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Is a Booster Dose of COVID-19 Vaccines Effective on Newly Dominant Omicron Subvariants Among University Students? Comparison Between BA.1 and BA.2 Dominancy

Short title: Booster dose in BA.1 and BA.2 dominancy

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HIGHLIGHTS

- A booster dose effectiveness is remains unclear against Omicron BA.2 subvariant.
- Updating evidence for students is essential to improve their vaccine acceptance.
- A booster dose reduced the infection rate of close contacts during BA.2 dominancy.
- Vaccine effectiveness tended to decrease in BA.2 dominancy than in BA.1 dominancy.

ABSTRACT

Background: Although the COVID-19 Omicron BA.1 subvariant was initially predominant, the BA.2 subvariant has now replaced it. Effectiveness of a booster dose vaccination for BA.2 remains unclear among university students.

Methods: We enrolled 562 Japanese university students who became a close contact and underwent polymerase chain reaction testing. We compared infection rates and cumulative incidence rates of severe fever among the students according to the COVID-19 vaccine doses received between BA.1-dominant (January 1–March 31, 2022) and BA.2-dominant (April 1–July 31, 2022) periods.

Results: Infection rates for BA.1 were 32% with three doses, 49% with two doses, and 68% in the unvaccinated (*P*=0.008). The odds ratio (OR) for infection following three doses during BA.1 was 0.46 (95% confidence interval [CI]=0.25−0.82, *P*=0.009). Infection rates for BA.2 were 45% with three doses, 62% with two doses, and 64% in the unvaccinated (*P*=0.02). The OR for infection following three doses during BA.2 was 0.50 (95% CI=0.31−0.82, *P*=0.006). Effectiveness of vaccine for BA.2 tended to decrease for both three (45% vs. 32%, *P*=0.06) and two doses (62% vs. 49%, *P*=0.07) compared with those for BA.1.

Conclusions: Booster dose effectiveness tended to decrease but remained significant against BA.2 subvariant predominancy among Japanese university students.

Keywords: COVID-19; Vaccine; Booster dose; Omicron; Subvariant; University

INTRODUCTION

After the first report of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on December 31, 2019, newly developed variants have repeatedly threatened the world. Since the end of November 2021, the Omicron variant has spread worldwide and rapidly replaced prior SARS-CoV-2 variants of concern. As of August 1, 2022, the Omicron variant has evolved into several subvariants including BA.1, BA.2, BA.2.12.1, BA.3, BA.4, and BA.5, which have sequentially increased their prevalence over time.[1,2] Among them, BA.1 initially surged and replaced the Delta variant to become the dominant subvariant worldwide. However, BA.2 has rapidly attained dominance in several countries due to its higher transmissibility compared with BA.1.[3] Although recent studies indicate that both BA.1 and BA.2 are highly resistant to neutralization by monoclonal antibody therapy and vaccine-induced immunity compared with the previous variants,[4,5] speeding up coverage with a booster dose vaccination is highly recommended under the Omicron emergency.[6] Missing learning opportunities due to COVID-19 infection and being a close contact of a COVID-19 patient have been raised as major concerns for university education. Although high levels of vaccine coverage are strongly required to minimize the impact of the COVID-19 pandemic on university education,[7] a certain amount of "vaccine hesitancy" is still occurring among university students.[8,9] Updating evidence of a booster dose vaccination for ongoing subvariants especially among the young population is needed to improve the students' vaccine acceptance. We previously reported the real-world effectiveness of a booster dose among Japanese university students during the BA.1-dominant period.[10] The present study aimed to investigate the effectiveness of a booster dose vaccination among Japanese university students during the BA.2-dominant period compared with the BA.1-dominant period.

MATERIALS AND METHODS

Study design

This observational study was conducted at Hiroshima University, Higashihiroshima and Hiroshima, Japan, from January 1 to July 31, 2022. As of January 1, 2022, 13,133 students (10,603 undergraduate students and 2,530 graduate students) were enrolled in Hiroshima University. They were firmly instructed to register on the online COVID-19 registration system of Hiroshima University when they became a close contact of a COVID-19 patient and were examined with a polymerase chain reaction (PCR) test for SARS-CoV-2. A close contact fulfilled the following criteria: (a) contact with a COVID-19 patient between 2 days before and 14 days after the onset of symptoms, (b) no use of masks, (c) distance of less than 1 meter during contact, and (d) more than 15 minutes of contact.[11] Direct physical contact during physical education and club activities was also considered to define a close contact. Information on the students' age, sex, vaccination status, symptoms, and the results of their PCR tests were collected using an online questionnaire. Severe fever was defined as fever $\geq$ 38.5℃. The students with a negative result at the first PCR test were followed up for at least 10 days from their last contact with a COVID-19 patient by public health services or the Hiroshima University Health Service Center. If new onset of symptoms occurred during the follow-up period, affected students were instructed to undergo PCR retesting, the results of which were also investigated using the online questionnaire. All registered students completed the questionnaire.

In Japan, the SARS-CoV-2 Omicron BA.1 subvariant, which replaced the Delta variant, became dominant at the beginning of January 2022, but dominance of the BA.2 subvariant arose at the end of March 2022.[12] Thus, students who were enrolled from January 1 to March 31 were grouped into the "BA.1-dominant period" and those enrolled from April 1 to July 31

were grouped into the "BA.2-dominant period". We compared the infection rates and cumulative incidence rates of severe fever among close contacts between these two periods according to the COVID-19 vaccine doses received.

This study was approved by the Ethical Committee of Hiroshima University (approval number: E−143−3). Informed consent was waived by the Institutional Review Board because of the observational nature of the study and because participant identifiers were completely encrypted before analysis.

Infection control measure policy against COVID-19 in the university

During the study period, wearing of non-woven masks was mandatory during all school activities except for outdoor exercise. Students were also instructed to use a non-woven mask and avoid close-contact settings as much as possible during their afterschool activities. The use of on-demand lectures was recommended except for practical training classes. Following the instruction of the Japanese Ministry of Health, Labour and Welfare, students infected with COVID-19 were required to quarantine for at least 10 days. Students coming into close contact with individuals infected with COVID-19 were required to quarantine for 7 days from the date of their last contact with the infected person.

COVID-19 vaccination

A third dose of either a BNT162b2 vaccine (Comirnaty, Pfizer–BioNTech, Mainz, Germany/New York, NY) or a half dose (50 μg) of an mRNA-1273 vaccine (Spikevax, Moderna, Cambridge, MA) was offered to all people aged 12 years or older who had received a second vaccination dose at least 6 months before from December 1, 2021, in Japan.[13] Vaccination was not mandatory for students at Hiroshima University, and the students decided themselves whether to get vaccinated. Three students had received only one dose of

vaccine, and those cases were counted as unvaccinated. Mass vaccinations for students were conducted at Hiroshima University using mRNA-1273 vaccine (first dose, from June 21 to July 2, 2021; second dose, from July 26 to August 2, 2021; third dose, from March 1–7 and 15–16, 2022). Thus, most vaccinated students received an mRNA-1273 vaccine during those periods. Although the ChAdOx1 nCoV-19 vaccine (Vaxzevria, AstraZeneca, Oxford, UK) was approved in May 2021, no students in the study population received this vaccine. In addition, no students had received a fourth vaccine dose during the study period.

Statistical analysis

Infection rate is presented as the percentage of the group total. Multiple comparisons of the infection rates and the cumulative incidence rates of severe fever between the three vaccine dose groups (three doses, two doses, and unvaccinated) were performed by Fisher's exact test followed by Steel-Dwass post hoc test. The odds ratio (OR) was calculated to estimate the effectiveness of three doses compared with two doses and unvaccinated. *P* values of <0.05 indicated statistical significance. JMP software version 15.0 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses.

RESULTS

Differences in vaccination status and infection rate between BA.1- and BA.2-dominant periods

In total, 562 students (age, 21.7 ± 3.0; male, 61%) were enrolled to the study. Among them, 230 (age, 21.6 ± 2.7; male, 66%) were included in the BA.1-dominant period, and 332 (age, 21.8 ± 3.1; male, 57%) were included in the BA.2-dominant period.

Figure 1 depicts the vaccination status and overall infection rates of students with close contact between the BA.1-dominant and BA.2-dominant periods. In the BA.1-dominant period, 68 (30%) students received three doses, 143 (62%) received two doses, and 19 (8%) were unvaccinated. In the BA.2-dominant period, 240 (72%) students received three doses, 78 (24%) received two doses, and 14 (4%) were unvaccinated ($P < 0.0001$, Figure 1A). Infection rates were not statistically different between the two periods (BA.1 dominant, 46% vs. BA.2 dominant, 50%, $P = 0.35$, Figure 1B).

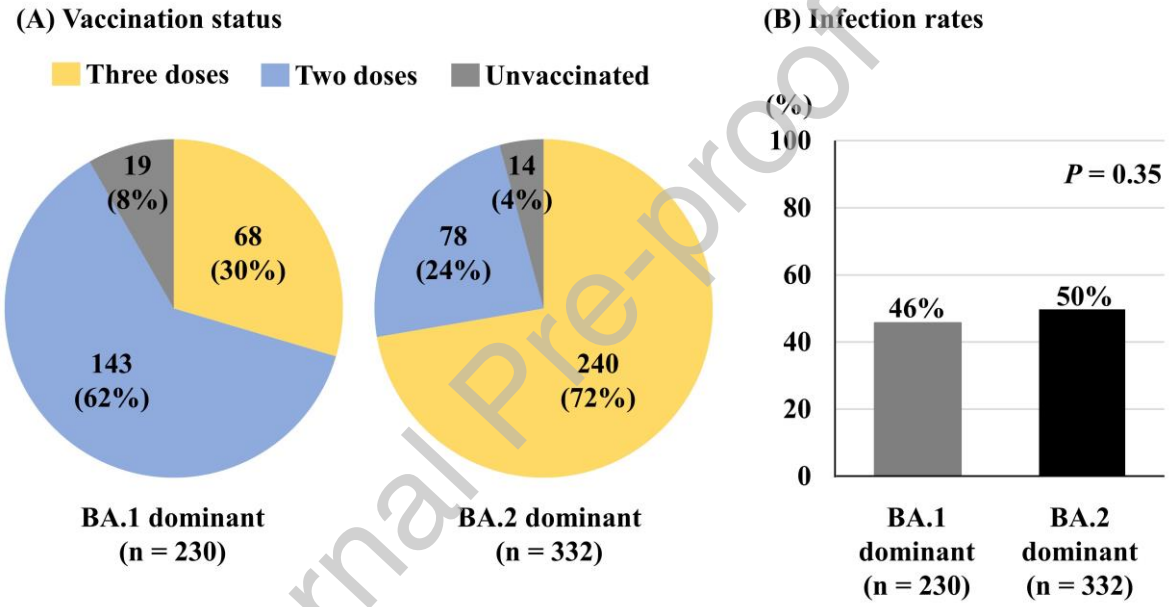

Fig. 1. Vaccination status and infection rates. Three students in the BA.1-dominant group had received only one dose of vaccine and were included in the unvaccinated group. BA.1-dominant period, from January 1, 2022 to March 31, 2022; BA.2-dominant period, from April 1, 2022 to July 31, 2022.

Vaccination status and infection rates among close contacts

Figure 2 compares vaccination status and infection rates between the close contacts. In the BA.1-dominant period, infection rates were 32% in students with three doses, 49% in those with two doses, and 68% in the unvaccinated, respectively ($P = 0.008$, Figure 2A). The

OR for infection with three doses during the BA.1-dominant period was 0.46 (95% confidence interval [CI] = 0.25−0.82, *P* = 0.009). In the BA.2-dominant period, infection rates were 45% in students with three doses, 62% in those with two doses, and 64% in the unvaccinated, respectively (*P* = 0.02, Figure 2B). The OR for infection with three doses during the BA.2-dominant period was 0.50 (95% CI = 0.31−0.82, *P* = 0.006).

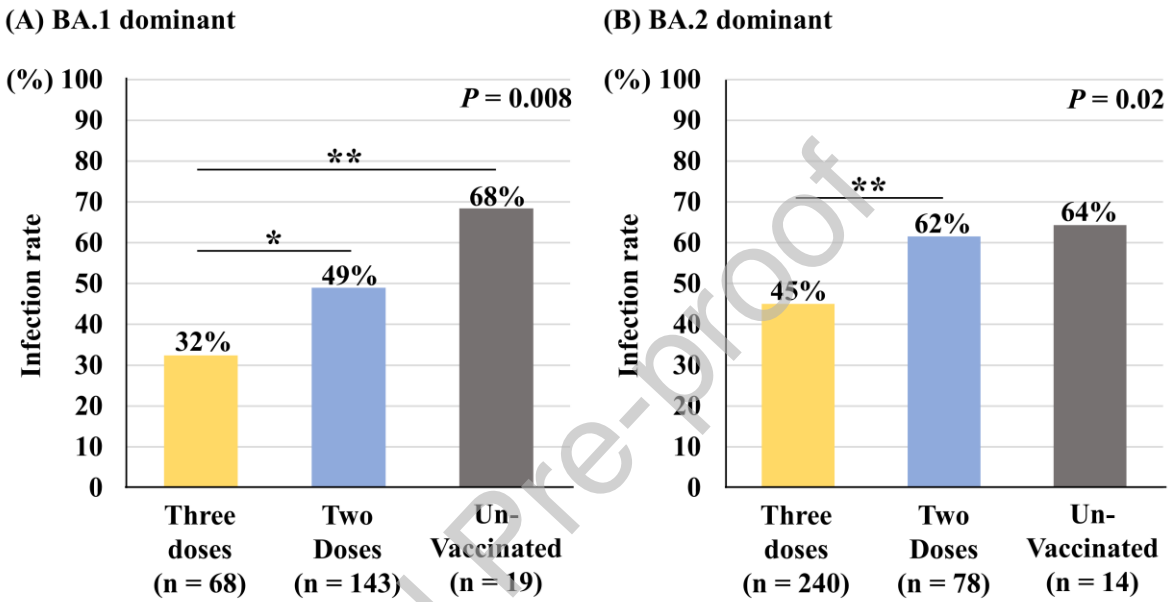

Fig. 2. Relation between vaccination status and infection rates. ** indicates *P* < 0.05 and * *P* < 0.10 by Steel-Dwass post hoc test. BA.1-dominant period, from January 1, 2022 to March 31, 2022; BA.2-dominant period, from April 1, 2022 to July 31, 2022.

Vaccine status and infection rates between BA.1- and BA.2-dominant periods

Figure 3 compares vaccine status and infection rates between the BA.1-dominant and BA.2-dominant periods. Although not statistically significant, the infection rates tended to be higher in the BA.2-dominant period compared with those in the BA.1-dominant period both for three doses (45% vs. 32%, *P* = 0.06, Figure 3A) and two doses (62% vs. 49%, *P* = 0.07, Figure 3B) of vaccine.

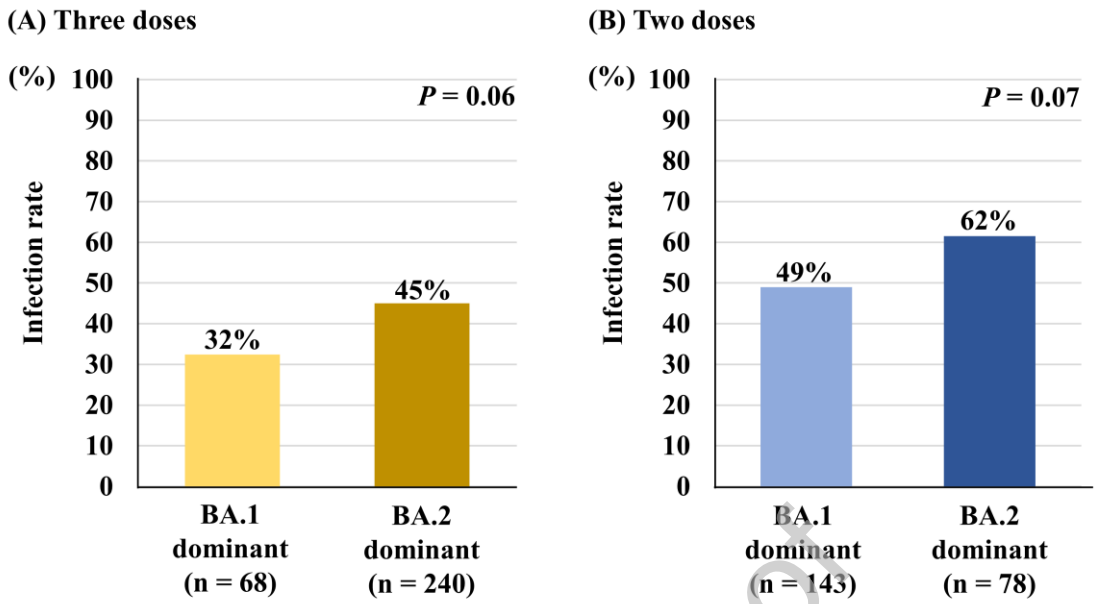

Fig. 3. Vaccine status and infection rates between the BA.1-dominant period (January 1, 2022 to March 31, 2022) and BA.2-dominant period (April 1, 2022 to July 31, 2022).

Vaccination status and severe fever among infected close contacts

The cumulative incidence rates of severe fever (≥ 38.5°C) were examined in close contacts who were infected (BA.1 dominant, n = 105; BA.2 dominant, n = 167). In the BA.1-dominant period, the cumulative incidence rates of severe fever were 5% in students with three doses, 16% in those with two doses, and 38% in the unvaccinated (P = 0.04, Figure 4A). The OR for infection with three doses during the BA.1-dominant period was 0.20 (95% CI = 0.02−1.59, P = 0.13). In the BA.2-dominant period, the cumulative incidence rates of severe fever were 13% in students with three doses, 33% in those with two doses, and 33% in the unvaccinated (P = 0.01, Figure 2B). The OR for infection with three doses during the BA.2-dominant period was 0.30 (95% CI = 0.14−0.65, P = 0.003).

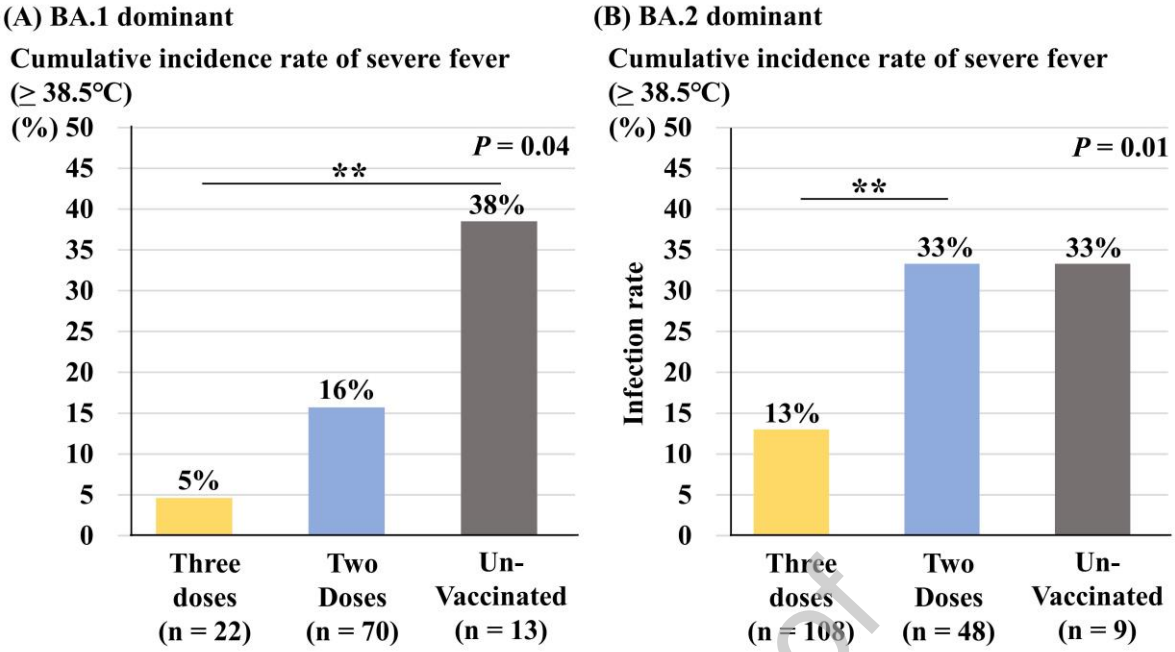

Fig. 4. Association between vaccine status and severe fever. ** indicates $P < 0.05$ by Steel-Dwass post hoc test. BA.1-dominant period, from January 1, 2022 to March 31, 2022; BA.2-dominant period, from April 1, 2022 to July 31, 2022.

DISCUSSION

The major findings of this study were that (a) three doses (booster dose) of vaccine were associated with a lower infection rate among close contacts in both the BA.1-dominant and BA.2-dominant periods, and (b) the infection rates with three doses and with two doses of vaccine tended to be higher in the BA.2-dominant versus BA.1-dominant period. Although the sample size was relatively small, this study is the first, to the best of our knowledge, to compare the effectiveness of a booster dose of vaccine between Omicron BA.1 and BA.2 subvariants spreading among university students.

The Omicron variant of SARS-CoV-2 emerged in November 2021 and rapidly replaced the previously dominant Delta variant because of its higher transmissibility and immune evasiveness.[3] Generally, the Omicron variant has the capacity to evade vaccine and natural

immunity due in part to several mutations in the spike protein region.[14] Recent studies showed that a booster dose vaccination significantly boosted neutralizing antibodies against both the BA.1 and BA.2 subvariants and suggested that booster doses are needed to maintain neutralizing antibody titers against the new subvariants.[15,16] Recently published reports provided real-world evidence of booster dose effectiveness during the BA.1-dominant period, although it decreased compared with the Delta-dominant period.[10,17–19] In contrast, the BA.2 variant is highly transmissible, and an early report from the United Kingdom stated that people infected with BA.2 were more likely to infect household contacts compared with those infected with BA.1.[20] The present study found that a booster dose remained effective during the BA.2-dominant period, in which the infection rate of close contacts was improved, as indicated by an OR of 0.50. However, the tendency for the effectiveness of both three and two doses to decrease during the BA.2-dominant period compared with the BA.1-dominant period may be due to the higher transmissibility of the BA.2 subvariant and the effect of waning immunity.[21,22] The overall infection rates were almost equal between the BA.1- and the BA.2-dominant periods, possibly because more students had received three doses of vaccine in the BA.2-dominant period.

During the COVID-19 pandemic, loss of learning opportunities has been raised as a major concern affecting school education. Distance education and school closures to prevent the in-school spread of COVID-19 resulted in significant learning losses.[23] A recent large-scale study showed that face-to-face learning was not contributing to the spread of COVID-19 in a university community in the setting of a mask and vaccine mandate.[24] A booster dose of vaccine can help to resume face-to-face learning with limited risk of classroom transmission. In Japan, as of August 1, 2022, students are being forced to undergo self-isolation for at least 10 days when they are infected, which can have considerable negative impacts on the education and mental health of those affected.[25] University students have

many opportunities to become a close contact due to their high activity through classes, clubs, and extracurricular activities, and by dining with a number of other students. A booster dose can play an important role in preventing infection in students in close contact with people infected with COVID-19 and in avoiding loss of education during the spread of BA.2.

There has been a certain amount of vaccine hesitancy especially in the young population.[26] Given the evidence that a booster provides additional protection against Omicron subvariants, understanding attitudes towards booster doses will be important for university health care. Suspicion of vaccine effectiveness is reported to be a major cause of vaccine hesitancy among university students, in addition to concerns regarding side effects and some political reasons.[9,27] Providing the most accurate and latest information on vaccine effectiveness and safety is essential to achieving higher vaccine acceptance. Although the present study provided evidence during the currently dominant spread of BA.2, another subvariant has almost replaced BA.2 dominance as of August 2022. Further evidence will be required sequentially, especially against the rapidly spreading Omicron subvariants such as BA.2.12.1, BA.4, and BA.5.

Study limitations

The present study has several limitations. First, the data came from a single university, and the sample size was relatively small. Second, although students were firmly instructed to register with the online system when they became a close contact, some cases may have been missed. In addition, interpretation of the definition of a close contact may vary individually. Third, the BA.1- and BA.2-dominant periods were determined based on a governmental announcement, and we did not examine the responsible subvariant in each student. Fourth, the date of vaccination and the status of vaccine-induced immunity were not examined. Finally, all included information was based on self-reporting by the students.

Conclusions

The effectiveness of a booster dose of COVID-19 vaccine tended to decrease but was still significant against Omicron BA.2 subvariant predominancy among Japanese university students. A booster dose may have an essential role in allowing the safe resumption of in-person learning and minimizing educational loses among university students.

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