Number of averted COVID-19 cases and deaths attributable to reduced risk in vaccinated individuals in Japan

*Taishi Kayano,[a] Misaki Sasanami,[a,1] Tetsuro Kobayashi,[a,1] Yura K. Ko,[b,1] Kanako Otani,[b,1] Motoi Suzuki,[b] and Hiroshi Nishiura [a]**

[a]Kyoto University School of Public Health, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
[b]Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, Tokyo 162-8640, Japan

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Summary

Background In Japan, vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initiated on 17 February 2021, mainly using messenger RNA vaccines and prioritizing health care professionals. Whereas nationwide vaccination alleviated the coronavirus disease 2019 (COVID-19)-related burden, the population impact has yet to be quantified in Japan. We aimed to estimate the numbers of COVID-19 cases and deaths prevented that were attributable to the reduced risk among vaccinated individuals via a statistical modeling framework.

Methods We analyzed confirmed cases registered in the Health Center Real-time Information-sharing System on COVID-19 (3 March–30 November 2021) and publicly reported COVID-19-related deaths (24 March–30 November 2021). The vaccination coverage over this time course, classified by age and sex, was extracted from vaccine registration systems. The total numbers of prevented cases and deaths were calculated by multiplying the daily risk differences between unvaccinated and vaccinated individuals by the population size of vaccinated individuals.

Findings For both cases and deaths, the averted numbers were estimated to be the highest among individuals aged 65 years and older. In total, we estimated that 564,596 (95% confidence interval: 477,020–657,525) COVID-19 cases and 18,622 (95% confidence interval: 6522–33,762) deaths associated with SARS-CoV-2 infection were prevented owing to vaccination during the analysis period (i.e., fifth epidemic wave, caused mainly by the Delta variant). Female individuals were more likely to be protected from infection following vaccination than male individuals whereas more deaths were prevented in male than in female individuals.

Interpretation The vaccination program in Japan led to substantial reductions in the numbers of COVID-19 cases and deaths (33% and 67%, respectively). The preventive effect will be further amplified during future pandemic waves caused by variants with shared antigenicity.

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Keywords: Averted burden; COVID-19; Statistical model; Vaccination; Epidemiology; Direct effectiveness

Introduction

Shortly after the emergence of severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), which causes coronavirus disease 2019 (COVID-19), the main interventions in 2020 were non-pharmaceutical, which are presently referred to as public health and social measures (PHSM). PHSM range from social distancing at a local level to widespread restrictions, such as lockdown policies, and have contributed to reducing virus transmission and buying time. However, these restrictions have curbed people's freedom and the adverse impact on social and economic activities has been substantial.[1–3] In this regard, vaccination has been a key player in epidemic control programs. The vaccine rollout against COVID-19 was launched in December

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*Corresponding author at: School of Public Health, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan.
E-mail address: nishiura.hiroshi.5r@kyoto-u.ac.jp (H. Nishiura).

[1] These authors contributed equally.

Research in context

Evidence before this study

The population impact of vaccination is principally evaluated by measuring direct and indirect effectiveness. Direct effectiveness is based on a comparison of risk between vaccinated and unvaccinated individuals whereas indirect effectiveness is focused on measures of reduced opportunities for infection owing to vaccination programs and reduced transmissibility among vaccinated individuals. When evaluating the unprecedented mass vaccination against coronavirus disease 2019 (COVID-19), it is vital to explore the direct effectiveness of vaccination such that the reduced risk of infection and death owing to the vaccination program can be objectively determined. We searched PubMed for research articles written in English from January 2020 to 18 March 2022 using the following keywords: ("SARS-CoV-2"[title] OR "COVID-19"[title]) AND ("direct effect*"[title] OR "averted"[title] OR "prevented"[title]) AND ("vaccination"[title]) AND ("mass" OR "campaign*" OR "program*") AND ("cases" OR "infections" OR "deaths"). Our search revealed eight published articles. Most studies (n = 7) investigated the number of COVID-19 cases, hospitalizations, and deaths averted by COVID-19 vaccination; of these, five evaluated the impact of vaccination in the presence of the Delta variant (B.1.617) of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The estimated values varied across regions and countries and depended on the size of the epidemic. A common finding was that the benefit of vaccination, especially of the first and second doses, was substantial. Other than studies in European countries and the United States, there has only been one related study in Israel and no relevant research has been published from the Western Pacific region. The present study is the first to report the number of COVID-19 cases and deaths averted owing to the vaccination program in Japan, as of 18 March 2022.

Added value of this study

Before widespread circulation of the Omicron (B.1.529) variant of SARS-CoV-2, many countries in the Western Pacific region experienced lower epidemic levels of COVID-19 infections than Western countries. To the best of our knowledge, the present study is the first to estimate the numbers of averted cases of SARS-CoV-2 infection and averted COVID-19-related deaths considered to be attributable to the mass vaccination program in Japan, a Western Pacific country that achieved two-dose vaccination coverage of 82% as of 18 March 2022. Using the national database of COVID-19 patients and publicly available information on the causes of death, we estimated that mass vaccination contributed to reducing the number of cases and deaths by 33% and 67%, respectively, from March to November 2021. Such substantial reductions were observed during sequential epidemic waves mainly caused by the Alpha (B.1.1.7) and Delta (B.1.617) variants. When analyzing estimates by age group, people aged 65 years and older benefitted more from vaccination than younger individuals.

Implications of all the available evidence

Many countries in the Western Pacific region experienced relatively lower epidemic levels than Western countries. Using readily available datasets such as vaccination coverage and surveillance records of cases stratified by age, sex, and vaccination history, we showed that a substantial reduction in the risk of infection and death can be objectively demonstrated in Japan. High coverage of mRNA vaccination (with BNT162b2 [Pfizer/BioNTech] and mRNA-1273 [Moderna] vaccines) led to substantial direct effects, preventing 560,000 cases and 19,000 deaths owing to COVID-19. Quantifying the direct effectiveness of vaccination can provide critical insights in the evaluation of vaccination programs as a whole, and similar methods may be applied to other country settings. In the present study, we mainly evaluated the fifth epidemic wave in Japan, caused by the Delta variant. The population impact of vaccination would be expected to be further amplified as the pandemic continues. Western Pacific countries can explore future epidemic waves by using the proposed framework, additionally accounting for the effect of booster immunization, waning immunity, and infections and deaths caused by an antigenically distinct variant with a different virulence level.

2020, mainly in high-income countries. Soon after, effects of COVID-19 vaccines such as a reduction in the number of cases, hospitalizations, and deaths, were evident in many countries, including Israel and the United Kingdom, among the first countries in the world to start mass vaccination.[4,5] A common strategy of vaccine rollout was that health care professionals were prioritized, followed by individuals aged 65 years and older and those with underlying comorbidities. Subsequently, vaccination programs began to allocate vaccines to younger and healthy people.[6,7] This particular approach was taken because a primary focus of mass vaccination programs in many countries has been to prevent cases of COVID-19 from becoming severe and to minimize the disease burden on health care systems more so than to prevent the spread of COVID-19.[7]

Whereas early evaluation of vaccination programs took place in Western countries where the incidence level was substantial, this was not the case in many countries belonging to the Western Pacific region that successfully maintained lower epidemic levels during the early period of the COVID-19 pandemic. As one of these countries, Japan maintained an incidence level lower than those of many European countries and the United States.[8] Even so, Japan experienced five large epidemic surges of SARS-CoV-2 infection between January 2020 and November 2021 involving more than 1·7 million cases and 18,000 deaths.[9] During this period, Japan used key PHSM to control the spread of COVID-19 based principally on voluntary restriction of contact, which was requested by the government but was not legally binding.[10] Whereas such countermeasures against COVID-19 greatly reduced virus transmission, the emergence of SARS-CoV-2 variants of concern, including the Alpha (B.1.529) and Delta (B.1.617) variants with elevated transmissibility compared with wild-type, has proven challenging. The fifth wave in July–September 2021 was mainly caused by the Delta variant, and the number of cases in August 2021 was the highest recorded since the start of the pandemic (Figure 1A). Regarding vaccination rollout, Japan launched a vaccination program, initially prioritizing health care professionals, from 17 February 2021.[11] A mass vaccination program then began on 12 April 2021, giving priority to those aged 65 years and older, people with pre-existing medical conditions, and workers in nursing homes.[12] From around the middle of June 2021, when vaccination coverage with the first dose among older people had reached approximately 50%, the program targets gradually and sequentially shifted to younger age groups, although the speed of vaccination was dependent on local governments (Figure 1A).[13] Initially, the targets of the vaccination program were individuals aged 16 years and older. However, the messenger RNA (mRNA) vaccine BNT162b2 (Pfizer/BioNTech) was approved for use in those aged ≥ 12 years on 1 June 2021; later, the mRNA-1273 (Moderna) vaccine was approved for those aged 12–15 years.[14] To boost vaccination coverage, the Japanese government initiated the "vaccination in the workplace" program on 21 June 2021.[15] The program invited large companies, initially restricted to those with more than 1000 workers, as well as universities and colleges, to vaccinate employees and students internally. By the end of November 2021, approximately 75% of the Japanese population had been vaccinated with the first dose of a COVID-19 vaccine, predominantly with the mRNA vaccine BNT162b2 (Pfizer/BioNTech) (83·2% of vaccinated individuals), followed by the mRNA-1273 (Moderna) vaccine (16·7% of vaccinated individuals).[13,16]

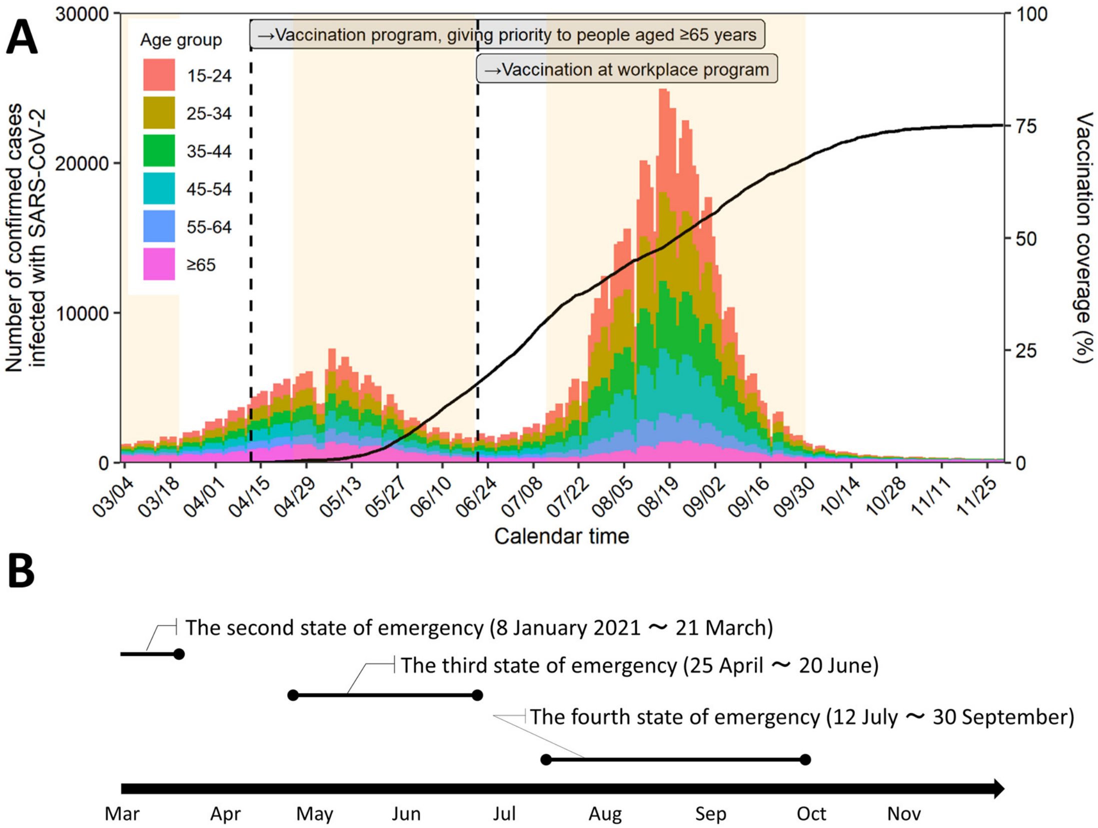

Figure 1. Epidemiological overview in Japan. (A) Confirmed cases of SARS-CoV-2 infection from 3 March to 30 November 2021 by age group (> 14 years) are shown (left-hand side vertical axis). The coverage of first dose vaccination is shown as a black line (right-hand side vertical axis). Dashed lines represent launch dates of the vaccination program, initially prioritizing those aged 65 years and older and the vaccination in the workplace program. Shaded areas highlighted in yellow represent the second, third, and fourth states of emergency, which were declared from 8 January to 21 March, from 25 April to 20 June, and from 12 July to 30 September 2021, respectively. (B) Timeline of the declarations of the state of emergency during the period of analysis. Each state of emergency period corresponds to the area highlighted in yellow in (A).

Vaccination programs have been evaluated in two ways, at the individual level and at the population level. With regard to the former, epidemiological studies in Israel have estimated that the BNT162b2 vaccine had 70%–90% effectiveness against infection, asymptomatic infection, COVID-19-related hospitalization, and death. These studies partially involved the Alpha variant.[5,17] Similar studies from the United Kingdom and the United States during the period when the Alpha variant was dominant in those countries have shown the high effectiveness of COVID-19 vaccines, particularly BNT162b2, which was estimated to be at least 80%.[18,19] Although the vaccine's effectiveness against the Delta variant appeared to be lower than that against the Alpha variant, the effectiveness of two doses was estimated to be at least around 80% and 60% for the BNT162b2 and ChAdOx1 (Oxford/AstraZeneca) vaccines, respectively.[20,21] Assessment of the population impact—the latter evaluation—was initially reported from Israel in September 2021, in which researchers calculated the averted number of infections, hospitalizations, and deaths related to COVID-19 owing to vaccination. The number of cases in Israel was reduced by one-third during the large epidemic wave between August and September 2021, and this reduction was attributed to mass vaccination.[22] Other studies showed that more than 445,000 cases and 22,000 deaths from January to September 2021 and approximately 470,000 deaths from December 2020 to November 2021 were prevented owing to COVID-19 vaccination in Italy and in the World Health Organization European region, respectively.[23,24] Additionally, other studies from the United States reported substantial numbers of averted cases, hospitalizations, and deaths related to COVID-19.[25,26]. However, evaluation of vaccination programs has yet to be reported from Western Pacific countries, where the incidence continued to remain low, especially during the period when the Delta variant was dominant. Therefore, quantifying the averted burden resulting from vaccination programs is critical to assessing vaccination policy in countries belonging to this region.

Since the beginning of the vaccination program in Japan, recording the daily number of vaccinated individuals in the registration system and surveillance data was mandated, and physicians were required to report the vaccination history of confirmed cases along with their age and sex. Here, we estimate the number of prevented COVID-19 cases and deaths that are attributable to the reduced risk of infection and death among vaccinated individuals. We used a simple statistical model based on the difference in risk between unvaccinated and vaccinated people, identifying host groups that experienced greater benefits than others.

Methods

Vaccination data

Vaccination coverage data were retrieved from two registration systems—the Vaccination Record System (VRS) and the Vaccination System (V-SYS); the former registers vaccination by age and the latter records the doses of vaccine distributed from central to local governments. Both data are aggregated as nationwide information. In general, people were registered in the VRS after they participated in the standard mass vaccination program. However, there could be a delay in reporting in real-time, and the number of vaccinated people was accumulated according to the date of reporting (the number of vaccinated individuals in the VRS was inconsistently reported, usually on weekdays). After integrating all vaccinated individuals registered in the VRS and V-SYS, we added 14 days to the date of vaccination to obtain the proportions of immunized people on certain days by age and sex. That is, we assumed that the vaccine was not effective after the first dose for the first 14 days, but that then there was an abrupt increase in vaccine-induced immunity. To integrate datasets from two independent systems of vaccination record, vaccinated people were divided into six different age groups: 15–24, 25–34, 35–44, 45–54, 55–64, and ≥ 65 years. People aged 12–14 years were included in the vaccination program, but they received the vaccine at the end of the program and vaccination coverage was far lower than for other age groups. Thus, for our analysis, we focused on those aged 15 years and older. Because prioritized vaccination for health care professionals was launched on 17 February 2021 in Japan, the dataset of immunized people was available 14 days later, that is, from 3 March 2021. The age-specific time-varying vaccination coverages by sex for people who were at least partially vaccinated or fully vaccinated are shown in Figure 2.

Daily incidence data

As of 30 November 2021, COVID-19 has been designated as an infectious disease requiring special attention in Japan. All individuals with suspected infection must be tested using PCR at a medical facility, followed by testing of their close contacts and movement restriction. Subsequently, all confirmed cases of COVID-19 are registered in the Health Center Real-time Information-sharing System on COVID-19 (HER-SYS) by health care facilities or local health centers in Japan, along with information on age, sex, date of onset, and vaccination status. After the data were de-identified and aggregated nationally, we analyzed confirmed cases reported from 3 March to 30 November 2021, the period corresponding to the observation period of vaccination rollout, and all confirmed cases were divided into the six age groups above. Approximately 8% of confirmed cases did not have information about vaccination status;

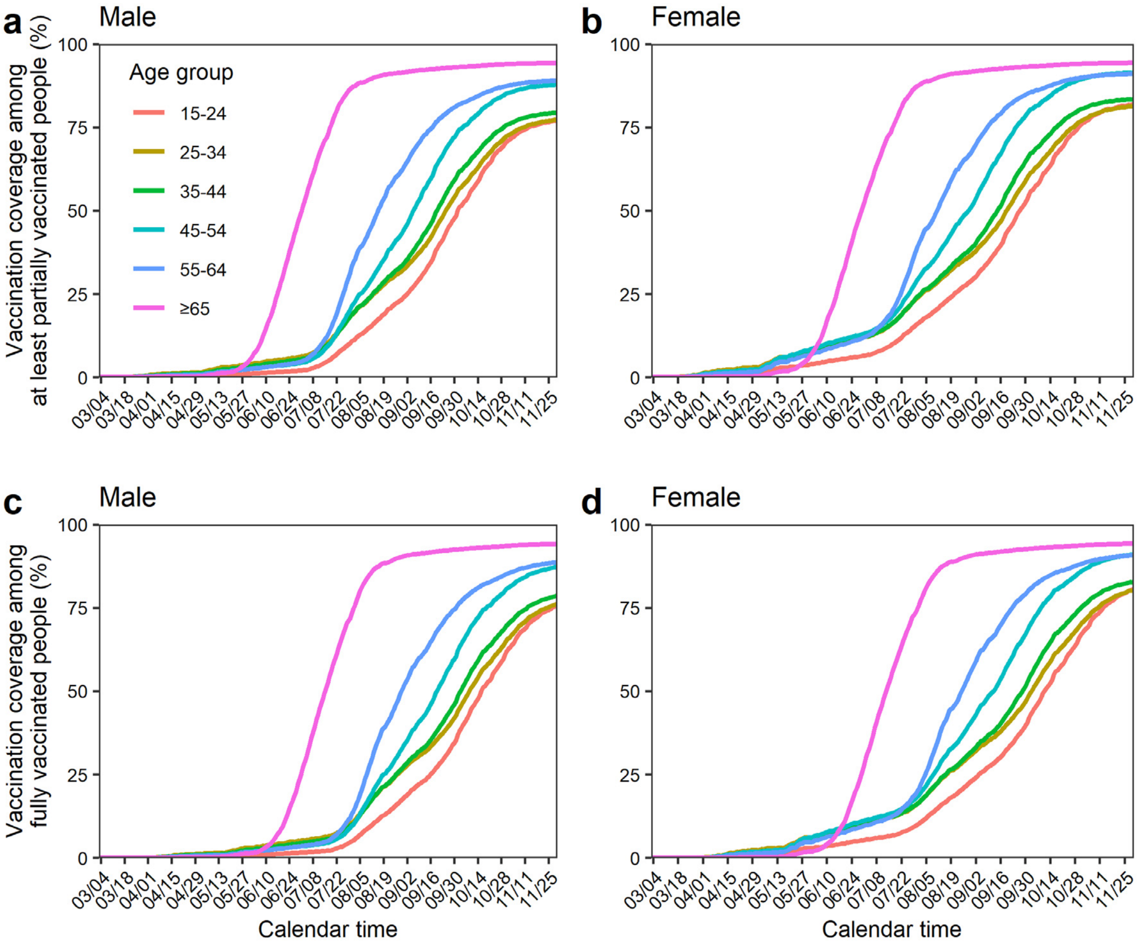

Figure 2. Estimated vaccination coverage among at least partially vaccinated and fully vaccinated people by sex. Vaccination coverage among at least partially vaccinated individuals by age group (> 14 years) from 3 March to 30 November 2021 for male (a) and female (b) individuals is shown. Additionally, vaccination coverage among fully vaccinated individuals by age group (> 14 years) from 3 March to 25 September 2021 for male (c) and female (d) individuals is shown. It is noted that all values take into account the delay in build-up of immunity.

therefore, we allocated these cases to either unvaccinated, partly vaccinated (only first dose), or fully vaccinated according to the distribution of vaccine status by age and sex, and the vaccination date registered in the HER-SYS, i.e., $c'_{i,a,b}(t) = c_{i,a,b}(t) + \frac{c_{i,a,b}(t)}{c_{0,a,b}(t)+c_{1,a,b}(t)+c_{2,a,b}(t)} c_{unknown,a,b}(t)$ where $c'_{i,a,\ b}$ is the reconstructed daily number of cases and $c_{i,a,\ b}$ is the daily number of confirmed cases or deaths in age group a of sex b, with vaccination status i, i.e., unvaccinated ($i = 0$), partly vaccinated (only first dose; $i = 1$), or fully vaccinated ($i = 2$). That is, a small number of cases without a known history of vaccination was proportionally distributed. COVID-19-related deaths have not been consistently registered in the HER-SYS; thus, we used death records available in the integrated data by the national broadcasting corporation.[27] Accounting for a reporting delay for each death, the dataset between 24 March and 30 November 2021 was used. Although the data for deceased cases were collected according to the date of death, the fifth wave of COVID-19 infections was nearly over by October. Thus, we believe that the impact on analysis owing to a reporting delay between infection and death, attributed to the infections in November, was minimal.

Estimation of the number of prevented cases and deaths

Using the abovementioned sets of information, the daily incidence (risk) among unvaccinated people ($\hat{r}_{\mathrm{unvac},a,b}$) and those who were at least partially vaccinated ($\hat{r}_{\geq\ 1\ \mathrm{dose},\ a,b}$) in age group a of sex b is expressed as:

$$\begin{cases} \hat{r}_{\mathrm{unvac},a,b}(t) = \dfrac{c'_{0,a,b}(t)}{N_{a,b} - N_{a,b}v_{\geq\ 1\ \mathrm{dose},\ a,b}(t)} \\ \hat{r}_{\geq\ 1\ \mathrm{dose},\ a,b}(t) = \dfrac{c'_{1,\ a,b}(t) + c'_{2,\ a,b}(t)}{N_{a,b}v_{\geq\ 1\ \mathrm{dose},\ a,b}(t)} \end{cases}, \qquad (1)$$

where $c'_{i,a,\,b}$ is the reconstructed daily number of confirmed cases or deaths in age group a of sex b, with vaccination status i, i.e., unvaccinated ($i = 0$), partly vaccinated (only first dose; $i = 1$), or fully vaccinated ($i = 2$). $v_{\geq 1\text{ dose},\,a,\,b}$ represents the vaccination coverage of people who received at least one dose in age group a of sex b. $N_{a,b}$ is the population size of age group a of sex b as of 1 January 2021 in Japan.[28] We then estimated $h_{a,\,b}$, the daily number of averted cases or deaths in age group a of sex b, given that at least partial vaccination had been received during the analysis period, as

$$h_{a,b}(t) = N_{a,b} v_{\geq 1\text{ dose},a,b}(t)\left(\hat{r}_{unvac,a,b}(t) - \hat{r}_{\geq 1\text{ dose},\,a,b}(t)\right) \tag{2}$$

As mentioned earlier, the analysis periods started from 3 March 2021 for averted cases and 24 March for averted deaths, respectively, but the endpoints for both periods were 30 November 2021. We estimated the daily incidence differences, measuring the risk reduction directly attributable to the vaccination program, and subsequently, the total number of averted cases or deaths, as

$$\sum_{t=3\text{ or }24\text{ Mar }2021}^{30\text{ Nov }2021} h_{a,b}(t). \tag{3}$$

We also estimated the vaccination coverage for fully vaccinated people ($v_{2\text{ dose}}$) by shifting the one-dose curve right by 14 days; that is, a 21-day gap between the first and second doses minus 7 days of delay required to build up immunity after receiving two-dose vaccination. Using the daily incidence for people who were fully vaccinated ($c'_{2,\,a,\,b}/N_{a,b}v_{2\text{ dose},\,a,\,b}$), we then estimated the number of prevented cases and deaths among fully vaccinated people. The 95% confidence intervals (CIs) of the averted number of cases and deaths were calculated based on the uncertainty of the risk difference between unvaccinated and vaccinated. We assumed that those cases and deaths were sufficiently captured by binomial distribution:

$$E\left(c'_{i,a,b}(t)\right) \sim B(n,p), \tag{4}$$

where n stands for the denominator of the incidence (r in Eq. 1) and p is the probability interpreted as r in the present study. We calculated the 95% CIs of prevented burdens using 1000 bootstrap iterations. It should noted that the computed uncertainty bounds does not account for serial dependence structure and thus may be conservative.

Role of the funding source

The funders of the present study had no role in study design, data analysis, data interpretation, or writing of the manuscript.

Ethical considerations

The conduct of this study adhered to the principles of the Declaration of Helsinki, and the research was approved by the Ethics Review Committee of Kyoto University (approval number R2673).

Results

As of 30 November 2021, the vaccination coverage among male individuals who were at least partially vaccinated was estimated to be 77·0%, 77·2%, 79·4%, 87·8%, 88·9%, and 94·2% among those aged 15–24, 25–34, 35–44, 45–54, 55–64, and ≥ 65 years, respectively (Figure 2A). By contrast, the vaccination coverage among female individuals who were at least partially vaccinated was estimated to be 81·8%, 81·3%, 83·4%, 91·4%, 91·0%, and 94·3% among those aged 15–24, 25–34, 35–44, 45–54, 55–64, and ≥ 65 years, respectively (Figure 2B). Earlier elevated vaccination coverage among those aged ≥ 65 years, in both male and female individuals, could be observed (Figure 2). The subsequent increase in vaccination coverage among younger people is evident from July 2021.

As a function of calendar month, the median daily incidence differences for confirmed cases of SARS-CoV-2 and COVID-19-related deaths per one million in each age group and sex stratum between unvaccinated and at least partially vaccinated individuals are shown in Table 1. Because the epidemic size of the fifth wave was at a record high level in August 2021, the estimated incidence differences in cases were estimated to be highest around that time. By contrast, the estimates of death risk differences were more evident in September, perhaps owing to a delay from diagnosis to death. Similarly, median daily incidence differences between unvaccinated and fully vaccinated individuals are shown in Table S1. Because most people vaccinated with one dose received a second dose of vaccine, the estimates in Table S1 only differed slightly from those in Table 1. The relationship of the daily incidence difference between unvaccinated and vaccinated individuals with COVID-19 cases over the study period by age group is illustrated in Figure S1.

The averted number of COVID-19 cases for the entire observation period was estimated to be 271,300 (95% CI: 230,194–314,632) and 293,297 (95% CI: 246,826–342,892) cases in male and female individuals, respectively. Moreover, we estimated that 10,938 (95% CI: 4174–19,334) male deaths and 7684 (95% CI: 2348–14,428) female deaths were prevented owing to the vaccination program. Figure 3 shows the age-specific cumulative number of averted cases and deaths by sex among at least partially vaccinated people. For both cases and deaths, the estimates of prevented counts were highest among older people. By 30 November

Age group	Overall analysis	Monthly analysis in 2021								
		March	April	May	June	July	August	September	October	November
Cases infected with SARS-CoV-2										
Male										
15–24	39·15 (15·28–90·75)	19·97 (12·88–31·89)	64·56 (47·71–83·24)	69·09 (56·25–99·9)	29·53 (24·5–34·65)	64·19 (35·34–109·35)	410·51 (296·64–535·75)	89·42 (45·8–177·1)	12·41 (7·44–18·62)	4·65 (2·66–6·83)
25–34	37·85 (16·6–85·38)	17·36 (12·5–23·98)	56·8 (42·06–71·07)	60·42 (48·05–82·53)	27 (20·8–32·11)	60·37 (38·49–112·93)	394·13 (304·65–510·42)	106 (49·27–177·54)	13·18 (8·74–20·8)	4·39 (2·31–7·35)
35–44	26·29 (10·98–59·26)	11·95 (9·15–16·95)	38·09 (26·77–48·54)	46·26 (35·31–55·36)	20·14 (14·76–24·06)	38·77 (25·23–68·49)	267·19 (187·89–311·03)	73·25 (37·32–119·33)	9·75 (5·49–16·82)	2·72 (1·34–4·35)
45–54	21·47 (10·18–49·15)	11·29 (8·55–15·1)	33·36 (23·44–42·85)	36·11 (24·76–48·64)	15·52 (11·66–18·95)	28·83 (17·62–53·49)	213·76 (145·17–256·23)	71·21 (37·74–114·75)	10·31 (6·37–14·85)	2·83 (1·29–4·88)
55–64	16·29 (7·6–40·2)	9·76 (7·55–13·29)	26·35 (18·84–37·82)	28·21 (17·71–38·54)	11·73 (7·12–14·36)	16·41 (10·55–27·68)	151·06 (94–189·65)	58·56 (35·22–103·17)	7·78 (3·45–12·66)	1·18 (−0·15–3·67)
≥ 65	12·1 (6·09–29·76)	9·57 (7·52–11·18)	17·39 (12·62–23·56)	17·07 (8·48–24·93)	5·95 (4·32–7·67)	10·97 (7·37–18·81)	143·96 (78·75–182·05)	62·49 (33·2–114·13)	10·91 (6·36–16·43)	1·24 (−0·27–3·36)
≥ 15	23·96 (9·7–60·98)	11·98 (8·9–17·62)	35·08 (21·4–52·99)	40·19 (23·04–58·59)	16·62 (9·09–25·55)	33·26 (15·49–65·55)	218·13 (147·93–341·63)	72·94 (39·37–131·15)	10·71 (6·1–16·65)	2·88 (0·9–5·21)
Female										
15–24	35·14 (13·82–80·18)	16·48 (11·55–25·32)	55·67 (29·06–67·91)	59·44 (46·68–81·94)	26·58 (20·8–32·57)	64·35 (37·47–100·71)	379·88 (307·38–472·45)	90·81 (45–173·3)	10·78 (7·15–15·36)	4·01 (1·78–6·96)
25–34	32·8 (14·48–72·81)	15·19 (12·01–20·58)	45·27 (33·48–58·78)	53·56 (41·26–73·11)	23·12 (18·59–27·89)	53·25 (33·62–92·29)	326·06 (271·35–404·47)	85·62 (45·43–153·64)	11·39 (7·55–16·22)	3·88 (1·74–6·25)
35–44	18·79 (8·73–42·48)	8·99 (6·97–11·77)	26·82 (19·01–35·94)	32·41 (25·11–41·57)	13·17 (9·95–16·48)	25·27 (14·83–43·6)	193·19 (141·36–234·95)	59·94 (30·75–104·24)	8·11 (4·75–13·15)	2·15 (0·75–3·8)
45–54	18·46 (9·31–41·77)	9·31 (7·14–12·05)	27·77 (18·95–37·08)	31·33 (22·27–39·58)	11·64 (9·44–14·33)	21·01 (15·16–39·84)	192·48 (125·92–236·09)	64·44 (36·44–110·07)	10·22 (6·28–16·25)	4·23 (1·97–6·98)
55–64	14·24 (7·11–33·3)	8·15 (6·46–10·5)	20·78 (13·14–27·74)	24·88 (18·29–32)	9·5 (6·95–12·32)	13·69 (9·13–24·04)	130·58 (83·61–167·47)	61·98 (27·95–96·99)	8·87 (4·88–14·61)	1·42 (0–3·87)
≥ 65	10·9 (5·57–28·39)	8·71 (7·28–9·95)	16·11 (10·66–22·81)	17·8 (12·2–22·89)	5·16 (3·26–6·93)	8·69 (5·93–16·99)	132·08 (78·63–173·86)	58·17 (34·12–92·57)	8·16 (4·56–15·54)	1·62 (0·23–3·79)
≥ 15	20·29 (8·55–51·82)	10·01 (7·5–14·5)	27·1 (17·02–41·96)	32·56 (21·46–48·27)	12·66 (7·88–21·02)	27·38 (12·91–55·1)	188·77 (129·26–285·71)	67·75 (37·09–114·2)	9·7 (5·77–15·19)	2·81 (0·89–5·35)
Deaths related to COVID-19										
Male										
15–24	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
25–34	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
35–44	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0·19)	0 (0–0·38)	0 (0–0)	0 (0–0)
45–54	0 (0–0·32)	0 (0–0)	0 (0–0·11)	0·11 (0–0·32)	0 (0–0·11)	0 (0–0)	0·17 (0–0·48)	0·74 (0·29–1·34)	0 (0–0·77)	0 (0–0)
55–64	0·21 (0–0·82)	0 (0–0·13)	0·13 (0–0·39)	0·4 (0·13–0·66)	0·27 (0–0·54)	0 (0–0·17)	0·44 (0–1·07)	2·54 (1·54–3·69)	0 (0–3·37)	0 (0–0)
≥ 65	1·8 (0·66–3·86)	1·09 (0·84–1·35)	0·9 (0·51–1·48)	2·73 (2·07–3·5)	1·93 (1·07–2·86)	0·92 (0·39–1·53)	3·55 (1·54–6·54)	10·23 (6·52–15·32)	2·7 (0–6·48)	0 (0–1·06)
≥ 15	0 (0–0·4)	0 (0–0·12)	0 (0–0·25)	0 (0–0·53)	0 (0–0·27)	0 (0–0·13)	0·14 (0–0·63)	0·34 (0–2·52)	0 (0–0·77)	0 (0–0)
Female										
15–24	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
25–34	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
35–44	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
45–54	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0·29)	0 (0–0)	0 (0–0)
55–64	0 (0–0)	0 (0–0)	0 (0–0·13)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0·31)	0·51 (0–1·63)	0 (0–0)	0 (0–0)
≥ 65	1·17 (0·41–2·42)	0·54 (0·4–0·74)	0·69 (0·45–0·99)	1·69 (1·2–2·22)	1·36 (0·89–1·83)	0·61 (0·2–1·12)	2 (0·89–3·88)	5·2 (3·13–8·29)	1·65 (0–4·32)	0 (0–0)
≥ 15	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0·19)	0 (0–0·91)	0 (0–0)	0 (0–0)

***Table 1*: Daily incidence differences in prevented cases and deaths between unvaccinated and at least partially vaccinated people by age, sex, and analysis period.**

Median daily incidence differences per 1,000,000 population are shown. Interquartile ranges are presented in parentheses.

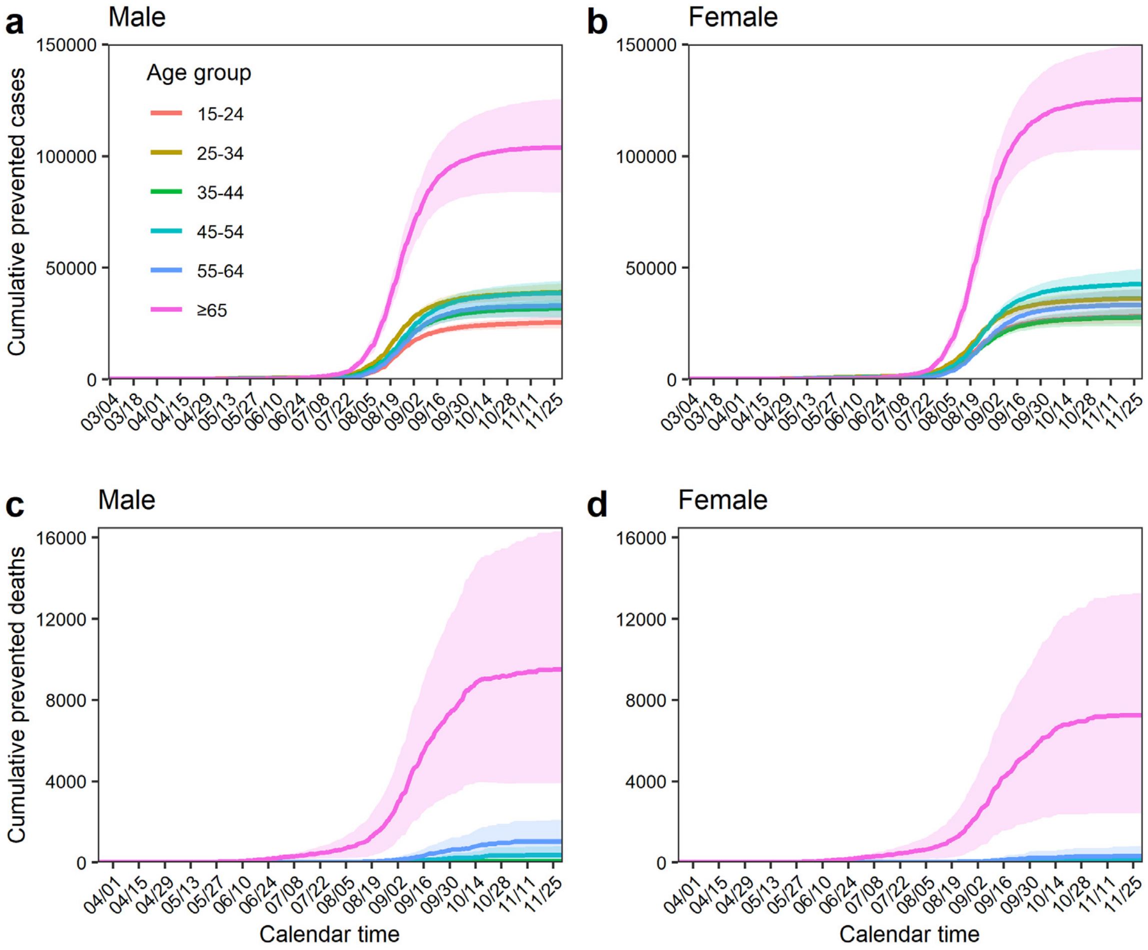

Figure 3. Cumulative numbers of prevented cases and deaths by sex that are attributed to the reduced risk among vaccinated individuals. Cumulative numbers of averted cases by age group (> 14 years) between 3 March and 30 November 2021 for male (a) and female (b) individuals are shown. Additionally, cumulative numbers of averted deaths by age group (> 14 years) between 24 March and 30 November 2021 for male (c) and female (d) individuals are shown. Each shaded area represents the 95% confidence interval.

2021, the averted number of cases among people aged 65 years and older was estimated to have been 103,637 (95% CI: 83,427–125,170) and 125,313 (95% CI: 102,679 –149,496) in male and female individuals, respectively. With regard to deaths, by 30 November, 9487 (95% CI: 3906–16,281) and 7277 (95% CI: 2379–13,362) deaths in male and female individuals, respectively, were estimated to have been prevented because of the risk reduction among vaccinated people compared with unvaccinated people.

Figure 4 shows the estimated cumulative number of cases and deaths prevented, along with the observed numbers, to illustrate the predicted number of cases and deaths without the vaccination program, that is, the "counterfactual" scenario. Without the vaccination program, an estimated 1,722,437 (95% CI: 1,634,589 –1,815,561) cases and 28,059 (95% CI: 16,003–43,122) deaths would have been observed. In other words, 564,596 (95% CI: 477,020–657,525) COVID-19 cases and 18,622 (95% CI: 6522–33,762) deaths were prevented owing to the vaccination program by the end of November 2021. Because the vaccine rollout was particularly accelerated before July (i.e., 1 month before the Tokyo Olympic Games), the discrepancies between the observed confirmed COVID-19 cases and COVID-19-related deaths and the estimated values become evident from around that period. However, the gaps between observed and counterfactual values later plateaued because the incidences during the fifth epidemic wave were greatly reduced. Table 2 summarizes the total number of prevented cases and deaths among at least partially vaccinated individuals, fully vaccinated

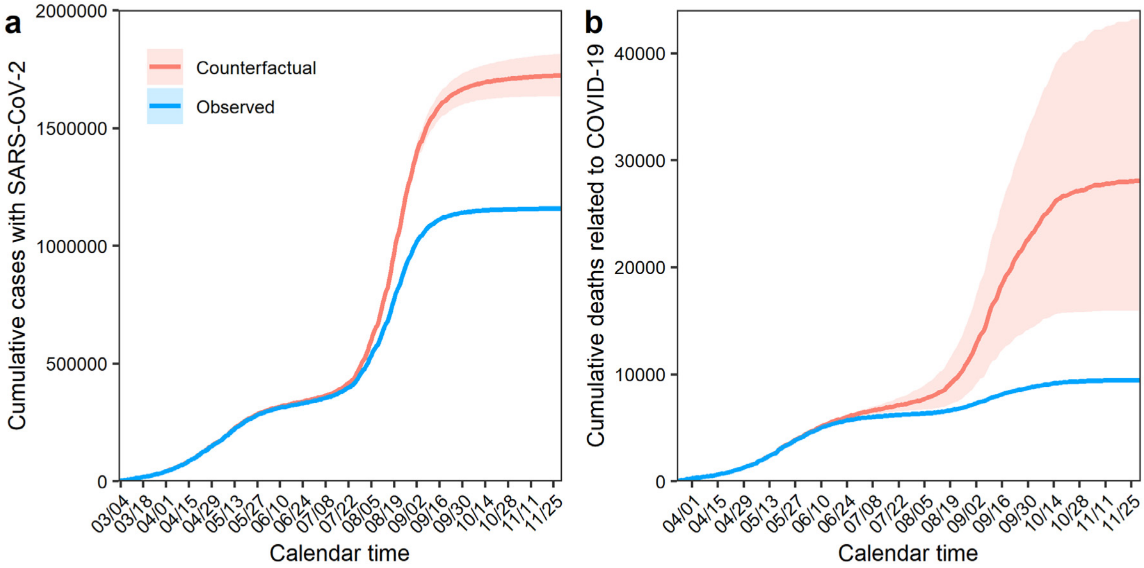

Figure 4. Counterfactual scenarios and total numbers of prevented cases and deaths that are attributable to the reduced risk among vaccinated individuals. Total number of averted cases from 3 March to 30 November 2021 (a) and averted deaths related to COVID-19 from 24 March to 30 November 2021 (b) are shown. Red lines represent actual observed COVID-19 cases and deaths, and blue lines represent the estimates of counterfactual scenarios without vaccination. Shaded areas describe 95% confidence intervals.

individuals, and partly vaccinated individuals during the study period.

Discussion

According to the Prime Minister's Office, the total number of available doses of COVID-19 vaccine in Japan reached more than 197 million by the end of November 2021, achieving vaccination coverage of 75% of the population.[13,16] In such a highly vaccinated county with widespread use of mRNA vaccines, we estimated that the vaccination program prevented 564,596 (95% CI: 477,020–657,525) COVID-19 cases and 18,622 (95% CI: 6522–33,762) COVID-19-related deaths, correlating with reductions of 33% and 67% in cases and deaths, respectively. The highest numbers of averted cases and deaths were seen among those aged 65 years and older for both men and women. Whereas 103,637 (95% CI: 83,427–125,170) and 125,313 (95% CI: 102,679 –149,496) cases in male and female individuals were prevented, the averted number of deaths was 9487 (95% CI: 3906–16,281) and 7277 (95% CI: 2379 –13,362) in male and female individuals, respectively.

To the best of our knowledge, the present study is the first to demonstrate the substantial direct benefit of the vaccination program in Western Pacific countries where a relatively low incidence of COVID-19 had been maintained prior to emergence of the Omicron variant. As a result of the rapid vaccine rollout and high vaccination coverage, we showed that more than 30% of COVID-19 cases and two-thirds of COVID-19-related deaths were prevented, especially among older people. During the fifth wave, the Delta variant acted as a trigger for another epidemic wave and incidences rose rapidly, coinciding with the start of the Tokyo Olympic Games. By comparing the observed values and counterfactual estimates, we objectively showed that the vaccination program substantially reduced the epidemiological impact during this period.

An important technical caveat is that the direct effectiveness of the vaccination program can be evaluated by simply comparing the daily incidence between vaccinated and unvaccinated individuals as a function of time, as was done in Israel.[22] This can be achieved when the vaccination coverage is available and when the vaccination history of cases is consistently recorded over time. However, it must be noted that, other than the direct effect as presented here, indirect effects have a tremendous impact on the epidemiological dynamics. In many countries with substantially high vaccination coverage, herd immunity was at least temporarily and locally achieved, and the disease incidence was greatly reduced. The total vaccination effect can be broken down into actual observations and counterfactual estimates, i.e., stacked additional cases/deaths if the vaccination program were not implemented. The effects can also be divided into indirect effects and direct effects, as per the following equation:

$$\text{Total vaccination effects} \\ = \text{Indirect effect} + \text{Direct effect}. \tag{5}$$

However, measuring the indirect effect is technically challenging; for example, we may have to compare the observed cumulative number of cases and deaths

Age group	Prevented outcomes			
	Cases infected with SARS-CoV-2		Deaths related to COVID-19	
At least partially vaccinated people				
	Male	Female	Male	Female
15–24	25,463 (22,700–28,304)	28,132 (24,918–31,495)	6 (0–19)	1 (-4–8)
25–34	38,931 (35,162–42,758)	36,183 (32,138–40,373)	15 (0–39)	1 (-15–16)
35–44	31,711 (28,001–35,557)	27,670 (23,718–31,823)	58 (-3–160)	20 (0–54)
45–54	38,653 (33,546–44,040)	42,704 (36,380–49,569)	347 (51–772)	69 (-4–189)
55–64	32,905 (27,358–38,803)	33,294 (26,994–40,136)	1023 (219–2062)	316 (-8–799)
≥ 65	103,637 (83,427–125,170)	125,313 (102,679–149,496)	9487 (3906–16,281)	7277 (2379–13,362)
≥ 15	271,300 (230,194–314,632)	293,297 (246,826–342,892)	10,938 (4174–19,334)	7684 (2348–14,428)
Fully vaccinated people				
	Male	Female	Male	Female
15–24	16,771 (14,992–18,606)	19,476 (17,256–21,785)	4 (0–13)	0 (-5–6)
25–34	27,764 (25,164–30,473)	26,628 (23,679–29,656)	10 (1–26)	1 (-9–11)
35–44	22,069 (19,581–24,673)	19,793 (16,997–22,722)	38 (0–104)	12 (-1–35)
45–54	24,674 (21,493–28,117)	27,456 (23,262–32,027)	221 (40–489)	41 (-2–110)
55–64	20,001 (16,465–23,831)	20,039 (15,943–24,601)	720 (149–1,451)	225 (10–569)
≥ 65	80,592 (64,535–97,988)	98,262 (80,048–117,887)	8097 (3453–13,723)	6190 (2108–11,241)
≥ 15	191,870 (162,230–223,688)	211,656 (177,185–248,679)	9090 (3643–15,805)	6469 (2102–11,971)
Partly vaccinated people				
	Male	Female	Male	Female
15–24	8692 (7717–9708)	8655 (7638–9696)	2 (0–7)	1 (-1–3)
25–34	11,167 (10,004–12,363)	9555 (8472–10,720)	5 (0–12)	0 (-6–5)
35–44	9642 (8409–10,859)	7877 (6718–9077)	20 (-2–60)	8 (2–18)
45–54	13,979 (12,068–15,946)	15,248 (13,117–17,519)	126 (9–280)	28 (0–70)
55–64	12,905 (10,902–15,057)	13,254 (11,068–15,549)	303 (60–628)	91 (-14–236)
≥ 65	23,045 (18,998–27,419)	27,051 (22,687–31,779)	1391 (496–2504)	1087 (290–2078)
≥ 15	79,430 (68,098–91,352)	81,641 (69,699–94,339)	1847 (564–3491)	1215 (270–2409)

***Table 2*:** Total number of prevented cases and deaths by age, sex, and vaccination status that are attributable to reduced risk among vaccinated individuals**.**

The study period of each outcome was from 3 March to 30 November 2021 and from 24 March to 30 November 2021 for cases and deaths, respectively. The 95% confidence intervals are presented in parentheses.

against theoretically reconstructed epidemic counterfactual scenarios, that is,

$$\begin{aligned}\text{Indirect effect} & \\ &= \mathrm{E}(C; \textit{no vaccination}) \\ &\qquad - \mathrm{E}(C; \textit{vaccination in the population}), \qquad (6)\end{aligned}$$

where C stands for the cumulative number of cases. The former term on the right-hand side requires very careful study design or simulations and we would need to know how many cases and deaths there would have been without the vaccination program. To compare our estimate of direct effect against possible indirect effect, we conducted an ad hoc analysis using a compartmental model (see Supplementary material). It was shown that indirect effect would lead to prevention of more than hundred times and thirty times greater number of cases and deaths, respectively, than those attributed to direct effect. The result indicates that indirect effect would involve enormously large population impact. For precise estimation, we need to carefully derive the indirect effect adjusting for other countermeasures, and developing an alternative counterfactual model for the estimation is our ongoing future study.

It is obvious that various PHSM including lockdowns have played crucial roles in suppressing the number of COVID-19 cases and deaths in many countries since the pandemic started. During the vaccination program, a state of emergency was declared three times in Japan, with the second state of emergency lasting from 7 January to 21 March 2021, which overlapped with the initial stage of the vaccination program prioritizing health care professionals (Figure 1B). Other states of emergency were declared between 25 April and 20 June and between 12 July and 30 September 2021 in the fourth and fifth epidemic waves, respectively. The coverage of each prefecture depended on the timing of its declaration, but Tokyo and Osaka, which usually bore the highest number of cases, were generally covered under the states of emergency. In the present study, we did not explicitly account for the impact of PHSM on the estimated numbers of averted cases and deaths. In other words, without PHSM, the size of the epidemic would be expected to be greater than that observed, and thus, the prevented cases and deaths would also have been elevated compared with those reported in the present study. Similar observations have been reported in Israel and other countries.[22–26] However, the median daily incidence differences in cases of the present study were estimated to be approximately 5 per 100,000 population, which were much lower than those in Israel (72 per 100,000 population).[22] Examining the ratios of the total number of prevented cases/deaths to observed values in both countries, the differences can be explained by the lower incidences themselves rather than waning immunity effects and incidence differences between unvaccinated and vaccinated people. Although Japan is a super-aging society, which imposes a greater COVID-19-related burden, PHSM and other interventions maintained the epidemic level and disease burdens at relatively low levels during the period of study.

Although our study mainly focused on the effects for at least partially vaccinated people, the total numbers of averted cases and deaths were also calculated according to vaccination status. Our estimates indicated that the effect of two doses contributed to reducing COVID-19 cases and deaths by 2·5 and 5·1 times, respectively, compared with one-dose vaccination. However, the effects of the first dose appeared not to be small, implying that we could expect a certain degree of vaccine effectiveness among partly vaccinated people. Furthermore, we explored the difference in outcomes by sex. The total number of cases prevented among female individuals was estimated to be 293,297 (95% CI: 246,826−342,892), which was higher than that among male individuals, estimated to be 271,300 (95% CI: 230,194−314,632). These estimates were influenced not only by the vaccination program but also by other factors such as the volume of the number of COVID-19 cases. Therefore, accounting for high-risk (socially active) behavior, it is reasonable that more cases/deaths were averted among male individuals aged 25−44 years than among female individuals. However, an estimated total 9487 (3906−16,281) deaths in male individuals were prevented, which was higher than this number in their female counterparts, estimated to be 7277 (2379−13,362). The same trends were recognized in all groups aged 15 years and older, which may be explained by the biological mechanisms underlying sex differences.

This study has four limitations. First, the averted number of hospitalizations was not consistently collected over time, precluding explicit estimation of the impact of vaccination on hospitalizations in Japan. Setting up hospitalization surveillance to systematically register and monitor admitted individuals along with their vaccination history would be required for this analysis. Second, we imposed an assumption that all individuals vaccinated with a first dose received a second dose at a constant interval. In Japan, the vaccination program explicitly recommended that people receive a second dose exactly 21 days after the first dose; however, there could have been discrepancies, particularly when using mRNA-1273 vaccine, which adopts a 28-day rather than 21-day interval. In fact, the vaccination rates at the end of 2021 among people who received the first dose and were fully vaccinated were 74·7% and 74·1%, respectively.[13] Third, we ignored waning immunity in our analysis. Vaccine-induced immunity gradually wanes, and a reduction in vaccine efficacy against SARS-CoV-2 has been observed in 6-month follow-up research.[29,30] Our study period was approximately 9 months, from March to November; however, the rate of vaccination was accelerated from June to August, and we believe that the impact of ignoring the effect of waning immunity would be minimal. Fourth, geographic heterogeneity in the vaccination rollout was not taken into account. For example, as of the end of October 2021, the lowest vaccination coverage for the first dose was estimated to be 62% in Okinawa, and the highest coverage was 76% in Akita.[16] An analysis focused on the impact of such gaps will be addressed in our future studies.

In the current study, we successfully quantified the direct effectiveness of the mass vaccination program in Japan. Substantial numbers of cases and deaths were prevented owing to mRNA vaccination, correlating to reductions of 33% and 67%, respectively, as compared with counterfactual scenarios without vaccination. Vaccine-induced immunity against SARS-CoV-2 is the safest and most effective means of reducing the number of COVID-19 cases and deaths, thereby limiting the burden on health care systems. The preventive effect of vaccination will be further amplified as the pandemic proceeds.

Using a statistical model, in the present study, we estimated the averted number of COVID-19 cases and deaths, by age and sex, that can be attributed to the reduced risk resulting from vaccination in Japan from March to November 2021. The estimated numbers were highest among those aged 65 years and older. For individuals who were at least partially vaccinated, we estimated that 564,596 (95% CI: 477,020−657,525) cases and 18,622 (95% CI: 6522−33,762) deaths were successfully prevented, representing a reduction in risk of 33% and 67%, respectively. Our findings confirm that the vaccination program was highly successful in Japan during the Delta variant epidemic wave. As vaccination continues among all eligible individuals, the preventive effects will be further amplified.

Contributors

All authors participated in the study design. T.K., M.S., T.K., K.Y., and K.O collected and retrieved the data. T.K. analyzed the data and H.N. evaluated the validity of analysis. T.K. drafted the manuscript, including the figures and tables. H.N. edited earlier versions of the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

Data on confirmed cases are available online (Open data, Ministry of Health, Labour and Welfare; https://www.mhlw.go.jp/stf/covid-19/open-data.html). Data on deaths are publicly available elsewhere.[27]

Declaration of interests

All authors declare no competing interests in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100571.

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Evaluating the COVID-19 vaccination program in Japan, 2021 using the counterfactual reproduction number

Taishi Kayano[1], Yura Ko[2,3], Kanako Otani[2], Tetsuro Kobayashi[1], Motoi Suzuki[2] & Hiroshi Nishiura[1]✉

Japan implemented its nationwide vaccination program against COVID-19 in 2021, immunizing more than one million people (approximately 1%) a day. However, the direct and indirect impacts of the program at the population level have yet to be fully evaluated. To assess the vaccine effectiveness during the Delta variant (B.1.617.2) epidemic in 2021, we used a renewal process model. A transmission model was fitted to the confirmed cases from 17 February to 30 November 2021. In the absence of vaccination, the cumulative numbers of infections and deaths during the study period were estimated to be 63.3 million (95% confidence interval [CI] 63.2–63.6) and 364,000 (95% CI 363–366), respectively; the actual numbers of infections and deaths were 4.7 million and 10,000, respectively. Were the vaccination implemented 14 days earlier, there could have been 54% and 48% fewer cases and deaths, respectively, than the actual numbers. We demonstrated the very high effectiveness of COVID-19 vaccination in Japan during 2021, which reduced mortality by more than 97% compared with the counterfactual scenario. The timing of expanding vaccination and vaccine recipients could be key to mitigating the disease burden of COVID-19. Rapid and proper decision making based on firm epidemiological input is vital.

Vaccination against coronavirus disease (COVID-19) was widely implemented at nationwide and global scale; therefore, its evaluation at population level, including direct and indirect effects, is key for assessing this policy program[1–3]. For instance, Japan implemented a nationwide vaccination program against COVID-19 in 2021 using mRNA vaccines and prioritizing health care professionals from February 2021, then older adults aged ≥ 65 years and those with underlying comorbidities, followed by younger individuals. For mass vaccination, the Pfizer/BioNTech mRNA vaccine (BNT162b2) using ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain was utilized. The Moderna vaccine (mRNA-1273) was also used for a part of the vaccination rollout and also for vaccination in the workplace. Immunization was conducted to cover more than one million people (approximately 1%) a day when the pace of vaccination was at its peak. Therefore, post-hoc evaluation is essential to understand how influential the program was at population level. Alongside the vaccination program, various public health and social measures (PHSM) were implemented, including the declaration of the state of emergency and contact tracing[4]. These measures aimed to suppress virus transmission even temporarily, thereby alleviating the burden on healthcare facilities and protecting the health infrastructure. Despite these efforts, the virus posed significant challenges, partly due to the emergence of new variants with elevated transmissibility including Alpha (B.1.1.7) and Delta (B.1.617.2) variants, imposing additional difficulties in controlling the spread of SARS-CoV-2[5–7].

In evaluating the indirect effects of vaccination owing to reduced opportunities for infection and decreased transmissibility (e.g., herd immunity effect), the epidemiological evaluation of population-level effectiveness calls for statistical methods[8–11]. For direct effects only (i.e., whether vaccinated individuals are protected biologically by comparing vaccinated and unvaccinated people), the estimation is simpler, as reported in many countries[12–16], including estimates in Japan[17]. However, evaluation of population-level effects are scarce (mainly in the United States and Israel)[18,19], although global estimates have been reported[20]. Whereas the indirect effectiveness of

[1]Kyoto University School of Public Health, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. [2]Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, Tokyo 162-8640, Japan. [3]Department of Virology, Tohoku University Graduate School of Medicine, Miyagi 980-8575, Japan. ✉email: nishiura.hiroshi.5r@kyoto-u.ac.jp

vaccination has been understudied, the related published studies imply that the impact of herd immunity has been substantial during the pre-Omicron period of the COVID-19 pandemic[18,19].

The present study is focused on the post-hoc evaluation of the vaccination program in Japan where the mortality impact of COVID-19 has been one of the lowest among countries belonging to the Organization for Economic Cooperation and Development[21]. Calculating the counterfactual scenario, herein, we aimed to estimate the total effectiveness of COVID-19 vaccination in Japan in 2021, during which the course of the primary series of the vaccination program was completed and third dose (or booster dose) was not administered yet. We further examined scenarios involving different timing and recipients of vaccination.

Results

Addressing age-dependent heterogeneity along with vaccination coverage, our transmission model successfully captured the observed data during the primary series of the vaccination program in Japan (Fig. 1 and Supplementary Fig. S8). Whereas the prototype model in Fig. 1 unrealistically assumed that observed cases represented all infected individuals (i.e., ascertainment bias factor at 1), hereinafter, we present results using other plausible reporting coverages, i.e., 0.125, 0.25, and 0.50, as shown in Supplementary Fig. S9 and Supplementary Table S1.

Hypothetical cumulative numbers of infections and deaths from February to November 2021 were explored in the absence of vaccination by different reporting coverages (Table 1). We found that the cumulative number of infections differed, from 63.3 million (95% CI 63.2–63.6) to 72.0 million (95% CI 71.4–72.6) cases for reporting coverages of 0.25 and 0.50, respectively. The possible cumulative number of deaths without vaccination ranged from 213,000 (95% CI 212–213) to 860,000 (95% CI 850–869) deaths for reporting coverage from 0.125 to 0.50. Compared with variations in cases, variations in deaths were broader because the infection fatality risk also varied by reporting coverage (Supplementary Figs. S10 and S11).

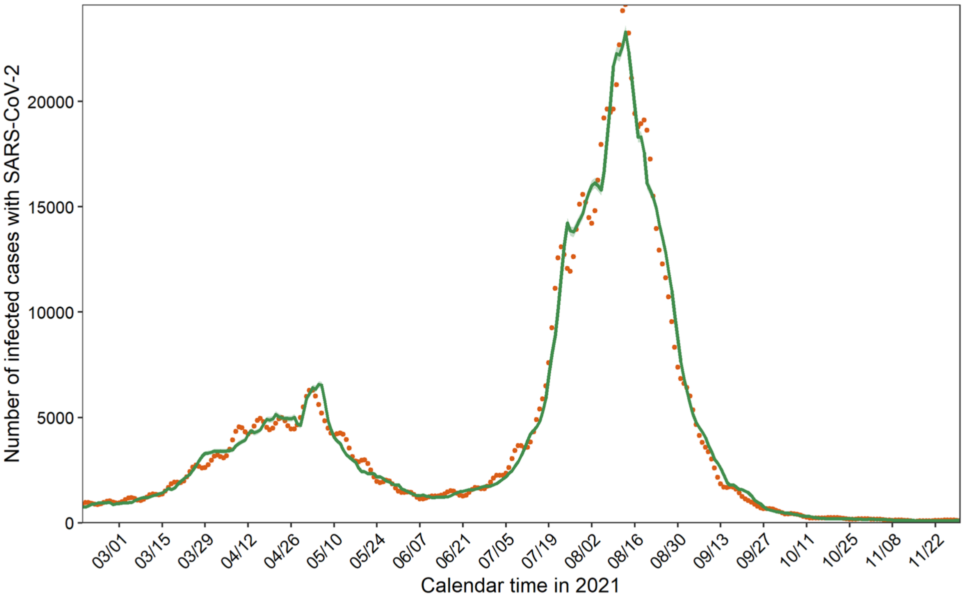

Figure 1. Comparison between predicted and observed infections with SARS-CoV-2. Orange dots represent the observed daily incidence of infection with SARS-CoV-2 during the primary series of the vaccination program from 17 February to 30 November 2021. Green line denotes the predicted daily incidence, computed by the transmission model, with 95% confidence intervals highlighted as light green areas. The observed number of COVID-19 cases is the same as the confirmed cases in this figure (i.e., we assumed that no ascertainment bias existed); in the main study, we examined realistic ranges of ascertainment bias.

Reporting coverage	Infections (thousand)	Deaths (thousand)
0.50	72,015 (71,406–72,621)[a]	860 (850–869)
0.25	63,344 (63,242–63,562)	364 (363–366)
0.125	71,457 (71,338–71,646)	213 (212–213)

Table 1. Cumulative numbers of infections and deaths owing to COVID-19 without vaccination according to reporting coverage. [a]Values inside the parentheses represent 95% confidence intervals computed using the parametric bootstrap method.

Here, we present the results based on the assumption that the reporting coverage was 0.25, i.e., the actual number of infections was four times greater than observed (confirmed) cases[22]. The epidemic size varied greatly with the counterfactual vaccination scenario (Fig. 2A). If the vaccination program had been conducted 14 days earlier than the actual pace, the peak of daily incidence would have decreased by 73%, i.e., 98,368 infections (or four times the observed) versus 26,149 (95% CI 24,354–27,952) infections in the early schedule scenario. However, if the program had taken place 14 days later than the actual schedule, the peak of daily incidence would have reached 263,220 (95% CI 250,387–276,173) infections, and the maximum daily incidence was estimated to be 33,004 (95% CI 30,996–35,258) infections in the elevated coverage scenario. Using the estimated number of infections over time, we calculated the effective reproduction number, interpreted as the average number of infections generated by a single primary case at a certain time (Fig. 2B). We also computed the line representing the effective reproduction number in the scenario without vaccination. The discrepancies among scenarios became recognizable when the vaccination program was accelerated around June–July 2021, sharing similar incidence patterns (Fig. 2A). Comparing Fig. 2A and B, the peak height of the effective reproduction number did not necessarily correspond to the magnitude of the epidemic.

Table 2 presents the cumulative number of infections with SARS-CoV-2 by age group and counterfactual scenario. Whereas the early schedule and elevated coverage scenarios respectively could have contributed to reductions of 54% and 47% overall, the late schedule scenario could have led to an increase in infections of 117%, reaching more than 10 million infections by the end of November 2021. In all examined scenarios, young adults aged 20–29 years yielded the greatest number of infections whereas the relative and absolute reductions with better vaccination programs than the actual program were comparable among people aged 10–49 years.

The cumulative numbers of deaths by age group and counterfactual scenario are summarized in Table 3. Mortality in older people was more sensitive to different vaccination scenarios. In the late schedule scenario, the relative increase in the number of deaths was estimated to be 50%, i.e., this scenario yielded more than 5000 additional deaths by the end of November 2021.

Discussion

Whereas Japan successfully implemented its primary series of vaccination against COVID-19, reaching 75% coverage by the end of November 2021[23], a pressing question has been how successful the program was during the pre-Omicron period. The present study revealed that without the vaccination program, the cumulative numbers of infections and deaths would have been 63.3 million (95% CI 63.2–63.6) and 364,000 (95% CI 363–366), respectively, assuming that confirmed cases represented 25% of infections. Despite the immense impact of the program, had vaccination been implemented 14 days earlier, there could have been 54% and 48% fewer cases and deaths, respectively, than the observed numbers. These figures represent the averted number of cases and deaths, and such estimates contrast to vaccine effectiveness (or efficacy) estimate at an individual level via randomized controlled trial or cohort study design, i.e., the averted number estimates require the vaccination coverage at the population level (possibly in real time), and additional datasets, including transmission dynamics, need to

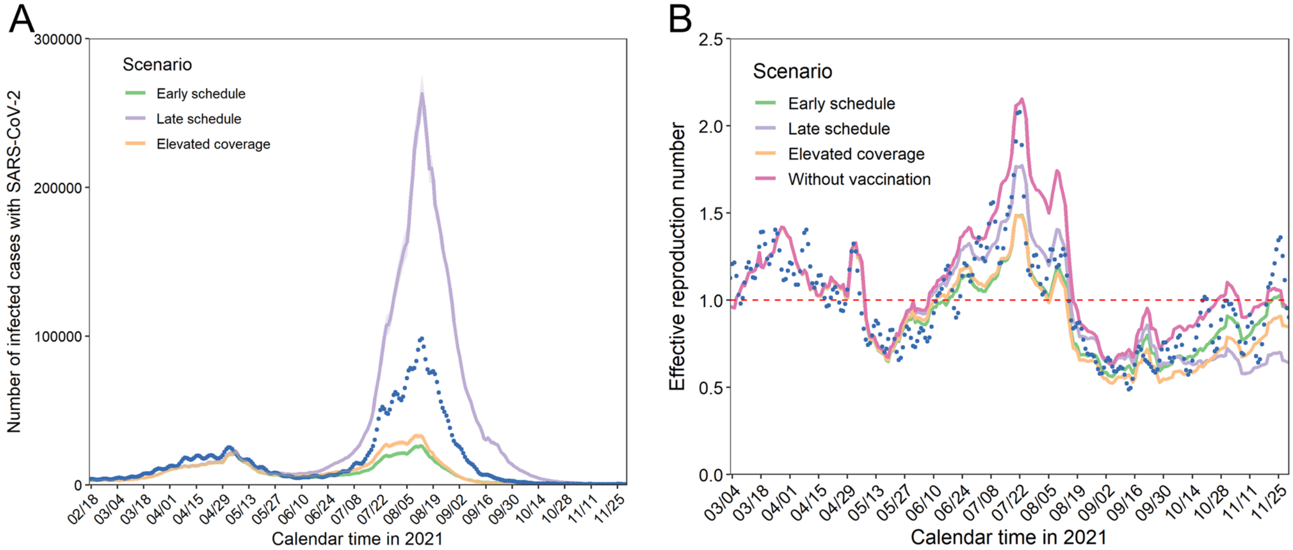

Figure 2. Impact of the primary series of the vaccination program on cases and the effective reproduction number. (**A**) Number of infections with SARS-CoV-2 from 17 February to 30 November 2021 according to counterfactual vaccination scenarios. Each line represents a different scenario with 95% confidence intervals highlighted as the light colored area; blue dots denote actual numbers of infections. (**B**) Effective reproduction number by vaccination scenario from 4 March to 30 November 2021. The colors are the same as in Fig. 3A. Blue dots represent the effective reproduction number estimated using the actual estimated infections shown in Fig. 3A. The pink-colored line represents the counterfactual scenario without vaccination. The red dashed line describes the threshold of the effective reproduction number, which is equal to 1. The number of infections was calculated assuming that the reporting coverage is 0.25.

Age group (years)	Scenario[a]	Estimate (thousand)	95% confidence interval	Relative change (%)[b]
0–9	Early	93	87–99	−72
	Late	498	477–518	50
	Elevated	109	103–115	−67
10–19	Early	324	304–345	−30
	Late	1677	1611–1740	260
	Elevated	375	354–398	−20
20–29	Early	537	508–567	−56
	Late	2470	2373–2563	101
	Elevated	597	565–629	−51
30–39	Early	314	295–332	−60
	Late	1545	1478–1610	95
	Elevated	356	336–376	−55
40–49	Early	344	324–364	−53
	Late	1731	1654–1804	134
	Elevated	391	369–413	−47
50–59	Early	266	251–281	−54
	Late	1303	1243–1361	126
	Elevated	303	287–320	−48
60–69	Early	120	114–127	−52
	Late	495	470–518	98
	Elevated	148	140–156	−41
70–79	Early	95	90–100	−43
	Late	286	272–299	71
	Elevated	110	104–116	−34
80–89	Early	57	54–61	−47
	Late	148	141–154	36
	Elevated	64	61–68	−41
≥90	Early	16	15–17	−63
	Late	43	41–45	2
	Elevated	18	17–19	−58
Total	Early	2166	2044–2290	-54
	Late	10,196	9761–10,607	117
	Elevated	2470	2337–2610	−47

Table 2. Cumulative numbers of infections with SARS-CoV-2 in the counterfactual scenarios. [a]Early: counterfactual scenario of a vaccination program implemented earlier that the actual schedule; Late: counterfactual scenario of a vaccination program implemented later that the actual schedule; Elevated: counterfactual scenario if the program had been implemented faster with higher vaccination coverage among adolescents and people aged 10–59 years. [b]Relative change represents a comparison between the computed number and observed number (i.e., reporting coverage = 0.25).

be analyzed to clarify the indirect effect of vaccination. The use of renewal process models enabled us to demonstrate the critical importance of the pace of the vaccination program and the prioritizing of vaccine recipients in determining the disease burden associated with COVID-19.

A critical take-home message from the present study is that the indirect effect of vaccination was enormous in Japan. The numbers of prevented infections and deaths were 13.5 and 36.4 times the empirically observed counts, respectively. In other words, the total effectiveness of the vaccination program in preventing infection and death was estimated at 92.6% and 97.2%, respectively. Of these fractions, the direct effect (i.e., comparison of risks between vaccinated and unvaccinated cases) that we estimated earlier[17] accounted for only 3.6% and 5.1%, respectively, and the indirect effect (i.e., comparison of risks between actual and counterfactual courses of the epidemic) was as large as 89.0% and 92.1% reductions in infections and deaths, respectively. Such differences were seen because the incidence in Japan remained relatively lower than those in Western countries owing to PHSM, e.g., less than 5% of the population was reported as a COVID-19 case by the end of 2021. Clarifying the total effectiveness of vaccination was facilitated by modeling to yield the counterfactual scenario, and our finding regarding the total effect echoes those of published studies[18,19]. Together with past evidence[18,19], consistent findings that the vaccination program prevented infections among half of the Japanese population and more than 90% of prevented deaths were owing to its indirect effect indicate that the vaccination program was enormously successful during the Delta variant epidemic wave during 2021 in Japan. The importance of indirect effect is what the present study contrasts to existing published studies[12–17] that only directly measured individual benefit of vaccination, including the averted cases, hospitalization, severe complication and death.

Age group (years)	Scenario[a]	Estimate (persons)	95% confidence interval	Relative change (%)[b]
0–9	Early	–	–	–
	Late	–	–	–
	Elevated	–	–	–
10–19	Early	2	2–2	−31
	Late	11	10–11	260
	Elevated	2	2–3	−19
20–29	Early	10	9–11	−56
	Late	46	44–49	102
	Elevated	11	10–12	−51
30–39	Early	27	24–29	−60
	Late	131	124–138	95
	Elevated	30	28–33	−55
40–49	Early	106	97–115	−53
	Late	533	504–562	135
	Elevated	122	113–131	−46
50–59	Early	301	276–326	−54
	Late	1465	1381–1547	126
	Elevated	348	320–376	−46
60–69	Early	533	480–587	−49
	Late	1998	1859–2138	92
	Elevated	663	602–727	−36
70–79	Early	1445	1296–1601	−40
	Late	4000	3684–4325	67
	Elevated	1700	1532–1877	−29
80–89	Early	2135	1874–2410	−44
	Late	5089	4608–5586	34
	Elevated	2444	2156–2748	−36
≥90	Early	717	565–880	−61
	Late	1831	1558–2119	−1
	Elevated	829	661–1009	−55
Total	Early	5274	4623–5960	−48
	Late	15,103	13,771–16,474	50
	Elevated	6150	5424–6916	−39

Table 3. Cumulative numbers of deaths associated with COVID-19 in the counterfactual scenarios. [a]Early: counterfactual scenario of a vaccination program implemented earlier that the actual schedule; Late: counterfactual scenario of a vaccination program implemented later that the actual schedule; Elevated: counterfactual scenario if the program had been implemented faster with higher vaccination coverage among adolescents and people aged 10–59 years. [b]Relative change represents a comparison between the computed number and observed number (i.e., reporting coverage = 0.25).

In many countries with greater incidence, including Brazil[15], Israel[14], Italy[12], United States[16] and countries that belong to WHO European Region[13], the direct effect was already enormous. Japan enjoyed smaller incidence by the end of 2021 and the direct effect was relatively limited[17], but the present study has been unique in that it demonstrated that the indirect effect can be inferred to be substantial using the effective reproduction number in a counterfactual scenario.

Another notable finding of this study is that our modeling approach enabled us to examine hypothetical scenarios in which the vaccination pace is accelerated. The cumulative numbers of infections in the early schedule and late schedule scenarios were estimated to be 2.2 million (95% CI 2.0–2.3) and 10.2 million (95% CI 9.8–10.6), respectively, which clearly led to substantial differences in mortality. Epidemiological studies can help policy makers recognize that a 1- or 2-week difference in the implementation of vaccination could yield completely different population impacts.

Published studies have indicated that prioritized vaccination for older people could minimize COVID-19 mortality if vaccines are not sufficiently available[24–28]. This was consistent with our finding, i.e., the early schedule scenario yielded better outcomes than the elevated coverage scenario. However, in our elevated coverage scenario (i.e., encouraging more adolescents and people aged 10–59 years to be vaccinated), the total effect was substantial, even when older people were not prioritized for vaccination. This demonstrates that vaccinating younger individuals with substantial transmission potential is a critical strategy in mitigating the magnitude of the epidemic for an entire population, including children aged < 10 years who were not eligible for the vaccination program. Taken together, the present study findings imply that, given a substantial vaccine supply and immunization capacity, allocating vaccines for younger adults in addition to prioritizing older adults could reduce the overall COVID-19 burden, as previously indicated[19,27,29–32].

So, how should we rate the vaccination program in Japan during the SARS-CoV-2 Delta variant epidemic wave? The Japanese government set a goal for the daily number of vaccinated people of one million in early May 2021 (which was achieved from late June to July), subsequently stating that the maximum number was to be 1.5 million in the later part of the same month[33]. In addition to mass vaccination with initial prioritization of older people and health care workers, the program of vaccination in the workplace aimed at expanding coverage started in late June 2021[34]. Our counterfactual scenario indicated that the observed vaccination program helped avoid the worst case. However, if the vaccination program had begun 2 weeks later than the observed schedule, substantial mortality could have occurred. Additionally, a surge in COVID-19 patients observed in July–September 2021 was the largest epidemic wave ever experienced in Japan, and the corresponding period fell under the state of emergency, which was based on a non-legally binding policy in which the government requested voluntary restriction of contacts[35]. Were PHSM not in place under the state of emergency, the number of infections could have been even greater than the observed number. Considering that our early schedule and elevated coverage schedule scenarios were realistic in their anticipated pace of vaccination, considerable mortality and resulting economic losses could have been mitigated. Perhaps more importantly, from a scientific point of view, evidence regarding the indirect impact of such interventions in real time using modeling techniques should be routinely accessible to policy makers during future pandemics.

Our study involved several technical limitations. First, as previously mentioned, during the research period, Japan experienced three state of emergency declarations: from 8 January to 21 March, from 25 April to 20 June, and from 12 July to 30 September 2021. Rather than incorporating the specific variable of a state of emergency into the model (e.g., quantified effectiveness of PHSM), we tried to indirectly capture its impact via estimating the effective reproduction number using several explanatory variables, including mobility. In fact, use of human mobility data as a predictor is recognized as reflecting the impact of PHSM[36–39]. It should be noted, however, that published studies have attempted to measure the population-level impact of both vaccination and PHSM over the course of time[40,41]. Second, the contact matrix used in the present study was quantified before the study period[42], and the next-generation matrix was calibrated during the course of the pandemic. At minimum, our time-dependent reproduction number helped capture the transmission dynamics over time and across ages (Fig. 1). Third, vaccine-induced immunity and immunity following natural infection were dealt with independently in the present study, and we did not account for the effect of waning immunity with the latter during the study period. We focused on the period shortly after vaccination and before the vaccination rollout, when approximately only 1% of the population experienced COVID-19 infection. Fourth, we did not take into account the heterogeneities over geographical space. Strictly speaking, the state of emergency covered different durations and areas according to prefecture, leading to specific variations in mobility information[43]. Finally, while vaccines against the Omicron variant, which is antigenically distinct, have shown reduced effectiveness compared to previously circulating variants[44,45], the population-level impact of those changes have yet to be understood well[46]. In line with this, we have yet to understand whether the indirect effects of vaccination continued to accumulate and played a pivotal role in responding to the Omicron variant and its subvariants, including XBB. Future studies should address the issue of population impact during Omicron era.

Conclusions

We demonstrated that the indirect effect of vaccination in Japan during 2021 was very large, with the vaccination program reducing mortality by more than 97%. The pace of vaccination and prioritization of vaccine recipients have been key to mitigating the mortality burden of COVID-19. In the future, firm and prompt policy-making process based on real-time understanding of the transmission dynamics under various vaccination scenarios is called for.

Methods

Conversion to infections

COVID-19 was designated a notifiable disease under the infectious disease law of Japan as of 2021. All individuals suspected of being infected with SARS-CoV-2 were tested via PCR or quantitative antigen test at medical facilities. They were then requested to remain in home isolation and undergo investigation by municipal public health centers to identify their close contacts. Information of confirmed cases (e.g., age and sex) was registered in the Health Center Real-time Information-sharing System on COVID-19 (HER-SYS) by medical facilities or municipal public health centers. Supplementary Fig. S1A shows the number of confirmed cases from the beginning of the primary series (the first and second doses) of the vaccination program through the end of November 2021. In the end of November 2021, SARS-CoV-2 in Japan was dominated by Delta variant to which the vaccine effectiveness was known to have been greatly diminished, sometimes by 10%, compared with other variants that circulated earlier[47–49].

The time of infection for all confirmed COVID-19 cases retrieved from HER-SYS was backcalculated using a previously estimated distribution of the interval between infection and illness onset, assumed to follow a log-normal distribution with a mean of 4.6 days and standard deviation (SD) of 1.8 days[50, 51]. Cases without a date of symptom onset were backcalculated using the time difference from symptom onset to reporting, assumed to follow a log-normal distribution with a mean of 2.6 days and SD of 2.1 days, as previously estimated using cases with information for the date of symptom onset. Non-parametric backcalculation was performed using the R-package “surveillance” (version 1.20.3). To address the issue of reporting bias, we explored different reporting coverages: 0.125, 0.25, 0.5, and 1.0 (no bias) by multiplying the backcalculated cases by 1 and dividing by reporting coverage to finally obtain the number of infections.

Immune fraction

SARS-CoV-2, all vaccinated individuals retrieved from the Vaccine Record System (VRS) were converted into immunized people according to time. The data comprised the sex, age, and date of vaccination for vaccinated individuals. We assumed that all people who received the first dose were subsequently vaccinated with the second dose at an interval of 21 days (Supplementary Fig. S1B). According to statistics of the VRS, there was a very small discrepancy in vaccination coverage between the first dose (75.19%) and the second dose (74.61%) as of the end of December 2021[52]; therefore, we could obtain a certain consensus on the usage data for people vaccinated with the first dose only. For the conversion, we used a profile of vaccine efficacy involving waning immunity for the primary series used by Gavish et al.[19], which was based on previous estimates[53,54]. Given the widespread use of the messenger RNA vaccine BNT162b2 (Pfizer/BioNTech) in Japan (more than 80% of individuals received this vaccine by the end of November 2021)[23], we assumed that published estimates could directly be applied to the case of Japan. Further details and background of the primary series in Japan's vaccination program are described elsewhere[17].

To adapt the following transmission model, we used the number of vaccinated individuals and the profile of vaccine efficacy to estimate the immune fraction in age group a at calendar time t, $l_{a,t}$, which is expressed as:

$$l_{a,t} = \frac{1}{n_a} \sum_{s=1}^{t-1} v_{a,t-s} h_s \tag{1}$$

where n_a is the population size in age group a in 2021[55], $v_{a,t}$ denotes the number of vaccinated individuals in age group a at calendar time t, and h_s represents the vaccine profile. Supplementary Fig. S2 displays the estimated immune fraction by age group.

Transmission model

We developed the time-dependent transmission model that accounts for heterogeneous transmission between age groups, fitting the model to observed incidence data and estimating unknown parameters. We used the following renewal equation to infer the transmission dynamics underlying the COVID-19 epidemic, which is described as:

$$i_{a,t} = \sum_{b=1}^{10} \sum_{\tau=1}^{t-1} \boldsymbol{R_{ab,t}} i_{b,t-\tau} g_\tau, \tag{2}$$

where $i_{a,t}$ represents the number of infections with SARS-CoV-2 in age group a at day t and g_τ indicates the probability density function of the generation interval, assumed to follow a Weibull distribution with a mean of 4.8 days and SD of 2.2 days[51,56]. $\boldsymbol{R_{ab,t}}$ denotes the effective reproduction number, interpreted as the average number of secondary cases in age group a generated by a single primary case in age group b at calendar time t. To capture the impact of vaccination, $\boldsymbol{R_{ab,t}}$ was decomposed as:

$$\boldsymbol{R_{ab,t}} = \left(1 - l_{a,t} - \frac{\sum_{k=1}^{t-1} i_{a,k}}{n_a}\right) \boldsymbol{K_{ab}} p h_t d_t c_t \tag{3}$$

where $\sum_{k=1}^{t-1} i_{a,k}$ represents the cumulative number of previous infections after 16 February 2021. $\boldsymbol{K_{ab}}$ is considered a next-generation matrix, which was modeled as $\boldsymbol{K_{ab}} = s_a \boldsymbol{m_{ab}}$, where s_a represents relative susceptibility and $\boldsymbol{m_{ab}}$ denotes the contact matrix; we rescaled a previously quantified next-generation matrix during the initial phase of the COVID-19 epidemic in 2021 attributable to the Alpha variant[57]. Because the oldest age group was ≥ 65 years in the previous estimate, we reconstructed the epidemic curve with new age groups: 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89 and ≥ 90 years and estimated $\boldsymbol{K_{ab}}$ by fitting the model to observed cases (Supplementary Fig. S3). The detailed methods are explained elsewhere[57,58]. We assumed that the contact rates among groups aged ≥ 70 years were the same as those aged ≥ 65 in the contact matrix, $\boldsymbol{m_{ab}}$, which is based on a social epidemiological survey conducted prior to the COVID-19 pandemic in Japan[42]. With respect to the above explanation, those early terms in Eq. (3) could capture the effective heterogeneous interactions between infectees and infectors, which accounts for the immune fraction owing to vaccination and infections among susceptible individuals (i.e., infectees). p denotes the scaling parameter involving all terms in Eq. (3) and h_t expresses the change in mobility. The variable, h_t, related to human mobility was decomposed as:

$$h_t = \omega^{community} \alpha_t^{community} + \omega^{house} \alpha_t^{house} + \omega^{work} \alpha_t^{work}, \tag{4}$$

where ω means the coefficient of human mobility in the community, household, or workplace relative to the community setting (i.e., $\omega^{community}$ is equivalent to 1). The coefficient, α_t, describes a proxy of the intensified contacts in three different settings retrieved from Google's COVID-19 community mobility report in Japan[59]. Those data were smoothed using a 7-day moving average (Supplementary Fig. S4). d_t represents the increase in transmissibility of the Delta variant compared with earlier variants, which was formulated as $d_t = ru_t$, where r is the scaling parameter for transmissibility and u_t represents the profile of increased transmissibility. We assumed that u_t increased with the detected proportion of COVID-19 cases owing to the Delta variant in Japan[60], which was modeled using a logistic curve. We then rescaled u_t up from 1 to a maximum of 1.5[61–63]. A comparison between the predicted and observed proportion is shown in Supplementary Fig. S5. d_t was parameterized as 1 before 20 May 2021, when we assumed that the proportion of infections with the Delta variant started to increase at population level. Finally, c_t expresses the influence of consecutive holidays, defined as more than 3 days in the present study. Moreover, we added "Obon season," the national religious season associated with Buddhist tradition, to those holidays. Not all consecutive days in this period (from 13 to 16 August 2021) were regarded as holidays; however, many Japanese people travel and/or visit their relatives during this season. We modeled c_t as $c_t = e\beta_t$, where e accounts for the coefficient of holiday influence and β_t was assigned 1 if the day was aligned with consecutive holidays; otherwise c_t was parameterized as 1.

Vaccination scenarios

We first computed the counterfactual scenario, i.e., without vaccination. We also explored three additional hypothetical scenarios: (1) the vaccination program was implemented sooner than the actual program, reaching a maximum number of vaccinated individuals 14 days earlier than the observed pace (hereafter "early schedule" scenario); (2) the vaccination schedule was delayed, reaching a peak in the number of vaccinated people 14 days slower than the observed pace ("late schedule" scenario); and (3) adolescents and people aged 10–59 years were vaccinated more and faster ("elevated" scenario). To explore different counterfactual scenarios, we first regressed the vaccination coverage using the logistic function by age group, which is modeled as:

$$E(v_{a,t}) = \frac{\pi^1}{1 + \exp(-\pi^2(t - \pi^3))}, \tag{7}$$

where π^1, π^2, and π^3 represent the carrying capacity (eventual coverage of the primary series), speed of increase in the vaccination coverage, and requisite duration for the half coverage of π^1 (also representing the peak day for the number of vaccinated individuals), respectively. We performed maximum likelihood estimation to estimate π^1, π^2, and π^3 by age group. Comparisons between the predicted and observed number of vaccinated people by age group are shown in Supplementary Fig. S6.

We assumed that the days with the maximum number of vaccinated people (i.e., days that 50% of the carrying capacity was achieved) were 14 days earlier in the Early scenario and later in the Late scenario than the observed. For the Elevated scenario, we assumed that people aged 10–59 years had earlier peaks in the number of vaccinated individuals, as with the Early scenario. Additionally, people aged 10–19 years and aged 20–49 years were assumed to reach 70% and 90% in eventual vaccination coverage (π^1), respectively. People aged ≥ 50 years had already reached more than 90% of the vaccination coverage by the end of November 2021. We did not consider vaccination among individuals aged less than 10 years because children were not eligible to be vaccinated during the primary series of the program in Japan. All scenarios of the vaccination program by age group are shown in Supplementary Fig. S7.

Likelihood function

We assumed that the daily counts of infections followed a Poisson distribution, and the likelihood function with unknown parameters, $\theta = \{p, \omega^{house}, \omega^{work}, r, e\}$, was represented as:

$$L(\theta; i_{a,t}) = \prod_t \prod_a \frac{E(i_{a,t})^{i_{a,t}} \exp(-E(i_{a,t}))}{i_{a,t}!} \tag{8}$$

By minimizing the loglikelihood function, we estimated θ. The 95% confidence intervals (CI) were calculated from 1000 bootstrap iterations using the multivariate normal distributions of the parameters. We estimated a series of parameters by reporting coverage in the present study. All estimated parameters with 95% CIs are shown in Supplementary Table S1. Supplementary Fig. S8 demonstrates the fitting outcome of the predicted and observed infections with SARS-CoV-2 by age group, with reporting coverage of 1 (i.e., no ascertainment bias). Supplementary Fig. S9 compares the predicted and observed infections by reporting coverage.

Using the estimated parameters, θ, we explored hypothetical scenarios by varying the timing and the recipients of vaccination. For this, we used infections already backcalculated 14 days back from the start of vaccination as the initial condition.

Effective reproduction number

Because the effective reproduction number in Japan conventionally uses an estimate for the entire population, we also calculated an effective reproduction number based on the total number of cases at calendar time t, R_t, in each counterfactual scenario using the total number of infections with SARS-CoV-2. Using an equation similar to Eq. (2), the total number of infections, i_t^{total}, was modeled as:

$$i_t^{total} = R_t \sum_{\tau}^{1-\tau} i_{t-\tau}^{total} g_\tau. \tag{9}$$

Assuming the daily case counts followed a Poisson distribution, we estimated R_t using maximum likelihood estimation[51].

Infection fatality risk

To compute the mortality impact, we estimated the age-specific infection fatality risk (IFR) according to reporting coverage in the present study. First, we formulated the cumulative number of deaths in age group a resulting from cases infected during the research period in unvaccinated and vaccinated individuals, respectively, which are described as:

$$\begin{cases} D_a^{unvaccinated} = IFR_a \sum_{t=17\text{Feb}2021}^{30\text{Nov}2021} (1-\epsilon_{a,t})\widehat{i}_{a,t} \\ D_a^{vaccinated} = IFR_a(1-VE_a) \sum_{t=17\text{Feb}2021}^{30\text{Nov}2021} \epsilon_{a,t}\widehat{i}_{a,t} \end{cases}, \tag{10}$$

where $\epsilon_{a,t}$ represents the time-varying proportion of vaccinated people among confirmed cases in age group a at calendar time t, and $\widehat{i}_{a,t}$ is the expected number of infections estimated from the transmission model. VE_a expresses the vaccine-induced reduction in mortality estimated in 2021 for Japan[64]. We obtained $\epsilon_{a,t}$ by modeling cases with a vaccination history registered in HER-SYS using a logistic function. The observed proportion was calculated as 7-day moving average and shifted − 5 days because of the conversion for the time of infection. Also, to account for the age groups used in the present study, people aged 10–19, 20–29, 30–39, 40–49, 50–59 and ≥ 60 years were utilized as people aged 15–24, 25–34, 35–44, 45–54, 55–64 and ≥ 65 years for the proportion retrieved from HER-SYS, respectively. Supplementary Fig. S10 shows the comparison between the model prediction and observed proportions.

To estimate IFR by age group, the following likelihood equation was used:

$$L\left(\lambda_a; \widehat{i}_{a,t}, D_a\right) = \prod \binom{\sum \widehat{i}_{a,t}}{D_a} \lambda_a^{D_a}\left(1-\lambda_a^{D_a}\right)^{\sum \widehat{i}_{a,t} - D_a}, \tag{11}$$

where λ_a denotes the risk of death in age group a, modeled as:

$$\lambda_a = \frac{(D_a^{unvaccinated} + D_a^{vaccinated})}{\sum \widehat{i}_{a,t}}. \tag{12}$$

D_a is the cumulative number of deaths reported from 10 March to 21 December 2021 in age group a, which was retrieved from the Ministry of Health, Labour and Welfare of Japan, accounting for the reporting delay of 21 days.[65] By minimizing the negative logarithm of Eq. (8), we estimated IFR_a. We performed this process for each reporting coverage. Supplementary Fig. S11 displays the estimated IFR by reporting coverage and age group. Finally, we estimated the cumulative number of deaths as an aggregation of $D_a^{unvaccinated}$ and $D_a^{vaccinated}$ in Eq. (7) according to different counterfactual scenarios of varying $\widehat{i}_{a,t}$. We only applied the first equation in Eq. (7), i.e., $D_a^{unvaccinated}$, for the counterfactual scenario in the absence of vaccination.

For calculation of the death toll, we altered only a parameter representing the requisite duration for the half coverage of a carrying capacity to coincide with changes in vaccine recipients in the counterfactual vaccination scenarios. Because of this exercise, we were able to model the specific proportion of vaccinated people among confirmed cases according to different vaccination scenarios. The principal idea of the logistic model is explained in the early subsection.

Ethical considerations

This study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained for reporting the diagnosis. The authors did not have an access to any individual identity information, and this research was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (approval number R2673).

Data availability

We were allowed to access the information on HER-SYS only for the purpose of analyzing the COVID-19 situation in Japan; therefore, this database is not publicly available. However, we shared the daily numbers of vaccinated individuals and reported cases not stratified by age group during the analysis. Hiroshi Nishiura should be contacted to request the data from this study.

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Author contributions

All authors participated in the study design. T.K., K.Y., K.O., and T.K. collected and retrieved the data. T.K. analyzed the data and H.N. evaluated the validity of the analysis. T.K. drafted the manuscript, including the figures and tables. H.N. edited earlier versions of the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to H.N.

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RESEARCH **Open Access**

Assessing the COVID-19 vaccination program during the Omicron variant (B.1.1.529) epidemic in early 2022, Tokyo

Taishi Kayano[1] and Hiroshi Nishiura[1*]

Abstract

Background Many countries, including high-income nations, struggled to control epidemic waves caused by the Omicron variant (B.1.1.529), which had an antigenically distinct evolution. Evaluating the direct and indirect effects of vaccination during the Omicron waves is essential to assess virus control policies. The present study assessed the population impacts of a vaccination program during the sixth wave caused by BA.1 and BA.2 from January to May 2022, in Tokyo.

Methods We analyzed the primary series and booster vaccination coverages and the confirmed cases stratified by vaccination history. We estimated the number of COVID-19 cases that were directly and indirectly prevented by vaccination. To estimate the direct impact, we used a statistical model that compared risks between unvaccinated and vaccinated individuals. A transmission model employing the renewal process was devised to quantify the total effect, given as the sum of the direct and indirect effects.

Results Assuming that the reporting coverage of cases was 25%, mass vaccination programs, including primary and booster immunizations, directly averted 640,000 COVID-19 cases (95% confidence interval: 624–655). Furthermore, these programs directly and indirectly prevented 8.5 million infections (95% confidence interval: 8.4–8.6). Hypothetical scenarios indicated that we could have expected a 19% or 7% relative reduction in the number of infections, respectively, compared with the observed number of infections, if the booster coverage had been equivalent to that of the second dose or if coverage among people aged 10–49 years had been 10% higher. If the third dose coverage was smaller and comparable to that of the fourth dose, the total number of infections would have increased by 52% compared with the observed number of infections.

Conclusions The population benefit of vaccination via direct and indirect effects was substantial, with an estimated 65% reduction in the number of SARS-CoV-2 infections compared with counterfactual (without vaccination) in Tokyo during the sixth wave caused by BA.1 and BA.2.

Keywords Immunization, COVID-19, Direct effect, Indirect effect, Population-level impact

Introduction

The COVID-19 pandemic has been a global health emergency since its emergence in late 2019 [1, 2]. Immunization programs have been an integral part of the response to this disease, which is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3–5]. Mass vaccination programs have two critical

*Correspondence:
Hiroshi Nishiura
nishiura.hiroshi.5r@kyoto-u.ac.jp
[1] Kyoto University School of Public Health, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

pathways to reduce population-level risk: direct and indirect effects [6, 7]. The direct effect of vaccination represents the reduction in the risk of infection or severe disease in vaccinated individuals compared with this risk in unvaccinated individuals. The indirect effect, often referred to as the total effect, results from preventing viral spread in the population, and this effect accumulates when vaccines are efficiently distributed among the population. To ensure successful viral control via mass vaccination and to inform public health policy, evaluating the direct and indirect impacts of vaccination programs is critical.

A small number of studies globally have investigated the population-level impact of COVID-19 vaccination [8–10]. For example, a modeling study in New York City, USA showed that the vaccination program reduced the magnitude of the epidemic during the Alpha (B.1.1.7) and Delta (B.1.617) variant waves, suggesting the importance of accelerating vaccine uptake [8]. A study in Austria measured the population impact of a mass vaccination campaign that took place after a large Beta variant (B.1.351) epidemic by comparing two similar districts, but was not a randomized clinical trial [9]. A statistical modeling study conducted in Israel concluded that the booster vaccination program made substantial direct and indirect contributions to reducing the number of infections, severe cases, and deaths during the Delta variant wave [10]. These studies demonstrate the importance of both the direct and indirect impacts of vaccination, and they highlight the potential for mass vaccination to mitigate the disease burden associated with COVID-19. Since the emergence of Omicron (B.1.1.529), including subvariants BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), BA.4 (B.1.1.529.4), and BA.5 (B.1.1.529.5), many countries have struggled to control the virus, partly because of its antigenically distinct evolution. Moreover, very few studies have evaluated vaccination programs at the population level during Omicron waves [11].

Controlling COVID-19 epidemics became more challenging with the emergence of the Omicron variant, partly owing to its increased secondary transmission in vaccinated populations compared with Alpha and Delta [12–17]. Evidence suggests that the vaccines were less effective against Omicron than against previously circulating variants [14, 18]. While the individual benefit of vaccination has been well characterized, the population-level impacts of vaccination during Omicron epidemics have yet to be clarified.

Community-acquired infections with Omicron BA.1 rose in late December 2021 in Japan, constituting the sixth epidemic wave. During this time, there were approximately 20,000 cases per day in Tokyo. This was the largest COVID-19 epidemic up to that point (Fig. 1A). Shortly before the Omicron epidemic, the booster program had been established in early December 2021, using mainly the Pfizer/BioNTech mRNA vaccine (BNT162b2) and the Moderna vaccine (mRNA-1273); the primary series was also still available (Fig. 1B). In late May 2022, another booster campaign (the fourth dose) was launched initially aiming to cover older people and people with underlying comorbidities. Around this time, the first Omicron BA.5 infections

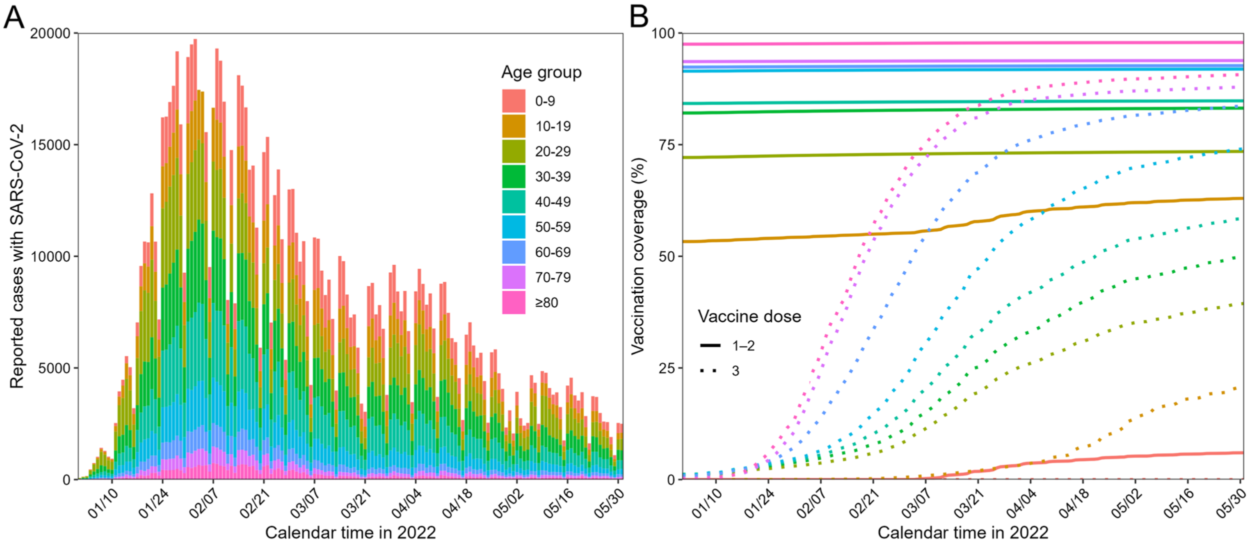

Fig. 1 Epidemiology of COVID-19 in Tokyo during the sixth wave, 2022. **A** Number of confirmed SARS-CoV-2 infections from January to May 2022 by age group. Each color represents the number of confirmed cases in each age group. **B** Vaccination coverage stratified by age group and dose (one or three). The period and color of the age group are the same as in Fig. 1A

were reported. Epidemiological and vaccination coverage data (Fig. 1) allowed us to reconstruct the transmission dynamics and quantify the population impacts of the vaccination program while focusing on the sixth wave caused by Omicron BA.1 and BA.2.

In the present study, we estimated the population-level impact of vaccination during the Omicron wave. The impact was estimated by distinguishing between the primary series and booster programs.

Methods

COVID-19 incidence data

In Japan, all patients diagnosed with COVID-19 at designated healthcare facilities were mandatorily reported to the local public health center in each prefecture under the Infectious Disease Law of 2022. Their personal information including age, sex, and vaccination history was electronically reported via the Health Center Real-time Information-sharing System on COVID-19 (HER-SYS). However, the completeness of the vaccination history information was limited, especially after the surge of Omicron infections in early 2022 [19, 20]. To address this challenge, we focused on the population impact of COVID-19 vaccination in Tokyo, which had more complete vaccination history data, rather than analyzing the impact for the entire country.

To estimate the direct impact, we used the confirmed COVID-19 cases stratified by vaccination history, as reported to the Tokyo metropolitan government. Although there was relatively thorough recordkeeping in Tokyo, the notification data included a small fraction of cases with incomplete vaccination history information (i.e., approximately 25% of cases were not accompanied by vaccination history). We thus performed the subsequent analyses using only complete data by employing a multiple imputation technique. Further explanation of the methods used and a data description can be found in the Additional file. Assuming a consistent delay of 5 days between infection and reporting, the epidemic curve of confirmed cases by the date of confirmation was back-calculated to the curve by the date of infection. The present study analyzed the data from January 1 to May 27, 2022 (21 weeks) during which the Omicron subvariants BA.1 and BA.2 were predominant.

To estimate the total effect, we used the same data stratified by age group. Details of the back-calculation procedure are provided in the Additional file. We estimated the number of infections by age group, assuming that the reporting coverage among all infected individuals was 0.25, i.e., one-quarter of the infections were detected and reported during the study period [21].

Vaccination coverage

Vaccinated individuals in Japan were registered in a national database called the Vaccine Record System (VRS). We extracted the information (age, vaccination date, and dose number (first or third dose)) of people who were vaccinated in Tokyo between January and May 2022. Because the discrepancy between the coverage of the first and second doses was small (0.6% as of June 1, 2022) according to the VRS, we assumed that all individuals who received a first dose subsequently received a second dose. Thus, our results can be interpreted as estimates for the "primary series" rather than for the first or second dose, specifically. To estimate the direct effect, the vaccination dates were shifted by 14 days into the future to allow for a delay to elicit the immune response [22, 23]. The population immune fractions by age group were then calculated. To compute the total effect, the dataset of vaccinated individuals was converted to that of the immune fraction of the population by using a vaccine efficacy estimate (see Additional file). The vaccinated individuals were divided into nine age groups: 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years; the incidence data were divided likewise. Lastly, we imposed a simplifying assumption that vaccine efficacy was independent of age.

Direct effect

The direct impact was calculated by comparing the risks between vaccinated and unvaccinated individuals. We estimated the total number of averted COVID-19 cases attributable to the direct effect by age group and by vaccine dose, i.e., the primary series or the booster program. The calculation was based on a statistical model whereby the immune fraction was multiplied by the weekly difference in incidence between unvaccinated and vaccinated people, i.e., the risk reduction directly attributable to vaccination, as explained elsewhere [24, 25]. To account for the reporting coverage, the estimates were multiplied by a factor of four to allow for comparison with the population-level impact, as noted above. Uncertainty in the estimates was based on iterations of multiple imputation; thus, the uncertainty reflects variation in the missing values rather than variation in the cases behind the epidemics. Further explanation of the method used is available in the Additional file.

Total effect

The total effect at the population level, consisting of the vaccine-induced protection that is conferred directly and indirectly, was evaluated by comparing the observed real-world data with a counterfactual scenario in which no vaccination program took place. To do this, we devised a transmission model that reconstructs the transmission dynamics over the period of analysis. A renewal equation was used, and the time-varying transmission model consisted of the incidence history, the effective reproduction number (i.e., the average number of infected cases generated by a single primary case at a given time), and the generation time. The effective reproduction number was expressed as a time-varying matrix that included the immune fraction attributable to the vaccination program, the reduced susceptible fraction owing to natural infection, the social contact matrix, and a weekly scaling parameter. Using the parameterized model and eliminating the vaccination impact (i.e., the immune fraction owing to vaccination) from the fitted transmission model allowed us to produce the counterfactual scenario in which the vaccination program had not taken place. Maximum likelihood estimation was performed to estimate the model parameters assuming that the daily incidence followed a Poisson distribution. The indirect effect was calculated as the gap between the total and direct effects. The 95% confidence intervals (CIs) for the total effectiveness were based on the parametric bootstrap method. We also assessed the impact of a third vaccine dose at the population level by varying the recipients and the coverage of the booster program as different counterfactual scenarios (Additional file).

Results

The total numbers of prevented COVID-19 cases directly attributable to vaccination by age group and vaccine dose in Tokyo, Japan, from January 1 to May 27, 2022, are shown in Table 1. These estimates were calculated using the confirmed case count; thus, the actual number of directly averted infections is greater. The absolute number of people who benefited from vaccination was highest for adults aged 30–39 years in the primary series program and ≥80 years in the booster program, with estimates of 86,181 (95% CI: 84,743–87,503) and 37,101 (95% CI: 35,649–38,780) people, respectively. Compared with the observed number of cases, the greatest relative reduction due to the direct effect was seen in people over 80 years of age and was estimated as −72% and −54% for the primary series and the booster program, respectively. The youngest age group (0–9 years old) had the lowest number of cases prevented by the primary series program (603 cases; 95% CI: 602–604), which corresponds to a 3% relative reduction compared with the observed count. Throughout the study period, 1–2 doses and a third dose reduced the total number of cases by 29% and 12%, respectively.

Table 1 Total number of COVID-19 cases averted owing to reduced risk in vaccinated individuals

Age group (years)	Vaccine dose[a]	Averted cases (95% confidence interval)	Relative change (%)[b]
0–9	Primary series	603 (602–604)	-0.3
	Booster	-	-
10–19	Primary series	65,755 (65,296–66,307)	-31.0
	Booster	2502 (2480–2532)	-1.7
20–29	Primary series	61,872 (60 935–62,910)	-22.0
	Booster	16,909 (16 737–17,063)	-7.1
30–39	Primary series	86,181 (84,743–87,503)	-29.7
	Booster	25,734 (25,382–26,015)	-11.2
40–49	Primary series	45,851 (44,425–47,165)	-19.6
	Booster	23,027 (22,605–23,441)	-10.9
50–59	Primary series	82,251 (80,529–83,825)	-43.4
	Booster	30,268 (29,656–30,858)	-22.0
60–69	Primary series	30,667 (29,400–31,917)	-38.6
	Booster	14,240 (13,786–14,759)	-22.6
70–79	Primary series	22,417 (21,182–23,432)	-40.8
	Booster	11,800 (11,169–12,389)	-26.6
≥80	Primary series	82,424 (79,777–85,023)	-72.5
	Booster	37,101 (35,649–38,780)	-54.3

[a] Primary series represents the vaccination program for the first and second dose, and booster represents the vaccination program for the third dose

[b] Relative change represents a comparison between the calculated counterfactual number and the observed confirmed cases

The transmission model allowed us to calculate the number of SARS-CoV-2 infections in the scenario in which the vaccination program had not taken place. Table 2 shows the age-dependent number of infections prevented by vaccination; these values represent the total impact of vaccination caused by direct and indirect effects. People aged 40–49 years had the highest number of infections averted, estimated at 1,509,663 (95% CI: 1,496,479–1,524,246) people owing to the primary series vaccination and 1,584,700 (95% CI: 1,567,932–1,601,394) people owing to the booster program. The lowest numbers of infections averted were estimated as 500,105 (95% CI: 494,024–506,749) and 471,383 (95% CI: 464,211–478,384) among those aged 70–79 years owing to the primary series plus booster program and ≥80 years owing to the booster program, respectively. However, the most notable relative change due to the total effect was also seen in people aged ≥70 years, with a relative reduction of approximately 80%. The youngest age group, 0–9 years, was again the least likely to benefit directly and indirectly from the vaccination program, yet a relative reduction of approximately 50% was achieved owing to the combined effect of the primary series and booster program.

The population-level impact by vaccine dose is illustrated in Fig. 2. The total impact was estimated at approximately 8.5–9.0 million infections averted by the

Table 2 Total number of averted SARS-CoV-2 infections attributable to a vaccination program by age group

Age group (years)	Vaccine dose[a]	Averted cases (95% confidence interval)	Relative change (%)[b]
0–9	Primary series and booster	1,375,249 (1,369,273–1,381,905)	-46.6
	Booster	1,425,061 (1,418,927–1,431,610)	-48.4
10–19	Primary series and booster	1,324,726 (1,317,489–1,331,570)	-55.8
	Booster	1,268,196 (1,261,495–1,274,982)	-53.8
20–29	Primary series and booster	2,264,996 (2,250,867–2,280,054)	-61.2
	Booster	2,411,696 (2,398,716–2,424,445)	-63.5
30–39	Primary series and booster	2,267,999 (2,254,956–2,283,361)	-64.0
	Booster	2,392,823 (2,378,472–2,407,955)	-65.9
40–49	Primary series and booster	2,265,627 (2,252,443–2,280,210)	-66.6
	Booster	2,340,664 (2,323,896–2,357,358)	-67.7
50–59	Primary series and booster	1,530,498 (1,518,872–1,544,057)	-71.9
	Booster	1,649,600 (1,634,595–1,664,511)	-73.9
60–69	Primary series and booster	842,916 (835,277–850,903)	-76.8
	Booster	894,544 (883,907–904,551)	-78.1
70–79	Primary series and booster	630,597 (624,516–637,241)	-79.3
	Booster	634,301 (626,165–642,737)	-79.4
≥80	Primary series and booster	636,801 (631,247–642,524)	-80.3
	Booster	596,883 (589,711–603,884)	-79.0

[a] Primary series and booster represents the combined vaccination programs for the first, second, and third doses, and booster represents the vaccination program for the third dos

[b] Relative change represents a comparison between the estimated counterfactual number of infections and the observed number of infections, considering a reporting coverage of 0.25

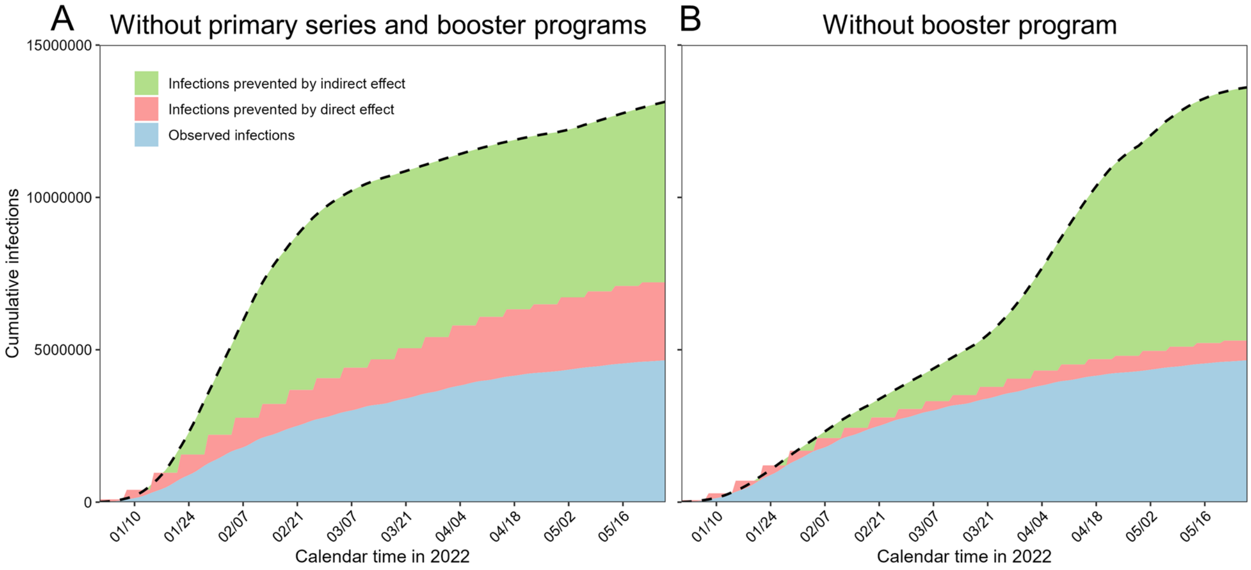

Fig. 2 Cumulative number of averted SARS-CoV-2 infections owing to vaccination. The cumulative number of SARS-CoV-2-infected individuals in Tokyo from January 1 to May 27, 2022 in the counterfactual scenario in which (**A**) the primary series and booster programs had not taken place and (**B**) the booster program had not taken place, stratified by type of protection. The blue area represents empirically observed data (confirmed cases divided by an ascertainment bias factor of 25%), the pink area represents infections averted owing to a direct effect, and the green area represents infections averted owing to an indirect effect. The indirect effect was calculated as the gap between the total and direct effects. Dashed lines indicate the cumulative number of infections in the counterfactual scenario with no vaccination program

end of May 2022. The direct effects differed between the programs; 2.6 million infections were prevented by the primary series plus booster program, and 0.6 million infections were prevented by the booster program alone. The indirect impact was obtained by subtracting the direct effect from the total effect, and the proportion of infections indirectly prevented was estimated to be a 70% and 93% total risk reduction owing to the primary series plus booster program and the booster program alone, respectively.

Finally, we explored three possible scenarios of booster dose vaccination by varying the recipients and their coverage (Table 3 and Fig. 3). The details of these counterfactual scenarios are provided in the Additional file. If the booster vaccination coverage was equivalent to that of the fourth dose, we would have experienced a larger epidemic in Tokyo in April and May 2022, reaching a total of 7,084,822 (95% CI: 7,026,286–7,141,322) infections (about half of Tokyo residents). However, if the booster vaccination coverage reached that of the primary series, the number of infections could have been limited to 3,760,075 (95% CI: 3,709,102–3,808,214), a 19% relative reduction compared with the observed number of infections. Moreover, a 10% increase in vaccination coverage among those aged 10–49 years would have reduced the number of infections by 7% by the end of May 2022.

Table 3 Cumulative number of SARS-CoV-2 infections in the counterfactual booster scenario

Age group (years)	Booster immunization coverage[a]	Averted cases (95% confidence interval)	Relative change (%)[b]
0–9	Equiv. to 2nd dose	617,501 (610,330–624,323)	-16.0
	Equiv. to 4th dose	983,421 (976,418–990,687)	33.8
	Elevated coverage	690,576 (684,180–696,569)	-6.0
10–19	Equiv. to 2nd dose	477,638 (471,417–483,874)	-18.4
	Equiv. to 4th dose	800,801 (793,776–807,502)	36.8
	Elevated coverage	540,508 (534,463–545,744)	-7.7
20–29	Equiv. to 2nd dose	684,634 (674,962–693,891)	-22.2
	Equiv. to 4th dose	1,344,003 (1,331,788–1,355,746)	52.8
	Elevated coverage	799,613 (791,240–806,938)	-9.1
30–39	Equiv. to 2nd dose	636,277 (627,136–644,993)	-22.1
	Equiv. to 4th dose	1,305,604 (1,293,596–1,317,961)	59.9
	Elevated coverage	747,156 (739,796–754,618)	-8.5
40–49	Equiv. to 2nd dose	608,320 (599,168–616,867)	-19.5
	Equiv. to 4th dose	1,182,119 (1,171,865–1,192,611)	56.4
	Elevated coverage	699,952 (691,723–707,332)	-7.4
50–59	Equiv. to 2nd dose	351,601 (345,798–3,56,991)	-18.3
	Equiv. to 4th dose	714,765 (708,054–721,741)	66.1
	Elevated coverage	412,497 (407,216–417,354)	-4.1
60–69	Equiv. to 2nd dose	164,808 (161,818–167,873)	-15.9
	Equiv. to 4th dose	340,978 (337,381–344,436)	74.0
	Elevated coverage	190,917 (188,132–193,644)	-2.6
70–79	Equiv. to 2nd dose	111,101 (108,918–113,236)	-14.9
	Equiv. to 4th dose	196,119 (194,075–198,270)	50.3
	Elevated coverage	127,683 (125,583–129,707)	-2.2
≥80	Equiv. to 2nd dose	108,193 (106,109–110,355)	-13.8
	Equiv. to 4th dose	217,011 (214,658–219,338)	72.9
	Elevated coverage	125,068 (123,036–127,109)	-0.3

[a] Equiv. to 2nd dose: in the counterfactual booster program scenario, the vaccination coverage was equivalent to that of the second dose; Equiv. to 4th dose: in the counterfactual booster program scenario, the vaccination coverage was equivalent to that of the fourth dose; Elevated coverage: vaccination coverage among people aged 10–49 years was assumed to be 10% higher than the observed coverage

[b] Relative change represents a comparison between the estimated counterfactual number of infections and the observed number of infections, considering a reporting coverage of 0.25

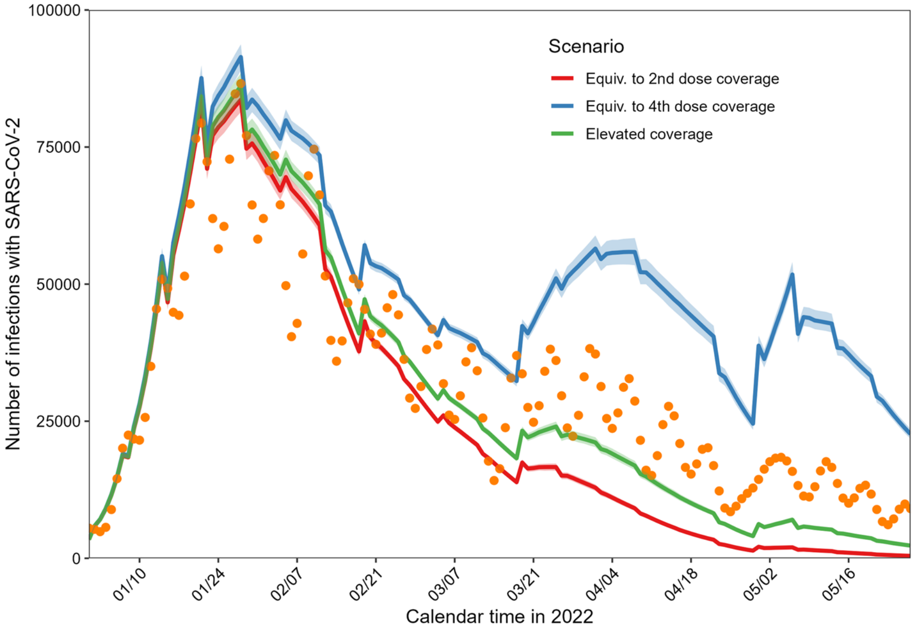

Fig. 3 Population-level impact in counterfactual scenarios of booster vaccination. The daily incidence of SARS-CoV-2 infections is shown by counterfactual scenario of booster vaccination in Tokyo. The orange dots represent the empirically observed data (confirmed cases divided by an ascertainment bias factor of 25%). Three scenarios were explored: (i) the vaccination coverage on the last day of the study period (May 27, 2022) was equivalent to that of the primary series (Equiv. to 2nd dose coverage), (ii) the vaccination coverage was equivalent to that of the second booster (i.e., the 4th dose), which was administered later in 2022 (Equiv. to 4th dose coverage), and (iii) the vaccination coverage among people aged 10–49 years was 10% greater than that of the observed third dose (Elevated coverage). Further details can be found in the Additional file

Discussion

The primary series and booster dose directly contributed to the prevention of 478,000 (95% CI: 467–489) and 162,000 (95% CI: 157–166) COVID-19 cases, representing 29% and 12% relative reductions, respectively, from January to May 2022 in Tokyo. The study period corresponded to the sixth COVID-19 wave in Japan during which the Omicron subvariants BA.1 and BA.2 were predominant. In combination, the primary series plus booster program contributed to directly and indirectly averting 8.5 million (95% CI: 8.4–8.6) SARS-CoV-2 infections. If the booster vaccination coverage had been similar to that of the second dose, or if the coverage among people aged 10–49 years had been 10% greater, the number of infections could have been additionally reduced by 19% and 7%, respectively.

We demonstrated that the population impact of vaccination was substantial in Tokyo even during the epidemics caused by Omicron subvariants BA.1 and BA.2. Overall, the indirect impact accounted for 70% of the total effect (Table S2). The booster dose alone had a smaller direct population impact than the primary series; the booster dose averted 646,000 infections, while the primary series averted 2.6 million infections. From the beginning of the Omicron variant epidemic, vaccine-induced immunity elicited by ancestral virus-based mRNA vaccines was known to have been weaker than that against earlier variants, including Delta. Nevertheless, the vaccination coverage in Japan was high, at greater than 95% for the primary series among older people. The population-level impact was also high even during the Omicron epidemic in 2022, protecting 54% of the population over 60 years of age in Tokyo from infection. Although the sixth wave from January to May 2022 was the largest in Japan by the end of the study period, we found that the population benefited from both direct and, more importantly, indirect protection. Although the Omicron variant was challenging to control, vaccination was a critical public health tool for mitigating COVID-19 [3, 11].

The population-level impact of vaccination was estimated to be greater during the period when the Delta variant predominated, with an estimated 84% relative case reduction in Israel [10], compared with that during the period when Omicron predominated, with an estimated 65% relative case reduction identified in the present study. This difference in impact can be explained by the reduced contribution of the indirect impact rather than the direct impact, because the period of Delta predominance was accompanied by more stringent suppression strategies to control viral transmission and greater vaccine effectiveness compared with the Omicron period

[18, 26]. However, the direct impact of the primary series program was still substantial more than a year later, and the booster program elicited additional population impact. This is good news for all populations, especially for those who were previously reluctant to be vaccinated. One of the advantages of studies using mathematical models is that the parameters can be changed, and hypothetical scenarios can be examined [4, 10, 27–29]. As we have shown, a higher vaccination coverage in the population leads to a greater indirect impact at the population level, even in the presence of antigenically distinct evolution, such as the emergence of the Omicron variant, emphasizing that mass vaccination can elicit herd immunity effect even though it may only be temporary.

Our estimates were derived from the sixth COVID-19 wave, which was dominated by Omicron subvariants BA.1 and BA.2; this epidemic was the last wave in Japan in which public health and social measure (PHSM) restrictions were in place. These measures shortened the opening hours of bars and restaurants and aimed to reduce contact in high-risk settings. These measures were in effect in Tokyo from January 21 to March 21, 2022. If the epidemic size had been greater in the absence of PHSMs, the total effect of vaccination would have been even larger. That is, the observed number of cases was affected by the interventions, and in the absence of the PHSMs, the population-level impact would have been larger than estimated.

In the present study, the population impact of vaccination was assessed as the number of averted COVID-19 cases or infections. The analysis could not be extended to include severe cases and deaths because the vaccination history of this population was not thoroughly recorded in any monitoring system in Japan. Considering that vaccination efficiently prevents severe complications in Omicron-infected individuals [3, 18, 30], it would be important to systematically link individual vaccination histories to surveillance or medical record datasets so that an explicit evaluation can be made.

There are several technical limitations to this study. First, estimating the exact number of infections was challenging because symptoms are lessened by vaccine-induced and naturally acquired immunity. The Ministry of Health, Labour, and Welfare conducted seroepidemiological surveys in a serial cross-sectional manner using blood donor data, but the surveys were not conducted regularly throughout the pandemic [31]. We used a reporting coverage of 0.25 as a reference to infer the number of infections during the analysis period in Tokyo [21], and additional sensitivity analyses were performed (see Additional file) with reference to Zhang & Nishiura [32]. Second, we focused on Tokyo because this population had robust data availability, but geographic heterogeneity in the population impact was not assessed. In prefectures with fewer transmissions, a smaller indirect impact might have been observed.

Following our study, additional sublineages (e.g., BA.4, BA.5, BF.7, BQ.1, and XBB) have emerged and have gradually replaced BA.1 and BA.2 partly because of their increased transmissibility, but more importantly because of their immune escape mechanisms. Age-dependent heterogeneity in the immune response has also become recognized, and different sequences of immunization (e.g., primary series vaccination followed by natural infection) have been shown to complicate our understanding of protection at the individual level. However, despite this complexity, the direct and indirect impacts of vaccination can be computed as long as the corresponding vaccination history data are available.

Conclusions

The primary series and booster vaccination programs prevented many SARS-CoV-2 transmission and contributed to a 65% reduction in infections during the epidemic wave dominated by Omicron BA.1 and BA.2 in Tokyo. Measuring the impact of COVID-19 vaccination can provide valuable information to guide public health policy and improve our understanding of population-level protection. It is critical to achieve high vaccination coverage to benefit from its valuable direct and indirect effects.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-023-08748-1.

Additional file 1: Supplementary Methods.Figure S1. Vaccine efficacy profile. **Figure S2.** Immune fraction owing to each vaccination program. **Figure S3.** Cumulative number of averted COVID-19 cases owing to the direct effect of the vaccination program. **Figure S4.** Total number of averted COVID-19 cases. **Figure S5.** Proportion of confirmed cases with unknown vaccination history. **Figure S6.** Flowchart of extracting COVID-19 cases for the analysis. **Figure S7.** Prediction accuracy of the deterministic approach to impute missing values for vaccination history. **Figure S8.** Cumulative number of prevented COVID-19 cases based on the deterministic approach. **Figure S9.** Total number of prevented COVID-19 cases based on the deterministic approach. **Figure S10.** Next-generation matrix. **Figure S11.** Cumulative number of SARS-CoV-2 infections: a sensitivity analysis to breakthrough infections.**Figure S12.** Weekly parameter by age group. **Figure S13.** Comparison between observed and predicted SARS-CoV-2 infections by age group. **Figure S14.** Comparison of the total number of observed and predicted SARS-CoV-2 infections assuming a reporting coverage is 0.25. **Figure S15.** Cumulative number of SARS-CoV-2 infections by reporting coverage. **Figure S16.** Comparison between observed and predicted vaccination coverage of the booster program by age group. **Figure S17.** Counterfactual scenarios of the booster vaccination coverage by age group. **Table S1.** Cumulative number of SARS-CoV-2 infections in the absence of vaccination by reporting coverage. **Table S2.** Comparison of population impact of vaccination at the end of the study period (May 27, 2022).

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Authors' contributions
All authors participated in the study design. T.K. analyzed the data, and H.N. evaluated the validity of the analysis. T.K. drafted the manuscript, including the figures and tables. H.N. edited earlier versions of the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials
The data analyzed in this study were publicly available and retrieved from the Tokyo Metropolitan Government, and temporal data of confirmed cases and vaccination coverage not stratified by age group are available at https://stopcovid19.metro.tokyo.lg.jp/.

Declarations

Ethics approval and consent to participate
This study was conducted adhering to the principles of the Declaration of Helsinki, and the research was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (approval number R2673).

Consent for publication
Not applicable

Competing interests
The authors declare no competing interests.

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