JIM Research Letter

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Three doses of mRNA COVID-19 vaccine protects from SARS-CoV-2 infections in Japan

Dear Editor,

Two doses of the coronavirus disease 2019 (COVID-19) vaccine have effectively prevented asymptomatic, symptomatic, and severe SARS-CoV-2 infection due to prior strains [1], although the rapid spread of Omicron strains in the community has been observed. Using data from 47 prefectures in Japan, we conducted an ecological study to explore the effect of a third vaccination on each regional outcome of COVID-19 primarily due to the newest strains.

Using government sources [2, 3], the proportion of vaccinated subjects per population in each prefecture, as of February 8, 2022, was obtained and divided into quartiles at quartile cutoff values. The proportions were subcategorized into those with exactly three, two to three, or no doses. We also extracted the number of COVID-19 cases and disease exacerbations within 2 weeks after February 15, when 1 week had passed since the vaccination status data were recorded. Our study was exempt from institutional review board review and required no informed consent because it used de-identified, publicly available data. Using Poisson regression, we estimated rate ratios (RRs) and their 95% confidence intervals (CIs) for COVID-19 incidence and severity. All analyses were performed with StataSE version 16. Bivariate maps were created to show the association of three-dose vaccination rates and COVID outcome per prefecture.

As on February 8, 2022, 9,140,466 (7.2%), 99,847,752 (79.1%), and 24,768,194 (19.6%) subjects received a third dose, two to three doses, and no dose of vaccines, respectively. In the 2 weeks from February 15, 2022, 773.0 (95% CI: 765.1–781.0) and 15.3 (95% CI: 14.2–16.4) per 100,000 Japanese people had newly confirmed COVID-19 and severe disease, respectively.

Prefectures with the highest proportion of three-dose vaccinations had significantly lower RRs than prefectures with the lowest proportion (incidence RR: 0.85 [95% CI, 0.81–0.88]; severity RR: 0.53 [95% CI, 0.36–0.78]) (Table 1). However, no clear patterns were observed for two to three doses (incidence RR: 1.02 [95% CI, 0.96–1.08]; severity RR: 1.11 [95% CI, 0.62–1.97]). Regarding no dose, some positive associations were observed (incidence RR: 1.14 [95% CI, 1.08–1.21]; severity RR: 1.68 [95% CI, 0.94–2.99).

In Figure S1, the colors indicating a stronger inverse association were slightly more observed for incidence rates (left panel) than for severity (right panel) in some geographical patterns.

Three-dose vaccination had a significant impact on COVID-19 outcomes in the 47 prefectures for both incidence and severity. This is consistent with findings from the United States that showed that a third vaccine dose was associated with a lower risk of SARS-CoV-2 infection and hospitalization in an individual-level data analysis [4]. The strengths of our study include the assessment of vaccine effect during the latest wave of the pandemic in Japan, primarily driven by the Omicron variant. Moreover, we set target regions homogeneously, minimizing background differences in the medical environment, including testing volumes and public measures. While there were positive associations between nonvaccination and COVID-19 incidence, the association was less clear for severity. This may be partly because of the limited number of severe cases in our study.

Study limitations include the failure to assess RR for mortality because of the short period of outcome evaluation and the use of raw data from a single country. Moreover, our study results should be interpreted cautiously when extrapolating to individuals within the area level of measurement, owing to the lack of individual data and inability to adjust for all potential confounding factors [5].

Our results support the promotion of three-dose vaccination to achieve successful containment of the pandemic. However, it is still unclear how this practice will protect against future SARS-CoV-2 infections, especially emerging variants.

Table 1. *Japanese COVID-19 incidence rate, severity rate, incidence rate ratio, and severity rate ratio with adjustment for clinical and socioeconomic characteristics*

Proportion of subjects	Incidence rate per 100,000 (95% CI)	Incidence RR (95% CI)			Severity rate per 100,000 (95% CI)	Severity RR (95% CI)		
		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
Vaccinated with three doses								
First quartile	835.4 (819.7–851.2))	(Ref)	(Ref)	(Ref)	28.85 (26.00–31.92)	(Ref)	(Ref)	(Ref)
Second quartile	895.9 (879.6–912.3)	1.07 (1.04–1.11)	1.02 (0.99–1.06)	0.96 (0.93–1.00)	7.74 (6.33–9.44)	0.44 (0.34–0.56)	0.90 (0.66–1.22)	0.49 (0.34–0.68)
Third quartile	594.9 (581.1–608.8)	0.75 (0.72–0.78)	0.91 (0.88–0.95)	0.92 (0.88–0.96)	7.06 (5.66–8.76)	0.37 (0.28–0.49)	0.81 (0.57–1.15)	0.63 (0.43–0.93)
Fourth quartile	452.8 (439.0–466.9)	0.72 (0.70–0.75)	0.88 (0.84–0.92)	0.85 (0.81–0.88)	7.20 (5.57–9.21)	0.50 (0.38–0.65)	0.66 (0.46–0.93)	0.53 (0.36–0.78)
Vaccinated with two to three doses								
First quartile	994.2 (977.1–1011.4)	(Ref)	(Ref)	(Ref)	28.91 (26.07–32.00)	(Ref)	(Ref)	(Ref)
Second quartile	739.7 (724.4–755.2)	0.79 (0.77–0.82)	0.94 (0.91–0.97)	1.01 (0.98–1.05)	8.00 (6.48–9.77)	0.31 (0.24–0.40)	0.42 (0.32–0.56)	0.69 (0.49–0.98)
Third quartile	661.2 (646.1–676.6)	0.81 (0.79–0.84)	0.90 (0.87–0.93)	0.90 (0.86–0.94)	7.71 (6.17–9.55)	0.41 (0.32–0.53)	0.81 (0.61–1.07)	1.06 (0.72–1.55)
Fourth quartile	427.0 (414.9–439.4)	0.59 (0.57–0.62)	0.97 (0.93–1.01)	1.02 (0.96–1.08)	3.20 (2.22–4.43)	0.16 (0.11–0.23)	0.58 (0.38–0.88)	1.11 (0.62–1.97)
Nonvaccinated								
First quartile	410.0 (396.9–423.4)	(Ref)	(Ref)	(Ref)	2.88 (1.89–4.23)	(Ref)	(Ref)	(Ref)
Second quartile	638.9 (625.8–652.3)	1.37 (1.31–1.42)	0.99 (0.95–1.03)	0.99 (0.94–1.04)	7.32 (6.01–8.92)	2.71 (1.71–4.31)	1.32 (0.81–2.17)	1.04 (0.61–1.78)
Third quartile	739.8 (724.5–755.4)	1.50 (1.44–1.56)	1.07 (1.02–1.12)	1.10 (1.04–1.16)	7.74 (6.26–9.50)	2.06 (1.27–3.35)	0.62 (0.36–1.04)	0.56 (0.32–0.99)
Fourth quartile	1009.9 (992.0–1028.1)	1.83 (1.76–1.91)	1.13 (1.08–1.18)	1.14 (1.08–1.21)	29.79 (26.82–33.09)	8.32 (5.39–12.87)	2.01 (1.26–3.21)	1.68 (0.94–2.99)

Note: Model 1 shows bivariate associations between the proportion of vaccinated participants and COVID-19 outcomes. In Model 2, we adjusted for socioclinical characteristics (percentage of the elderly population, smoking rate, obesity rate, incidence of diabetes mellitus, and educational attainment). Model 3 further adjusts for regional characteristics (population density, Gini coefficient, and number of physicians, public health nurses, and acute care hospital beds per population). These socioeconomic data were extracted from multiple government surveys [Statistics Bureau, Ministry of Internal Affairs and Communications. Statistics. Accessed February 9, 2022. https://www.stat.go.jp/english/data/index.html]. Pearson's correlation coefficients of the proportion of vaccinated persons with three doses versus two to three doses, three doses versus no dose, and two to three doses versus no dose were –0.2879, 0.2719, and –0.9960, respectively.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ref, reference; RR, rate ratio.

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Conflicts of Interest

Katsuyuki Hotta received honoraria from Pfizer, AZ, Chugai, Lilly, Takeda, MSD, BMS, Ono, Taiho, and Boehringer-Ingelheim unrelated to the work, and grants from MSD, AZ, Chugai, Lilly, BMS, and Abbvie unrelated to the work. Etsuji Suzuki has no conflicts of interest. Eiki Ichihara has received honoraria from Eli Lilly Japan, and research funds from MSD, Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Janssen Pharmaceutical K.K. unrelated to the work. Katsuyuki Kiura received consulting fees from Daiichi Sankyo Co., Ltd., honoraria from Eli Lilly Japan K.K., Novartis International AG, Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Pfizer Japan Inc., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K., MSD K.K., Boehringer Ingelheim Co., Ltd., AstraZeneca K.K., and Daiichi Sankyo Co., Ltd., and grants from Daiichi Sankyo Co., Ltd., TEIJIN Pharma Ltd., Pfizer Japan Inc., SHIONOGI & Co., Ltd., Boehringer Ingelheim Co., Ltd., Nippon Kayaku Co., Ltd., Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., KYORIN Pharmaceutical Co., Ltd., MSD K.K., Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K., Merck Biopharma Co., Ltd, Novartis International AG, and Takeda Pharmaceutical Co., Ltd., unrelated to the work the work.

Author Contributions

Katsuyuki Hotta: Conceptualization-Equal, Formal analysis-Equal, Investigation-Equal, Methodology-Equal, Project administration-Equal, Writing original draft-Equal, Writing review & editing-Equal; Etsuji Suzuki: Investigation-Equal, Methodology-Equal, Writing original draft-Equal, Writing review & editing-Equal; Eiki Ichihara: Writing review & editing-Equal; Katsuyuki Kiura: Writing review & editing-Equal

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Bivariate maps showing the results of a crude analysis of the association of three-dose vaccination rates with COVID-19 incidence rate (A) and severity rate (B) at the prefecture level occurring within 2 weeks from 15, February 2022. The vaccination rate in each prefecture was obtained at the time of February 8, 2022. Both vaccination and COVID-19 outcome data were divided into tertiles at tertile cutoff values. We expressed a total of nine patterns with color coding, based on the combination of the two variables. Prefectures with high vaccination rates and low COVID-19 outcomes are highlighted in purple, and prefectures with low vaccination rates and high COVID-19 outcomes are highlighted in yellow-green.

[Correction included on 06 June 2022 after original online publication: The Supplementary figure legend has been updated.]

