1. Booster VE against SARS-CoV-2 for two different periods of time, without considering the Immunosenescence. Incidence per million of inhabitants.

Vaccine	Period	Fully Vaccinated hospitalizations	Booster hospitalizations	Booster VE (95% CI)
CoronaVac	Oct-Dec 21	19.2949	0.5916	96.93% (96.35 - 97.51)
	Jan - Mar 22	87.6454	16.1136	81.62% (80.99 - 82.23)
AZD1222	Oct-Dec 21	38.9221	1.3390	96.56% (96.13 - 97.12)
	Jan - Mar 22	128.0328	34.8373	72.79% (72.20 - 73.37)
BNT162b2	Oct-Dec 21	5.3537	0.0883	98.35% (97.52 - 99.18)
	Jan - Mar 22	24.1829	2.2162	90.84% (89.92 - 91.75)
Ad26.COV2.S	Oct-Dec 21	1.3349	0.1638	87.73% (83.65 - 91.80)
	Jan - Mar 22	2.1686	0.9012	58.44% (53.43 - 63.46)
Missing manufacturer information	Oct-Dec 21	0.8933	0.1502	83.19% (77.03 - 89.34)
	Jan - Mar 22	6.8709	1.6788	75.57% (72.90 - 78.24)

Figure 2 shows the profile of in-hospital mortality and recovery for January 2021 (Figure 2a), with predominance of the Gamma variant, October to December 2021 (Figure 2b) with the predominance of Delta, and January to March 2022 (Figure 2c) with the predominance of the Omicron variant, for children and adolescents (0-17 years old), adults (18-59 years old), and elderly (Over 60 years old), in vaccinated and unvaccinated patients. Regardless of the variant, once hospitalized, the proportion of recovery and death outcomes is approximately the same in all age groups. Moreover, for all variants considered here, the proportion of recovered children is higher than for adults. The attack rate obtained from

epidemiological models [15], serological surveys [16, 17], or estimates obtained from average Infection Fatality Ratio must be considered with care due to the higher reinfection rate by the Omicron variant.

Figure 2. In-hospital mortality and recovery for (a) January 2021 with the predominance of the Gamma variant infections among the hospitalized patients, (b) October to December 2021, with the predominance of Delta and (c) January to March 2022 with the predominance of the Omicron variant. “A” stands for Unvaccinated and Recovered patients, “B” for Unvaccinated and Dead, “C” for Vaccinated and Recovered, and “D” for Vaccinated and Dead. Age was stratified into three groups: Child (0-17 years old), Adult (18-59 years old) and Elderly (Over 60 years old).

Discussion

Gamma and Delta variants were dominant during the year of 2021, resulting in two overlapping outbreaks, with similar hospitalization rates for infections caused by each variant. By the end of 2021 the Omicron variant was detected and became the leading cause of hospitalization by January 2022. At the beginning of the pandemic hospitalizations were in a great proportion of elderly individuals (Over 60 years old). In Brazil, during the same period, approximately half of COVID-19 severe cases occurred in this age group, accounting for 73% of deaths [18]. But now there is proportion of 85% of fully vaccinated individuals between the elderly population, while the proportion of the vaccinated population with less than thirty years old is much lower [19]. Another relevant factor impacting the age profile among the hospitalized population is the reduced VE for the Omicron variant. Moreover, due to the initial limited availability of vaccines for COVID-19 in Brazil, only targeted people who belonged to risk groups such as health workers, the elderly, indigenous populations, and institutionalized individuals were vaccinated. Vaccination by age started with those above 85 years and older and was gradually reduced for younger groups, with the younger population remaining exposed to the virus for a longer period, with booster doses for these individuals administered only from September 2021.

Despite the proven efficacy of vaccines and with a significant proportion of the population immunized, COVID-19 remains a public health concern, as the number of new hospitalizations and deaths due to the disease remains important. Between late 2021 and early 2022, the moving average of daily cases increased worldwide, with a peak of more than four million new cases in a single day on 26 January 2022 [20]. In Brazil this number was close to 300,000 cases per day on the 5 February 2022, with a strong impact on the healthcare system [21]. An important contributing factor to this situation was the emergence of the Omicron variant, first reported the 26 November 2021 in South Africa, and classified as a variant of concern (VOC) by the WHO in later that month [22]. The Omicron variant was responsible for the majority of cases by January 2022 and estimated four times more transmissible than the Delta variant.

Most of the approved and available vaccines for COVID-19 target the Spike (S) glycoprotein site from the original SARS-CoV-2 (Wuhan-01 strain) for the neutralizing antibodies, due to its role in the virus infection and in the adaptive immune response [23]. Studies have demonstrated that the Omicron variant mutation

in its S glycoprotein epitope, including mutations within the receptor-binding domain (RBD), allow it to evade the antibody response and thus threatening measures to contain the infection. Such mutations result in resistance to neutralizing antibodies and are associated with reduced vaccine effectiveness. However, it is not completely clear to what extent T-cells are able to recognize this variant. The existing vaccines may not be able to provide proper protection against the Omicron variant infection, even if they reduce its risk of hospitalization and death [24]. Booster doses have been proven an effective alternative in reducing the new COVID-19 cases.

Evidence points to the critical relevance of booster doses in reducing hospitalizations. At first booster doses in Brazil were administered after 180 days after the second dose (or single dose for the Janssen vaccine), but now this delay was reduced to 120 days. Based on the available data, the optimal delay is between 105 and 120 days (Tables S2-S3).

Studies conducted with the CoronaVac and BNT162b2 vaccines with different vaccine regimes have shown that Omicron neutralization is weak or undetectable after complete immunization with two doses. Moreover, such studies and reports demonstrate that the booster dose can effectively prevent infection, hospitalizations and deaths from COVID-19 [25-27]. As pointed out above, for both CoronaVac and BNT162b2 vaccines, studies have shown that it is important to consider the interval between the second dose and the booster dose, as immunity declines over time [28].

Regarding other vaccine platform technologies, such as adenoviral vector vaccines, it was also shown that for the vaccine AZD1222 a third dose booster significantly increased the antibody levels against the Omicron variant [29]. Serum from individuals collected one month after receiving the booster dose was able to neutralize the action of the Omicron variant at levels like those observed one month after the second dose against the Delta variant, while two doses of AZD1222 yielding an effective protection against the Delta variant [30].

Although the Omicron variant being less lethal in the population, it did not differ much for the elderly population, who remain at risk due to the natural age-related decline in VE. In contrast, the VE behavior decreased for hospitalized children in the 0 to 17 years old group with the omicron variant (Table S2-S3). A cross-sectional analysis of the hospitalizations and in-hospital deaths between 1st January 2022 and 23 March 2022 may suggest that the vaccination schedule should be updated to use only vaccines of a similar class of BNT162b2 to immunize the elderly people.

Brazil has no mass testing policy, with self-tests only approved by the end of February 2022 but with no planned availability in the public health sector, where all treatments and medications are free. Also, there is no policy for the incorporation of effective drugs for the treatment of COVID-19 in this the public health sector up to March 2022, which must be compared to the United Kingdom, where these drugs were responsible for the change in hospitalization outcomes in groups with greater probability of evolving to severity, as the elderly, when treated in the first few days of symptoms [31]. Due to the protection

guaranteed by the vaccines and the characteristics of the Omicron variant, which causes milder symptoms, the number of deaths has not grown at the same rate as the number of cases.

Considering that the aged population in Brazil received as primary vaccination regimen the CoronaVac or AZD1222 vaccines, the present discussion strongly reinforces the need for an increased protection of this population before the austral autumn/winter, preferably integrated with the influenza vaccination campaign that is already consolidated by the public immunization plan in Brazil. Finally, the analysis shows that, regardless of age group, the death ratio among hospitalized people remains the same for any of the studied periods (Table S4).

Methods

This is a retrospective cohort study of COVID-19 hospitalization in the Brazilian public health system of 959,812 SARS-CoV-2 infected patients from a multicenter, nationwide database in Brazil from 1st January 2021 to 23 March 2022. The limitations of this study are: I. the Brazilian public health system represents 70% of all hospital beds in the country and II. the rough dataset presented some data gaps, so we considered only data where the outcome of death or survival is given.

We tested whether the Omicron cohort had reduced severity in outcomes differed from the Gamma and Delta cohorts, within hospitalized patients in the Brazilian public health system. The vaccination status documented in hospitalized patients (CoronaVaC, AZD1222, BNT162b2 and Ad26.COV2.S) and age were used in the evaluation. Separate analyses were performed on patients stratified into three age groups (0-17 years old), adults (18-60 years old), and elderly (over 60 years old). The in-hospital mortality outcome was examined in the studied time window.

Data availability

In this study, we followed the Brazilian Personal Data Protection General Law. The anonymized data is publicly available at https://opendatasus.saude.gov.br/dataset/srag-2021-e-2022 downloaded on 24 March 2022. Any information for assessing the databases must be addressed to the Brazilian Ministry of Health at https://datasus.saude.gov.br/ and requests can be addressed to dadosabertos@saude.gov.br.

References

1. Tanriover, M.D. et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* ***398***, 213-222 (2021). https://doi.org/10.1016/S0140-6736(21)01429-X.

2. Voysey, M. et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* ***397***, 99-111 (2021). https://doi.org/10.1016/S0140-6736(20)32661-1.

3. Polack, F.P.C. et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N. Engl. J. Med.* ***383***, 2603-2615 (2020). https://doi.org/10.1056/NEJMoa2034577.

4. Sadoff, J. et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N. Engl. J. Med.* ***384***, 2187-2201 (2021). https://doi.org/10.1056/NEJMoa2101544.

5. https://covid19.who.int/. Accessed on March 10, 2022.

6. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed on March 10, 2022.

7. Li, B. et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant. *Nat. Commun.* **13**, 460 (2022). https://doi.org/10.1038/s41467-022-28089-y

8. Allen, H. et al. Preprint at *medRxiv* https://doi.org/10.1101/2022.02.15.22271001 (2022).

9. Murray, C.J.L. COVID-19 will continue but the end of the pandemic is near. *Lancet* **399**, 417-419 (2022). https://doi.org/10.1016/S0140-6736(22)00100-3

10. Filho, T.M.R., Moret, M.A. & Mendes, J.F.F. A Transnational and Transregional Study of the Impact and Effectiveness of Social Distancing for COVID-19 Mitigation. *Entropy* **23**, 1530 (2021). https://doi.org/10.3390/e23111530

11. Wang, L et al. Preprint at *medRxiv* https://doi.org/10.1101/2021.12.30.21268495 (2022).

12. Report 50 - Hospitalisation risk for Omicron cases in England. Available at: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-50-severity-omicron/ (2022).

13. Feikin, D.R. et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* **399**, 924-944 (2022). https://doi.org/10.1016/S0140-6736(22)00152-0

14. Rocha Filho, T.M. et al. Optimization of COVID-19 vaccination and the role of individuals with a high number of contacts: A model based approach. *PLoS ONE* **17**(3): e0262433 (2022). https://doi.org/10.1371/journal.pone.0262433

15. Rocha Filho, T.M. et al. A data-driven model for COVID-19 pandemic – Evolution of the attack rate and prognosis for Brazil. *Chaos, Solitons and Fractals* **152**, 111359 (2021). https://doi.org/10.1016/j.chaos.2021.111359

16. Silveira, M.F., Barros, A.J.D, Horta BL, Pellanda LC, Victora GD, Dellagostin OA. Population-based surveys of antibodies against SARS-cov-2 in southern Brazil. *Nat. Med.* **26**, 1196–1199 (2020). https://doi.org/10.1038/s41591-020-0992-3.

17. Soroepi MSP: Serial soroepidemiological survey to monitor the prevalence of SARS-cov-2 infection in the municipality of São Paulo, SP, brazil. 2020. https: //www.monitoramentocovid19.org/. Accessed April, 28 (2021).

18. Pietrobon, A.J., Teixeira, F.M.E. & Sato, M.N. Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Front. Immunol. **11**, 579220 (2020). https://doi.org/10.3389/fimmu.2020.579220

19. Victora, C.G., Castro, M.C., Gurzenda, S., Medeiros, A.C., França, G.V.A., & Barros, A.J.D. Estimating the early impact of vaccination against COVID-19 on deaths among elderly people in Brazil: Analyses of routinely-collected data on vaccine coverage and mortality. *EClinicalMedicine* **38**, 101036 (2021). https://doi.org/10.1016/j.eclinm.2021.101036

20. https://covid19.who.int/

21. https://covid19.who.int/region/amro/country/br

22. https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern

23. Sadarangani, M., Marchant, A. & Kollmann, T.R. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. *Nat Rev Immunol* **21**, 475-484 (2021). https://doi.org/10.1038/s41577-021-00578-z

24. Willyard, C. The omicron wave's surprising lessons for long-term immunity. Immunologists have raced to work out how to protect against new variants of SARS-CoV-2. Their research has yielded a wealth of insights. *Nature* **602**, 22-25 (2022). https://doi.org/10.1038/d41586-022-00214-3

25. Pérez-Then, E., Lucas, C., Monteiro, V.S. *et al.* Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. *Nat Med* (2022). https://doi.org/10.1038/s41591-022-01705-6

26. Cheng, S.M.S., Mok, C.K.P., Leung, Y.W.Y. *et al.* Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med* (2022). https://doi.org/10.1038/s41591-022-01704-7

27. Gruell, H., Vanshylla, K., Tober-Lau, P. *et al.* mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. *Nat Med* (2022). https://doi.org/10.1038/s41591-021-01676-0

28. Pajon, R., Doria-Rose, N.A., Shen, X., Schmidt, S.D., O'Dell, S., McDanal, C. et al. SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination. *N Engl J Med* **386**, 1088-1091 (2022). https://doi.org/10.1056/NEJMc2119912

29. Dejnirattisai W, Huo J, Zhou D, Zahradník J, Supasa P, Liu C. et al. Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. *bioRxiv* preprint doi: https://doi.org/10.1101/2021.12.03.471045 (2021)

30. Sheikh, A. McMenamin, J., Taylor, B. et al. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet **397**, 2461- 2462 (2021).

31. https://www.nhs.uk/conditions/coronavirus-covid-19/self-care-and-treatments-for-coronavirus/treatments-for-coronavirus/

Figures

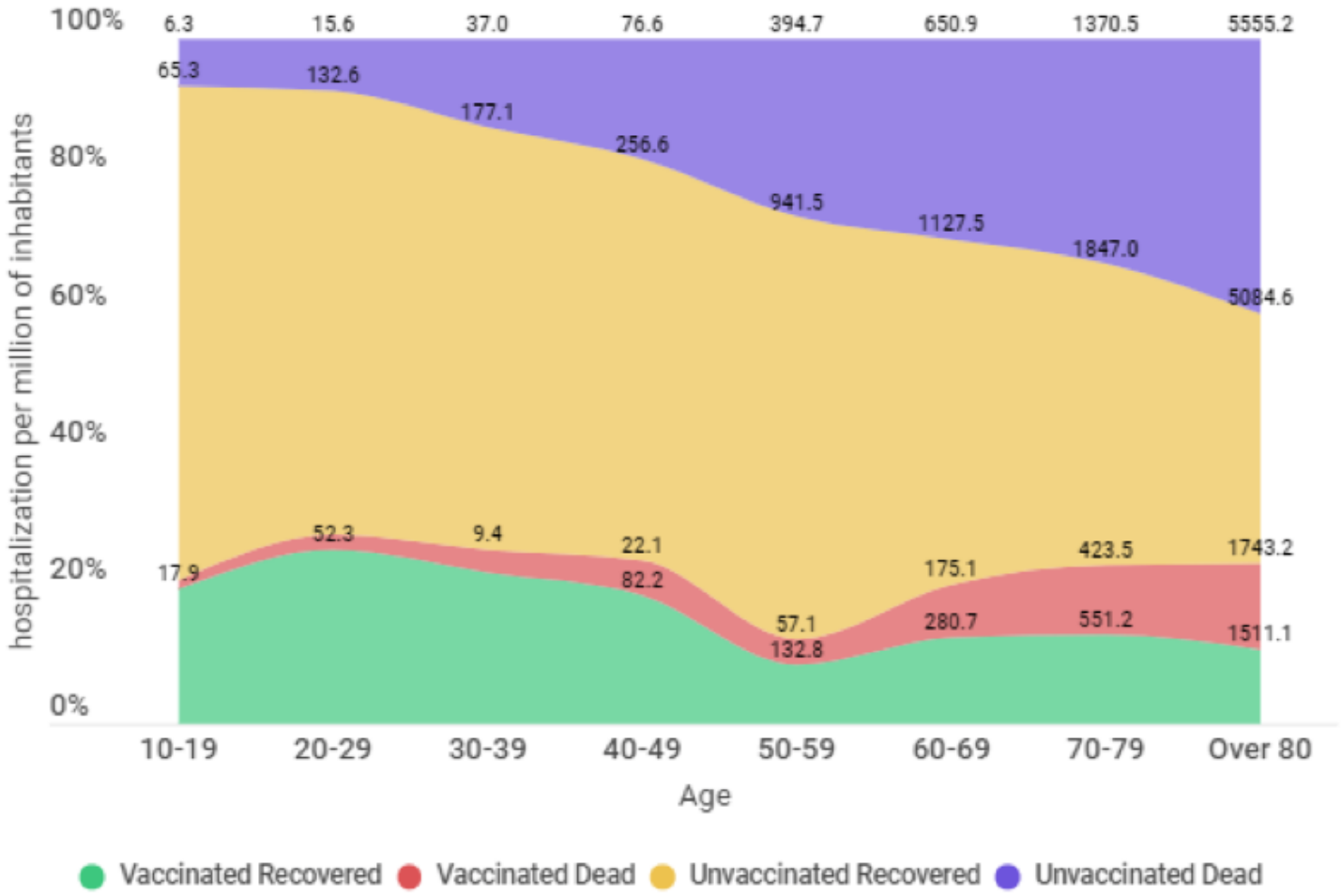

Figure 1

Hospitalizations and in-hospital deaths per million inhabitants between 1st January 2022 and 23 March 2022, according to vaccination status and age group. Unvaccinated include partially vaccinated individuals.

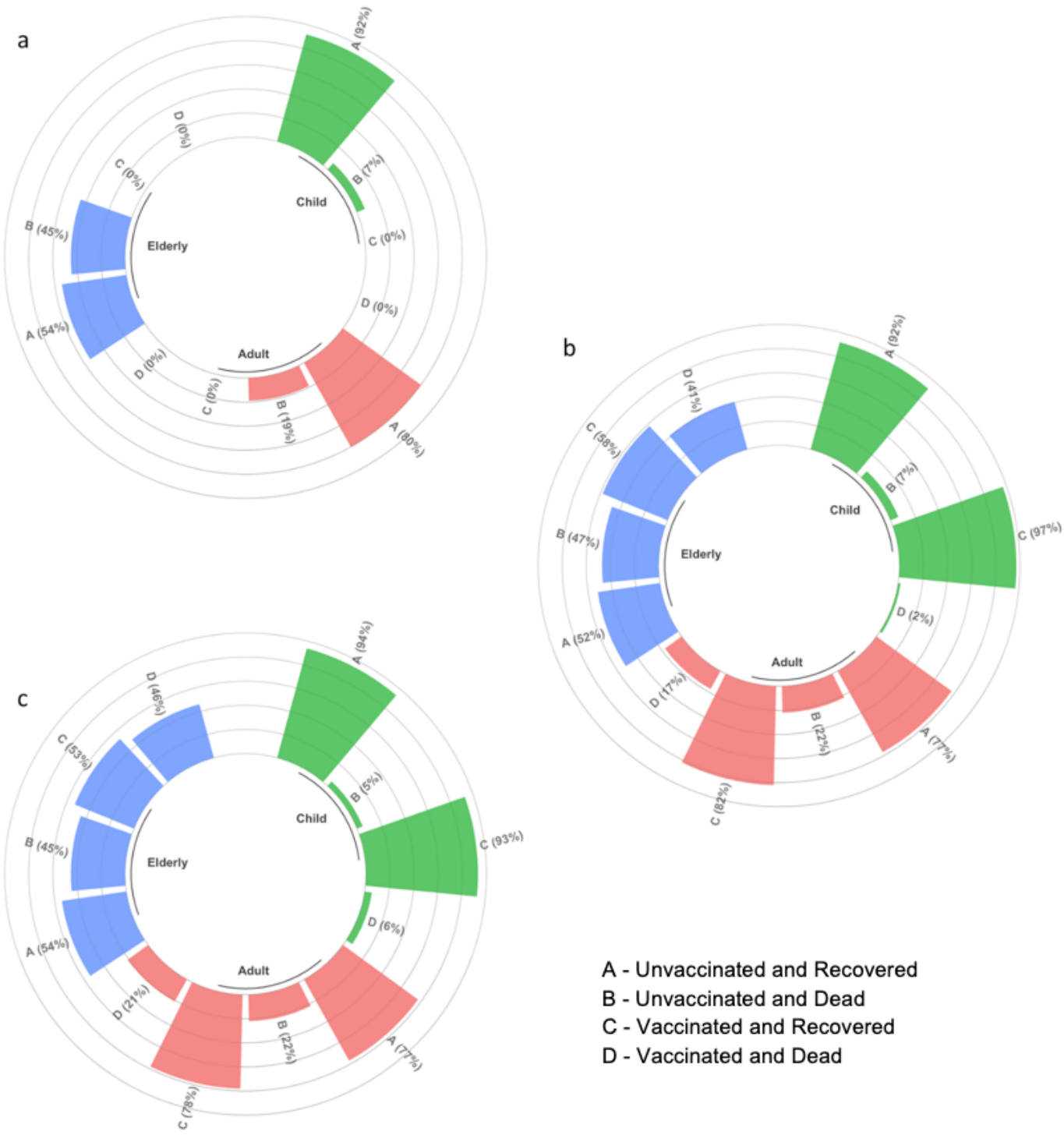

Figure 2

In-hospital mortality and recovery for (a) January 2021 with the predominance of the Gamma variant infections among the hospitalized patients, (b) October to December 2021, with the predominance of Delta and (c) January to March 2022 with the predominance of the Omicron variant. “A” stands for Unvaccinated and Recovered patients, “B” for Unvaccinated and Dead, “C” for Vaccinated and Recovered, and “D” for Vaccinated and Dead. Age was stratified into three groups: Child (0-17 years old), Adult (18-59 years old) and Elderly (Over 60 years old).

Supplementary Files

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- SupplementaryData.docx