Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines

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I, Takeshi Arashiro, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

SARS-CoV-2 transmission and disease with varying severity occur through a complex interplay of public health and social measures (non-pharmaceutical interventions), behavior, social background, past infection, and vaccination. The emergence of new variants and the potential waning of vaccine-induced immunity further complicated the situation. Teasing apart and analyzing the association between these factors was vital for informing policies and risk communication. This PhD aimed to (1) elucidate social and behavioral risk factors associated with SARS-CoV-2 infection and (2) evaluate COVID-19 vaccine effectiveness (VE) for both symptomatic infection and severe disease in Japan and the Philippines.

These were mainly done by setting up and conducting multi-center case-control studies in healthcare facilities in both countries. Multiple socio-behavioral factors were associated with SARS-CoV-2 infection, including social gatherings and school/work, many of which were in line with the policy/risk communication implemented. Some of these factors, together with anxiety, were monitored over time, together with the number of reported cases in Japan. A triangulation approach using community controls (in addition to test-positive and test-negative individuals) with an online survey to assess the behavioral risk factors was explored and showed the potential usefulness of using such control groups. The prospective approach enabled exploration of the influence of preventive measures such as mask-wearing and high-risk behaviors on estimates of COVID-19 VE against symptomatic infection. This was an important consideration for COVID-19, where differential exposures may exist between vaccinated and unvaccinated individuals due to, for example, vaccine passports. In Japan, COVID-19 VE against symptomatic infection was continuously monitored through the Alpha-dominant period, Delta-dominant period, Omicron-dominant period (including BA.1/BA.2 and BA.5 to differentiate immune escape and waning immunity), and also for Omicron-containing bivalent vaccines. Also, the association between SARS-CoV-2 infection and influenza vaccination status was assessed as a negative control exposure (during the period with extremely low influenza activity) with no association found. In the Philippines, ethics and alignment with internal stakeholders proved challenging and the study was initiated after the first Omicron peak. Biases due to complex immune histories made it challenging to assess VE against symptomatic infection, but the results did suggest a possible moderate effect of boosters. Further, in Japan, online survey data on the general population was utilized to identify socio-behavioral factors associated with the lack of intention to receive COVID-19 vaccines and to inform vaccination policy further.

Next, emerging evidence suggested that VE wanes against mild symptomatic infection and is also less effective in the setting of Omicron. This resulted in the target product profile shifting to severe disease with an increasing need to evaluate VE against severe disease. Therefore, VE against severe COVID-19 was also evaluated in hospitals that admit severe COVID-19 cases in each country. In doing so, data on various severity levels (hospitalization, oxygen use, invasive mechanical ventilation use, and death) and on whether oxygen use was due to COVID-19 or other diseases among those who

tested positive for SARS-CoV-2 were collected. This was because incidental infection found during hospital admission screening was an issue in using a database to conduct VE studies due to lower VE against infection than against severe diseases with past studies showing a wide range of VE estimates against hospitalization. VE of 2 doses of COVID-19 was high in the pre-Omicron period and moderate to high against Omicron for multiple severe outcomes in both countries. Among categories with sufficient sample sizes, there was a consistent trend towards higher VE for more severe and specific outcomes. These results demonstrate the usefulness of severe and specific outcomes to accurately measure VE, as recommended in World Health Organization (WHO) guidance in the setting of intense transmission as seen during Omicron. Additionally, in collaboration with the WHO Western Pacific Regional Office, a practical protocol to implement COVID-19 VE studies was also developed for use in other countries.

Finally, to inform future health emergencies, epidemics, and potential pandemics, the challenges and lessons learned from setting up and executing operational research to evaluate public health interventions, including non-pharmaceutical interventions and vaccines, were summarized.

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Table of Abbreviations/Glossary

AZD1222	COVID-19 vaccine developed by AstraZeneca/Oxford University
BNT162b2	COVID-19 vaccine developed by Pfizer/BioNTech
CoronaVac	COVID-19 vaccine developed by SinoVac
COVID-19	Coronavirus disease 2019
HICs	High-income countries
LMICs	Low- and middle-income countries
LSHTM	London School of Hygiene and Tropical Medicine
MHLW	Ministry of Health, Labour and Welfare, Japan
mRNA-1273	COVID-19 vaccine developed by Moderna/NIAID
NIID	National Institute of Infectious Diseases, Japan
NU	Nagasaki University, Japan
PCR	Polymerase chain reaction
PGH	Philippine General Hospital, the Philippines
RCT	Randomized controlled trial
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SLH	San Lazaro Hospital, the Philippines
VE	Vaccine effectiveness
WHO	World Health Organization
WPRO	WHO Western Pacific Regional Office

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally [1]. SARS-CoV-2 transmission occurs through a complex interplay of public health and social measures (non-pharmaceutical interventions), high-risk behaviors, social background, past infection, and vaccination. The emergence of new variants and the potential waning of vaccine-induced immunity further complicated the situation. Teasing apart and analyzing the association between these factors was vital for informing policies and risk communication. This PhD aims to (1) elucidate social and behavioral risk factors associated with SARS-CoV-2 infection and (2) evaluate COVID-19 vaccine effectiveness (VE) in Japan and the Philippines.

Literature Review

Note related to evolving situations regarding COVID-19 during PhD period

The number of papers published on COVID-19 exponentially grew during the three years of my PhD (2021-2024), and there were many evolving contexts. In this chapter, I focus mainly on the representative, most relevant/important, and overarching reviews and references. Also, many studies cited were from the first few years (2020-2021) of the pandemic and the first year of my PhD, when an extensive literature search was done to identify gaps in knowledge to initiate the PhD projects. The ones that are more relevant in or specific to each chapter are included in the reference list of each paper rather than this chapter.

Coronavirus disease (COVID-19): clinical features

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally [1-2]. In most individuals, SARS-CoV-2 infection results in mild respiratory disease (common cold or influenza-like symptoms), especially in healthy young individuals [3-5]. However, in a small but meaningful proportion of individuals, conditions deteriorate and cause respiratory failure with oxygen use, mechanical ventilation, and/or death. Such exacerbation happens more frequently among older adults and individuals with certain underlying conditions [6-8]. Complications such as cardiovascular conditions such as ischemic heart disease can also occur [9]. Even among those who recover only from mild illness, a condition called long-COVID can happen, where malaise and other chronic symptoms for several months to years [10-11]. Prior to the PhD program, the PhD candidate took care of and published case reports of both mild infection and severe disease resulting in death very early in the phase of the pandemic (early 2020), which is considered the first English case reports from Japan and one of the earliest reports from outside of China [3,11].

Coronavirus disease (COVID-19): transmission

The transmission is considered to occur “through the air” [12]. However, COVID-19 may have specific characteristics where transmission occurs efficiently, including aerosol transmission, especially in poorly ventilated and/or crowded indoor settings [13-16]. Direct contact and fomite transmission is also considered to be possible, although the risk is generally considered to be low [12,17-18]. The incubation period is a few days to up to two weeks for pre-Omicron SARS-CoV-2 [19-20]. For the Omicron variant, the incubation period is thought to be shorter [19-20]. The

infectious period is thought to be up to 10 days for mild infection based on viral isolation data of respiratory samples [21-22].

Behavioral and socioeconomic factors associated with SARS-CoV-2 infection

In Japan, since early in the course of the epidemic, the government has been promoting avoidance of the "three Cs," which represent (1) closed spaces, (2) crowded places, and (3) close-contact settings that are considered to be high-risk [23-24]. These "three Cs" were easy for the public to remember, and with relatively successful control of the epidemic in Japan, the World Health Organization (WHO) also started to promote this message [25-26]. However, these were based on limited anecdotal and circumstantial information from cluster investigations without control or comparison groups [27-28]. Also, at the beginning of the pandemic, contact tracing was done to identify close contacts, but containment through cluster investigation became increasingly challenging with an increase in the number and proportion of cases with no history of close contact [29]. Other countries, including the Philippines, have also been seeing a similar surge in cases with no history of close contact [30-31]. These circumstances led to the need to understand behavioral and social factors associated with SARS-CoV-2 infection to inform public health policy and to provide evidence-based risk communication. Many studies have investigated risk factors associated with SARS-CoV-2 infection [32-42]. The majority of these studies assessed risks among healthcare workers or close contacts, probably due to ease of follow-up and higher positivity [32-33]. There have only been a handful of studies in the United States and Europe to identify potential factors that are causally associated with an increased risk of infection among the general public. These studies identified risks such as dining at restaurants, not teleworking, and not wearing a face covering in enclosed spaces [34-42]. Since some risk factors are universal while others may be context/setting-specific, conducting such studies in each country would be important.

COVID-19 vaccine effectiveness against symptomatic infection

Interim results from RCTs demonstrated around 95% efficacy for two mRNA vaccines produced by BioNTech/Pfizer and Moderna/NIAID and 70.4% efficacy for a viral vector vaccine produced by Oxford/AstraZeneca [43-48]. Furthermore, several real-world VE studies have evaluated different types of vaccines at the initial roll-out, including CoronaVac (Sinovac), with numerous studies following during the PhD period (2021-2024) [49-57]. Although these VE studies initially demonstrated moderate to high VE similar to the efficacy shown in RCTs, further analyses after half a year showed conflicting results, with some studies showing varying degrees of waning [58-63]. There

was also concern regarding the emergence of SARS-CoV-2 variants that can escape immunity [64-71]. Furthermore, there has been scarce evidence of VE in the context of changes in social and public health measures/policies. Since many factors can affect VE estimates, such as the emergence of SARS-CoV-2 variants, waning immunity, and social and public health measures, VE studies are prone to various biases inherent to observational studies; it is important to collect data prospectively, including factors that influence VE measures. There were also very few epidemiological studies evaluating the effectiveness of COVID-19 vaccines in Asia and low- and middle-income countries (LMICs) generally. This was also the case when literature screening was done at the time of thesis writing (February 2024), where only reports published in peer-reviewed journals from LMICs in Asia were four reports from Malaysia (which is an upper-middle income country) [72-75].

It is not necessary or recommended for all countries introducing COVID-19 vaccines to conduct VE evaluation studies, as they require extensive resources and technical expertise and would need to be balanced with other response activities. However, it would be valuable for more LMICs to conduct VE studies for several reasons, including (1) evaluation of vaccines that are mainly distributed in these countries, such as CoronaVac, (2) confirmation that vaccine distribution networks in these countries ensure that the vaccines remain active (with, for example, no cold chain breach), (3) considerably different cumulative infection burdens among countries (e.g., individuals with prior infection are protected against subsequent infection/disease), (4) substantial variation in public health and social measures and policies/risk communication activities among countries, (5) vaccine confidence within and among surrounding countries, and (6) capacity building to conduct operational research to inform public health response in LMICs for COVID-19 pandemics and for future epidemics and pandemics.

COVID-19 vaccine effectiveness against severe disease

As RCTs generally enroll younger and healthy individuals who are less likely to develop severe COVID-19, it is important but challenging to measure VE against COVID-19 requiring severe disease such as hospitalization. This question can only be answered in observational studies. Indeed, several studies have been done in several countries with similar or higher VE (over 90%) compared to VE against any infection or symptomatic (mild) infection before the emergence of the Omicron variant with high immune escape capacity [49-50, 54-57, 76-80]. Even though VE against COVID-19 hospitalization is more durable than VE against mild infection, there is some evidence of waning [58-71]. Furthermore, VE against COVID-19 hospitalization is reported to be slightly lower against the

Omicron variant (approximately 85%) compared to the non-variant, Alpha variant, and Delta variant, with a booster dose resulting in recovering high VE (>90%) [68-71, 77-80]. Data on VE against hospitalization for CoronaVac (Sinovac), especially during the Omicron era, is very limited. Also, studies evaluating COVID-19 VE in Asia and LMICs are very limited, especially for VE against hospitalization. With the emergence of the Omicron variant, there was emerging evidence suggesting that VE was also less effective against Omicron. Also, there was another set of emerging evidence that VE wanes against mild symptomatic infection. This resulted in the target product profile shifting to severe disease with an increasing need to evaluate VE against severe disease [81-82].

Gaps in Knowledge and Research Questions

Similar to the Literature Review, the number of papers published on COVID-19 grew exponentially during the three years of my PhD (2021-2024), and there were evolving contexts in many aspects. Therefore, the PhD work attempted to not only focus on novelty (which quickly became non-novel with multiple reports or outdated in terms of data to directly inform policy [e.g., waning VE and VE against variants]) but also to aim for overall scientific contributions to inform the COVID-19 pandemic/epidemic response as well as future epidemics and pandemics of emerging and re-emerging diseases.

Numerous publications report COVID-19 VE estimates using existing surveillance and clinical databases. However, scarce reports consider behavioral factors that may bias VE estimates since data on behaviors and infection prevention measures are not available in existing data sources. It is infrequently reported for individuals to alter their behavior based on vaccination status for other diseases. This was a unique but important consideration for COVID-19, where differential exposures may exist between vaccinated and unvaccinated individuals due to vaccine passports and perceptions of protection. Through a prospective approach, I first aimed to elucidate factors associated with SARS-CoV-2 infections in Japan and the Philippines. Second, I included some of these identified risk factors in the analysis to aim for more accurate VE estimates and to assess the influence of behavior on VE estimates. I next aimed to utilize online survey data to examine how vaccinees and non-vaccinees differ regarding sociodemographic and behavioral factors to inform VE estimates further. Furthermore, the multi-country approach allowed for exploring cultural differences in risk factors and evaluating multiple vaccine types.

As the pandemic progressed, there was emerging evidence suggesting that VE wanes against mild symptomatic infection and is also less effective in the setting of Omicron. This resulted in the target product profile shifting to severe disease with an increasing need to evaluate VE against severe disease. Therefore, VE against severe COVID-19 was aimed at being evaluated in hospitals that admit severe COVID-19 cases in each country. In doing so, I planned to collect data on whether medical interventions, such as oxygen use, were due to COVID-19 or other diseases among those who tested positive for SARS-CoV-2 since incidental infection found at the time of hospital admission with unrelated conditions was an issue in using a database to conduct VE studies as such analyses had not been done globally.

Additionally, in collaboration with the World Health Organization Western Pacific Regional Office and through a WHO consultancy, the studies' findings were to be disseminated internally, and a practical protocol to implement COVID-19 VE studies was planned to be developed for use in other countries.

Finally, in order to inform future health emergencies, epidemics, and potential pandemics, challenges and lessons learned were aimed to be summarized through the experience of setting up and executing operational research to evaluate public health interventions, including non-pharmaceutical

interventions and vaccines, as well as dissemination of results to rapidly inform policies and risk communication during the COVID-19 pandemic.

The current project ultimately aimed to inform how we may be better prepared to rapidly set up operational research to inform policies and risk communication in future epidemics and pandemics of emerging and re-emerging diseases.

Specific Objectives

Objective 1	
Objective 1A	To elucidate behavioral and demographic risk factors associated with SARS-CoV-2 infection in Japan
Objective 1B	To elucidate behavioral and demographic risk factors associated with SARS-CoV-2 infection in the Philippines
Objective 2	
To understand temporal changes in anxiety and high-risk behaviors during the COVID-19 pandemic and to identify social and behavioral factors associated with no intention to receive COVID-19 vaccines among the general public in Japan	
Objective 3	
Objective 3A	To estimate the real-world effectiveness of COVID-19 vaccines against symptomatic infection in Japan
Objective 3B	To estimate the real-world effectiveness of COVID-19 vaccines against symptomatic infection in the Philippines
Objective 3C	To develop a practical protocol to implement COVID-19 VE studies in collaboration with the WHO Western Pacific Regional Office and share research output to inform policies/risk communication strategies and experience for potential expansion of VE studies within the Western Pacific Region and beyond
Objective 3D	To estimate the real-world effectiveness of COVID-19 vaccines against severe disease in Japan
Objective 3E	To estimate the real-world effectiveness of COVID-19 vaccines against severe disease in the Philippines
Objective 4	
To examine the influence of high-risk behaviors on estimates of COVID-19 VE	

Methods

Objective 1

Objective 1A: To elucidate behavioral and demographic risk factors associated with SARS-CoV-2 infection in Japan

Objective 1B: To elucidate behavioral and demographic risk factors associated with SARS-CoV-2 infection in the Philippines

Methods

Design

The study was a multi-center/multi-country case-control study conducted in Japan and the Philippines. Participants were recruited in healthcare facilities (primary care clinics and fever clinics (clinics specifically set up for COVID-19 testing)) in Japan and triage swabbing sites in the Philippines. SARS-CoV-2 testing was done routinely in these sites. Individuals who were tested were recruited in order of presentation and included upon agreement to participate. There was an additional exploratory control set up in Japan from the general population using a pool of online survey panel members from a list owned by a marketing research company.

Enrollment criteria

For those who were enrolled at healthcare facilities, the inclusion criterion was symptomatic individuals tested for SARS-CoV-2 for diagnostic purposes. Individuals were considered as symptomatic if they had any of the following: fever above 37.5°C, malaise, chills, joint pain, headache, runny nose, cough, sore throat, shortness of breath, gastrointestinal symptoms (vomiting, diarrhea, stomach ache), and loss of taste/smell. Exclusion criteria included individuals younger than the age of 18 in the Philippines and 20 in Japan (drinking age in respective countries, as there are questions regarding alcohol consumption in the questionnaire); individuals who did or could not consent to participate in the study; and individuals who could not complete the questionnaire by themselves; individuals who had already participated in this study; or individuals who required immediate treatment.

For those enrolled as exploratory control, the inclusion criterion was individuals residing in the Kanto Region (since healthcare facilities that participated were all located in the Kanto Region) who agreed to participate in the study among those who voluntarily registered to be panel members of a marketing research company. Exclusion criteria included the same exclusion criteria were applied other than the last criterion and individuals who had symptoms or who tested positive for SARS-CoV-2 within 14 days were excluded (as they should not be considered “controls”).

Sampling method

All individuals tested for SARS-CoV-2 were requested to complete the questionnaire administered via paper-based questionnaire (Japan) or by a research nurse (Philippines).
The following information below was collected for analysis: general information (including sociodemographic factors); symptoms in the past two weeks; preventive measures such as mask-wearing in the past two weeks; history of close contact in the past two weeks; history of work/school/travel in the past two weeks; behaviors such as social gatherings in the past two weeks; and COVID-19 vaccination status.
The Japanese questionnaire was mainly the same as the one used in the Philippines, with the addition of questions/multiple choice answers to fit the local context; these include monthly household income, monthly expenditures, vaccine types (that are only rolled out in the Philippines), going to church.
As for the exploratory control in Japan, the ones who agreed to participate in the online survey were among those who voluntarily registered to be panel members of a marketing research company (anyone can register). As of January 2022, the company had approximately 5.41 million active panel members who had responded to at least one questionnaire in the past year (4.3% of the 126.15 million population in Japan). In exchange for responding to questionnaires, panel members receive points that can be exchanged for products and services from partner companies. The marketing research company disseminated the questionnaire from February 12, 2022, until a predefined sample size of 300 individuals answered the questionnaire (see sample size calculation below).

Ascertainment of cases and controls (except for the exploratory control)
To classify patients as SARS-CoV-2 positive or negative, we used testing for diagnosis purposes among symptomatic individuals.

Sample size calculation
Exposure probabilities would vary depending on factors and contexts, but as an example, dining at a restaurant was 28%, and teleworking was 53% among the control group in a prior U.S. study [1]. With 30-50% of controls having the exposures of interest, a 10% positivity rate for SARS-CoV-2 among those who are tested, a two-tailed significance level of 5%, and 80% power, enrollment of 135-145 cases and 1400-1500 controls are needed to detect a minimal OR of 2. Considering potential missing data, differences in exposure probabilities, multivariable analyses/sub-analyses, and evaluation of VE, we continued enrollment for the duration of the study period even after reaching this initial target.
As for the exploratory control, with 30-50% of controls having the exposures of interest, a two-tailed significance level of 5%, and 80% power, enrollment of 207-210 controls (assuming a 2:1 ratio for cases:controls) was needed to detect a minimal OR of 2. Therefore, we enrolled 300 individuals.

Ethics approval

The study in Japan was approved by the research ethics committee at the National Institute of Infectious Diseases and study sites (hospitals and clinics). Ethics approval was obtained from San Lazaro Hospital and Philippine General Hospital for the study in the Philippines. Ethics approval is also obtained from the ethics committee at the London School of Hygiene and Tropical Medicine.

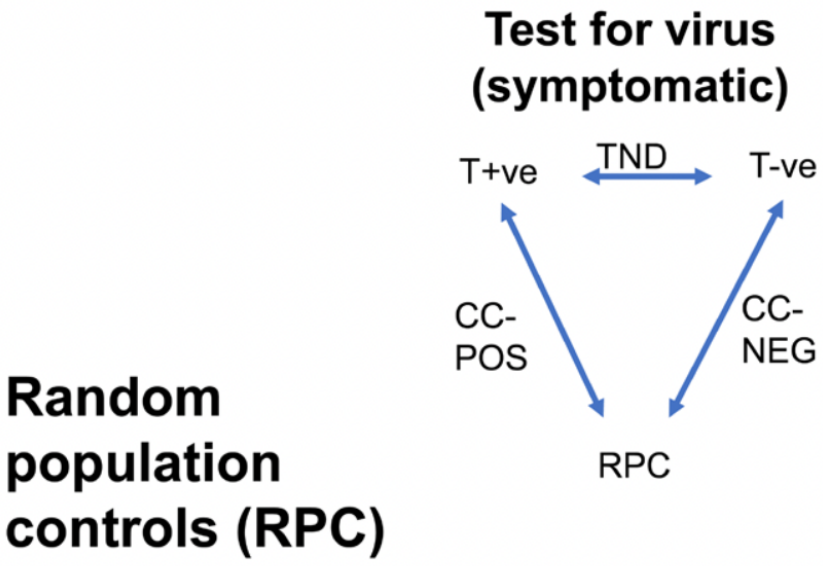
Note on case-control studies with test-negative design

Many objectives, including this one, were fulfilled using test-negative case-control studies. Although there are some important limitations, including selection bias, a test-negative design (in which individuals tested for SARS-CoV-2 with negative results serve as controls) has been utilized extensively for the evaluation of VE for infectious diseases such as influenza and COVID-19, as this design is efficient and can somewhat control for healthcare-seeking behavior [83-85]. Estimating VE using the test-negative design is more straightforward to interpret because of the antigen specificity of the vaccines. However, using a test-negative design to understand disease risk is an emerging concept, necessitating careful interpretation [86]. It is possible that test-negative individuals also share some risk factors with cases, as controls may also be symptomatic [86]. Although ideal controls would be randomly selected individuals who test negative and arise from the same population as the cases, this is not possible for us due to feasibility. We considered utilizing other additional controls while formulating the protocol. One potential method is to have an accompanying person (AP) as a control, but individuals getting tested for SARS-CoV-2 who are not severely ill often go to healthcare facilities alone to keep the AP from becoming a close contact, so it was not feasible in our setting (APs are usually not allowed in the medical facilities for this reason). Another option is individuals who are getting tested with no symptoms and are not a close contact of a case. However, there is the issue of why these individuals are getting tested in the first place. In Japan, people who get tested despite being asymptomatic are usually at high risk of exposure by the nature of their occupation (e.g., healthcare workers and other specific occupations) or behaviors (individuals who engage in high-risk recreational behaviors regularly, individuals who are constantly worried about getting infected [e.g., mysophobia], individuals traveling overseas, etc.). Asymptomatic individuals getting tested for such reasons would not serve as a representative sample of the source population that gave rise to the cases. The final option is to have traditional hospital controls who visit other departments, such as surgery and orthopedics. However, these would not be appropriate since these individuals are older on average and have a very skewed distribution for the factors that we are and are not interested in, including potential confounding factors. Also, there are no such departments in many of our study sites in Japan, as they are small clinics. Often, matching the traits of cases with controls in a case-control study can be very challenging. We concluded that the baseline and demographic traits among cases and controls would be most similar with a test-negative approach, as the two groups would be sourced from those presenting to the same medical facilities for testing (e.g., health-seeking behaviors)—and as long as participants complete the questionnaire before receiving their test results, the influence of social desirability bias should be minimal. Also, if controls were infected with other

viruses due to similar exposures, the odds ratio (OR) for SARS-CoV-2 infection would underestimate the true association. In other words, our design would detect differences in the magnitude of a particular risk factor or risk factors that would be specific to COVID-19. In fact, although many respiratory pathogens (e.g., influenza virus and *Streptococcus pneumoniae*) have been present at extremely low levels during the study period so far, at least partially due to social and public health measures, we have continued to see repeated SARS-CoV-2 epidemics. This suggests that SARS-CoV-2 has unique features that allow it to circulate even under strict public health and social measures. Finally, the threshold for testing was low for SARS-CoV-2 at the time of the study (more so in Japan than in the Philippines) and having any one of the very broad spectrum of COVID-19-like signs/symptoms, not just respiratory symptoms, would trigger testing and hence inclusion in the study. Therefore, we expected to identify at least some risk factors identified in other studies that utilized similar methods to elucidate risk factors. To explore whether this is a valid way to choose controls, we also planned to set up an additional exploratory control in Japan from the general public using a pool of survey panel members from a list owned by a marketing research company.

Analysis plan

Sociodemographic information, past medical history, and exposure status overall and by test status (test-positive or test-negative) were described. To investigate factors associated with SARS-CoV-2 infection, univariate analysis was used to calculate ORs and their 95% confidence intervals (CIs). Multivariable analysis was also done with appropriate *a priori*-determined covariates. Regarding missing data, a complete case analysis was performed initially, but imputation was done as needed. As for the analysis utilizing exploratory controls, the triangulation approach, as described below, was used. Specifically, ORs were calculated for (1) a comparison between test-positive and test-negative who visited healthcare facilities (test-negative design; TND), (2) a comparison between test-positive and participants of online survey (CC-POS), and (3) a comparison between test-negative and participants of online survey (CC-NEG). All statistical analyses were performed using Stata.



Vandenbroucke et al. (2020) Epidemiology (note that the actual participants for the study were not random population control, but rather, participants who agreed to participate in the online survey among those who voluntarily registered to be panel members of a marketing research company)

Objective 2

To understand temporal changes in anxiety and high-risk behaviors during the COVID-19 pandemic and to identify social and behavioral factors associated with no intention to receive COVID-19 vaccines among the general public in Japan

Background on the methods

SARS-CoV-2 transmission and the epidemic magnitude are heavily influenced by the attitude and behavior of each individual within a community. Therefore, in this objective, I describe temporal changes in anxiety and high-risk behaviors to see if they are useful as an early indicator of COVID-19 epidemic trends. After the rollout of the vaccines has stabilized, addressing individuals with the highest risk of developing severe or fatal COVID-19 who do not intend to be vaccinated has become paramount as we transition to the endemic phase. This was especially true in Japan, as most individuals were not protected from natural infection for years after the pandemic started [87-88]. Several studies have addressed reasons behind this hesitancy at the early stage of vaccine rollout [89-92], but evidence on attitudes toward the risk of infection and prevention and risk behaviors is scarce. Furthermore, the importance of booster doses (third or fourth) has been suggested for COVID-19 vaccines due to waning immunity and the emergence of variants. However, some individuals received the primary series but not the booster doses.

Methods

Design

The study was a retrospective analysis of an online serial cross-sectional survey on life during the COVID-19 pandemic conducted monthly by a marketing research company since the beginning of the pandemic. The total number of survey participants was 2,500 (250 participants for each gender and 10-year age group, from 20s through 60s).

Sampling method

The nationwide survey participants were those who voluntarily registered to be panel members of a marketing research company (anyone can register). As of January 2022, the company had approximately 5.41 million active panel members who had responded to at least one questionnaire in the past year (4.3% of the 126.15 million population in Japan). In exchange for responding to questionnaires, panel members receive points that can be exchanged for products and services from partner companies.

Sample size calculation

Since this is a retrospective analysis of a survey conducted by a marketing research company, the company determined the sample size.

Ethics approval

The Institutional Review Board of the National Institute of Infectious Diseases, Japan, reviewed and exempted this study from ethics approval as the raw data were anonymized.

Analysis plan

A descriptive analysis was undertaken to summarize various sociodemographic and behavioral factors as a whole and by vaccination intent. I also used publicly available data on COVID-19 cases in Japan (published by the Ministry of Health, Labour and Welfare) and data on human mobility (purchased from Agoop Corp). To investigate factors associated with COVID-19 vaccination intent, ORs and their 95% CIs were calculated using univariate analysis. Multivariable analysis was also performed with appropriate covariates. Ordinary logistic regression was used as matching was not done to select controls. Since the survey was conducted voluntarily, there was concern that the survey participants could differ from the general population of Japan. Therefore, we compared the survey participants and the general population for (1) the proportion of individuals vaccinated twice by age group and (2) geographic region of residence in an attempt to evaluate the generalizability of our findings. In addition, the reasons for lack of intention to receive COVID-19 booster vaccines were described. One thing to note is that, I could not differentiate between vaccination hesitancy and being anti-vaccination since the study was a retrospective analysis of an online serial cross-sectional survey by a marketing research company and I had no control over what questions with multiple choices are included in the questionnaire. Therefore, the individuals with a lack of intention to receive vaccines would include both individuals with vaccination hesitancy and individuals who are anti-vaccination. All statistical analyses were performed using Stata.

Objective 3

Objective 3A: To estimate the real-world effectiveness of COVID-19 vaccines against symptomatic infection in Japan

Objective 3B: To estimate the real-world effectiveness of COVID-19 vaccines against symptomatic infection in the Philippines

Background on the methods

Unlike in the U.K., there is no systematic collection of testing data in Japan. Also, there is a system to collect vaccination records called the "Vaccination Record System (VRS)," where local governments register vaccination records. Due to legal restrictions, individual-level data from VRS cannot be accessed at the national level (and thus, even though the PhD candidate was also a staff at the National Institute of Infectious Diseases, Japan, there was no access to the VRS). In the Philippines, the Department of Health requires the submission of Case Investigation Forms (CIFs) when individuals are tested for SARS-CoV-2. There is also a system to collect vaccination records. These would potentially be a good data source for evaluating VE. However, access to these data is difficult to obtain, and careful assessment of data quality and completeness is necessary. Therefore, in Japan and the Philippines, we decided to prospectively collect data in clinics and hospitals routinely testing for SARS-CoV-2. These challenges allowed us to consider a prospective collection of data, including factors that influence VE measures, including variables that are not routinely collected, such as preventive measures taken by the participants.

Methods

Design

The platform was the same as the one used in Objective 1 (a multi-center/multi-country case-control study [test-negative design]).

Enrollment criteria, sampling method, and ascertainment of cases and controls

It is the same as Objective 1, except that in Japan, the minimum age was lowered to 16 to increase the sample size for evaluating vaccine effectiveness.

Sample size calculation

Assuming 10% positivity, expected COVID-19 vaccine coverage of 30%, and 90% VE, 207 cases and 1864 controls are needed for precision of the lower CI boundary of 10%. A larger sample size will be necessary if VE estimates are considered to be lower due to the emergence of new variants and waning immunity.

Ethics approval

Same as Objective 1.

Analysis plan

Sociodemographics, past medical history, and vaccination status overall and by test status (test-positive or test-negative) were described. Univariate analysis was used to calculate ORs and their 95% CIs. Multivariable analysis was also done with appropriate covariates. VE was estimated by 1-(adjusted ORs) X100%. Ordinary logistic regression was used as matching is not done to select controls. Regarding missing data, a complete case analysis was performed initially, but imputation was done as needed. All statistical analyses were performed using Stata.

Objective 3C: To develop a practical protocol to implement COVID-19 VE studies in collaboration with the WHO Western Pacific Regional Office and share research output to inform policies/risk communication strategies and experience for potential expansion of VE studies within the Western Pacific Region and beyond

Background

As COVID-19 vaccination programs were being rolled out, countries were encouraged to conduct real-world VE studies, especially in the context of the emergence of new variants and waning immunity. In doing so, close guidance was needed to ensure the efficient implementation of quality studies. Standard WHO guidance was available regarding the evaluation of COVID-19 VE [93-95]. However, this guidance was generic in nature; more concrete and specific guidance and protocols/manuals are required to implement these studies, such as one using a test-negative design. Also, technical assistance was needed to provide further support to countries in the Western Pacific Region in adapting and implementing the guidance and protocol.

Methods

An Agreement for the Performance of Work contract between WHO and Nagasaki University was made to seek additional funding for the study in the Philippines. The PhD candidate was a part-time unpaid consultant for WHO to implement the below terms of reference and to facilitate the dissemination of data obtained to inform public health policies in the Western Pacific Region.

1. Developing the generic protocol/guidance on COVID-19 VE studies using the test-negative design for the Region

A generic protocol/guidance that can potentially be applied in countries in the Western Pacific Region was developed. If other regions request it, the protocol/guidance could also be extended to them. The protocol/guidance included a data collection guide (detailed steps on initial implementation), potential inclusion/exclusion criteria, a statistics/data analysis plan, and a data collection and analysis template. Experience in Japan and the Philippines was incorporated as appropriate to make the protocol/guidance practical.

2. Executing COVID-19 VE studies as model cases in the Philippines and Japan

First, the PhD candidate developed the protocol specifically for the study in the Philippines (adapting from the above-mentioned generic protocol for the Region) to be submitted for ethics and technical review at local sites. Second, the PhD candidate oversaw the study implementation, including logistics, etc. The support was done both remotely and on-site (via PhD candidate's visit(s) to the Philippines).

3. Sharing research output to inform policies/risk communication strategies and experience for potential expansion of VE studies within the Region and beyond

Country experience in Japan and the Philippines was shared. For Japan, lessons in implementation and preliminary results were shared. For the Philippines, lessons in implementation were shared. Technical assistance was also provided if countries in the Region other than Japan and the Philippines expressed interest in conducting VE studies. Although it is not feasible for the studies in Japan and the Philippines, I proposed integrating COVID-19 VE studies into existing influenza-like illness/severe acute respiratory illness surveillance systems in other countries.

Finally, after the study implementation in Japan and the Philippines, challenges and lessons learned were summarized through the experience of setting up and executing operational research to evaluate public health interventions, including non-pharmaceutical interventions and vaccines, as well as dissemination of results to rapidly inform policies and risk communication during the COVID-19 pandemic to inform future health emergencies, epidemics, and potential pandemics.

Objective 3D: To estimate the real-world effectiveness of COVID-19 vaccines against severe disease in Japan
Objective 3E: To estimate the real-world effectiveness of COVID-19 vaccines against severe disease in the Philippines

Background

With the emergence of the Omicron variant, there was emerging evidence suggesting that VE was also less effective against Omicron. Also, there was another set of emerging evidence that VE wanes against mild symptomatic infection. This resulted in the target product profile shifting to severe disease with an increasing need to evaluate VE against severe disease. Therefore, VE against severe COVID-19 was also evaluated in hospitals that admit severe COVID-19 cases in each country. In doing so, I collected data on whether medical interventions, such as oxygen use, were due to COVID-19 or other diseases among those who tested positive for SARS-CoV-2 since incidental infection found at the time of hospital admission with unrelated conditions was an issue in using a database to conduct VE studies.

Methods

Design

The study was a multi-center/multi-country case-control study conducted in Japan and the Philippines. Patients admitted with COVID-19 are considered cases, while patients admitted with other conditions are considered controls. In Japan, hospitalization criteria change vastly over time depending on the availability of beds, variant detection, and frailty, so enrollment was done only among patients requiring oxygen. Although this study was mainly a retrospective chart review, when vaccination data were missing, patients or their family members were contacted by phone to fill in the information in Japan. In the Philippines, various hospital records (medical charts, Case Investigation Forms (CIFs), etc.) were referred to obtain vaccination history information as much as possible.

Enrollment criteria

The inclusion criterion in Japan was patients aged ≥16 years who were hospitalized in participating hospitals with respiratory failure (i.e., requiring oxygen therapy) between August 1, 2021, and June 30, 2022. The inclusion criterion in the Philippines was patients aged ≥16 years who were hospitalized in San Lazaro Hospital between March 1, 2021 and December 30, 2022.
Exclusion criteria included patients who were previously enrolled (only the first eligible admission is included); patients with an unknown symptom onset date; patients with admission ≥15 days after onset; patients with onset during hospitalization; patients tested either ≥8 days before or ≥15 days after onset; patients tested ≥15 days before or ≥15 days after admission; patients currently on home oxygen therapy or home mechanical ventilation; patients started oxygen therapy ≥15 days before or ≥15 days after admission; patients started invasive mechanical ventilation ≥15 days before or ≥20

days after admission; patients with past SARS-CoV-2 infection ≥ three months before admission; or patients with immunodeficiency or current use of immunosuppressants.
The rationale for including patients tested up to 7 days before onset and excluding those tested earlier is that patients may have been tested on routine asymptomatic screening. Still, the likelihood of testing positive is lower ≥8 days before onset. Also, the rationale for including patients who were tested up to 14 days before admission and excluding those who were tested ≥15 days before admission is that it takes from a few days to 2 weeks from symptom onset for patients to develop severe disease, and these patients may be tested right after onset and later hospitalized. Finally, the rationale for including patients tested up to 14 days after the onset of illness is that viral load, as measured by PCR, continues to be high for severe cases in the second week of illness and would likely continue to be positive if the cases are true COVID-19 cases.

Ascertainment of cases and controls
Regardless of test type, patients who tested positive before or after admission based on the above inclusion and exclusion criteria were defined as cases; patients who tested negative before or after admission based on the above criteria were defined as controls.
To measure VE, I used various severe outcomes, including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation, death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than other differential diagnoses), and progression from oxygen use to mechanical ventilation or death. "True" severe COVID-19 outcome was based on the judgment of the treating physicians (record on the chart), trained nurse or pharmacist responsible for chart review, as well as the primary investigator (final decision). For controls, I included all patients who required oxygen to measure VE against all severe outcomes (thus, it is not strictly a test-negative design).
The chart review was conducted to ensure that at least six months had passed since participants were hospitalized, allowing sufficient time for participants to reach the final discharge outcome.

Sample size calculation
The sample size was determined by the number of patients admitted to participating hospitals during the study period. However, based on a priori sample size calculations (assuming a 1:1 ratio between cases and controls, expected COVID-19 vaccine coverage of 80%, and 90% VE, 89 patients are needed in each group for the precision of a lower CI boundary of 10%), we considered that our design would allow for adequately precise VE estimates.

Ethics approval
It is the same as Objective 1 (except that Philippine General Hospital did not participate in this one).

Analysis plan

Patient characteristics were described overall and by case/control status. A severe disease risk score was developed to be incorporated as a covariate. Based on published reports [6-8], we assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, pregnancy while hospitalized, or overweight; the points were added up to calculate the risk score for each patient. Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group (categorical), sex, risk score categories (0, 1, 2, 3-4, 5+; categorical), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of the admitting hospital, and calendar week of hospitalization (biweekly). To estimate VE against progression from oxygen use to mechanical ventilation or death among COVID-19 patients, additional adjustments were made for the use of antivirals, monoclonal antibody therapy, steroids, anti-inflammatory drugs (tocilizumab or baricitinib), anticoagulation, and proning. (Post-viva note: the analysis was done including these factors, but based on the discussion during the viva, it was noted that how these factors should be treated in an attempt to measure VE against disease progress among COVID-19 requires further exploration in the future.) Ordinary logistic regression was used as matching is not done to select controls. VE was estimated using the following equation: VE = 1-(adjusted ORs) X100%, including VE against disease progression. A complete case analysis was performed regarding missing data. Co-circulation of influenza and COVID-19 can result in biased VE estimates as the propensity to get vaccinated may be similar for COVID-19 and influenza vaccines [96]. In theory, the same concern applies to *Streptococcus pneumoniae* pneumonia and pneumococcal vaccination. Therefore, we decided to collect information on influenza or *Streptococcus pneumoniae* pneumonia status. All statistical analyses will be performed using Stata.

Potential Sources and Implications of Biases for VE Evaluation

VE studies are important to assess the capacity of COVID-19 vaccines in the context/setting of (1) emergence of variants, (2) waning immunity, and (3) vaccine types/boosters when RCTs are no longer ethical, but due to their observational nature, careful consideration is necessary to reduce bias. The table below lists potential biases and how we plan to approach them.

Bias	Problem	Approach to reduce bias
Care seeking behavior/access to care	Those more likely to get vaccines seek care more, and thus are more likely to be cases	Test-negative design can partially address this
Care seeking based on vaccine status	Vaccinated persons are less likely to seek care/testing for COVID-19-like illness due to perception of protection	(Breakthrough infection is common enough that individuals are expected to get tested even after vaccination)
Collider bias	Health seeking and SARS-CoV-2 infection both lead to testing	Adjust for health seeking behaviors
Confounding factors	Potential confounding factors include age, sex, race/ethnicity, socioeconomic status, occupation, chronic medical conditions, close contact history, date of onset/specimen collection, and priority groups for vaccination	Include these factors in the questionnaire and adjust as appropriate
Diagnostic bias	Health workers more likely to test unvaccinated persons for COVID-19	Ask health workers to not decide who to test based on vaccination status
Misclassification of the outcome	False positives and false negatives	Use PCR that has high sensitivity and specificity; sensitivity analysis on symptomatic individuals with onset within two weeks
Misclassification of the exposure	Measurement error/vaccine effect may start before/after a specified cut-off for considering an individual vaccinated	Ascertain vaccination history with vaccine certificate (Philippines; partly in Japan) and administrative records (Philippines; may be incomplete)
Non-specific vaccine effect	Vaccine prevents diseases for which controls seek care	Not possible to control for but the magnitude is expected to be small due to antigenic specificity
Prior infection	Individuals with known prior SARS-CoV-2 infection are less likely to get vaccinated. Also, if there is unreported prior infection with unvaccinated individuals experiencing more of this unreported prior infection, VE would be underestimated. if individuals	Adjust for prior infection (self-reported); perform sensitivity analysis excluding those with prior SARS-CoV-2 infection (although presence of unreported infection could not be controlled and would result in inaccurate VE)

	with prior infections (that are not reported) are less likely to get vaccinated due to the perception of protection, VE would also be underestimated.	
Spurious waning	Unvaccinated individuals become immune through natural infection faster than vaccinated individuals	Conduct the study soon after vaccine introduction

Reference: Evaluation of COVID-19 vaccine effectiveness interim guidance [89]

Objective 4

To examine the influence of high-risk behaviors on estimates of COVID-19 VE

Background

SARS-CoV-2 transmission occurs through a complex interplay of public health and social measures (non-pharmaceutical interventions), high-risk behaviors, social background, past infection, and vaccination. For example, due to vaccine passports and perceptions of protection, differential exposures may exist between vaccinated and unvaccinated individuals. Therefore, it is critical to account for these factors when estimating COVID-19 VE in order to produce accurate results. Our prospective approach enables exploration of the influence of preventive measures such as mask-wearing and high-risk behaviors on estimates of COVID-19 VE. To elaborate further, high-risk behaviors can potentially act as effect modifiers (e.g., differential behavioral patterns can result in different VE), mediators (e.g., vaccination can trigger high-risk behaviors, and in turn, can trigger infection), or confounders (e.g., Individuals who would like to get engaged in high-risk behaviors [such as going to restaurants, bars, or nightclubs] as underlying characteristics are more likely to get vaccinated. This is because, without vaccination, they are not allowed to do so in the context where a domestic vaccination passport is introduced since the law or regulation requires the presentation of a vaccination passport to enter such venues).

Methods

A multi-center/multi-country case-control study using data from Objective 1 and Objective 3A/B. Dining at restaurants/bars at night with alcohol consumption in a group was used as a proxy for high-risk behaviors.

Analysis plan

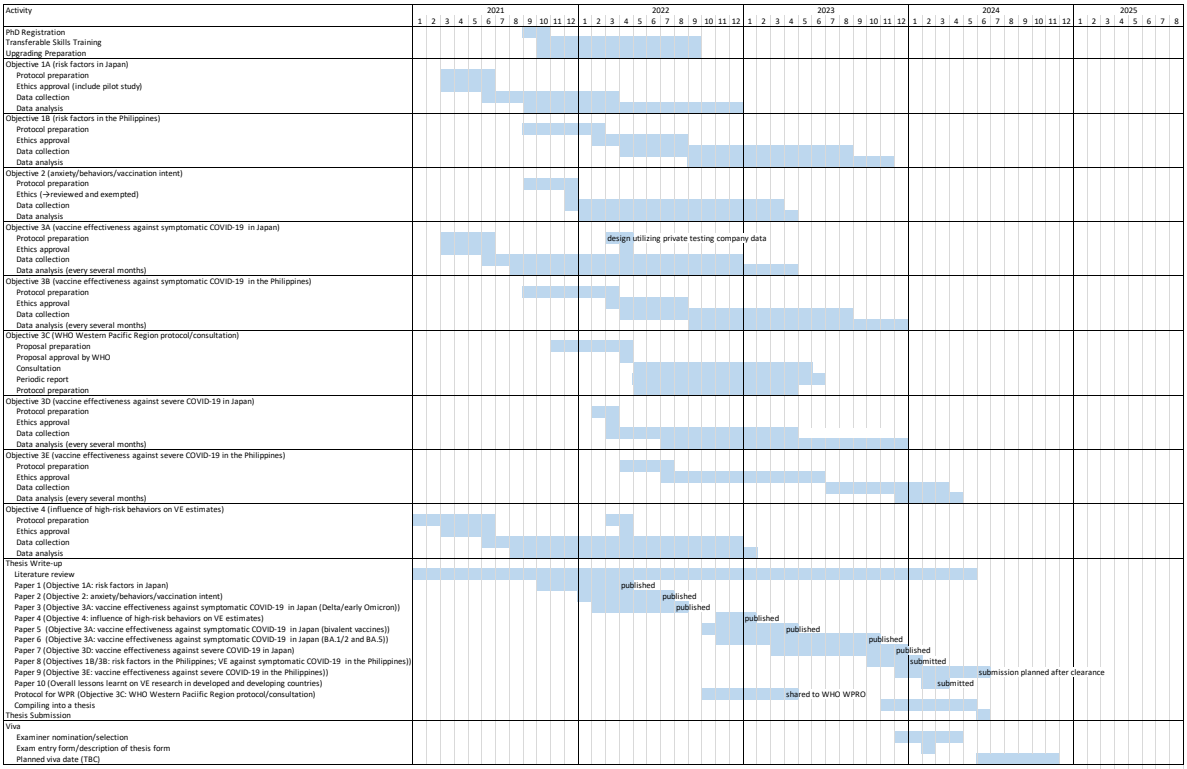
VE adjusted for mask-wearing and high-risk behaviors was estimated. VE stratified by vaccination status and high-risk behaviors was also estimated. Here, I simulated a hypothetical scenario as the following to examine high-risk behaviors as confounders. As a base-case scenario where all individuals are not engaging in high-risk behaviors, I compared unvaccinated individuals with no high-risk behavior and individuals who are fully vaccinated with no high-risk behaviors (this, in fact, imitates the scenario when initial randomized controlled studies for COVID-19 vaccine candidates were conducted where many countries were strictly implementing public health and social measures and almost all individuals were not engaged in high-risk behaviors). On the other hand, in a "domestic vaccination passport" scenario, where only vaccinated individuals are allowed to engage in high-risk behaviors, unvaccinated individuals with no high-risk behavior were compared with individuals who are fully vaccinated with high-risk behaviors. The important assumptions here are that (1) high-risk behaviors act as confounders where individuals who would like to get engaged in

high-risk behaviors are more likely to get vaccinated (and, by definition of being “high-risk”, those who would like to get engaged in high-risk behaviors are more likely to get infected), (2) majority of individuals engage in high-risk behaviors if there is no legal restriction or sense of protection (this is truly the case in Japan where the majority of individuals go out to restaurants/bars at night with alcohol consumption in a group within two week period), and (3) domestic vaccination passport is strictly implemented where unvaccinated individuals are prohibited to engage in high-risk behaviors where vaccinated individuals are allowed to engage in such behaviors.

Overall, it is important to note is that the context where vaccine efficacy for COVID-19 was measured via randomized controlled studies was vastly different from the context where vaccine effectiveness was measured. Also, perhaps, high-risk behaviors can act as mediators, effect modifiers on top of confounders. Therefore, it is important to acknowledge that VE estimates are context-specific rather than being universal. Furthermore, in the future, it would be important to further explore how public health and social measures and behaviors play a role, especially in the context where the lay public is more aware of infectious disease threats and alters their prevention measures. These points were added to the objective 4 method section.

PhD Timeline

Due to the public health importance and urgency of the COVID-19 project, upon consultation and thorough discussion with the supervisors and other stakeholders, some of the studies were planned from March 2021 and implemented before PhD registration in September 2021. The ethics application for LSHTM was cleared after registration (data already collected before ethics application clearance were treated as a retrospective analysis, although the study was planned and implemented mainly by the PhD candidate). Data analyses and manuscript writing were done after registration. See the detailed timeline on the next page.


Activity
2021
2022
2023
2024
2025
PhD Registration
Transferable Skills Training
Upgrading Preparation
Objective 1A (risk factors in Japan)
Protocol preparation
Ethics approval (include pilot study)
Data collection
Data analysis
Objective 1B (risk factors in the Philippines)
Protocol preparation
Ethics approval
Data collection
Data analysis
Objective 2 (anxiety/behaviors/vaccination intent)
Protocol preparation
Ethics (→reviewed and exempted)
Data collection
Data analysis
Objective 3A (vaccine effectiveness against symptomatic COVID-19 in Japan)
Protocol preparation
design utilizing private testing company data
Ethics approval
Data collection
Data analysis (every several months)
Objective 3B (vaccine effectiveness against symptomatic COVID-19 in the Philippines)
Protocol preparation
Ethics approval
Data collection
Data analysis (every several months)
Objective 3C (WHO Western Pacific Region protocol/consultation)
Proposal preparation
Proposal approval by WHO
Consultation
Periodic report
Protocol preparation
Objective 3D (vaccine effectiveness against severe COVID-19 in Japan)
Protocol preparation
Ethics approval
Data collection
Data analysis (every several months)
Objective 3E (vaccine effectiveness against severe COVID-19 in the Philippines)
Protocol preparation
Ethics approval
Data collection
Data analysis (every several months)
Objective 4 (influence of high-risk behaviors on VE estimates)
Protocol preparation
Ethics approval
Data collection
Data analysis
Thesis Write-up
Literature review
Paper 1 (Objective 1A: risk factors in Japan)
published
Paper 2 (Objective 2: anxiety/behaviors/vaccination intent)
published
Paper 3 (Objective 3A: vaccine effectiveness against symptomatic COVID-19 in Japan (Delta/early Omicron))
published
Paper 4 (Objective 4: influence of high-risk behaviors on VE estimates)
published
Paper 5 (Objective 3A: vaccine effectiveness against symptomatic COVID-19 in Japan (bivalent vaccines))
published
Paper 6 (Objective 3A: vaccine effectiveness against symptomatic COVID-19 in Japan (BA.1/2 and BA.5))
published
Paper 7 (Objective 3D: vaccine effectiveness against severe COVID-19 in Japan)
published
Paper 8 (Objectives 1B/3B: risk factors in the Philippines; VE against symptomatic COVID-19 in the Philippines))
submitted
Paper 9 (Objective 3E: vaccine effectiveness against severe COVID-19 in the Philippines))
submission planned after clearance
Paper 10 (Overall lessons learnt on VE research in developed and developing countries)
submitted
Protocol for WPR (Objective 3C: WHO Western Pacific Region protocol/consultation)
shared to WHO WPRO
Compiling into a thesis
Thesis Submission
Viva
Examiner nomination/selection
Exam entry form/description of thesis form
Planned viva date (TBC)

Output List of this PhD

Peer-reviewed Journal Publications

Published

1. **Arashiro T[*],** Arima Y, Muraoka H, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. *Influenza Other Respir Viruses.* 2022 Sep;16(5):952-961. doi: 10.1111/irv.12992. **([*]first and corresponding author)**
2. **Arashiro T[*],** Arima Y, Stucky A, et al. Social and Behavioral Factors Associated with Lack of Intent to Receive COVID-19 Vaccine, Japan. *Emerg Infect Dis.* 2022 Sep;28(9):1909-1910. doi: 10.3201/eid2809.220300. **([*]first and corresponding author)**
3. **Arashiro T[*],** Arima Y, Muraoka H, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). *Clin Infect Dis.* 2022 Aug 3:ciac635. doi: 10.1093/cid/ciac635. **([*]first and corresponding author)**
4. **Arashiro T[*],** Arima Y, Kuramochi J, et al. Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. *Euro Surveill.* 2023 Jan;28(4). doi: 10.2807/1560-7917.ES.2023.28.4.2300034. **([*]first and corresponding author)**
5. **Arashiro T[*],** Arima Y, Kuramochi J, et al. Effectiveness of BA.1- and BA.4/BA. 5-Containing Bivalent COVID-19 mRNA Vaccines Against Symptomatic SARS-CoV-2 Infection During the BA.5-Dominant Period in Japan. *Open Forum Infect Dis.* 2023;10(6):ofad240. doi:10.1093/ofid/ofad240. **([*]first and corresponding author; Editor's Choice)**
6. **Arashiro T[*],** Arima Y, Kuramochi J, et al. Immune escape and waning immunity of COVID-19 monovalent mRNA vaccines against symptomatic infection with BA.1/BA.2 and BA.5 in Japan. *Vaccine.* 2023;S0264-410X(23)01194-5. doi:10.1016/j.vaccine.2023.10.021. **([*]first and corresponding author)**
7. **Arashiro T[*],** Miwa M, Nakagawa H,et al. COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: A multicenter case-control study (MOTIVATE study). *Vaccine.* 2023 Dec 18:S0264-410X(23)01480-9. doi: 10.1016/j.vaccine.2023.12.033. **([*]first and corresponding author)**

Submitted/prepared and to be submitted

8. **Arashiro T[*],** et al. Socio-behavioral factors associated with SARS-CoV-2 infection and COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines: a prospective case-control study (FASCINATE-P study). (Revision submitted; [*]**first and corresponding author)**

9. **Arashiro T*,** et al. Factors associated with COVID-19 in-hospital death and COVID-19 vaccine effectiveness against COVID-19 hospitalization in the Philippines during pre-Omicron and Omicron period: a descriptive and case-control study (MOTIVATE-P study) **(**Under internal clearance; ***first and corresponding author)**
10. **Arashiro T*,** et al. Lessons from COVID-19 vaccine effectiveness studies conducted in response to the COVID-19 pandemic in Japan and the Philippines **(**Under peer review; ***first and corresponding author)**

Peer Review Activities

Invited and completed over 40 manuscripts (including some revisions) for peer review for multiple journals, including Clinical Infectious Diseases, Eurosurveillance, International Journal of Epidemiology, Epidemiology and Infection, Influenza and Other Respiratory Viruses, Journal of Epidemiology, Vaccine, Vaccine: X, Open Forum Infectious Diseases, BMC Infectious Diseases, BMC Public Health, PLOS ONE, Western Pacific Surveillance and Response Journal, Journal of Medical Virology, Japanese Journal of Infectious Diseases (the official journal of NIID), Tropical Medicine and Health.

Government Reports related to PhD (Japan)

1. **Arashiro T**, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness against severe disease during Delta and Omicron-dominant periods. National Institute of Infectious Diseases, Japan [in Japanese]. 2023. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/12019-covid19-9999-2.html
2. **Arashiro T**, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (fifth report): bivalent vaccine effectiveness. National Institute of Infectious Diseases, Japan [in Japanese]. 2022. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/11688-covid19-9999.html
3. **Arashiro T,** et al. Monitoring the flow of people at major stations, downtown areas, etc., as well as the anxiety and risk behavior of the general public, to help understand and evaluate the spread of COVID-19. *Infectious Agent Surveillance Report. National Institute of Infectious Diseases*, 43:285-286 [in Japanese]. 2022. https://www.niid.go.jp/niid/ja/typhi-m/iasr-reference/2605-related-articles/related-articles-514/11704-514r09.html
4. **Arashiro T**, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (fourth report): vaccine effectiveness during BA.5-dominant period. National Institute of Infectious Diseases, Japan [in Japanese]. 2022. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/11405-covid19-999.html
5. **Arashiro T**, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (third report): vaccine effectiveness during Omicron variant-

dominant period. National Institute of Infectious Diseases, Japan [in Japanese]. 2022. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10966-covid19-71.html

6. **Arashiro T,** et al. Antibody response in individuals diagnosed with COVID-19 after COVID-19 vaccination. *Infectious Agent Surveillance Report. National Institute of Infectious Diseases*, 43, 18 [in Japanese]. 2022. https://www.niid.go.jp/niid/ja/2019-ncov/2488-idsc/iasr-news/10832-503p02.html
7. **Arashiro T,** et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (second report): vaccine effectiveness during Delta variant-dominant period. National Institute of Infectious Diseases, Japan [in Japanese]. 2021. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10757-covid19-61.html
8. **Arashiro T,** et al. Preliminary report on case-control study to evaluate behavioral risk factors associated with SARS-CoV-2 infection. National Institute of Infectious Diseases, Japan [in Japanese]. 2021. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10692-covid19-59.html
9. **Arashiro T,** et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (first report). National Institute of Infectious Diseases, Japan [in Japanese]. 2021. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10614-covid19-55.html
10. **Arashiro T,** Suzuki T. Introduction of COVID-19 Vaccines in Japan: Basics of mRNA vaccines and viral vector vaccines. *Infectious Agent Surveillance Report. National Institute of Infectious Diseases*, 42, 36 [in Japanese]. 2021. https://www.niid.go.jp/niid/ja/typhi-m/iasr-reference/2536-related-articles/related-articles-492/10182-492r06.html

Other Invited Publications

1. Invited Book Chapter: **Arashiro T,** Suzuki T. Chapter on COVID-19 Vaccines. Vaccine 2nd edition: From Basic Science to Clinical Practice. the Japanese Society for Vaccinology. [in Japanese] (draft submitted).
2. Invited article in academic society journal: **Arashiro T,** Suzuki T. Development, rollout, and challenges of COVID-19 vaccines in Japan and globally (invited review). **Uirusu.** 2021 71(1):41-44. [in Japanese].

Conference and Meeting Presentations and Conference Session Chair

1. Invited oral presentation: **Arashiro T.** Evaluation of COVID-19 vaccine effectiveness. The 26th Annual Meeting of the Japanese Society for Vaccinology, November 2022
2. Co-chair: Session on influenza vaccine effectiveness. OPTIONS XI for the Control of Influenza, September 2022

3. Poster presentation: **Arashiro T, et al**. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan (FASCINATE study): implications for studies of influenza and other respiratory viruses. OPTIONS XI for the Control of Influenza, September 2022
4. Invited oral presentation: **Arashiro T.** Invited presentation: Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan with the plan for the Philippines and beyond. World Health Organization, Western Pacific Regional Office COVID-19 Incident Management Support Team meeting, June 2022
5. Invited oral presentation: **Arashiro T.** Evaluation of COVID-19 vaccine effectiveness. The 63rd Annual Meeting of the Japanese Society of Clinical virology, June 2022

Contribution of PhD Candidate, Supervisors, and Other Stakeholders

Publications

For all publications listed in the previous chapter, the PhD candidate was the one who wrote the original draft and published them as the first author and (for peer-reviewed publications) the corresponding author.

Case-control study in Japan (risk factor analysis/VE against symptomatic disease)

PhD candidate: conceptualization (main), design (main), recruitment of participating healthcare facilities and private testing companies (main), data acquisition (main/support), data analysis (main), writing – original draft (main), funding acquisition (support/main)

PhD supervisors: supervision, writing – review and editing

Relevant stakeholders:

1. Participating healthcare facilities and site investigator: data acquisition (support), writing – review and editing
2. Private testing companies: data acquisition (support), writing – review and editing
3. Supervisors (Yuzo Arima and Motoi Suzuki) and other staff at NIID: conceptualization (support), supervision, funding acquisition (support/main), writing – review and editing

Case-control study in the Philippines (risk factor analysis/VE against symptomatic disease)

PhD candidate: conceptualization (main), design (main), recruitment of hospital site (Philippine General Hospital) (main), data acquisition (main/support), data analysis (main), writing – original draft (main), funding acquisition (main)

PhD supervisors: recruitment of hospital site (existing collaborative office at San Lazaro Hospital) (main), planning (support), supervision (main), writing – review and editing

Relevant stakeholders:

1. SLH and SLH-Nagasaki University Collaborative Research Office (Joy Potenciano Calayo, Jack Suzuki, Marie Dimol, Reby Marie Garcia, Greco Mark Malijan, Kristal An Agrupis, Mary Jane Salazar, Mary Ann Salazar): data acquisition (main/support), logistics support (main), writing – review and editing
2. Philippine General Hospital (Regina Pascua Berba, Cecile Dungog, Jonathan Rivera): data acquisition (main/support), logistics support (main), writing – review and editing
3. World Health Organization (Jinho Shin): provision of funding (partial), writing – review and editing

Analysis using data from a marketing research company

PhD candidate: conceptualization (main), design (main), data analysis (main), writing – original draft (main), funding acquisition (support/main)
PhD supervisors: supervision, writing – review and editing
Relevant stakeholders:

1. Cross Marketing Inc.: data acquisition (main)
2. Supervisors (Yuzo Arima and Motoi Suzuki) and other staff at NIID: supervision, funding acquisition (main/support), writing – review and editing

Case-control study in Japan (VE against severe COVID-19)

PhD candidate: conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (main/support), data analysis (main), writing – original draft (main), funding acquisition (main/support)
PhD supervisors: supervision, writing – review and editing
Relevant stakeholders:

1. Participating healthcare facilities and site investigator and research nurses: data acquisition (main/support), writing – review and editing
2. Supervisors (Yuzo Arima and Motoi Suzuki) and other staff at NIID: supervision, funding acquisition (main/support), writing – review and editing

Case-control study in the Philippines (VE against severe COVID-19)

PhD candidate: conceptualization (main), design (main), data acquisition (main/support), data analysis (main), writing – original draft (main), funding acquisition (main)
PhD supervisors: recruitment of hospital sites (existing collaborative office at San Lazaro Hospital) (main), supervision, writing – review and editing
Relevant stakeholders:

1. SLH and SLH-Nagasaki University Collaborative Research Office (Rontgene Solante, Grace Go, Edna Miranda, Michelle Carandang-Cuvin, Jack Suzuki, Marie Dimol, Reby Marie Garcia, Greco Mark Malijan, Kristal An Agrupis, Mary Jane Salazar, Mary Ann Salazar): data acquisition (main/support), logistics support (main), writing – review and editing
2. World Health Organization (Jinho Shin): provision of funding (partial), writing – review and editing

Protocol development and technical assistance for the World Health Organization

PhD candidate: conceptualization (main), design (main), writing of the proposal (main), consultancy (main), writing of the protocol (main), funding acquisition (main)
PhD supervisors: supervision
Relevant stakeholders:

1. World Health Organization (Jinho Shin): provision of funding, supervision

Paper 1 : Behavioral risk factors in Japan

Arashiro T[*], Arima Y, Muraoka H, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. **Influenza Other Respir Viruses.** 2022 Sep;16(5):952-961. doi: 10.1111/irv.12992. **([*]first and corresponding author)**

Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 1A.

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SECTION A – Student Details

Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Influenza and Other Respiratory Viruses		
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ORIGINAL ARTICLE

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Behavioral factors associated with SARS-CoV-2 infection in Japan

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Abstract

Background: The relative burden of COVID-19 has been less severe in Japan. One reason for this may be the uniquely strict restrictions imposed upon bars/restaurants. To assess if this approach was appropriately targeting high-risk individuals, we examined behavioral factors associated with SARS-CoV-2 infection in the community.

Methods: This multicenter case–control study involved individuals receiving SARS-CoV-2 testing in June–August 2021. Behavioral exposures in the past 2 weeks were collected via questionnaire. SARS-CoV-2 PCR-positive individuals were cases, while PCR-negative individuals were controls.

Results: The analysis included 778 individuals (266 [34.2%] positives; median age [interquartile range] 33 [27–43] years). Attending three or more social gatherings was associated with SARS-CoV-2 infection (adjusted odds ratio [aOR] 2.00 [95% CI 1.31–3.05]). Attending gatherings with alcohol (aOR 2.29 [1.53–3.42]), at bars/restaurants (aOR 1.55 [1.04–2.30]), outdoors/at parks (aOR 2.87 [1.01–8.13]), at night (aOR 2.07 [1.40–3.04]), five or more people (aOR 1.81 [1.00–3.30]), 2 hours or longer (aOR 1.76 [1.14–2.71]), not wearing a mask during gatherings (aOR 4.18 [2.29–7.64]), and cloth mask use (aOR 1.77 [1.11–2.83]) were associated with infection. Going to karaoke (aOR 2.53 [1.25–5.09]) and to a gym (aOR 1.87 [1.11–3.16]) were also associated with infection. Factors not associated with infection included visiting a cafe with others, ordering takeout, using food delivery services, eating out by oneself, and work/school/travel-related exposures including teleworking.

Conclusions: We identified multiple behavioral factors associated with SARS-CoV-2 infection, many of which were in line with the policy/risk communication implemented in Japan. Rapid assessment of risk factors can inform decision making.

KEYWORDS
coronavirus disease 2019 (COVID-19), health risk behaviors, public health and social measures, risk factors, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally.[1] Japan has been no exception, but the relative burden of COVID-19 after 2 years has not been as severe as in many other countries, with fewer cumulative cases and deaths relative to the population despite its aging population.[2] Many factors may have contributed to this, such as the tireless efforts of public health centers in extensive contact tracing including backward tracing (source investigation), high mask-wearing adherence, maintaining greater physical distance, and strict infection prevention and control measures at health-care/long-term care facilities.[3,4] Among these, one intriguing hypothesis is the unique policy with a focused approach targeting restaurants and bars to reduce business hours at night and prohibiting the serving of alcohol.[5] As the Japanese government's response against COVID-19 is based on the Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response, Japan has declared a state of emergency several times during the course of the pandemic.[6] However, unlike many other countries, there were no strict restrictions imposed on individual citizens such as lockdowns and obligatory curfews. Rather, there were voluntary requests to stay at home and engage in basic infection prevention measures such as proper mask wearing/hand hygiene. In comparison, restaurants and bars were ordered to suspend business if they cannot operate without serving alcohol, to stop serving alcohol, and to reduce business hours at night until 8:00 p.m. in prefectures with high transmission. Non-compliant businesses were disclosed publicly. This specific approach towards restaurants and bars was based on individual case data and cluster investigations with a theoretical rationale that dining or drinking alcohol at restaurants and bars with others (i.e., social gatherings involving food or drinks) provides occasion to interact face to face for a prolonged period without masks and that the influence of alcohol can further lead to laxity of infection prevention measures.[7] Also, an increase in the frequency and proportion of cases with no history of close contact[8] made containment through cluster investigation increasingly challenging and highlighted the lack of understanding regarding risk factors for infection at the community level. These circumstances led to the need to confirm through epidemiological data, with inclusion of a control group, whether behaviors such as social gatherings are indeed risk factors for SARS-CoV-2 infection to inform public health policy and provide evidence-based risk communication. Therefore, we initiated a multicenter case–control study to evaluate risk factors associated with SARS-CoV-2 infection, focusing on social gatherings involving food or drinks. We examined various social settings and further explored other behaviors as potential risk factors.

2 | METHODS

2.1 | Study design and setting

Our study, Factors Associated with SARS-CoV-2 Infection And The Effectiveness of COVID-19 vaccines (FASCINATE study), is a multicenter case–control study in health-care facilities in Japan with two objectives: (1) to elucidate risk factors associated with SARS-CoV-2 infection and (2) to estimate the effectiveness of COVID-19 vaccines.

Participating health-care facilities are routinely testing outpatients using polymerase chain reaction (PCR) to diagnose SARS-CoV-2 infection. For this report, data from six health-care facilities in the Kanto region (Tokyo and neighboring metropolitan prefectures) on individuals recruited during June 8–August 1, 2021, were analyzed.

2.2 | Inclusion and exclusion criteria

Individuals who were tested for SARS-CoV-2 were included. Exclusion criteria were (1) individuals younger than 20 years (as alcohol drinking is illegal for these individuals), (2) individuals who did or could not consent to participate in the study, (3) individuals who could not complete the questionnaire by themselves, (4) individuals who had already participated in this study, (5) individuals who required immediate treatment, and (6) individuals with history of close contact (because an infection, if confirmed, is most likely due to this specific contact rather than exposures asked about in the questionnaire). For this report, we excluded asymptomatic individuals and individuals vaccinated at least once as COVID-19 vaccination can influence behaviors.

2.3 | Questionnaire and classification of cases/controls

A paper or web-based questionnaire (according to individual preference) was administered before PCR results were available to avoid social desirability bias, where individuals who test positive may be less likely to report potentially high-risk behaviors. The questionnaire was optimized based on a pilot study done at two sites.[9] We defined social gathering as getting together with one or more persons that does not cohabitate with the participant. Cases were defined as PCR-confirmed SARS-CoV-2 positive individuals, while controls were defined as PCR-negative individuals.

2.4 | Data analysis

Logistic regression to identify associations between behavioral risk factors and SARS-CoV-2 infection was conducted adjusting for age group, sex, presence of comorbidities, educational attainment, place of residence, past SARS-CoV-2 infection, health-care facility in which SARS-CoV-2 testing was done, and calendar week. These potential confounders were determined *a priori*.[10,11] Data analyses were performed using STATA version 17.0.

3 | RESULTS

3.1 | Participant characteristics

A total of 992 symptomatic individuals were enrolled from six medical facilities during the study period; we excluded 44 due to unknown symptom onset, 16 due to being tested ≥15 days after symptom onset, and 154 due to being vaccinated (Figure 1). The final analysis included 778 individuals with 266 (34.2%) positive cases. The median age (interquartile range [IQR]) was 33 (27–43) years, 386 were males (49.6%), and 182 (23.4%) had comorbidities (Table 1); 758 (97.4%) were Japanese nationals and most foreigners were from East Asia.

3.2 | Factors related to 3Cs and five situations in the past 2 weeks

Since early in the pandemic, the Japanese government has been promoting avoidance of the "3Cs," representing (1) closed spaces, (2) crowded places, and (3) close-contact settings, which are considered high-risk based on characteristics of early clusters.[12] These "3Cs" were easy for the public to remember and the World Health Organization also began promoting this message.[13] Additionally, since fall 2020, the government started to promote avoidance of "five situations," namely, (1) social gatherings that include alcohol consumption, (2) large group gatherings that involve eating and/or drinking for an extended period of time, (3) conversing without a mask, (4) cohabitation in small living quarters, and (5) relocating to a different area.[12] We first examined factors among the above that could be measured (Table 2). Those who attended large gatherings that involve eating and/or drinking for an extended period of time in the past 2 weeks had particularly higher odds of infection compared with those who did not (adjusted odds ratio [aOR] 2.36 [1.38–4.05]).

3.3 | Association between social gatherings with food/drinks in various settings in the past 2 weeks and SARS-CoV-2 infection

We further examined the association between social gatherings that involve eating and/or drinking in various settings and SARS-CoV-2 infection (Table 2). The odds of infection increased with increased frequency of social gatherings; those who attending social gatherings three or more times had higher odds of infection compared with those who did not (aOR 2.00 [95% CI 1.31–3.05]). We examined this association in detail, specifically by presence of alcohol, location of gathering, and time of day. The odds of infection were substantially higher among individuals who attended social gatherings with alcohol at least once compared with those who did not (aOR 2.29 [95% CI 1.53–3.42]). Social gatherings without alcohol were not associated with infection. When we compared the location of social gatherings, the odds of infection were higher among individuals who had gatherings only at home (aOR 2.10 [95% CI 0.92–4.77]), visited bars or restaurants (aOR 1.55 [95% CI 1.04–2.30]), and had gatherings involving food/drinks outdoors/at parks (aOR 2.87 [95% CI 1.01–8.13]), all compared with those who did not. Moreover, the odds of infection among individuals who attended social gatherings at night were double that of those who did not (aOR 2.07 [95% CI 1.40–3.04]). Attending social gatherings only in the daytime was not associated with infection.

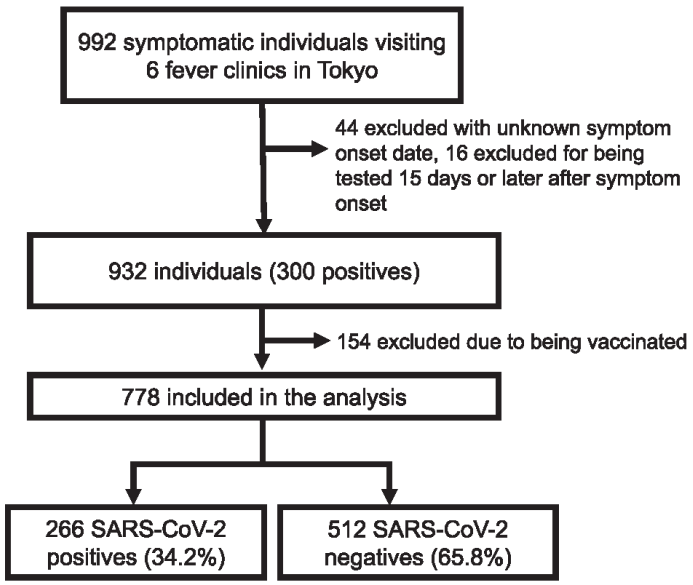

FIGURE 1 Flow diagram of study participants

3.4 | Association between other behaviors related to food/drinks in the past 2 weeks and SARS-CoV-2 infection

To compare the above findings on social gatherings that involve eating and/or drinking, we examined whether other behaviors related to food/drinks were associated with SARS-CoV-2 infection (Table 2). Unlike social gatherings, the odds of infection were not higher among individuals who visited a cafe with others (aOR 1.08 [95% CI 0.75–1.57]), ordered takeout (aOR 0.80 [95% CI 0.56–1.15]), used food delivery services (aOR 1.40 [95% CI 0.97–2.01]), and ate out by oneself (aOR 0.79 [95% CI 0.54–1.13]), all compared with those who did not.

3.5 | Association between size, duration, and mask wearing among participants of social gatherings in the past 2 weeks and SARS-CoV-2 infection

The government requested individuals attending social gatherings involving food/drinks to limit these gatherings to five people and to less than 2 hours and to consider use of masks except for when consuming food/drinks.[14] We assessed whether these factors were indeed associated with infection (Table 2). Specifically, those who attended a social gathering involving food/drinks and/or went to a cafe with others in the past 2 weeks were asked how many people attended the gathering, how long the gathering continued at maximum, and when the attendees had their masks on (cafe use was included here as we hypothesized that it also provides occasion to talk face to face for a prolonged period without masks). The odds of infection were higher among individuals who attended gatherings of five or more people (aOR 1.81 [95% CI 1.00–3.30]) and for individuals who attended for 2 hours or longer (aOR 1.76 [95% CI 1.14–2.71]), both compared with those who did not attend gatherings. Regarding mask wearing, the odds of infection were higher among those who did not wear a mask or took it off when seated (aOR 4.18 [95% CI 2.29–7.64]). This association was similar when the mask-wearing practices of other attendees at the gathering was assessed (aOR 3.74 [95% CI 2.13–6.55]).

3.6 | Association between type of mask used in the past 2 weeks and SARS-CoV-2 infection

Three types of masks are mainly used among the public in Japan: medical/surgical masks, cloth masks, and polyurethane masks. The Japanese government recommends use of medical/surgical masks rather than cloth or polyurethane masks based on a computer simulation model,[15] but epidemiological data were lacking. Therefore, we examined the association between mask type and infection (Table 3). The odds of infection were higher among individuals who used cloth masks (aOR 1.77 [95% CI 1.00–3.30]) and slightly higher among individuals who used polyurethane masks (aOR 1.47 [95% CI 0.91–2.38]), both compared with those who used medical/surgical masks. When we stratified dichotomously by whether the participants attended social gatherings or visited a cafe with others, the aforementioned association between infection and cloth or polyurethane mask use compared with medical/surgical mask use was only present among individuals who attended social gatherings or visited a cafe with others.

TABLE 1 Demographic and clinical characteristics of the study participants

	All (n = 778)	Test-positive (n = 266)	Test-negative (n = 512)
Age in years, n (%)			
20–29	307 (39.5)	115 (43.2)	192 (37.5)
30–39	228 (29.3)	77 (28.9)	151 (29.5)
40–49	145 (18.6)	41 (15.4)	104 (20.3)
50–59	77 (9.9)	30 (11.3)	47 (9.2)
60–69	20 (2.6)	3 (1.1)	17 (3.3)
70–79	1 (0.1)	0 (0.0)	1 (0.2)
Sex, n (%)			
Male	386 (49.6)	141 (53.0)	245 (47.9)
Female	392 (50.4)	125 (47.0)	267 (52.2)
Educational attainment, n (%); missing = 6			
Middle school or less	10 (1.3)	5 (1.9)	5 (1.0)
High school	130 (16.8)	56 (21.1)	74 (14.6)
Junior college/technical college	171 (22.2)	58 (21.9)	113 (22.3)
Undergraduate or graduate school	461 (59.7)	146 (55.1)	315 (62.1)
Place of residence, n (%); missing = 2			
Home	760 (97.9)	257 (97.4)	503 (98.2)
Hospital or long-term care facility	2 (0.3)	1 (0.4)	1 (0.2)
Dormitory or other	14 (1.8)	6 (2.3)	8 (1.6)
Comorbidities, n (%)			
Yes	182 (23.4)	71 (26.7)	111 (21.7)
No	596 (76.6)	195 (73.3)	401 (78.3)
Smoking, n (%); missing = 2			
Never smoker	441 (56.8)	134 (50.8)	307 (60.0)
Past smoker	176 (22.7)	57 (21.6)	119 (23.2)
Current smoker	159 (20.5)	73 (27.7)	86 (16.8)
Days from onset to SARS-CoV-2 test[a]; missing = 4			
	2 (1–3)	2 (1–3)	2 (1–3)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 10			
Yes	118 (15.4)	49 (18.7)	69 (13.6)
No	650 (84.6)	213 (81.3)	437 (86.4)
Past SARS-CoV-2 infection, n (%); missing = 18			
Yes	13 (1.7)	3 (1.2)	10 (2.0)
No	747 (98.3)	255 (98.8)	492 (98.0)

[a]Median (interquartile range).

3.7 | Association between behaviors not related to food/drinks in the past 2 weeks and SARS-CoV-2 infection

We next looked at behaviors that do not involve eating/drinking that are considered to be risk factors based on case/cluster investigations in Japan[7] (Table 4). The odds of infection were not higher among individuals who attended indoor events and gatherings (aOR 1.45 [95% CI 0.76–2.76]) and outdoor events and gatherings (aOR 1.34 [95% CI 0.67–2.69]), both compared with those who did not. The odds of infection were lower among individuals who went to department stores and shopping malls (aOR 0.64 [95% CI 0.45–0.91]) compared with those who did not. In contrast, the odds of infection were higher among individuals who attended karaoke with others (aOR 2.53 [95% CI 1.25–5.09]) and individuals who visited a gym (aOR 1.87 [95% CI 1.11–3.16]), both compared with those who did not.

3.8 | Association between behaviors related to work/school and travel in the past 2 weeks and SARS-CoV-2 infection

We lastly examined whether behaviors related to work/school were associated with SARS-CoV-2 infection (Table 4). The odds of infection

TABLE 2 Association of SARS-CoV-2 infection with various activities/situations

	Test-positive, n (%)	Test-negative, n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
Having a conversation at a close distance (within arm's reach)				
No	142 (53.4)	283 (55.3)	1	1
Yes	124 (46.6)	229 (44.7)	1.08 (0.80–1.45)	0.92 (0.65–1.30)
Closed spaces with poor ventilation/air exchange				
No	225 (84.6)	460 (89.8)	1	1
Yes	41 (15.4)	52 (10.2)	1.61 (1.04–2.50)	1.24 (0.76–2.03)
Large gatherings that involve eating and/or drinking for an extended period of time				
No	221 (83.1)	471 (92.0)	1	1
Yes	45 (16.9)	41 (8.0)	2.34 (1.49–3.68)	2.36 (1.38–4.05)
Crowded places				
No	189 (71.1)	378 (73.8)	1	1
Yes	77 (29.0)	134 (26.2)	1.15 (0.83–1.60)	1.03 (0.71–1.50)
Cohabitation in small living quarters				
No	250 (94.0)	472 (92.2)	1	1
Yes	16 (6.0)	40 (7.8)	0.76 (0.41–1.38)	0.77 (0.39–1.53)
Frequency of social gatherings attended that involved eating/drinking				
0 (did not attend)	75 (28.9)	208 (41.8)	1	1
1	38 (14.6)	85 (17.1)	1.24 (0.78–1.97)	1.37 (0.81–2.31)
2	42 (16.2)	73 (14.7)	1.60 (1.00–2.53)	1.60 (0.94–2.72)
≥3	105 (40.4)	132 (26.5)	2.21 (1.53–3.19)	2.00 (1.31–3.05)
Presence or absence of alcohol in social gatherings that involved eating/drinking				
Did not attend	74 (28.8)	207 (41.8)	1	1
No alcohol	38 (14.8)	111 (22.4)	0.96 (0.61–1.51)	0.93 (0.56–1.55)
With alcohol	145 (56.4)	177 (35.8)	2.29 (1.62–3.23)	2.29 (1.53–3.42)
Location of social gatherings attended that involved eating/drinking				
Did not go out to eat	75 (31.9)	208 (43.5)	1	1
Only at home	16 (6.8)	21 (4.4)	2.11 (1.05–4.26)	2.10 (0.92–4.77)
Restaurants/bars[b]	134 (57.0)	239 (50.0)	1.55 (1.11–2.18)	1.55 (1.04–2.30)
Outdoors/parks[c]	10 (4.3)	10 (2.1)	2.77 (1.11–6.93)	2.87 (1.01–8.13)
Time of day of social gatherings attended that involved eating/drinking				
Did not go out to eat	75 (28.9)	208 (41.8)	1	1
Daytime only	20 (7.7)	76 (15.3)	0.73 (0.42–1.28)	0.76 (0.41–1.42)
Evening/night	165 (63.5)	214 (43.0)	2.14 (1.53–2.98)	2.07 (1.40–3.04)
Visiting a cafe with others				
No	140 (58.1)	306 (64.3)	1	1
Yes	101 (41.9)	170 (35.7)	1.30 (0.95–1.78)	1.08 (0.75–1.57)
Ordering takeout				
No	160 (64.5)	291 (60.8)	1	1
Yes	88 (35.5)	188 (39.3)	0.85 (0.62–1.17)	0.80 (0.56–1.15)
Food delivery				
No	149 (58.7)	309 (63.5)	1	1
Yes	105 (41.3)	178 (36.6)	1.22 (0.90–1.67)	1.40 (0.97–2.01)
Eating out by oneself				
No	150 (59.1)	281 (57.6)	1	1
Yes	104 (40.9)	207 (42.4)	0.94 (0.69–1.28)	0.79 (0.55–1.13)

(Continues)

TABLE 2 (Continued)

	Test-positive, n (%)	Test-negative, n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
Maximum number of people attended including oneself				
Did not go out to eat/drink or to a cafe	61 (28.6)	169 (39.2)	1	1
<5 people	112 (52.6)	213 (49.4)	1.46 (1.00–2.11)	1.31 (0.86–2.00)
≥5 people	40 (18.8)	49 (11.4)	2.26 (1.36–3.77)	1.81 (1.00–3.30)
Maximum time spent				
Did not go out to eat/drink or to a cafe	61 (25.4)	169 (36.3)	1	1
<2 h	51 (21.3)	118 (25.3)	1.20 (0.77–1.86)	1.01 (0.61–1.65)
≥2 h	128 (53.3)	179 (38.4)	1.98 (1.37–2.87)	1.76 (1.14–2.71)
Mask wearing (study participant)				
Did not go out to eat/drink or to a cafe	61 (25.0)	169 (36.4)	1	1
Wore at all times except when eating/drinking	28 (11.5)	72 (15.5)	1.08 (0.64–1.82)	0.96 (0.53–1.73)
Took mask off when food/drink was served	100 (41.0)	185 (39.9)	1.50 (1.02–2.19)	1.29 (0.84–2.00)
Did not wear one/took mask off when seated	55 (22.5)	38 (8.2)	4.01 (2.42–6.66)	4.18 (2.29–7.64)
Mask wearing (others)				
Did not go out to eat/drink or to a cafe	61 (26.2)	169 (37.1)	1	1
Wore at all times except when eating/drinking	20 (8.6)	51 (11.2)	1.09 (0.60–1.97)	0.96 (0.49–1.86)
Took mask off when food/drink was served	89 (38.2)	190 (41.8)	1.30 (0.88–1.91)	1.12 (0.72–1.74)
Did not wear one/took mask off when seated	63 (27.0)	45 (9.9)	3.88 (2.40–6.28)	3.74 (2.13–6.55)

[a]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, past SARS-CoV-2 infection, health-care facility, and calendar week.
[b]Individuals may or may not have history of gathering at home.
[c]Individuals may or may not have history of gathering at home, restaurants, and bars.

TABLE 3 Association of SARS-CoV-2 infection with type of mask used

	Test-positive, n (%)	Test-negative, n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
Type of mask used regularly				
Medical/surgical mask	134 (55.6)	340 (69.4)	1	1
Cloth mask	53 (22.0)	82 (16.7)	1.64 (1.10–2.44)	1.77 (1.11–2.83)
Polyurethane mask	53 (22.0)	68 (13.9)	1.97 (1.31–2.98)	1.47 (0.91–2.38)
No mask	1 (0.4)	0 (0.0)	N/A	N/A
Type of mask used regularly (individuals who *did not* report attending social gathering or visiting a cafe with others)				
Medical/surgical mask	33 (61.1)	114 (68.7)	1	1
Cloth mask	11 (20.4)	32 (19.3)	1.19 (0.54–2.61)	1.48 (0.51–4.29)
Polyurethane mask	10 (18.5)	20 (12.1)	1.73 (0.74–4.05)	0.75 (0.24–2.37)
No mask	0 (0.0)	0 (0.0)	N/A	N/A
Type of mask used regularly (individuals who reported attending social gathering or visiting a cafe with others)				
Medical/surgical mask	98 (53.9)	219 (70.9)	1	1
Cloth mask	42 (23.1)	46 (14.9)	2.04 (1.26–3.30)	2.03 (1.16–3.56)
Polyurethane mask	41 (22.5)	44 (14.2)	2.08 (1.28–3.39)	1.62 (0.91–2.89)
No mask	1 (0.6)	0 (0.0)	N/A	N/A

[a]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, past SARS-CoV-2 infection, health-care facility, and calendar week.

were not higher among individuals who have work/school (aOR 1.01 [95% CI 0.60–1.69]) and who attended work/school full time (aOR 1.11 [95% CI 0.65–1.90]), compared with those who did not or who attended work/school part time. As millions of people commute each day in metropolitan prefectures in crowded trains, many were afraid of being infected on these trains, but the odds of infection were not higher among those who used trains to commute (aOR 0.84 [95% CI 0.57–1.24]). Teleworking was also encouraged by the government,

TABLE 4 Association of SARS-CoV-2 infection with behaviors other than going out to eat/drink

	Test-positive, n (%)	Test-negative, n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
Indoor events/gathering[b]				
No	219 (90.9)	432 (92.1)	1	1
Yes	22 (9.1)	37 (7.9)	1.17 (0.68–2.04)	1.45 (0.76–2.76)
Outdoor events/gathering[b]				
No	221 (91.7)	435 (94.4)	1	1
Yes	20 (8.3)	26 (5.6)	1.51 (0.83–2.77)	1.34 (0.67–2.69)
Department stores and shopping malls				
No	116 (46.8)	189 (39.1)	1	1
Yes	132 (53.2)	294 (60.9)	0.73 (0.54–1.00)	0.64 (0.45–0.91)
Karaoke with others				
No	227 (90.4)	463 (96.1)	1	1
Yes	24 (9.6)	19 (3.9)	2.58 (1.38–4.80)	2.53 (1.25–5.09)
Gym				
No	212 (83.5)	432 (89.8)	1	1
Yes	42 (16.5)	49 (10.2)	1.75 (1.12–2.72)	1.87 (1.11–3.16)
Work/school				
No	32 (12.2)	77 (15.2)	1	1
Yes	231 (87.8)	430 (84.8)	1.29 (0.83–2.01)	1.01 (0.60–1.69)
Work/school full time[c]				
Part time	28 (12.5)	65 (15.4)	1	1
Full time	196 (87.5)	358 (84.6)	1.27 (0.79–2.04)	1.11 (0.65–1.90)
Use trains to commute[c]				
No	79 (34.2)	133 (30.9)	1	1
Yes	152 (65.8)	297 (69.1)	0.86 (0.61–1.21)	0.84 (0.57–1.24)
Frequency of teleworking/attending online classes[c,d]				
0%	98 (51.3)	180 (51.3)	1	1
25%	34 (17.8)	45 (12.8)	1.39 (0.83–2.31)	1.17 (0.63–2.17)
50%	17 (8.9)	46 (13.1)	0.68 (0.37–1.25)	0.71 (0.36–1.43)
75%	21 (11.0)	30 (8.6)	1.29 (0.70–2.37)	1.55 (0.78–3.10)
Almost 100%	21 (11.0)	50 (14.3)	0.77 (0.44–1.36)	0.99 (0.51–1.91)
Residing/visiting an urban location[e]				
Never	15 (5.9)	55 (11.0)	1	1
Residing an urban location	180 (70.6)	326 (65.5)	2.02 (1.11–3.69)	3.46 (1.52–7.84)
Visiting an urban location	60 (23.5)	117 (23.5)	1.88 (0.98–3.60)	2.43 (1.11–5.33)
Travel				
No travel	224 (92.2)	418 (94.1)	1	1
Business travel	5 (2.1)	12 (2.7)	0.78 (0.27–2.23)	1.05 (0.32–3.47)
Non-business travel	14 (5.8)	14 (3.2)	1.87 (0.87–3.98)	1.56 (0.65–3.73)

[a]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, past SARS-CoV-2 infection, health-care facility, and calendar week.
[b]Gatherings include events, social groups, and school extracurricular activities.
[c]Restricted to individuals with work and/or school.
[d]Restricted to individuals who work full time.
[e]Surrounding areas of city centers/major train stations.

but the odds of infection were not lower among individuals who teleworked/attended online classes almost 100% of the time (aOR 0.99 [95% CI 0.51–1.91]), compared with those who did not. When asked about travel-related factors, the odds of infection were higher among individuals who reside in an urban location (aOR 3.46 [95% CI 1.52–7.84]) or visited an urban location (aOR 2.43 [95% CI

1.11–5.33]), compared with those who did not, respectively. In contrast, the odds of infection were not higher among individuals who traveled on business (aOR 1.05 [95% CI 0.32–3.47]) or for non-business purposes (aOR 1.56 [95% CI 0.65–3.73]), compared with those who did not travel.

4 | DISCUSSION

In this multicenter case–control study, we investigated the association between various behavioral factors and SARS-CoV-2 infection in the community setting. First, we found that attending social gatherings with food/drinks was associated with SARS-CoV-2 infection. We strengthened our findings and those of previous reports[16–18] by showing the association in a dose-dependent manner, with the odds of infection increasing with increasing frequency of social gatherings in the past 2 weeks. We also investigated the details of specific settings of social gatherings that were associated with infection. First, attending social gatherings with alcohol was associated with infection. When we examined the location of gatherings, attending gatherings at restaurants or bars was associated with infection. This finding was consistent with previous ecological/modeling and case–control studies where going to restaurants or bars was associated with infection.[16–18] As there were strict restrictions imposed upon restaurants and bars in Japan, there was a concern that people may choose to have gatherings at home or out on public streets/parks, with 10% of young people reporting that they had done the latter.[19] Indeed, individuals who had social gatherings exclusively at home had higher odds of infection, and attending gatherings outdoors or at parks was associated with infection. Attending a gathering at night was also associated with infection. The reason may be that social gatherings at night tend to be longer in duration, and individuals may become more intoxicated and care less about infection prevention measures. In contrast to the findings on social gatherings, ordering takeout, using food delivery services, and eating out by oneself were not associated with infection. This is expected as these behaviors would not substantially increase contact with others; our findings provide opportunity for the food industry to sustain its business. Details about how these gatherings took place also mattered; attending a gathering with five or more people or gathering lasting 2 hours or longer was associated with infection. Not wearing a mask or taking it off when seated at the gathering was also associated with infection, supporting the idea of "mask-dining" (taking off the mask only when putting food in the mouth or sipping drinks and keeping the mask on while talking, while waiting for food/drinks to be served, and after finishing meals), which has been recommended by the government when at restaurants and bars. On a related note, regular use of cloth or polyurethane masks was associated with infection, specifically among individuals who attended social gatherings or visited a cafe with others. In addition to source control, the association here suggested the protective effect of medical/surgical masks,[20] and individuals who engage in high-risk behaviors may benefit from wearing medical/surgical masks. We could not evaluate associations with any mask use, as the mask-wearing adherence was high.

We identified some factors unrelated to social gatherings, namely, karaoke and gym use, which are also known to be hotspots for clusters.[7] Shopping at department stores and shopping malls was negatively associated with infection. This may have been because individuals in metropolitan areas visit department stores to buy products for use at home, although there have been reported clusters in these settings.[21] Unlike in previous reports from the United States and France,[18,22] we did not find a negative association between teleworking and infection, which may reflect the difference in the magnitude of epidemics or the amount of physical contact at the work place.

These findings collectively indicate that, although epidemiological evidence was scarce at the time of implementation of the targeted policies in Japan, the policies appropriately targeted high-risk individuals and activities/situations. Our results highlight the importance of rapidly assessing and identifying modifiable behavioral risk factors for SARS-CoV-2 infection and of informing risk communication and shaping public health policy with targeted approaches tailored to each country's situation, in addition to universal recommendations. Targeted approaches can have substantial financial consequences to individuals, so appropriate social security and welfare policies should be paired with restrictions imposed.

This study had several limitations. First, biases inherent in observational studies such as recall bias and residual confounding are possible. Second, controls may have been infected with other viruses due to similar exposures, which can underestimate the odds ratio (Supporting Information). Third, our primary analyses were complete case analyses. However, when we did sensitivity analyses to impute missing exposure variables in each analysis, findings were similar. Finally, identified risk factors may be country/region/culture-specific and time-dependent due to changes in COVID-19-related policies and behaviors, as well as emergence of SARS-CoV-2 variants.

In conclusion, we identified multiple behavioral factors associated with SARS-CoV-2 infection, particularly in various settings of social gatherings. These factors may be country/culture-specific and time-dependent due to changes in COVID-19-related policies and behaviors, so continuous monitoring in various settings is important to inform decision making.

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AUTHOR CONTRIBUTIONS

Takeshi Arashiro: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; visualization; funding acquisition. **Yuzo Arima:** Conceptualization; formal analysis; methodology; resources; supervision. **Hirokazu**

Muraoka: Investigation. **Akihiro Sato:** Investigation. **Kunihiro Oba:** Investigation. **Yuki Uehara:** Investigation. **Hiroko Arioka:** Investigation. **Hideki Yanai:** Investigation. **Naoki Yanagisawa:** Investigation. **Yoshito Nagura:** Investigation. **Yasuyuki Kato:** Investigation. **Hideaki Kato:** Investigation. **Akihiro Ueda:** Investigation. **Koji Ishii:** Investigation. **Takao Ooki:** Investigation. **Hideaki Oka:** Investigation. **Yusuke Nishida:** Investigation. **Ashley Stucky:** Formal analysis; investigation; visualization. **Reiko Miyahara:** Formal analysis; methodology. **Chris Smith:** Conceptualization; formal analysis; methodology; supervision. **Martin Hibberd:** Conceptualization; formal analysis; methodology; supervision. **Koya Ariyoshi:** Conceptualization; formal analysis; methodology; supervision. **Motoi Suzuki:** Conceptualization; formal analysis; funding acquisition; methodology; supervision.

DATA AVAILABILITY STATEMENT

Individual-level data of patients included in this manuscript after de-identification are considered sensitive and will not be shared. The study methods and statistical analyses are all described in detail in Section 2 and throughout the manuscript.

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REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. 2021. Accessed April 4, 2022. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
3. National Institute of Infectious Diseases. Active case investigation on COVID-19 cases (In Japanese). 2021. Accessed April 4, 2022. https://www.niid.go.jp/niid/ja/2019-ncov/2559-cfeir/10800-covid19-02.html
4. Tanaka A, Yamamoto S, Miyo K, et al. Seroprevalence of antibodies against SARS-CoV-2 in a large national hospital and affiliated facility in Tokyo, Japan. *J Infect*. 2021;82(4):e1-e3. doi:10.1016/j.jinf.2021.01.010
5. Cabinet Secretariat, Government of Japan. COVID-19 information and resources: measures to be taken based on the basic response policy. 2020. Accessed April 4, 2022. https://corona.go.jp/en/emergency/
6. Cabinet Secretariat, Government of Japan. Summary on the state of emergency due to COVID-19 (In Japanese). 2020. Accessed April 4, 2022. https://corona.go.jp/news/news_20200421_70.html
7. Furuse Y, Sando E, Tsuchiya N, et al. Clusters of coronavirus disease in communities, Japan, January-April 2020. *Emerg Infect Dis*. 2020;26(9):2176-2179. doi:10.3201/eid2609.202272
8. Tokyo Metropolitan Government. Updates on COVID-19 in Tokyo. 2020. Accessed April 4, 2022. https://stopcovid19.metro.tokyo.lg.jp/en/monitoring
9. National Institute of Infectious Diseases. National Institute of Infectious Diseases: Case-control study to evaluate behavioral risk factors of SARS-CoV-2 infection: preliminary report of a pilot study (In Japanese). 2021. Accessed April 4, 2022. https://www.mhlw.go.jp/content/10900000/000807662.pdf
10. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436. doi:10.1038/s41586-020-2521-4
11. Hawkins RB, Charles EJ, Mehaffey JH. Socio-economic status and COVID-19-related cases and fatalities. *Public Health*. 2020;189:129-134. doi:10.1016/j.puhe.2020.09.016
12. Ministry of Health, Labour and Welfare. Information on health and medical consultation. 2020. Accessed April 4, 2022. https://www.mhlw.go.jp/stf/covid-19/kenkou-iryousoudan_00006.html
13. World Health Organization. Considerations for implementing and adjusting public health and social measures in the context of COVID-19. 2021. Accessed April 4, 2022. https://www.who.int/publications/i/item/considerations-in-adjusting-public-health-and-social-measures-in-the-context-of-covid-19-interim-guidance
14. Cabinet Secretariat, Government of Japan. COVID-19 response: efforts to prevent the spread of infection (In Japanese). 2020. Accessed April 4, 2022. https://corona.go.jp/proposal/
15. RIKEN Center for Computational Science. Prediction and prevention of SARS-CoV-2 droplet infection in indoor environment (In Japanese). 2021. Accessed April 4, 2022. https://www.r-ccs.riken.jp/wp/wp-content/uploads/2021/03/210304tsubokura.pdf
16. Chang S, Pierson E, Koh PW, et al. Mobility network models of COVID-19 explain inequities and inform reopening. *Nature*. 2021;589(7840):82-87. doi:10.1038/s41586-020-2923-3
17. Fisher KA, Tenforde MW, Feldstein LR, et al. Community and close contact exposures associated with COVID-19 among symptomatic adults ≥18 years in 11 outpatient health care facilities—United States, July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(36):1258-1264. doi:10.15585/mmwr.mm6936a5
18. Galmiche S, Charmet T, Schaeffer L, et al. Exposures associated with SARS-CoV-2 infection in France: a nationwide online case-control study. *Lancet Reg Health Eur*. 2021;7:100148 doi:10.1016/j.lanepe.2021.100148
19. Tokyo Metropolitan Government. Results of the online questionnaire to young people in Tokyo (In Japanese). 2021. Accessed April 4, 2022. https://www.metro.tokyo.lg.jp/tosei/hodohappyo/press/2021/05/25/20.html
20. Bundgaard H, Bundgaard JS, Raaschou-Pedersen DET, et al. Effectiveness of adding a mask recommendation to other public health measures to prevent SARS-CoV-2 infection in Danish mask wearers: a randomized controlled trial. *Ann Intern Med*. 2021;174(3):335-343. doi:10.7326/M20-6817
21. National Institute of Infectious Diseases. Proposal on infection prevention measures to owners, employees, and occupational health staff of department stores and shopping malls (In Japanese). 2021. Accessed April 4, 2022. https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10579-covid19-18.html
22. Fisher KA, Olson SM, Tenforde MW, et al. Telework before illness onset among symptomatic adults aged ≥18 years with and without COVID-19 in 11 outpatient health care facilities—United States, July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1648-1653. doi:10.15585/mmwr.mm6944a4

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Supporting Information

COVID-19 situation in Japan during the study period
During this period, transmission intensity was relatively high and cases detected were increased from 20 to 160 per 100 000 population in Tokyo, with a state of emergency in effect during June 8-20 as well as July 12-August 1, and a semi-state of emergency during June 21-July 11. The study period was the replacement period from the alpha variant to the delta variant in the Kanto area.

Symptomatic infection
We considered individuals as symptomatic if they had any of the following: fever above 37.5°C, malaise, chills, joint pain, headache, runny nose, cough, sore throat, shortness of breath, gastrointestinal symptoms (vomiting, diarrhea, stomach ache), and loss of taste/smell.

Definition of comorbidities
Comorbidities included any one of the following: hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.

Choice of controls
A test-negative design (individuals tested for SARS-CoV-2 with negative results serve as controls) has been established and utilized extensively for the evaluation of vaccine effectiveness for infectious diseases such as influenza and COVID-19; this is because of the antigen specificity of the vaccines.[1-5] As for risk factor analysis, it is possible that test-negative individuals also share some risk factors with the cases as the controls are also symptomatic. Although ideal controls would be individuals randomly selected, tested negative, and from the same population as the cases, this was not possible for us due to feasibility. We considered utilizing other additional controls while formulating the protocol. One potential method was to have an accompanying person (AP) as a control, but individuals getting tested for SARS-CoV-2 who are not severely ill often go to health-care facilities alone to keep the AP from becoming a close contact, so it was not feasible in our setting (APs are usually not allowed in the medical facilities for this reason). Another option was individuals who are getting tested with no symptoms and without close contact. However, there is an issue of why these individuals are getting tested in the first place. In Japan, people who get tested despite being asymptomatic are usually at high risk of exposure by nature of their occupation (e.g. health-care workers and other specific occupations) or behaviors (individuals who engage in high-risk recreational behaviors regularly, individuals who are constantly worried about getting infected [e.g. mysophobia], individuals travelling overseas, etc.). Asymptomatic individuals getting tested for such reasons would not serve as a representative sample of the source population that gave rise to the cases. The final option was classical hospital controls who visit other departments such as surgery and orthopedics. However, these would not be appropriate since these individuals are a lot older on average and very different in terms of factors that we are and are not interested in, including potential confounding factors. Also, there are no such departments in many of our study sites as they are small clinics. Often, it can be very challenging to match the traits of cases with controls in a case-control study.[6] We concluded that the behavioral and demographic traits among cases and controls would be most similar as they were sourced from those presenting to the same medical facilities for testing (e.g. health-seeking behaviors), and as long as participants complete the questionnaire before receiving their test results, the influence of social desirability bias should be minimal. Also, if controls are infected with other viruses due to similar exposures, the odds ratio for SARS-CoV-2 infection would be an underestimate of the true association. In other words, our design would detect differences in magnitude of a particular risk factor or risk factors that would be specific for COVID-19. In fact, even though many respiratory pathogens (influenza virus, *Streptococcus pneumoniae*, etc.) were circulating at extremely low levels during the study period, at least partially due to social and public health measures, we are seeing SARS-CoV-2 epidemics repeatedly. This suggests that SARS-CoV-2 has unique features that allow it to circulate even under strict public health and social measures. Finally, the threshold for testing was low for SARS-CoV-2 in Japan at the time of the study and any one of very broad spectrum of symptoms would trigger testing and be included in the study, not just individuals with respiratory symptoms. Therefore, at the start of the investigation, we expected to see at least some risk factors identified in other studies that utilized similar methods to elucidate risk factors.[7-9]

Sample size calculation
Assuming 10% positivity (based on data when the study was planned),[8] 30-50% of controls having the exposures of interest, a two-tailed significance level of 5%, and 80% power, enrollment of approximately 70-80

cases and 700-800 controls was needed to detect a minimal odds ratio of 2. We planned to continue enrollment even after reaching this target to allow for sub-analysis and continued assessment of risk factors that may be time-varying.

References

1. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021;384:1412–1413.
2. Dean NE, Hogan JW, Schnitzer ME. Covid-19 vaccine effectiveness and the test-negative design. *N Engl J Med*. 2021;385:1431–1433.
3. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine*. 2013;31:2165–2168.
4. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med*. 2021;385:585–594.
5. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev *Vaccines*. 2014;13:1571–1591.
6. Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls CMJE, Pearce N. A test-negative design with additional population controls can be used to rapidly study causes of the SARS-CoV-2 epidemic. *Epidemiology*. 2020;31:836–843.
7. Fisher KA, Tenforde MW, Feldstein LR, et al. Community and close contact exposures associated with COVID-19 among symptomatic adults ≥18 years in 11 outpatient health care facilities - United States, July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1258–1264.
8. Fisher KA, Olson SM, Tenforde MW, et al. Telework before illness onset among symptomatic adults aged ≥18 years with and without COVID-19 in 11 outpatient health care facilities - United States, July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1648–1653.
9. Tenforde MW, Fisher KA, Patel MM. Identifying COVID-19 risk through observational studies to inform control measures. *JAMA*. 2021;325:1464–1465.

Paper 2 : Factors associated with lack of vaccination intent in Japan

Arashiro T*, Arima Y, Stucky A, et al. Social and Behavioral Factors Associated with Lack of Intent to Receive COVID-19 Vaccine, Japan. **Emerg Infect Dis.** 2022 Sep;28(9):1909-1910. doi: 10.3201/eid2809.220300. **(*first and corresponding author)**

PhD candidate contributions:
Conceptualization (main), design (main), data acquisition (done by a marketing research company), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: MHLW)

The paper is based on Objective 2.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

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Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Emerging Infectious Diseases		
When was the work published?	July 6, 2022		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualization (main), design (main), data acquisition (done by a marketing research company), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: MHLW)

SECTION E

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Date	February 25, 2024

Social and Behavioral Factors Associated with Lack of Intent to Receive COVID-19 Vaccine, Japan

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Persons in Japan who did not intend to receive COVID-19 vaccines after widespread rollout were less likely than others to engage in preventive measures or to be afraid of getting infected or infecting others. They were also not less likely to engage in potentially high-risk behaviors, suggesting similar or higher exposure risks.

COVID-19 vaccines have become a critical tool in pandemic control (*1*). In Japan, BNT162b2 (Pfizer-BioNTech, https://www.pfizer.com), mRNA-1273 (Moderna, https://www.modernatx.com), and ChAdOx1 nCoV-19 (AZD1222; Oxford/AstraZeneca, https://www.astrazeneca.com) have been approved, but use of ChAdOx1 nCoV-19 has been minimal. For the Omicron variant, 2 doses of mRNA vaccines might not be highly protective against symptomatic infection, but early data suggest they are still highly protective against severe disease and that a booster dose provides further protection (*2*–*4*). Addressing persons at highest risk for severe or fatal COVID-19 who do not intend to be vaccinated has become paramount as we transition to the endemic phase, which is especially true in Japan because most persons are not protected by natural infection (*5*). Several studies have addressed reasons behind this hesitancy at the early stage of vaccine rollout (*6*–*9*), but evidence on attitudes toward risk for infection and prevention and risk behaviors is scarce.

We retrospectively analyzed an online survey about life during the COVID-19 pandemic conducted by a marketing research company in Japan during November 26–28, 2021, after the vaccine rollout had stabilized and 70% of the population had received 2 doses. The total number of survey participants was 2,500 (250 participants for each sex and 10-year age group, 20–60 years of age) (Appendix, https://wwwnc.cdc.gov/EID/article/28/9/22-0300-App1.pdf). We extracted sociodemographic information, vaccination status (choices included vaccinated once, vaccinated twice, unvaccinated with intention to be vaccinated, unvaccinated without intention to be vaccinated, and prefer not to answer), attitudes toward COVID-19-related issues (e.g., whether participants were afraid of getting infected), and behaviors in the previous week (e.g., preventive measures such as mask-wearing and potentially high-risk behaviors such as visiting bars or restaurants) (*10*). For vaccination status, we categorized the first 3 options into vaccinated or intend to be vaccinated and the last 2 choices into no intention to be vaccinated, because persons who preferred not to answer likely did not intend to be vaccinated but were unwilling to disclose this information. Depending on the social or behavioral factor, we adjusted for potential confounders that were determined a priori (*6*–*9*). This study was reviewed and exempt from ethics approval by the Institutional Review Board of the National Institute of Infectious Diseases, Japan.

Overall, 2,069 (82.8%) participants had received 2 doses, 35 (1.4%) had received 1 dose, 95 (3.8%) were not vaccinated but intended to be, 203 (8.1%) had no intention of being vaccinated, and 98 (3.9%) preferred not to answer. By age group, proportions of vaccinated persons were similar to those in the general population of Japan (Appendix). The proportions of participants residing in each geographic region were also similar to the national distribution (Appendix). Compared with men 60–69 years of age, men 20–39 years of age, as well as women 20–40 years of age, were ≥2-fold more likely to have no intention of being vaccinated (Appendix Table 1). Persons who did not intend to be vaccinated were less likely to be afraid of getting infected (adjusted odds ratio [aOR] 2.32, 95% CI 1.53–3.53), family members getting infected (aOR 2.50, 95% CI 1.68–3.71), infecting others (aOR 2.58, 95% CI 1.73–3.84), and bed shortages caused by a surge in severe COVID-19 cases (aOR 1.89, 95% CI 1.25–2.87). Persons who did not intend to be vaccinated also did not plan to receive a third (booster) dose, but 74% of persons who had received or intended to receive vaccines also intended to receive a booster dose. Persons without intention to be vaccinated were more likely to report not wearing a mask (aOR 2.01, 95% CI 1.52–2.65) and not using hand sanitizer (aOR 1.90, 95% CI 1.47–2.47) in the previous week. These persons were less likely to have gone shopping for nonessential goods in the past week (aOR 0.70, 95% CI 0.51–0.97), but no association was seen between vaccination intent and refraining from meeting with others (aOR

1.20, 95% CI 0.87–1.65) or going to crowded places or traveling (aOR 1.11, 95% CI 0.83–1.47). We also saw no association between vaccination intent and meeting noncohabitating friends, acquaintances, or family members (aOR 0.73, 0.47–1.12); dining out (aOR 0.92, 0.65–1.30); going out socially (aOR 0.87, 0.59–1.27); traveling (aOR 0.51, 0.22–1.22); or going to a gym (aOR 1.08, 0.64–1.83). We obtained similar results when we excluded persons who preferred not to answer regarding their vaccination status.

Persons who did not intend to receive COVID-19 vaccines were less likely to engage in preventive measures or be afraid of getting infected or infecting others, but we observed no association between vaccine intention and engaging in potentially high-risk behaviors. These results suggest that these nonintenders have similar or higher exposure risks compared with vaccinees and intenders. Similar surveys might be considered in other countries to understand vaccine denial and inform policies and risk communication.

Limitations of our study include selection bias and recall bias. Social desirability bias might be an issue, but this survey about life during the pandemic was not administered as an assessment about COVID-19 vaccination intent.

Acknowledgment

We thank the marketing research company for providing the original survey data.

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References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic [cited 2022 Jun 5]. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med. 2022;386:1532–46. https://doi.org/10.1056/NEJMoa2119451
3. Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants [Erratum in: Nat Med. 2022;28:1095]. Nat Med. 2022;28:1063–71. https://doi.org/10.1038/s41591-022-01753-y
4. United Kingdom Health Security Agency. COVID-19 vaccine surveillance reports [cited 2022 Jun 5]. https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports
5. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20:533–4. https://doi.org/10.1016/S1473-3099(20)30120-1
6. Nomura S, Eguchi A, Yoneoka D, Kawashima T, Tanoue Y, Murakami M, et al. Reasons for being unsure or unwilling regarding intention to take COVID-19 vaccine among Japanese people: a large cross-sectional national survey. Lancet Reg Health West Pac. 2021;14:100223. https://doi.org/10.1016/j.lanwpc.2021.100223
7. Yoda T, Katsuyama H. Willingness to receive COVID-19 vaccination in Japan. Vaccines (Basel). 2021;9:48. https://doi.org/10.3390/vaccines9010048
8. Machida M, Nakamura I, Kojima T, Saito R, Nakaya T, Hanibuchi T, et al. Acceptance of a COVID-19 vaccine in Japan during the COVID-19 pandemic. Vaccines (Basel). 2021;9:210. https://doi.org/10.3390/vaccines9030210
9. Okubo R, Yoshioka T, Ohfuji S, Matsuo T, Tabuchi T. COVID-19 vaccine hesitancy and its associated factors in Japan. Vaccines (Basel). 2021;9:662. https://doi.org/10.3390/vaccines9060662
10. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses. 2022; 16:952–61. https://doi.org/10.1111/irv.12992

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Social and Behavioral Factors Associated with Lack of Intent to Receive COVID-19 Vaccine, Japan

Appendix

Survey Background

The participants in the nationwide survey were those who voluntarily registered to be a panel member of a marketing research company. As of January 2022, the company had ≈5.41 million active panel members who have responded to ≥1 questionnaire in the past year (4.3% of 126.15 million population in Japan). In exchange for responding to questionnaires, panel members receive points that can be exchanged for products and services from partner companies.

The survey was conducted exclusively in Japanese. Although foreigners are an important consideration when formulating vaccination policy, they comprise only 2.2% (2.75 million out of 126.15 million) of the total population in Japan (*1*). The survey participants came from all 47 prefectures of Japan.

Comparison of Survey Participants and General Population of Japan

Since the survey was conducted on a voluntary basis, there was concern that the survey participants could differ from the general population of Japan. Therefore, we compared the survey participants and the general population for (1) proportion of persons vaccinated twice by age group and (2) geographic region of residence, in an attempt to evaluate the generalizability of our findings.

Data on the proportion of vaccinated persons in the general population by age group were only available for the date of accessing the data (i.e., February 14, 2022), but the national proportion of persons vaccinated twice has remained similar (73.0% on November 26, 2021, compared to 74.4% on February 14, 2022) (*2*). The proportion of individuals vaccinated twice among the survey participants was similar to the national distribution (Appendix Table 2). The proportions of participants residing in each geographic region were also similar to national proportions (Appendix Table 3).

Appendix Table 1. Association between lack of intention to receive COVID-19 vaccination and various social and behavioral factors based on a questionnaire conducted in late November 2021, Japan

Category	No intention to be vaccinated (n = 301)	Vaccinated or intend to be vaccinated (n = 2,199)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age group, years/sex				
60–69/Male	16 (5.3)	234 (10.6)	1	-
50–59/Male	23 (7.6)	227 (10.3)	1.48 (0.76–2.88)	-
40–49/Male	27 (9.0)	223 (10.1)	1.77 (0.93–3.37)	-
30–39/Male	44 (14.6)	206 (9.4)	3.12 (1.71–5.70)	-
20–29/Male	43 (14.3)	207 (9.4)	3.04 (1.66–5.56)	-
60–69/Female	23 (7.6)	227 (10.3)	1.48 (0.76–2.88)	-

Category	No intention to be vaccinated (n = 301)	Vaccinated or intend to be vaccinated (n = 2,199)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
50–59/Female	20 (6.6)	230 (10.5)	1.27 (0.64–2.52)	-
40–49/Female	36 (12.0)	214 (9.7)	2.46 (1.33–4.56)	-
30–39/Female	31 (10.3)	219 (10.0)	2.07 (1.10–3.89)	-
20–29/Female	38 (12.6)	212 (9.6)	2.62 (1.42–4.84)	-
Region of residence				
Hokkaido/Tohoku	36 (12.0)	259 (11.8)	1	-
Kanto	97 (32.2)	848 (38.6)	0.82 (0.55–1.24)	-
Chubu	60 (19.9)	347 (15.8)	1.24 (0.80–1.94)	-
Kinki	56 (18.6)	416 (18.9)	0.97 (0.62–1.51)	-
Chugoku/Shikoku	20 (6.6)	162 (7.4)	0.89 (0.50–1.59)	-
Kyushu	32 (10.6)	167 (7.6)	1.38 (0.82–2.31)	-
Marital status*				
Married, divorced, or widowed	130 (43.2)	1,353 (61.5)	1	1
Never married	171 (56.8)	846 (38.5)	2.10 (1.65–2.68)	1.85 (1.40–2.44)
Presence of children*				
Yes	84 (27.9)	1,036 (47.1)	1	1
No	217 (72.1)	1,163 (52.9)	2.30 (1.77–3.00)	2.01 (1.51–2.68)
Presence of cohabitants*				
Yes	203 (67.4)	1,730 (78.7)	1	1
No	98 (32.6)	469 (21.3)	1.78 (1.37–2.31)	1.66 (1.26–2.17)
Household income, Japanese Yen*				
4–10 million	60 (19.9)	832 (37.8)	1	1
>10 million	17 (5.7)	189 (8.6)	1.25 (0.71–2.19)	1.40 (0.79–2.48)
3–4 million	27 (9.0)	212 (9.6)	1.77 (1.09–2.85)	1.76 (1.08–2.86)
<3 million	80 (26.6)	406 (18.5)	2.73 (1.92–3.90)	2.90 (2.01–4.18)
Prefer not to answer	117 (38.9)	560 (25.5)	2.90 (2.08–4.03)	3.15 (2.24–4.41)
Occupation type*				
Business person (general)	71 (23.6)	604 (27.5)	1	1

Category	No intention to be vaccinated (n = 301)	Vaccinated or intend to be vaccinated (n = 2,199)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Business person (management)	5 (1.7)	143 (6.5)	0.30 (0.12–0.75)	0.33 (0.13–0.86)
Business person (executive)	5 (1.7)	40 (1.8)	1.06 (0.41–2.78)	1.45 (0.54–3.87)
Staff at public office or nonprofit organization, teacher	10 (3.3)	106 (4.8)	0.80 (0.40–1.61)	0.83 (0.41–1.68)
Contract worker	28 (9.3)	125 (5.7)	1.91 (1.18–3.07)	2.41 (1.47–3.95)
Self-employed (industry/commercial)	9 (3.0)	66 (3.0)	1.16 (0.55–2.43)	1.54 (0.72–3.29)
Self-employed (small office/home office)	3 (1.0)	8 (0.4)	3.19 (0.83–12.3)	4.15 (1.03–16.7)
Agriculture, forestry, fishery	1 (0.3)	9 (0.4)	0.95 (0.12–7.57)	1.19 (0.14–9.95)
Specialist (lawyer, healthcare worker)	6 (2.0)	72 (3.3)	0.71 (0.30–1.69)	0.77 (0.32–1.85)
Part-time employee	46 (15.3)	331 (15.1)	1.18 (0.80–1.75)	1.41 (0.92–2.16)
Homemaker	33 (11.0)	322 (14.6)	0.87 (0.56–1.35)	1.18 (0.72–1.94)
Student	17 (5.7)	78 (3.6)	1.85 (1.04–3.31)	1.61 (0.86–3.03)
Unemployed/retired	55 (18.3)	243 (11.1)	1.93 (1.31–2.82)	2.76 (1.83–4.16)
Other occupation	12 (4.0)	52 (2.4)	1.96 (1.00–3.85)	2.23 (1.12–4.42)
Being afraid of getting infected†				
Slightly to very afraid	263 (87.4)	2,082 (94.7)	1	1
Not at all	38 (12.6)	117 (5.3)	2.57 (1.74–3.79)	2.32 (1.53–3.53)
Being afraid of family members getting infected‡				
Slightly to very afraid	258 (85.7)	2,083 (94.7)	1	1
Not at all	43 (14.3)	116 (5.3)	2.99 (2.06–4.35)	2.50 (1.68–3.71)
Being afraid of infecting others†				
Slightly to very afraid	258 (85.7)	2,076 (94.4)	1	1
Not at all	43 (14.3)	123 (5.6)	2.81 (1.94–4.07)	2.58 (1.73–3.84)
Being afraid of bed shortages due to a surge in severe COVID-19 cases†				
Slightly to very afraid	263 (87.4)	2,077 (94.5)	1	1
Not at all	38 (12.6)	122 (5.6)	2.46 (1.67–3.62)	1.89 (1.25–2.87)

Category	No intention to be vaccinated (n = 301)	Vaccinated or intend to be vaccinated (n = 2,199)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Intention to receive COVID-19 booster vaccine (third dose)				
Yes	0 (0.0)	1,688 (76.8)	1	1
No	203 (67.4)	319 (14.5)	N/A	N/A
Prefer not to answer	98 (32.6)	192 (8.7)	N/A	N/A
Mask-wearing in the past week†				
Yes	188 (62.5)	1,759 (80.0)	1	1
No	113 (37.5)	440 (20.0)	2.40 (1.86–3.10)	2.01 (1.52–2.65)
Use of hand sanitizer in the past week†				
Yes	159 (52.8)	1,570 (71.4)	1	1
No	142 (47.2)	629 (28.6)	2.23 (1.75–2.85)	1.90 (1.47–2.47)
Handwashing with soap in the past week†				
Yes	135 (44.9)	1,370 (62.3)	1	1
No	166 (55.2)	829 (37.7)	2.03 (1.59–2.59)	1.88 (1.45–2.43)
Refrain from using public transport in the past week§				
Yes	60 (19.9)	457 (20.8)	1	1
No	241 (80.1)	1,742 (79.2)	1.05 (0.78–1.42)	1.05 (0.76–1.43)
Refrain from meeting others (including for work) in the past week†				
Yes	56 (18.6)	508 (23.1)	1	1
No	245 (81.4)	1,691 (76.9)	1.31 (0.97–1.79)	1.20 (0.87–1.65)
Refrain from going to crowded places such as events, traveling, or restaurants/bars in the past week‡				
Yes	78 (25.9)	654 (29.7)	1	1
No	223 (74.1)	1,545 (70.3)	1.21 (0.92–1.59)	1.11 (0.83–1.47)
Teleworking or remote learning in the past week†				
Yes	31 (10.3)	232 (10.6)	1	1
No	270 (89.7)	1,967 (89.5)	1.03 (0.69–1.53)	0.94 (0.61–1.45)
Gathering information about preventive measures against COVID-19 in the past week†				
Yes	55 (18.3)	626 (28.5)	1	1
No	246 (81.7)	1,573 (71.5)	1.78 (1.31–2.42)	1.56 (1.14–2.15)
Going shopping to buy food and essential goods in the past week‡				
No	101 (33.6)	611 (27.8)	1	1

Category	No intention to be vaccinated (n = 301)	Vaccinated or intend to be vaccinated (n = 2,199)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Yes	200 (66.5)	1,588 (72.2)	0.76 (0.59–0.98)	0.90 (0.69–1.19)
Going shopping to buy non-essential goods in the past week‡				
No	247 (82.1)	1,646 (74.9)	1	1
Yes	54 (17.9)	553 (25.2)	0.65 (0.48–0.89)	0.70 (0.51–0.97)
Meeting friends, acquaintances, or family members who live separately (noncohabitants) in the past week‡				
No	274 (91.0)	1,932 (87.9)	1	1
Yes	27 (9.0)	267 (12.1)	0.71 (0.47–1.08)	0.73 (0.47–1.12)
Going to work/school in the past week‡				
No	196 (65.1)	1,111 (50.5)	1	1
Yes	105 (34.9)	1,088 (49.5)	0.55 (0.43–0.70)	0.58 (0.43–0.79)
Going out to eat in the past week‡				
No	256 (85.1)	1,801 (81.9)	1	1
Yes	45 (15.0)	398 (18.1)	0.80 (0.57–1.11)	0.92 (0.65–1.30)
Going out socially in the past week‡				
No	264 (87.7)	1,902 (86.5)	1	1
Yes	37 (12.3)	297 (13.5)	0.90 (0.62–1.29)	0.87 (0.59–1.27)
Traveling in the past week†				
No	295 (98.0)	2,109 (95.9)	1	1
Yes	6 (2.0)	90 (4.1)	0.48 (0.21–1.10)	0.51 (0.22–1.22)
Going to a gym in the past week¶				
No	283 (94.0)	2,071 (94.2)	1	1
Yes	18 (6.0)	128 (5.8)	1.03 (0.62–1.71)	1.08 (0.64–1.83)
Going to yoga in the past week¶				
No	281 (93.4)	2,114 (96.1)	1	1
Yes	20 (6.6)	85 (3.9)	1.77 (1.07–2.93)	1.84 (1.10–3.11)

*Odds ratio adjusted for age group/sex and region.

†Odds ratio adjusted for age group/sex, region, marital status, presence of children, presence of cohabitants, household income, and occupation.

‡Odds ratio adjusted for age group/sex, region, marital status, presence of children, presence of cohabitants, and household income.

§Odds ratio adjusted for age group/sex, region, household income, and occupation.

¶Odds ratio adjusted for age group/sex, region, and household income.

Appendix Table 2. Proportions of individuals vaccinated twice among survey participants and the general population of Japan

Age group, years	Survey participants (%)	General population*
20–29	75.4	79.0
30–39	77.2	79.4
40–49	82.8	83.0
50–59	88.6	90.8
60–69	89.8	89.5

*Based on published data from the Vaccination Record System (*2*).

Appendix Table 3. Proportions of individuals residing in each geographic region among survey participants and the general population of Japan

Region of residence	Survey participants (%)	General population*
Hokkaido/Tohoku	11.8	10.9
Kanto	37.8	34.6
Chubu	16.3	16.8
Kinki	18.9	17.7
Chugoku/Shikoku	7.3	8.7
Kyushu	8.0	11.3

*Based on data from the 2020 Census (*1*).

References

1. 2020 Census: Outline of the results [in Japanese]. 2021 Nov 30 [cited 2022 Jun 5]. https://www.stat.go.jp/data/kokusei/2020/kekka/pdf/outline_01.pdf

2. Vaccination record system [in Japanese] [cited 2022 Jun 5]. https://www.kantei.go.jp/jp/content/nenreikaikyubetsu-vaccination_data.pdf

Paper 3 : VE against symptomatic infection in Japan (Delta/early Omicron)

Arashiro T*, Arima Y, Muraoka H, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). **Clin Infect Dis.** 2022 Aug 3:ciac635. doi: 10.1093/cid/ciac635. **(*first and corresponding author)**
Clinical Infectious Diseases journal is the original place of publication and Oxford University Press is the publisher.

PhD candidate contributions:
Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 3A.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Clinical Infectious Diseases		
When was the work published?	September 1, 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

SECTION E

Student Signature	Takeshi Arashiro
Date	February 25, 2024

Supervisor Signature	Chris Smith
Date	February 25, 2024

Clinical Infectious Diseases

MAJOR ARTICLE

Coronavirus Disease 19 (COVID-19) Vaccine Effectiveness Against Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection During Delta-Dominant and Omicron-Dominant Periods in Japan: A Multicenter Prospective Case-control Study (Factors Associated with SARS-CoV-2 Infection and the Effectiveness of COVID-19 Vaccines Study)

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Background. Although several coronavirus disease 2019 (COVID-19) vaccines initially showed high efficacy, there have been concerns because of waning immunity and the emergence of variants with immune escape capacity.

Methods. A test-negative design case-control study was conducted in 16 healthcare facilities in Japan during the Delta-dominant period (August-September 2021) and the Omicron-dominant period (January-March 2022). Vaccine effectiveness (VE) against symptomatic severe acute respiratory syndrome coronavirus 2 infection was calculated for 2 doses for the Delta-dominant period and 2 or 3 doses for the Omicron-dominant period compared with unvaccinated individuals.

Results. The analysis included 5795 individuals with 2595 (44.8%) cases. Among vaccinees, 2242 (55.8%) received BNT162b2 and 1624 (40.4%) received messenger RNA (mRNA)-1273 at manufacturer-recommended intervals. During the Delta-dominant period, VE was 88% (95% confidence interval [CI], 82–93) 14 days to 3 months after dose 2 and 87% (95% CI, 38–97) 3 to 6 months after dose 2. During the Omicron-dominant period, VE was 56% (95% CI, 37–70) 14 days to 3 months since dose 2, 52% (95% CI, 40–62) 3 to 6 months after dose 2, 49% (95% CI, 34–61) 6+ months after dose 2, and 74% (95% CI, 62–83) 14+ days after dose 3. Restricting to individuals at high risk of severe COVID-19 and additional adjustment for preventive measures (ie, mask wearing/high-risk behaviors) yielded similar estimates, respectively.

Conclusions. In Japan, where most are infection-naïve, and strict prevention measures are maintained regardless of vaccination status, 2-dose mRNA vaccines provided high protection against symptomatic infection during the Delta-dominant period and moderate protection during the Omicron-dominant period. Among individuals who received an mRNA booster dose, VE recovered to a high level.

Keywords. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); test-negative design; vaccine effectiveness; SARS-CoV-2 variants.

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally [1]. The speed of vaccine development has been unprecedented, with randomized controlled studies [2–5] and several real-world vaccine effectiveness (VE) studies early after the vaccine rollout [6–9] demonstrating high efficacy/effectiveness for 2 messenger RNA (mRNA) vaccines (BNT162b2 [Pfizer/BioNTech] and mRNA-1273 [Moderna]) and a viral vector vaccine (AZD1222 [AstraZeneca]). However, subsequent observational studies evaluating mid- to long-term effectiveness against symptomatic infection suggested waning immunity [10–13]. Further complicating the situation, in November 2021, a new variant, B.1.1.529 (Omicron), which harbors numerous mutations in the spike protein was detected in South Africa. Initial in vitro neutralization studies suggested substantial immune escape capacity [14–16]. Early epidemiological studies from the United Kingdom and the United States retrospectively analyzing surveillance or clinical data suggested low to no VE against symptomatic disease caused by the Omicron variant [17–19]. However, evidence from elsewhere has been limited, and VE studies in mostly infection-naïve populations would provide additional evidence to inform policies and risk communication. In Japan, a national seroprevalance study was conducted by the Ministry of Health, Labour and Welfare in December 2021, before the Omicron wave in Japan. Even in Tokyo, where the COVID-19 case notification rate has been one of the highest in Japan throughout the pandemic, only 2.8% were seropositive for nucleocapsid protein, which is considered to be the marker for past infection, but not for COVID-19 vaccination because the vaccines rolled out in Japan only code for spike protein (the previously mentioned 3 vaccines) [20]. Here, we report the results of a multicenter test-negative design case-control study conducted in Japan to evaluate VE against symptomatic SARS-CoV-2 infection during the Delta- and Omicron-dominant periods. We evaluated VE against 2 doses for the Delta-dominant period and 2 or 3 doses for the Omicron-dominant period.

METHODS

COVID-19 Vaccination Rollout in Japan

In Japan, BNT162b2, mRNA-1273, and AZD1222 have been approved for use since February 2021. The use of AZD1222 has been extremely limited and the majority of individuals received either BNT162b2 or mRNA-1273 (Supplementary Methods) [21].

Study Design and Setting

Our study, Factors Associated with SARS-CoV-2 Infection and the Effectiveness of COVID-19 vaccines is a multicenter case-control study in healthcare facilities in Japan with 2 objectives: (1) to elucidate behavioral and demographic risk factors associated with SARS-CoV-2 infection and (2) to estimate the real-world effectiveness of COVID-19 vaccines. Participating healthcare facilities have fever clinics that routinely test individuals using polymerase chain reaction (PCR) for diagnostic purposes. This report includes data from 16 healthcare facilities in the Kanto region (Tokyo and 4 surrounding metropolitan prefectures), where the reported COVID-19 case counts and rate per population have been one of the highest throughout the pandemic relative to other regions in Japan. For this report, individuals who were tested between 1 August 2021 and 31 March 2022 were included.

Definition of Delta- and Omicron-Dominant Periods and Nonepidemic Period

Based on data from variant-specific PCR that can detect the L452R mutation, which is present in the Delta variant but absent in the Alpha and Omicron variants, by 1 August 2021, the Delta variant was estimated to be responsible for more than 90% of SARS-CoV-2 infections in Japan, replacing the Alpha variant [22]. Therefore, we defined 1 August to 30 September 2021 as the Delta-dominant period (Figure 1). By the beginning of October, the number of reported COVID-19 cases decreased rapidly and reached <1 case per 100 000 population. This low level lasted until the end of December 2021. Therefore, we defined 1 October to 31 December 2021 as the nonepidemic period. In early January 2022, the number of cases rose rapidly owing to introduction of the Omicron variant, with Omicron estimated to be responsible for more than 90% of SARS-CoV-2 infections [23]. Therefore, we defined 1 January to 31 March 2022 as the Omicron-dominant period.

Inclusion and Exclusion Criteria

The inclusion criterion was all symptomatic individuals aged ≥20 years (Supplementary Methods). Individuals who did not or could not consent to participate in the study, individuals who required immediate lifesaving treatment, and individuals who had previously participated in this study were excluded. At the analysis stage, we also excluded individuals who had unknown symptom onset, were tested ≥15 days after symptom onset, or were tested during the nonepidemic period.

Classification of Exposures and Outcome

A paper or web-based (according to the subject's preference) questionnaire was administered before the test results were available to avoid social desirability bias. Vaccination status (number of doses, vaccine manufacturer, and date of each dose) was recorded based on the questionnaire (via a copy of the vaccine record/certificate) and checked for plausibility. Vaccination status was classified into 7 categories: (1) not vaccinated, (2) dose 1 or ≤13 days after dose 2 (partially vaccinated), (3) 14 days–3 months (14–90 days) after dose 2, (4) 3–6 months

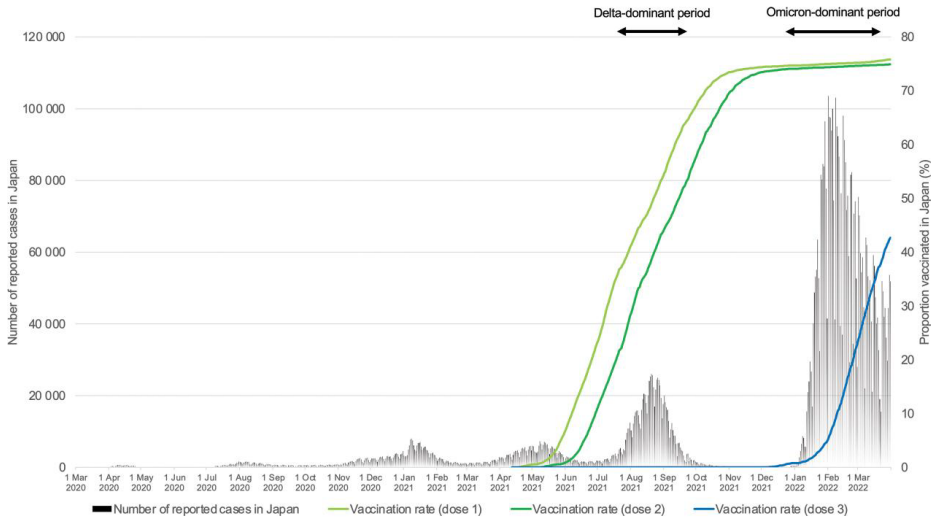

Figure 1. Number of reported COVID-19 cases since the beginning of the pandemic and proportion of individuals vaccinated in Japan by dose number. (Data sources: Ministry of Health, Labour and Welfare, Japan [https://www.mhlw.go.jp/stf/covid-19/open-data.html] and Digital Agency, Japan [https://info.vrs.digital.go.jp/dashboard]). COVID-19, coronavirus disease 2019.

(91–180 days) after dose 2, (5) >6 months (181 days) after dose 2, (6) ≤13 days after dose 3 (booster dose), and (7) ≥14 days after dose 3. SARS-CoV-2 PCR was done at each medical facility or commercial company for diagnostic purposes; PCR-positive individuals were considered cases and PCR-negative individuals were controls.

Data Analysis

Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group, sex, presence of any comorbidity (Supplementary Methods), educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility in which SARS-CoV-2 testing was done, and calendar week. These potential confounders were determined a priori based on published reports [7–13]. VE against symptomatic SARS-CoV-2 infection was estimated using the following equation: VE = (1 − adjusted odds ratio [aOR]) × 100%. In secondary exploratory analysis, we further adjusted the odds ratios for preventive measures, including mask-wearing (4 categories: wore at home and outside, wore outside at all times, wore only when having conversations, almost never wore masks) and high-risk behavior (dining at a restaurant/bar at night with alcohol consumption in a group was used as a proxy; this provides the occasion to talk face-to-face for a prolonged period without masks in an intoxicated state and was identified as a major risk factor associated with SARS-CoV-2 infection [24]) in an attempt to control for differential exposures between vaccinated and unvaccinated individuals. We also performed a subanalysis by restricting the analysis to individuals who either were ≥65 years or had any comorbidities, who have higher risk of developing severe COVID-19. Furthermore, although complete case analysis was done in primary analyses, multiple imputation by chained equations was performed as a sensitivity analysis. We used the same variables used in the primary analyses to impute missing data and to further calculate aOR and VE. Data analyses were performed using STATA version 17.0.

Ethics Statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval number 1332). Ethics approval was also sought from medical facilities that required review from on-site committees.

RESULTS

Characteristics of the Study Participants

A total of 7157 individuals were enrolled from 16 medical facilities during the study period; 339 were excluded because of unknown symptom onset and 87 were excluded because of being tested ≥15 days after symptom onset (Figure 2). Individuals tested during the nonepidemic period were also excluded. The

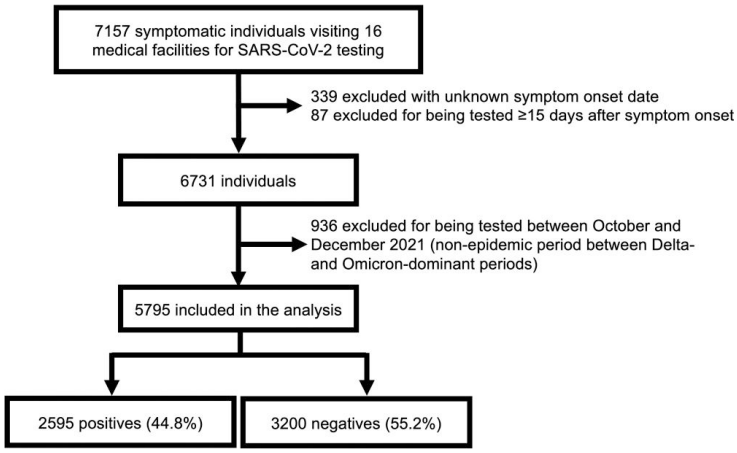

Figure 2. Flow diagram of the study participants.

final analysis included 5795 individuals with 2595 (44.8%) positive cases. The median age (interquartile range) was 35 (27–46) years, 2896 (50.0%) were males, and 1491 (25.7%) had comorbidities (Table 1). Although data on race/ethnicity were not collected, 5684 (98.5%; 25 missing) were Japanese nationals and most foreigners were from East Asia, so we expected most study participants to be Asians. Almost all (5589, 97.5%) lived in a home, rather than a hospital/care facility or dormitory, and 953 (16.8%) reported having undergone SARS-CoV-2 diagnostic testing in the past month. Median (interquartile range) time from onset to SARS-CoV-2 testing was 1 (1–3) days; 1256 (21.7%) had history of close contact. Among those vaccinated at least once, 2242 (55.8%) received BNT162b2, 1624 (40.4%) received mRNA-1273, 94 (2.3%) received other types/heterologous regimen, and 60 (1.5%) were of unknown vaccine type. The median interval between the first 2 doses was 21 days for BNT162b2 and 28 days for mRNA-1273, as per manufacturer instructions. The median interval between the primary series and the booster dose was 214 days (7.1 months).

Characteristics of participants during the Delta- and Omicron-dominant periods are in Supplementary Table 1. Compared with participants in the Delta-dominant period, those in the Omicron-dominant period were more likely to be vaccinated (because of the rollout timeline), slightly less likely to have history of close contact, slightly more likely to have past SARS-CoV-2 infection, slightly more likely to have been vaccinated with BNT162b2, and more likely to be engaged in high-risk behaviors (possibly because a state of emergency was in effect during the Delta-dominant period). Otherwise, the participants' characteristics were similar between the 2 periods.

Vaccine Effectiveness by Period Since COVID-19 Vaccination During the Delta-dominant Period

During the Delta-dominant period, VE estimates were 65% (95% confidence interval [CI], 54–74) for participants who received dose 1 only or were ≤13 days since dose 2 (partially vaccinated), 88% (95% CI, 82–93) for 14 days to 3 months after dose 2, and 87% (95% CI, 38–97) for 3–6 months after dose 2, all compared with unvaccinated individuals (Figure 3, Supplementary Table 2). Because the Delta-dominant period was during the early rollout phase of the 2-dose regimen, there were no individuals who had received 2 doses over 6 months ago or a booster dose (Figure 1).

Vaccine Effectiveness by 2 or 3 Doses and Period Since COVID-19 Vaccination During the Omicron-dominant Period

During the Omicron-dominant period, VE estimates were 34% (95% CI, −20–64) for individuals who received dose 1 or were ≤13 days since dose 2 (partially vaccinated), 56% (95% CI, 37–70) for 14 days to 3 months after dose 2, 52% (95% CI, 40–62) for 3–6 months after dose 2, and 49% (95% CI, 34–61) for >6 months after dose 2, all compared with unvaccinated individuals (Figure 3, Supplementary Table 2). VE estimates after dose 3 were 67% (95% CI, 47–79) for ≤13 days after dose 3 and 74% (95% CI, 62–83) for ≥14 days after dose 3. When comparing 3 doses vs 2 doses after 6 months, aOR was 0.49 (0.34–0.71), which translated to a relative VE of 51% (95% CI, 29–66).

Secondary Analysis Accounting for Preventive Measures, Subanalysis Among Individuals With Higher Risk of Developing Severe COVID-19, and Sensitivity Analysis Using Multiple Imputation

Secondary analysis with additional adjustments for preventive measures including mask wearing and high-risk behaviors was performed. These VE estimates were similar to those in

Table 1. Demographic and Clinical Characteristics of the Study Participants

	All (n = 5795)	Test Positive (n = 2595)	Test Negative (n = 3200)
Age in years, n (%)			
20–29	1960 (33.8)	924 (35.6)	1036 (32.4)
30–39	1601 (27.6)	666 (25.7)	935 (29.2)
40–49	1145 (19.8)	566 (21.8)	579 (18.1)
50–59	677 (11.7)	295 (11.4)	382 (11.9)
60–69	272 (4.7)	107 (4.1)	165 (5.2)
70–79	107 (1.9)	32 (1.2)	75 (2.3)
80+	33 (0.6)	5 (0.2)	28 (0.9)
Sex, n (%); missing = 6 (0.1%)			
Male	2896 (50.0)	1352 (52.1)	1544 (48.3)
Female	2893 (50.0)	1241 (47.9)	1652 (51.7)
Educational attainment, n (%); missing = 74 (1.3%)			
Middle school or less	160 (2.8)	86 (3.4)	74 (2.3)
High school	1317 (23.0)	623 (24.4)	694 (21.9)
Junior college/ technical college	1261 (22.0)	576 (22.5)	685 (21.7)
Undergraduate or graduate school	2983 (52.1)	1273 (49.8)	1710 (54.1)
Place of residence, n (%); missing = 59 (1.0%)			
Home	5589 (97.5)	2488 (97.1)	3101 (97.7)
Hospital or long-term care facility	16 (0.3)	7 (0.3)	9 (0.3)
Dormitory or other	131 (2.3)	67 (2.6)	64 (2.0)
Comorbidity,[a] n (%)			
Yes	1491 (25.7)	588 (22.7)	903 (28.2)
No	4304 (74.3)	2007 (77.3)	2297 (71.8)
Occupation, n (%)			
Healthcare worker	300 (5.2)	107 (4.1)	193 (6.0)
Other	5495 (94.8)	2488 (95.9)	3007 (94.0)
Smoking, n (%); missing = 32 (0.6%)			
Never-smoker	3185 (55.3)	1401 (54.3)	1784 (56.0)
Past smoker	1350 (23.4)	619 (24.0)	731 (23.0)
Current smoker	1228 (21.3)	559 (21.7)	669 (21.0)
Days from onset to SARS-CoV-2 test; exact onset date missing = 7 (0.1%)[b]	1 (1–3)	2 (1–3)	1 (1–3)
History of close contact, n (%)			
Yes	1256 (21.7)	714 (27.5)	542 (16.9)
No/unknown	4539 (78.3)	1881 (72.5)	2658 (83.1)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 104 (1.8%)			
Yes	953 (16.8)	406 (16.0)	547 (17.4)
No	4738 (83.3)	2140 (84.1)	2598 (82.6)
Past SARS-CoV-2 infection, n (%); missing = 134 (2.3%)			
Yes	250 (4.4)	74 (2.9)	176 (5.7)
Ancestral strain-dominant period (2020–February 2021)	108 (1.9)	35 (1.4)	73 (2.3)
Ancestral-to-Alpha replacement period (March–May 2021)	43 (0.8)	12 (0.5)	31 (1.0)
Alpha-to-Delta replacement period (June–July 2021)	17 (0.3)	8 (0.3)	9 (0.3)
Delta-dominant period (August–December 2021)	47 (0.8)	9 (0.4)	38 (1.2)
Multiple infections	1 (0.0)	0 (0.0)	1 (0.0)
Period of infection missing	34 (0.6)	10 (0.4)	24 (0.8)
No	5411 (95.6)	2472 (97.1)	2939 (94.4)
Number of COVID-19 vaccinations received, n (%); missing = 96 (1.7%)			
0	1617 (28.4)	922 (36.2)	695 (22.1)
1	323 (5.7)	126 (4.9)	197 (6.3)
2	3430 (60.2)	1382 (54.2)	2048 (65.0)
3	329 (5.8)	119 (4.7)	210 (6.7)
Vaccine type, n (%); missing among those vaccinated = 62/4082 (1.5%)			
BNT162b2	2242 (55.8)	905 (56.5)	1337 (55.3)
mRNA-1273	1624 (40.4)	629 (39.3)	995 (41.2)
Others/heterologous	94 (2.3)	39 (2.4)	55 (2.3)
Unknown	60 (1.5)	29 (1.8)	31 (1.3)
Interval between dose 1 and 2 for Pfizer/ BioNTech (days)[b,c]	21 (21–22)	21 (21–22)	21 (21–22)
Interval between dose 1 and 2 for Moderna (d)[b,c]	28 (28–31)	28 (28–31)	28 (28–31)
Interval between dose 2 and 3 (d)[b,c]	214 (197–226)	215 (196–226)	213 (198–225)
Interval between dose 3 and SARS-CoV-2 testing[d]	17 (0–108)	15 (1–108)	18 (0–93)
Mask-wearing in the past 2 weeks; missing = 90 (1.6%)			
Wore at home and outside	456 (8.0)	215 (8.4)	241 (7.6)
Wore outside at all times	5108 (89.5)	2261 (88.6)	2847 (90.3)
Wore only when having conversations	131 (2.3)	70 (2.7)	61 (1.9)
Almost never wore masks	10 (0.2)	6 (0.2)	4 (0.1)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol consumption), n (%); missing = 344 (6.3%)			
Yes	1578 (29.0)	776 (32.1)	802 (26.5)
No	3873 (71.1)	1644 (67.9)	2229 (73.5)

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.

[b]Median (interquartile range).

[c]Among individuals with exact dates for both doses.

[d]Median (range).

the primary analysis during both the Delta-dominant period (86–88% vs 87–88% after 2 doses, respectively) and the Omicron-dominant period (52–55% vs 49–56% after 2 doses and 78% vs 74% after 3 doses, respectively) (Table 2). A subanalysis of individuals who were at higher risk of developing severe COVID-19 was done; this yielded results similar to or slightly higher than those observed for the entire study population (Table 3). There were 96 (1.7%) participants who did not report the number of COVID-19 vaccinations received, and among those who did report, 238 (4.1%) did not report the vaccination date. Multiple imputation of missing data yielded similar VE

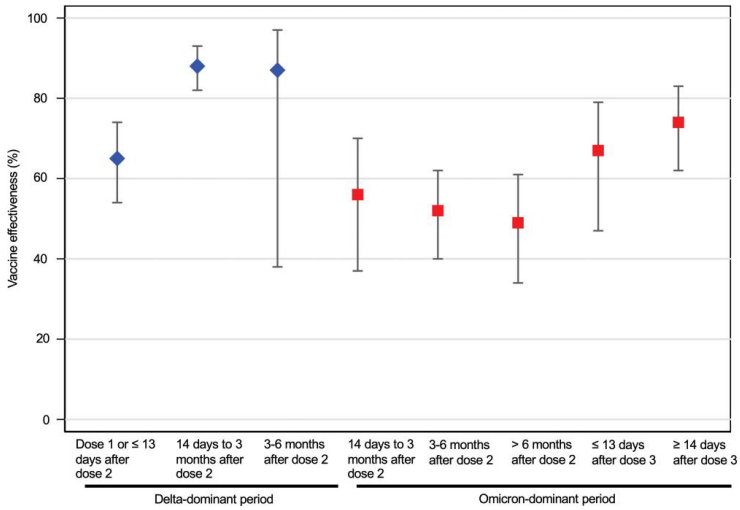

Figure 3. Vaccine effectiveness against symptomatic severe acute respiratory syndrome coronavirus 2 infection by period since coronavirus disease 2019 vaccination during the Delta-dominant period (diamonds) and Omicron-dominant periods (squares), all compared with unvaccinated individuals. Diamonds and squares indicate point estimates and error bars indicate 95% confidence intervals.

estimates for both the Delta- and Omicron-dominant periods (Supplementary Table 3).

DISCUSSION

In this multicenter, test-negative, case-control study in Japan, we evaluated VE for 2 doses of COVID-19 vaccine during the Delta-dominant period and 2 or 3 doses of COVID-19 vaccine during the Omicron-dominant period. In agreement with many other observational studies [18, 19, 25], 2 doses provided high (VE of 80%–90%) protection during the Delta-dominant period for up to 6 months. Because the Delta-dominant period abruptly ended in Japan, likely partly owing to the rollout of 2-dose regimens, we could not assess the long-term effectiveness against the Delta variant.

On the other hand, during the Omicron-dominant period, VE estimates were approximately 50% after 2 doses up to and beyond 6 months in our study. Although these VE estimates against the Omicron variant were substantially lower than those against the Delta variant, they were higher than what was observed in the United Kingdom and the United States, where VE estimates against the Omicron variant were reported to be 0%–10% after 3 months [17–19]. Several factors may have contributed to VE estimates being higher in Japan than in other countries. First, in Japan, the government has not actively implemented policies to relax social and public health measures specifically for vaccinated individuals using vaccine certificates/passports. Rather, the government has been continuously communicating to the public to continue practicing infection prevention measures such as mask-wearing and physical distancing even after vaccination. VE estimates would be underestimated if vaccinated individuals are more likely to engage in high-risk behaviors from perceived protection from infection or by relaxation of mask-wearing and physical distancing mandates/policies only among vaccinees or utilization of vaccine certificates/passports to allow vaccinees to engage in high-risk behaviors. In fact, some countries reported negative VE estimates during the Omicron wave, possibly from biases arising from different levels of risk between vaccinees and nonvaccinees [26, 27]. In contrast, the baseline risk of infection among vaccinees and nonvaccinees may have been more similar in Japan, resulting in estimates less affected by this bias. This is partly supported by the results of the secondary analysis that adjusted for prevention measures including mask wearing and high-risk behaviors. Indeed, among the study participants, only 10 of 5705 (0.2%) reported not wearing masks, and 9 of the 10 individuals who reported not wearing masks were not vaccinated. Furthermore, differential propensity for vaccination by past infection status can be a concern in estimating VE. For example, if individuals with past infection choose not to be vaccinated because of perceived protection, as observed in the United Kingdom [28], VE would be underestimated. Moreover, in Japan, only 2.8% of individuals in Tokyo (which is in the Kanto region) were antinucleocapsid antibody positive before the Omicron-dominant period, indicating that most of the population was infection-naïve, in stark contrast to the United Kingdom (approximately 30%) and the United States (33.5%)

Table 2. Vaccine Effectiveness Against Symptomatic SARS-CoV-2 During the Delta- and Omicron-dominant Period by Time Since Vaccination With Additional Adjustment for Preventive Measures

Vaccination Status	Adjusted Odds Ratios (95% CI)[a]	Vaccine Effectiveness, % (95% CI)
(A) Delta-dominant period		
Unvaccinated	1	N/A
Dose 1 or within 13 d of dose 2	0.36 (0.27–0.48)	64 (52–73)
14 d to 3 mo after dose 2	0.12 (0.08–0.20)	88 (80–92)
3–6 mo after dose 2	0.14 (0.03–0.65)	86 (35–97)
(B) Omicron-dominant period		
Unvaccinated	1	N/A
Dose 1 or within 13 d of dose 2	0.71 (0.38–1.32)	29 (−32–62)
14 d to 3 mo after dose 2	0.45 (0.31–0.66)	55 (34–69)
3–6 mo after dose 2	0.46 (0.37–0.58)	54 (42–63)
>6 mo after dose 2	0.48 (0.37–0.63)	52 (37–63)
Within 13 d of dose 3	0.31 (0.19–0.50)	69 (50–81)
≥14 d after dose 3	0.22 (0.14–0.33)	78 (67–86)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N/A, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, calendar week, mask-wearing, and high-risk behaviors in the past 2 weeks.

Table 3. Vaccine Effectiveness Against Symptomatic SARS-CoV-2 During the Delta- and Omicron-Dominant Period by Time Since Vaccination Among Individuals With Higher Risk of Developing Severe COVID-19 (≥65 Years of Age or Having at Least 1 Comorbidity)

Vaccination Status	Test Positive, n (%)	Test Negative, n (%)	Adjusted Odds Ratios (95% CI)[a]	Vaccine Effectiveness, % (95% CI)
(A) Delta-dominant period				
Unvaccinated	111 (72.6)	113 (36.0)	1	N/A
Dose 1 or within 13 d of dose 2	29 (19.0)	81 (25.8)	0.24 (0.13–0.45)	76 (65–87)
14 d to 3 mo after dose 2	13 (8.5)	116 (36.9)	0.10 (0.04–0.23)	90 (77–96)
3–6 mo after dose 2	0 (0.0)	4 (1.3)	N/A	N/A
(B) Omicron-dominant period				
Unvaccinated	78 (18.4)	45 (7.8)	1	N/A
Dose 1 or within 13 days of dose 2	4 (1.0)	9 (1.6)	0.37 (0.09–1.41)	63 (−41 to 91)
14 d to 3 mo after dose 2	19 (4.5)	38 (6.5)	0.50 (0.23–1.09)	50 (−9 to 77)
3–6 mo after dose 2	162 (38.3)	258 (44.4)	0.34 (0.20–0.57)	66 (43–80)
>6 mo after dose 2	122 (28.8)	145 (25.0)	0.36 (0.20–0.62)	64 (38–80)
Within 13 d of dose 3	15 (3.6)	27 (4.7)	0.19 (0.08–0.48)	81 (52–92)
≥14 d after dose 3	23 (5.4)	59 (10.2)	0.18 (0.08–0.38)	82 (62-92)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N/A, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

[20, 29, 30]. This allowed us to calculate VE estimates in a mostly infection-naïve population. Our study also had a low proportion of individuals with past SARS-CoV-2 infection (4.4%), for which we were also able to account for in our analysis. Finally, Japan followed manufacturer-recommended intervals between the first and second doses, similar to the United States but different from the United Kingdom, where the interval was up to 12 weeks, including for mRNA vaccines with a recommended dose interval of 3–4 weeks for the primary series. Some in vitro studies have suggested that a longer interval provides better protection against variants [31], so careful interpretation is warranted in extrapolating findings from countries with different intervals especially in the setting of emerging variants. The immune profile against SARS-CoV-2 is becoming increasingly diversified because of a complex combination of exposure to vaccines and infection with various lineages/variants, likely generating heterogeneity in protective immunity. It would be challenging but valuable to tease apart various immune histories in future studies.

Last, we found that the VE after 3 doses of COVID-19 vaccine was high (74%) in this study. This was consistent with previous studies done in countries that are rolling out a booster dose [17–19]. Continued monitoring will be necessary to evaluate mid- to long-term effectiveness against the Omicron variant, as early reports from the United Kingdom and Israel indicate waning effectiveness several months after dose 3 [17, 32].

Limitations

This study has several limitations. First, biases inherent in observational studies are possible. Using a detailed questionnaire, we attempted to minimize confounding that is not necessarily accounted for in studies that retrospectively evaluate routine surveillance data, but unmeasured and residual confounding could have occurred. Individuals who are SARS-CoV-2 negative may be less likely to make an effort to recall exposures such as vaccination history. To avoid these sources of bias, we administered the questionnaires before the test results were available. Because we did not have a system to link test results with vaccination history, we asked participants to refer to their vaccine records/certificates. Approximately 39% of individuals reported carrying their vaccine record; others were asked to refer to their diary/calendar for accuracy. Second, although the test-negative design is widely used to estimate VE because it is efficient and can control for some healthcare-seeking behavior, it has some potential shortcomings as well [33]. Third, as the vaccine rollout progresses and vaccination rates stabilize, vaccinated and unvaccinated individuals may differ in characteristics other than vaccination status. However, as noted previously, such biases may be less of an issue in Japan. Also, booster vaccination was restricted to individuals who had their second dose ≥6 months before, meaning those who were eligible during the Omicron-dominant period would have consisted mostly of the earliest recipients of the vaccine, such as healthcare workers and those aged ≥65 years, which we accounted for in our analysis. Fourth, some VE estimates were calculated based on very

low numbers, resulting in wide CIs. Fifth, our primary analyses were complete case analyses. However, in this study, missing data on vaccination status were minimal and sensitivity analysis with multiple imputation of missing data resulted in similar estimates. Sixth, we did not assess VE against asymptomatic infection, severe cases, or death. Finally, we were not able to classify individual COVID-19 cases as infected with the Omicron or Delta variant. However, because there was a 3-month nonepidemic period with very few cases between these 2 periods, misclassification was likely minimal.

Conclusions

In Japan, where most of the population is infection-naïve and strict prevention measures at the government and individual levels are maintained regardless of vaccination status, 2-dose mRNA vaccines provided high protection against symptomatic infection during the Delta-dominant period and moderate protection during the Omicron-dominant period several months after the second dose. Among individuals who received an mRNA booster dose, VE recovered to a high level in the short-term.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 29 April 2022.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020; 383:2603–15.
3. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021; 384:403–16.
4. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021; 385:1761–73.
5. Sahly HM E, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021; 385:1774–85.
6. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021; 384:1412–3.
7. Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021; 70:495–500.
8. Pilishvili T, Fleming-Dutra KE, Farrar JL, et al. Interim estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna COVID-19 vaccines among health care personnel–33 U.S. sites, January—March 2021. MMWR Morb Mortal Wkly Rep 2021; 70:753–8.
9. Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ 2021; 374:n1943.
10. Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med 2022; 386:340–50.
11. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021; 385:e83.
12. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med 2021; 385:e85.
13. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021; 398:1407–16.
14. Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature 2022; 602:654–6.
15. Lu L, Mok BW, Chen LL, et al. Neutralization of severe acute respiratory syndrome coronavirus 2 omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. Clin Infect Dis 2022; 75:e822–6.
16. Dejnirattisai W, Shaw RH, Supasa P, et al. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. Lancet 2022; 399:234–6.
17. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022; 386:1532–46.
18. Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. JAMA 2022; 327:639–51.
19. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med 2022; 28:1063–71.
20. Ministry of Health, Labour and Welfare, Japan. Preliminary results of the national seroprevalence study [in Japanese]. Available at: https://www.mhlw.go.jp/content/10900000/000898612.pdf. Accessed 29 April 2022.
21. Cabinet Public Affairs Office, Cabinet Secretariat. COVID-19 vaccines [in Japanese]. Available at: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html. Accessed 29 April 2022.
22. Kobayashi Y, Arashiro T, Otsuka M, et al. Analysis on replacement of SARS-CoV-2 variants with L452R mutation in Japan [in Japanese]. Infectious Agents Surveillance Report 2021; 42:265–7.
23. Ministry of Health, Labour and Welfare, Japan. Variant-specific PCR results [in Japanese]. Available at: https://www.mhlw.go.jp/content/10900000/000892298.pdf. Accessed 29 April 2022.
24. Arashiro T, Arima Y, Muraoka H, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses 2022; 16:952–61. 10.1111/irv.12992.
25. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. N Engl J Med 2021; 385:585–94.
26. Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against omicron or delta infection. medRxiv 2022. doi:10.1101/2021.12.30.21268565.
27. Hansen CH, Schelde AB, Moustsen-Helm IR, et al. Vaccine effectiveness against SARS-CoV-2 infection with the omicron or delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: a Danish cohort study. medRxiv 2022. doi:10.1101/2021.12.20.21267966.
28. Office for National Statistics, United Kingdom. Coronavirus (COVID-19) Infection Survey technical article: Analysis of characteristics associated with vaccination uptake. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19infectionsurveytechnicalarticleanalysisofcharacteristicsassociatedwithvaccinationuptake/2021-11-15. Accessed 29 April 2022.
29. UK Health Security Agency. COVID-19 vaccine surveillance report: 28 April 2022 (week 17). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1072064/Vaccine-surveillance-report-week-17.pdf. Accessed 29 April 2022.
30. Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of infection-induced SARS-CoV-2 antibodies–United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022; 71:606–8.
31. Grunau B, Goldfarb DM, Asamoah-Boaheng M, et al. Immunogenicity of extended mRNA SARS-CoV-2 vaccine dosing intervals. JAMA 2022; 327:279–81.
32. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance–VISION Network, 10 states, August 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022; 71:255–63.
33. Li KQ F, Shi X, Miao W, et al. Double negative control inference in test-negative design studies of vaccine effectiveness. ArXiv 2022:arXiv:2203.12509v2.

Supplementary Material

Supplementary Methods

COVID-19 vaccination rollout in Japan

As of 31 March 2022, 78 751 544 doses of BNT162b2, 16 056 950 doses of mRNA-1273, and 58 374 doses of AZD1222 were rolled out as second doses nationwide [21]. The primary series (doses 1 and 2) followed manufacturer-recommended intervals (21 days for BNT162b2 and 28 days for mRNA-1273). The rollout of the mRNA booster doses was initiated in December 2021 and individuals became eligible 6-7 months after the second dose, depending on local availability.

Definition of symptomatic individuals

We defined symptomatic individuals as individuals with any of the following: fever ≥37.5°C, malaise, chills, joint pain, headache, runny nose, cough, sore throat, shortness of breath, gastrointestinal symptoms (vomiting, diarrhea, stomachache), and loss of taste/smell.

Definition of comorbidity

We defined comorbidity as any of the following: hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.

Supplementary Table 1. Demographic and clinical characteristics of the study participants during the Delta- and Omicron-dominant periods

(a) Delta-dominant period

	All (n = 1805)	Test positive (n = 724)	Test negative (n = 1081)
Age in years, n (%)			
20-29	648 (35.9)	278 (38.4)	370 (34.2)
30-39	494 (27.4)	187 (25.8)	307 (28.4)
40-49	348 (19.3)	149 (20.6)	199 (18.4)
50-59	197 (10.9)	81 (11.2)	116 (10.7)
60-69	75 (4.2)	20 (2.8)	55 (5.1)
70-79	32 (1.8)	8 (1.1)	24 (2.2)
80+	11 (0.6)	1 (0.1)	10 (0.9)
Sex, n (%); missing = 0			
Male	873 (48.4)	403 (55.7)	470 (43.5)
Female	932 (51.6)	321 (44.3)	611 (56.5)
Educational attainment, n (%); missing = 28 (1.5%)			
Middle school or less	44 (2.5)	26 (3.7)	18 (1.7)
High school	374 (21.1)	150 (21.1)	224 (21.0)
Junior college/technical college	424 (23.9)	182 (25.6)	242 (22.7)
Undergraduate or graduate school	935 (52.6)	354 (49.7)	581 (54.5)
Place of residence, n (%); missing = 18 (1.0%)			
Home	1723 (96.4)	681 (95.4)	1042 (97.1)
Hospital or long-term care facility	5 (0.3)	2 (0.3)	3 (0.3)
Dormitory or other	59 (3.3)	31 (4.3)	28 (2.6)
Comorbidity,[a] n (%)			
Yes	474 (26.3)	161 (22.2)	313 (29.0)
No	1331 (73.7)	563 (77.8)	768 (71.1)
Occupation, n (%)			
Healthcare worker	91 (5.0)	20 (2.8)	71 (6.6)
Other	1714 (95.0)	704 (97.2)	1010 (93.4)
Smoking, n (%); missing = 7 (0.4%)			
Never-smoker	976 (54.3)	360 (49.9)	616 (57.2)
Past smoker	421 (23.4)	179 (24.8)	242 (22.5)
Current smoker	401 (22.3)	182 (25.2)	219 (20.3)
Days from onset to SARS-CoV-2 test; exact onset date missing = 4 (0.2%)[b]	2 (1-3)	2 (1-3)	2 (1-3)
History of close contact, n (%)			
Yes	407 (22.5)	214 (29.6)	193 (17.8)
No/unknown	1398 (77.5)	510 (70.4)	888 (82.2)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 43 (2.4%)			
Yes	312 (17.7)	115 (16.3)	197 (18.6)
No	1450 (82.3)	589 (83.7)	861 (81.4)
Past SARS-CoV-2 infection, n (%); missing = 58 (3.2%)			
Yes	64 (3.7)	7 (1.0)	57 (5.5)

Ancestral strain-dominant period (2020 to February 2021)	42 (2.4)	6 (0.9)	36 (3.4)
Ancestral-to-Alpha replacement period (March-May 2021)	16 (0.9)	0 (0.0)	16 (1.5)
Alpha-to-Delta replacement period (June-July 2021)	2 (0.1)	1 (0.1)	1 (0.1)
Delta-dominant period (August-December 2021)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple infections	0 (0.0)	0 (0.0)	0 (0.0)
Period of infection missing	4 (0.2)	0 (0.0)	4 (0.4)
No	1683 (96.3)	694 (99.0)	989 (94.6)
Number of COVID-19 vaccinations received, n (%); missing = 39 (2.2%)			
None	1035 (58.6)	561 (79.4)	474 (44.8)
One	272 (15.4)	99 (14.0)	173 (16.3)
Two	459 (26.0)	47 (6.7)	412 (38.9)
Three	0 (0.0)	0 (0.0)	0 (0.0)
Vaccine type, n (%); missing among those vaccinated = 5 (0.7%)			
BNT162b2	374 (51.5)	86 (60.1)	288 (49.4)
mRNA-1273	347 (47.8)	56 (39.2)	291 (49.9)
Others/heterologous	1 (0.1)	0 (0.0)	1 (0.2)
Unknown	4 (0.6)	1 (0.7)	3 (0.5)
Interval between dose 1 and 2 for Pfizer/BioNTech (days)[b,c]	21 (21-21)	21 (21-23)	21 (21-21)
Interval between dose 1 and 2 for Moderna (days)[b,c]	28 (28-31)	28 (26-28)	28 (28-31)
Interval between dose 2 and 3 (days)[b,c]	N/A	N/A	N/A
Mask-wearing in the past 2 weeks; missing = 36 (2.0%)			
Wore at home and outside	148 (8.4)	63 (8.9)	85 (8.0)
Wore outside at all times	1558 (88.1)	609 (85.9)	949 (89.5)
Wore only when having conversations	56 (3.2)	33 (4.7)	23 (2.2)
Almost never wore masks	7 (0.4)	4 (0.6)	3 (0.3)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol present), n (%); missing = 98 (5.4%)			
Yes	368 (21.6)	177 (26.1)	191 (18.5)
No	1339 (78.4)	500 (73.9)	839 (81.5)

(b) Omicron-dominant period

	All (n =3990)	Test positive (n =1871)	Test negative (n =2119)
Age in years, n (%)			
20-29	1312 (32.9)	646 (34.5)	666 (31.4)
30-39	1107 (27.7)	479 (25.6)	628 (29.6)
40-49	797 (20.0)	417 (22.3)	380 (17.9)
50-59	480 (12.0)	214 (11.4)	266 (12.6)
60-69	197 (4.9)	87 (4.7)	110 (5.2)
70-79	75 (1.9)	24 (1.3)	51 (2.4)
80+	22 (0.6)	4 (0.2)	18 (0.9)

Sex, n (%); missing = 6 (0.2%)			
Male	2023 (50.8)	949 (50.8)	1074 (50.8)
Female	1961 (49.2)	920 (49.2)	1041 (49.2)
Educational attainment, n (%); missing = 46 (1.2%)			
Middle school or less	116 (2.9)	60 (3.3)	56 (2.7)
High school	943 (23.9)	473 (25.6)	470 (22.4)
Junior college/technical college	837 (21.2)	394 (21.3)	443 (21.1)
Undergraduate or graduate school	2048 (51.9)	919 (49.8)	1129 (53.8)
Place of residence, n (%); missing = 41 (1.0%)			
Home	3866 (97.9)	1807 (97.8)	2059 (98.0)
Hospital or long-term care facility	11 (0.3)	5 (0.3)	6 (0.3)
Dormitory or other	72 (1.8)	36 (2.0)	36 (1.7)
Comorbidity,[a] n (%)			
Yes	1017 (25.5)	427 (22.8)	590 (27.8)
No	2973 (74.5)	1444 (77.2)	1529 (72.2)
Occupation, n (%)			
Healthcare worker	209 (5.2)	87 (4.7)	122 (5.8)
Other	3781 (94.8)	1784 (95.4)	1997 (94.2)
Smoking, n (%); missing = 25 (0.6%)			
Never-smoker	2209 (55.7)	1041 (56.0)	1168 (55.4)
Past smoker	929 (23.4)	440 (23.7)	489 (23.2)
Current smoker	827 (20.9)	377 (20.3)	450 (21.4)
Days from onset to SARS-CoV-2 test; exact onset date missing = 3 (0.1%)[b]	1 (1-2)	1 (1-2)	1 (1-2)
History of close contact, n (%)			
Yes	849 (21.3)	500 (26.7)	349 (16.5)
No/unknown	3141 (78.7)	1371 (73.3)	1770 (83.5)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 61 (1.5%)			
Yes	641 (16.3)	291 (15.8)	350 (16.8)
No	3288 (83.7)	1551 (84.2)	1737 (83.2)
Past SARS-CoV-2 infection, n (%); missing = 76 (1.9%)			
Yes	186 (4.8)	67 (3.6)	119 (5.8)
Ancestral strain-dominant period (2020 to February 2021)	66 (1.7)	29 (1.6)	37 (1.8)
Ancestral-to-Alpha replacement period (March-May 2021)	27 (0.7)	12 (0.7)	15 (0.7)
Alpha-to-Delta replacement period (June-July 2021)	15 (0.4)	7 (0.4)	8 (0.4)
Delta-dominant period (August-December 2021)	47 (1.2)	9 (0.5)	38 (1.8)
Multiple infections	1 (0.0)	0 (0.0)	1 (0.1)
Period of infection missing	30 (0.8)	10 (0.5)	20 (1.0)
No	3728 (95.3)	1778 (96.4)	1950 (94.3)
Number of COVID-19 vaccinations received, n (%); missing = 57 (1.4%)			
None	582 (14.8)	361 (19.6)	221 (10.6)
One	51 (1.3)	27 (1.5)	24 (1.2)
Two	2971 (75.5)	1335 (72.5)	1636 (78.2)
Three	329 (8.4)	119 (6.5)	210 (10.0)

Vaccine type, n (%); missing among those vaccinated = 57/3351 (1.7%)			
BNT162b2	1868 (56.7)	819 (56.1)	1049 (57.2)
mRNA-1273	1277 (38.8)	573 (39.3)	704 (38.4)
Others/heterologous	93 (2.8)	39 (2.7)	54 (2.9)
Unknown	56 (1.7)	28 (1.9)	28 (1.5)
Interval between dose 1 and 2 for Pfizer/BioNTech (days)[b,c]	21 (21-22)	21 (21-22)	21 (21-22)
Interval between dose 1 and 2 for Moderna (days)[b,c]	28 (28-31)	28 (28-31)	28 (28-31)
Interval between dose 2 and 3 (days)[b,c]	214 (197-226)	215 (196-226)	213 (198-225)
Interval between dose 3 and SARS-CoV-2 testing [d]	17 (0-108)	15 (1-108)	18 (0-93)
Mask-wearing in the past 2 weeks; missing = 54 (1.3%)			
Wore at home and outside	308 (7.8)	152 (8.3)	156 (7.5)
Wore outside at all times	3550 (90.2)	1652 (89.6)	1898 (90.7)
Wore only when having conversations	75 (1.9)	37 (2.0)	38 (1.8)
Almost never wore masks	3 (0.1)	2 (0.1)	1 (0.1)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol present), n (%); missing = 246 (6.2%)			
Yes	1210 (32.3)	599 (34.4)	611 (30.5)
No	2534 (67.7)	1144 (65.6)	1390 (69.5)

[a] Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.
[b] Median (interquartile range).
[c] Among individuals with exact dates for both doses.
[d] Median (range).

Supplementary Table 2. Vaccine effectiveness against symptomatic SARS-CoV-2 during the Delta-and Omicron-dominant period by time since vaccination

(a) Delta-dominant period

Vaccination status	Test positive, n (%)	Test negative, n (%)	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	561 (79.7)	474 (45.2)	1	N/A
Dose 1 or ≤ 13 days after dose 2	111 (15.8)	265 (25.3)	0.35 (0.26-0.46)	65 (54-74)
14 days to 3 months after dose 2	30 (4.3)	289 (27.6)	0.12 (0.07-0.18)	88 (82-93)
3-6 months after dose 2	2 (0.3)	21 (2.0)	0.13 (0.03-0.62)	87 (38-97)

(b) Omicron-dominant period

Vaccination status	Test positive, n	Test negative, n	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	361 (20.7)	221 (11.2)	1	N/A
Dose 1 or ≤ 13 days after dose 2	30 (1.7)	28 (1.4)	0.66 (0.36-1.20)	34 (-20-64)
14 days to 3 months after dose 2	74 (4.2)	169 (8.5)	0.44 (0.30-0.63)	56 (37-70)
3-6 months after dose 2	767 (44.0)	971 (49.1)	0.48 (0.38-0.60)	52 (40-62)
> 6 months after dose 2	400 (22.9)	394 (19.9)	0.51 (0.39-0.66)	49 (34-61)
≤ 13 days after dose 3	47 (2.7)	66 (3.3)	0.33 (0.21-0.53)	67 (47-79)
≥ 14 days after dose 3	65 (3.7)	130 (6.6)	0.25 (0.17-0.38)	74 (62-83)

[a] Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

Supplementary Table 3. Vaccine effectiveness against symptomatic SARS-CoV-2 during the Omicron-dominant period by time since vaccination with multiple imputation

(a) Delta-dominant period

Vaccination status	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	1	N/A
Dose 1 or ≤ 13 days after dose 2	0.33 (0.25-0.44)	67 (56-75)
14 days to 3 months after dose 2	0.11 (0.07-0.17)	89 (83-93)
3-6 months after dose 2	0.13 (0.03-0.61)	87 (39-97)

(b) Omicron-dominant period

Vaccination status	Adjusted odds ratios (95% CI)[a]	Vaccine effectiveness, % (95% CI)
Unvaccinated	1	N/A
Dose 1 or ≤ 13 days after dose 2	0.71 (0.39-1.29)	29 (-29-61)
14 days to 3 months after dose 2	0.41 (0.29-0.59)	59 (41-71)
3-6 months after dose 2	0.50 (0.40-0.62)	50 (38-60)
> 6 months after dose 2	0.53 (0.41-0.68)	47 (32-59)
≤ 13 days after dose 3	0.33 (0.21-0.52)	67 (48-79)
≥ 14 days after dose 3	0.25 (0.17-0.37)	75 (63-83)

[a] Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

Paper 4 : Influence of high-risk behaviors on VE estimates

Arashiro T*, Arima Y, Kuramochi J, et al. Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. **Euro Surveill.** 2023 Jan;28(4). doi: 10.2807/1560-7917.ES.2023.28.4.2300034. **(*first and corresponding author)**

PhD candidate contributions:

Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 4.

The following, as a reference, is the details of the data presented in the Paper 4:

Influence of high-risk behaviors on estimates of COVID-19 VE: Results (BA.1/BA.2-dominant period)

Vaccination status (Omicron-dominant period)	Test positive, n	Test negative, n	aOR (95%CI)	Vaccine effectiveness, % (95%CI)
Unvaccinated with no high-risk behavior	204	118	ref	ref
Unvaccinated with high-risk behavior	140	86	1.30 (0.86-1.95)	-30 (-95-14)
Partially vaccinated	30	28	0.69 (0.37-1.30)	31 (-30-63)
14 days after dose 2 with no high-risk behaviors	787	1014	0.44 (0.33-0.59)	56 (41-67)
14 days after dose 2 with high-risk behaviors	387	453	0.64 (0.47-0.86)	36 (14-53)
Dose 3	119	210	0.28 (0.19-0.40)	72 (60-81)

p<0.001

Adjusted for: Age group, Sex, Presence of comorbidities, Occupation (healthcare workers or not), SARS-CoV-2 test in the past month, Prior infection, History of close contact, Testing facility, Calendar week, Mask wearing

Arashiro et al. (2023) Eurosurveillance

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First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?	Eurosurveillance		
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Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	

Stage of publication	Choose an item.

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

SECTION E

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Date	December 2, 2023

Supervisor Signature	Chris Smith
Date	February 25, 2024

LETTER

Letter to the editor: Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies

Takeshi Arashiro[1,2,3,4], Yuzo Arima[1], Jin Kuramochi[5,6], Hirokazu Muraoka[7], Akihiro Sato[8], Kumi Chubachi[9], Kunihiro Oba[10], Atsushi Yanai[11], Hiroko Arioka[11], Yuki Uehara[12,13], Genei Ihara[14], Yasuyuki Kato[15], Naoki Yanagisawa[16], Yoshito Nagura[17], Hideki Yanai[18], Akihiro Ueda[19], Akira Numata[20], Hideaki Kato[21], Hideaki Oka[22], Yusuke Nishida[22], Takao Ooki[23], Yuki Nidaira[5], Ashley Stucky[1], Tadaki Suzuki[2], Chris Smith[3,4], Martin Hibberd[3], Koya Ariyoshi[4], Motoi Suzuki[1]

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Article submitted on 16 Jan 2023 / accepted on 24 Jan 2023 / published on 26 Jan 2023

To the editor: We read with interest the article by van Ewijk et al. [1] regarding the influence of people's behaviour on vaccine effectiveness (VE) estimates against coronavirus disease (COVID-19). We commend the authors' effort in prospectively collecting detailed exposure history. The authors concluded that it is not necessary to collect data on risk behaviour in a test-negative case–control study, but we believe this conclusion is not fully supported by the data. The VE may be underestimated when there is relaxation of mask/physical distancing policies only among vaccinees or implementation of domestic vaccine certificates/passports to allow vaccinees to engage in high-risk behaviours, as outlined in World Health Organization guidance [2]. In fact, the Netherlands used a 'coronavirus entry pass' from 25 September 2021 (midway through the study period), requiring visitors to present the pass at bars, restaurants, events and cultural venues [3]. If the authors had captured this exposure information (i.e. high-risk behaviours associated with this pass), they would probably have seen differing VE estimates with and without adjustments for high-risk behaviours as only the vaccinated would have been allowed to engage in these behaviours. Conversely and counterintuitively, in Table 1, the test-positive group exhibited more frequent mask wearing and more individuals without close contact. The questionnaire could have perhaps asked for more specific exposures such as visiting restaurants/bars, in line with the coronavirus entry pass and previous reports that showed these activities to be high-risk [4,5]. Furthermore, observed waning immunity may partially be due to the introduction of the coronavirus entry pass halfway through the study (i.e. spurious waning), which could have been accounted for with the collection of specific exposures.

There is a previously published report suggesting that policies differentially targeting the vaccinated and unvaccinated would alter VE estimates. A study in New York showed that VE estimates declined simultaneously

across different time cohorts after lifting mask mandates exclusively for fully vaccinated individuals, which cannot be explained by waning immunity [6]. Although this potential association was ecological in nature, the study suggested that behavioural changes such as mask wearing may influence VE estimates.

We previously published a similar study adjusting for high-risk behaviours and mask wearing as well as testing behaviour [7]. We also did not see a large difference in COVID-19 VE estimates before and after adjusting for behaviours. This is expected because the Japanese government did not introduce policies differentially targeting the vaccinated and unvaccinated; and our incorporation of high-risk behaviours and mask wearing as covariates strengthened our observational findings. We also did an exploratory secondary analysis to estimate VEs of 2-dose mRNA vaccine recipients among those who did or did not engage in high-risk behaviours (dining at restaurants/bars at night with alcohol consumption in a group was used as a proxy [5]) compared with unvaccinated individuals who did not engage in high-risk behaviours during the BA.1/BA.2-dominant period, assuming a hypothetical scenario of vaccine passport introduction. The resulting VE estimate was significantly lower among vaccinees with high-risk behaviours (36%; 95% confidence interval (CI): 14–53) than among vaccinees with no high-risk behaviours (56%; 95% CI: 41–67; $p<0.001$), indicating that VE can be underestimated by 20% via vaccine passport introduction.

When estimating VE, we assume a causal relationship between vaccination and infection/disease [8] and we rely on observational studies as trials are often not ethically possible. Therefore, we need to carefully consider potential confounders and biases in the design and analysis. These potential confounders are not uniform for any disease or context. This notion is becoming increasingly important as infectious diseases are attracting the attention of the public and influencing behaviours, while more observational studies utilise existing data sources, which may not always contain the information necessary for the appropriate analysis.

Conflict of interest

Takeshi Arashiro is an unpaid consultant for the World Health Organization. The other authors declare no conflicts of interest.

Authors' contributions

Conception: TA, YA, JK, HM, ASa, KC, KO, AY, HA, YU, GI, YK, NY, YNa, HY, AU, AN, HK, HO, YNis, TO, YNid, ASt, TS, CS, MH, KA, MS.

Drafting of the manuscript: TA.

Critical revision of the manuscript for important intellectual content: TA, YA, JK, HM, ASa, KC, KO, AY, HA, YU, GI, YK, NY, YNa, HY, AU, AN, HK, HO, YNis, TO, YNid, ASt, TS, CS, MH, KA, MS.

References

1. van Ewijk CE, Kooijman MN, Fanoy E, Raven SF, Middeldorp M, Shah A, et al. COVID-19 vaccine effectiveness against SARS-CoV-2 infection during the Delta period, a nationwide study adjusting for chance of exposure, the Netherlands, July to December 2021. Euro Surveill. 2022;27(45):2200217. https://doi.org/10.2807/1560-7917.ES.2022.27.45.2200217 PMID: 36367011
2. World Health Organization (WHO). Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination: interim guidance, 1 October 2022: second addendum to Evaluation of COVID-19 vaccine effectiveness: interim guidance. Geneva: WHO; 2022. Available from: https://apps.who.int/iris/handle/10665/363344
3. Government of the Netherlands. Netherlands to reopen further with coronavirus entry passes. Amsterdam: Government of the Netherlands; 2021. Available from: https://www.government.nl/latest/news/2021/09/14/netherlands-to-reopen-further-with-coronavirus-entry-passes
4. Fisher KA, Tenforde MW, Feldstein LR, Lindsell CJ, Shapiro NI, Files DC, et al. Community and close contact exposures associated with COVID-19 among symptomatic adults ≥18 years in 11 outpatient health care facilities – United States, July 2020. MMWR Morb Mortal Wkly Rep. 2020;69(36):1258-64. https://doi.org/10.15585/mmwr.mm6936a5 PMID: 32915165
5. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses. 2022;16(5):952-61. https://doi.org/10.1111/irv.12992 PMID: 35470969
6. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. COVID-19 vaccine effectiveness by product and timing in New York State. medRxiv. https://doi.org/10.1101/2021.10.08.21264595
7. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). Clin Infect Dis. 2022;ciac635. https://doi.org/10.1093/cid/ciac635 PMID: 35918782
8. Sullivan SG, Cowling BJ. "Crude vaccine effectiveness" is a misleading term in test-negative studies of influenza vaccine effectiveness. Epidemiology. 2015;26(5):e60. https://doi.org/10.1097/EDE.0000000000000343 PMID: 26133018

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Any supplementary material referenced in the article can be found in the online version.

Paper 5 : VE against symptomatic infection in Japan (bivalent vaccines)

Arashiro T*, Arima Y, Kuramochi J, et al. Effectiveness of BA.1- and BA.4/BA. 5-Containing Bivalent COVID-19 mRNA Vaccines Against Symptomatic SARS-CoV-2 Infection During the BA.5-Dominant Period in Japan. Open Forum Infect Dis. 2023;10(6):ofad240. doi:10.1093/ofid/ofad240. **(*first and corresponding author; Editor's Choice)**

Open Forum Infectious Diseases journal is the original place of publication and Oxford University Press is the publisher.

PhD candidate contributions:

Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 3A.

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Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

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Student Signature	Takeshi Arashiro
Date	February 25, 2024

Supervisor Signature	Chris Smith
Date	February 25, 2024

Open Forum Infectious Diseases

BRIEF REPORT

Effectiveness of BA.1- and BA.4/BA.5-Containing Bivalent COVID-19 mRNA Vaccines Against Symptomatic SARS-CoV-2 Infection During the BA.5-Dominant Period in Japan

Takeshi Arashiro,[1,2,3,4] Yuzo Arima,[1] Jin Kuramochi,[5,6] Hirokazu Muraoka,[7] Akihiro Sato,[8] Kumi Chubachi,[9] Atsushi Yanai,[10] Hiroko Arioka,[10] Yuki Uehara,[11,12] Genei Ihara,[13] Yasuyuki Kato,[14] Naoki Yanagisawa,[15] Akihiro Ueda,[16] Hideaki Kato,[17] Hideaki Oka,[18] Yusuke Nishida,[18] Yuki Nidaira,[5] Takahiro Asami,[19] Torahiko Jinta,[20] Akira Nakamura,[21] Kunihiro Oba,[22] Daisuke Taniyama,[23] Kei Yamamoto,[18] Katsushi Tanaka,[17] Kankuro Ueshima,[24] Tetsuji Fuwa,[24] Ashley Stucky,[1] Tadaki Suzuki,[2] Chris Smith,[3,4] Martin Hibberd,[3] Koya Ariyoshi,[4] and Motoi Suzuki[1]

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In this multicenter, prospective, test-negative, case-control study in Japan, the effectiveness of both BA.1-containing and BA.4/BA.5-containing bivalent coronavirus disease 2019 mRNA vaccines against symptomatic infection during the BA.5-dominant period was high compared with no vaccination (65% and 76%) and moderate compared with monovalent vaccines administered over half a year earlier (46% combined).

Keywords. COVID-19; SARS-CoV-2; SARS-CoV-2 variants; test-negative design; vaccine effectiveness.

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https://doi.org/10.1093/ofid/ofad240

Although mRNA vaccines against coronavirus disease 2019 (COVID-19) initially showed high efficacy and effectiveness, waning immunity and the repeated emergence of variants with immune escape capacity caused concern [1]. To combat this, bivalent vaccines containing mRNA coding for the ancestral strain and either omicron subvariant BA.1 or BA.4/BA.5 were developed by both Pfizer/BioNTech and Moderna. In Japan, both BA.1-containing and BA.4/BA.5-containing bivalent vaccines were approved for use on September 20 and October 13, 2022, respectively. Because these bivalent vaccines were approved based on in vitro and animal model data, quality real-world epidemiological data are urgently needed to assess their real-world vaccine effectiveness (VE). Japan provides a uniquely suited population to estimate VE, because over two thirds of the population are considered infection-naive based on a nationwide seroprevalence study among blood donors with infection-induced seroprevalence of 26.5% in mid-November 2022 and with a relatively stable testing strategy [2, 3]. In this study, we report the results of a multicenter prospective, test-negative design, case-control study conducted in Japan to evaluate the effectiveness of bivalent vaccines against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the BA.5-dominant period.

METHODS

Patient Consent Statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval numbers 1332 and 1392). The study is conducted with a waiver of informed consent granted by the ethics committee.

Study Design and Setting

The COVID-19 vaccination rollout in Japan is detailed in the Supplementary Methods. Our study, Factors Associated with SARS-CoV-2 Infection And The Effectiveness of COVID-19 vaccines (FASCINATE study), is a multicenter, prospective, case-control study in healthcare facilities in Japan [4]. This report includes individuals who visited 1 of 10 healthcare facilities in an outpatient setting due to COVID-19-like symptom(s) in the Kanto region (Tokyo and 3 surrounding metropolitan prefectures) between September 20 and December 31, 2022. During this period, BA.5 was estimated to be responsible for 75%–100% of SARS-CoV-2 infections in the Kanto region [5].

Inclusion and Exclusion Criteria

The inclusion criterion was all individuals aged ≥16 years. Individuals who did not or could not consent to participate in the study, required immediate lifesaving treatment, or had

Table 1. Demographic and Clinical Characteristics of the Study Participants

Characteristics	All (n = 6191)	Test Positive (n = 3498)	Test Negative (n = 2693)
Age in Years, n (%)			
16–19	300 (4.9)	181 (5.2)	119 (4.4)
20–29	1719 (27.8)	900 (25.7)	819 (30.4)
30–39	1505 (24.3)	793 (22.7)	712 (26.4)
40–49	1243 (20.1)	743 (21.2)	500 (18.6)
50–59	897 (14.5)	591 (16.9)	306 (11.4)
60–69	347 (5.6)	200 (5.7)	147 (5.5)
70+	180 (2.9)	90 (2.6)	90 (3.3)
Sex, n (%); missing = 18 (0.3%)			
Male	3404 (55.1)	1976 (56.7)	1428 (53.2)
Female	2769 (44.9)	1512 (43.4)	1257 (46.8)
Comorbidity,[a] n (%)			
Yes	1525 (24.6)	824 (23.6)	701 (26.0)
No	4666 (75.4)	2674 (76.4)	1992 (74.0)
Occupation, n (%)			
Healthcare/long-term care worker	427 (6.9)	203 (5.8)	224 (8.3)
Other	5764 (93.1)	3295 (94.2)	2469 (91.7)
Days from onset to SARS-CoV-2 Test; Exact Onset Date Missing = 7 (0.1%)[b]	1 (1–2)	1 (1–2)	1 (1–2)
History of Close Contact, n (%)			
Yes	658 (10.6)	425 (12.2)	233 (8.7)
No/unknown	5533 (89.4)	3073 (87.9)	2460 (91.4)
SARS-CoV-2 Diagnostic Test in the Past Month, n (%); Missing = 200 (3.2%)			
Yes	898 (15.0)	446 (13.2)	452 (17.4)
No	5093 (85.0)	2945 (86.9)	2148 (82.6)
Past SARS-CoV-2 Infection, n (%); Missing = 74 (1.2%)			
Yes	647 (10.6)	94 (2.7)	553 (20.8)
Ancestral strain-dominant period (2020–February 2021)	37 (0.6)	14 (0.4)	23 (0.9)
Ancestral-to-alpha replacement period (March–May 2021)	12 (0.2)	6 (0.2)	6 (0.2)
Alpha-to-delta replacement period (June–July 2021)	24 (0.4)	9 (0.3)	15 (0.6)
Delta-dominant period (August–December 2021)	42 (0.7)	16 (0.5)	26 (1.0)
BA.1/BA.2-dominant period (January–June 2022)	294 (4.8)	35 (1.0)	259 (9.7)
BA.5-dominant period (July 2022)	202 (3.3)	8 (0.2)	194 (7.3)
Multiple infections	6 (0.1)	1 (0.0)	5 (0.2)
Period of infection missing	30 (0.5)	5 (0.1)	25 (0.9)
No	5471 (89.4)	3364 (97.3)	2107 (79.2)
Number of Vaccinations Received, n (%); Missing = 66 (1.1%)			
0	668 (10.9)	442 (12.8)	226 (8.5)
1	63 (1.0)	33 (1.0)	30 (1.1)
2	1380 (22.5)	811 (23.5)	569 (21.3)
3	2945 (48.1)	1617 (46.8)	1328 (49.8)
4	947 (15.5)	492 (14.2)	455 (17.1)
5	122 (2.0)	62 (1.8)	60 (2.3)
Vaccine Type for All Doses Received, n (%)			
BNT162b2 (Pfizer/BioNTech)	2349 (43.1)	1325 (44.0)	1024 (41.9)
mRNA-1273 (Moderna)	1127 (20.7)	633 (21.0)	494 (20.2)
Heterologous mRNA	1410 (25.8)	761 (25.2)	649 (26.6)
BA.1-containing bivalent	227 (4.2)	121 (4.0)	106 (4.3)
BA.4/BA.5-containing bivalent	344 (6.3)	175 (5.8)	169 (6.9)
Interval between ba.1-containing bivalent vaccine and SARS-CoV-2 Testing,[b] days	37 (17–54)	39 (20–57)	34 (15–54)
Interval between BA.4/BA.5-containing bivalent vaccine and SARS-CoV-2 testing,[b] days	21 (9–33)	22 (8–33)	21 (11–33)
Interval between BA.1-containing bivalent vaccine and SARS-CoV-2 testing among individuals who received the bivalent vaccine ≥14 days before,[b] days	42 (28–57)	42 (31–59)	43 (28–54)
Interval between BA.4/BA.5-containing bivalent vaccine and SARS-CoV-2 testing among individuals who received the bivalent vaccine ≥14 days before,[b] days	30 (23–44)	30 (24–45)	29 (22–44)
Doses of Monovalent Vaccines Received Before Bivalent Vaccine (Among Individuals Who Received Bivalent Vaccine)			

Table 1. Continued

Characteristics	All (n = 6191)	Test Positive (n = 3498)	Test Negative (n = 2693)
2	51 (8.9)	22 (7.4)	29 (10.6)
3	399 (69.9)	213 (72.0)	186 (67.6)
4	121 (21.2)	61 (20.6)	60 (21.8)
Mask Wearing in the Past 2 Weeks, Missing = 132 (2.1%)			
Wore at home and outside	414 (6.8)	235 (6.9)	179 (6.8)
Wore outside at all times	5263 (86.9)	2987 (87.2)	2276 (86.5)
Wore only when having conversation	349 (5.8)	189 (5.5)	160 (6.1)
Almost never wore masks	33 (0.5)	16 (0.5)	17 (0.7)
High-Risk Behaviors in the Past 2 Weeks (Went to Restaurant/Bar at Night With Alcohol Present), n (%); Missing = 195 (3.1%)			
Yes	2081 (34.7)	1183 (34.8)	898 (34.6)
No	3915 (65.3)	2216 (65.2)	1699 (65.4)

Abbreviation: mRNA, messenger ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.

[b]Median (interquartile range).

previously participated in this study were excluded. In the analysis, we also excluded individuals who had unknown symptom onset time, were tested ≥15 days after symptom onset, received vaccine types other than mRNA vaccines, or received unknown vaccine types.

Classification of Exposures and Outcome

A questionnaire was administered before the test results were available to minimize social desirability bias. Vaccination status was recorded based on the questionnaire via a copy of the vaccine record/certificate and checked for plausibility. Vaccination status was classified into 17 categories: (1) not vaccinated, (2) dose 1 or ≤13 days after dose 2, (3) 14 days–3 months (14–90 days) after dose 2, (4) 3–6 months (91–180 days) after dose 2, (5) >6 months (181 days) after dose 2, (6) ≤13 days after dose 3 (first booster dose), (7) 14 days–3 months (14–90 days) after dose 3, (8) 3–6 months (91–180 days) after dose 3, (9) >6 months (181 days) after dose 3, (10) ≤13 days after dose 4 (second booster dose), (11) 14 days–3 months (14–90 days) after dose 4, (12) 3–6 months (91–180 days) after dose 4, (13) >6 months (181 days) after dose 4, (14) ≤13 days after BA.1-containing bivalent vaccine, (15) ≥14 days after BA.1-containing bivalent vaccine, (16) ≤13 days after BA.4/BA.5-containing bivalent vaccine, and (17) ≥14 days after BA.4/BA.5-containing bivalent vaccine (categories 1–13 include monovalent recipients only). Severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (PCR) was done at each medical facility or commercial company for diagnostic purposes; PCR-positive individuals were considered cases and PCR-negative individuals were controls.

Data Analysis

Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for the following a priori determined covariates: age group, sex, presence of any comorbidity, occupation (healthcare/long-term care worker or not), SARS-CoV-2 diagnostic test in the past month, self-reported past SARS-CoV-2 infection (categorized by the period of infection), history of close contact, healthcare facility that the participant visited, calendar week, mask wearing, high-risk behavior (dining at a restaurant/bar at night with alcohol consumption in a group as a proxy [6, 7]), and influenza vaccination status for the 2022–2023 season. The VE against symptomatic SARS-CoV-2 infection was estimated using the following equation: VE = (1 − adjusted odds ratio [aOR]) × 100%. In addition to absolute VE ([aVE] VE comparing the vaccinated and unvaccinated), we calculated relative VE ([rVE] VE comparing individuals who received the bivalent vaccine vs individuals who only received monovalent doses 3–6 months earlier/6+ months earlier) to evaluate the added effect of the bivalent vaccine. Based on a priori knowledge that time since vaccination contributes more to VE compared to doses received [8] and due to sample size restrictions, we did not categorize by the number of monovalent vaccines received. Finally, we calculated the aOR of SARS-CoV-2 infection comparing ≥14 days after the bivalent vaccine against 14 days–3 months after the third or fourth dose of monovalent vaccines for a head-to-head comparison of monovalent versus bivalent vaccines. We also calculated the aOR of SARS-CoV-2 infection by influenza vaccination status to assess the risk of bias. During the study period, influenza activity was extremely low in Japan [9]. Data analyses were performed using STATA version 17.0.

RESULTS

A total of 6955 individuals were enrolled from 10 medical facilities; 170 were excluded for unknown symptom onset date, 33 for being tested ≥15 days after symptom onset, and 561 for

Table 2. Absolute and Relative Effectiveness of BA.1- or BA.4/BA.5-Containing Bivalent Vaccine Against Symptomatic SARS-CoV-2 by Dose Number and Time Since Vaccination During the BA.5-Dominant Period

Vaccination Status	Test Positive, n	Test Negative, n	Adjusted Odds Ratios (95% CI)[a]	Vaccine Effectiveness, % (95% CI)
Comparison Between Vaccinated Versus Unvaccinated				
Unvaccinated	442	226	1	NA
Dose 1 or ≤13 days after dose 2	36	31	0.54 (.29–1.00)	46 (0–71)
14 days–3 months after dose 2	52	38	0.68 (.40–1.16)	32 (–16–60)
3–6 months after dose 2	34	24	0.58 (.31–1.07)	42 (–7–69)
>6 months after dose 2	571	436	0.58 (.46–.74)	42 (26–54)
≤13 days after dose 3	0	1	NA	NA
14 days–3 months after dose 3	70	115	0.24 (.16–.35)	76 (65–84)
3–6 months after dose 3	364	373	0.45 (.35–.58)	55 (42–65)
>6 months after dose 3	987	664	0.50 (.40–.63)	50 (37–60)
≤13 days after dose 4	9	3	1.27 (.25–6.45)	NA
14 days–3 months after dose 4	119	150	0.33 (.23–.47)	67 (53–77)
3–6 months after dose 4	120	99	0.39 (.26–.59)	61 (41–74)
>6 months after dose 4	6	1	1.78 (.21–15.30)	NA
≤13 days after BA.1-containing bivalent	21	24	0.29 (.14–.51)	71 (49–86)
≤13 days after BA.4/BA.5-containing bivalent	65	57	0.32 (.20–.51)	68 (49–80)
≥14 days after BA.1-containing bivalent	95	76	0.35 (.23–.53)	65 (47–77)
≥14 days after BA.4/BA.5-containing bivalent	112	116	0.24 (.17–.35)	76 (65–83)
Comparison Between Bivalent Vaccine Versus 3–6 Months After Monovalent Dose[b]				
Unvaccinated	442	226	NA	NA
Dose 1 or ≤13 days after monovalent dose[b]	45	35	NA	NA
14 days–3 months after monovalent dose[b]	241	303	NA	NA
3–6 months after monovalent dose[b]	518	496	1	NA
>6 months after monovalent dose[b]	1564	1101	NA	NA
≤13 days after bivalent dose	86	81	0.72 (.49–1.04)	28 (–4–51)
≥14 days after bivalent dose	207	192	0.65 (.49–.85)	35 (15–51)
Comparison Between Bivalent Vaccine Versus >6 Months After Monovalent Dose[b]				
Unvaccinated	442	226	NA	NA
Dose 1 or ≤13 days after monovalent dose[b]	45	35	NA	NA
14 days–3 months after monovalent dose[b]	241	303	NA	NA
3–6 months after monovalent dose[b]	518	496	NA	NA
>6 months after monovalent dose[b]	1564	1101	1	NA
≤13 days after bivalent dose	86	81	0.60 (.42–.86)	40 (14–58)
≥14 days after bivalent dose	207	192	0.54 (.42–.70)	46 (30–58)
Comparison Between Bivalent Vaccine Versus 14 Days–3 Months After 3 or 4 Doses of Monovalent Vaccines				
Unvaccinated	442	226	NA	NA
Dose 1 or dose 2	703	533	NA	NA
14 days–3 months after 3rd or 4th monovalent dose	189	265	1	NA
3–6 months after 3rd or 4th monovalent dose	484	472	1.52 (1.18–1.96)	NA
>6 months after 3rd or 4th monovalent dose	993	665	1.77 (1.38–2.28)	NA
≤13 days after bivalent dose	86	81	1.09 (.73–1.63)	–9 (–63 to 27)
≥14 days after bivalent dose	207	192	0.99 (.72–1.36)	1 (–36 to 28)

Abbreviations: CI, confidence interval; NA, not available (includes categories with small sample size or irrelevant comparisons); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Adjusted for age group, sex, presence of comorbidities, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, calendar week, mask wearing, high-risk behavior, and influenza vaccination status for the 2022–2023 season.

[b]Regardless of doses received.

receiving vaccine types other than monovalent mRNA vaccines or receiving an unknown vaccine type. The final analysis included 6191 individuals with 3498 (56.5%) positive cases. The median age was 36 (interquartile range [IQR], 27–48) years (other demographic and clinical characteristics are in Table 1 and the Supplementary Table). The aVE of bivalent vaccine (regardless of subvariant coded) was 72% (95% confidence interval [CI], 61–80). When stratified by subvariant coded in the bivalent vaccine, the aVE of BA.1-containing bivalent vaccine was 65% (95% CI, 47–77), and the aVE of BA.4/BA.5-containing bivalent vaccine was 76% (95% CI, 65–83) (Table 2). The rVE comparing bivalent vaccine (regardless of

subvariant coded) versus monovalent vaccines post-3–6 months was 35% (95% CI, 15–51), whereas rVE comparing bivalent vaccine versus monovalent vaccines post-6 months was 46% (95% CI, 30–58). The aOR of SARS-CoV-2 infection comparing bivalent vaccine ≥14 days versus 14 days–3 months after 3 or 4 doses of monovalent vaccine was 0.99 (95% CI, .72–1.36) (median interval between the bivalent vaccine and SARS-CoV-2 testing 34 days [IQR, 24–49]; median interval between the monovalent vaccine and testing 66 days [IQR, 49–80]). The aOR of SARS-CoV-2 infection by influenza vaccination status was 0.95 (95% CI, .79–1.13).

DISCUSSION

In this multicenter, test-negative study in Japan, we found that aVE of BA.1-containing bivalent COVID-19 vaccines was 65% and that of BA.4/BA.5-containing bivalent vaccines was 76% during the BA.5-dominant period, both against symptomatic infection. Only a few published studies have assessed the effectiveness of BA.4/BA.5-containing bivalent VE, mostly against severe COVID-19 [10–12]. Our estimate of aVE against symptomatic infection was higher than that observed in a US study on BA.4/BA.5-containing bivalent vaccines [10]. This may be due to substantial differences in the proportion of previously infected individuals as well as public health and social measures (eg, high frequency of mask wearing in Japan regardless of vaccination status). We also included a number of factors to adjust for potential differences between vaccinated and unvaccinated individuals. Similar to the US study, rVE was moderate (46%) with more added benefit with a longer period since the last monovalent vaccine. The head-to-head comparison soon after monovalent and bivalent vaccines did not result in the superiority of the bivalent vaccine during the BA.5-dominant period (aOR, 0.99). However, there are some important limitations in this comparison because monovalent booster vaccines became unavailable after introduction of the bivalent vaccine. Overall, although aVE was high in our study, the bivalent vaccine was not superior to the monovalent vaccine, and aVE was lower than that observed for the monovalent primary series against the ancestral strain, alpha, and delta variants (85%–95%) [4, 13]. This is in line with immune imprinting against the ancestral strain as suggested in other studies [14, 15].

This study has several limitations. First, biases and confounding inherent in observational studies are possible. We attempted to minimize these by adjusting for various factors, and there was no association between influenza vaccination and SARS-CoV-2 testing. Second, because we did not have a system to link test results with vaccination history, we asked participants to refer to their vaccine records/certificates and (if not in possession) diary/calendar for accuracy. Third, wide CIs for some estimates warrant careful interpretation of point estimates. Fourth, our analysis was a complete case analysis. Finally, our VE estimates were short term and require continued assessment to monitor mid- to long-term effectiveness.

CONCLUSIONS

In conclusion, we found that bivalent COVID-19 VE was high compared with no vaccination and moderate compared with monovalent vaccines administered over half a year earlier. Although there was evidence suggestive of immune imprinting, our results support the continued rollout of bivalent vaccines.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. TA, YA, and MS conceived of and designed the study. All authors contributed to the acquisition, analysis, and/or interpretation of the data. TA wrote the first draft of the manuscript. All authors provided critical input to the manuscript for important intellectual content.

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Potential conflicts of interest. TA is an unpaid consultant for the World Health Organization. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub: COVID-19 data, vaccine effectiveness studies. Available at: https://view-hub.org/covid-19/effectiveness-studies. Accessed 14 April 2023.
2. Ministry of Health, Labour and Welfare/National Institute of Infectious Diseases, Japan. [Seroprevalence among blood donors]. Available at: https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/11729-covid19-82.html. Accessed 14 April 2023.
3. Arashiro T, Arai S, Kinoshita R, et al. National seroepidemiological study of COVID-19 after the initial rollout of vaccines: before and at the peak of the omicron-dominant period in Japan. Influenza Other Respir Viruses 2023; 17: e13094.
4. Arashiro T, Arima Y, Muraoka H, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and omicron-dominant periods in Japan: a multi-center prospective case-control study (factors associated with SARS-CoV-2 infection and the effectiveness of COVID-19 vaccines study). Clin Infect Dis 2023; 76:e108–15.
5. Ministry of Health, Labour and Welfare, Japan. [Estimated subvariant prevalence via SARS-CoV-2 genomic surveillance using specimen from commercial company]. Available at: https://www.mhlw.go.jp/content/10900000/001039363.pdf. Accessed 14 April 2023.
6. Arashiro T, Arima Y, Muraoka H, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses 2022; 16:952–61.
7. Arashiro T, Arima Y, Kuramochi J, et al. Letter to the editor: importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. Euro Surveill 2023; 28:2300034.
8. National Institute of Infectious Diseases, Japan. [Influenza activity compared to past 10 years]. Available at: https://www.niid.go.jp/niid/ja/flu-m/813-idsc/map/130-flu-10year.html. Accessed 14 April 2023.
9. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. Results of COVID-19 vaccine effectiveness studies: an ongoing systematic review (page 16). Available at: https://view-hub.org/sites/default/files/

2023-03/COVID19%20VE%20Studies_Forest%20Plots_Omicron_0.pdf. Accessed 14 April 2023.
10. Link-Gelles R, Ciesla AA, Fleming-Dutra KE, et al. Effectiveness of bivalent mRNA vaccines in preventing symptomatic SARS-CoV-2 infection—increasing community access to testing program, United States, September–November 2022. MMWR Morb Mortal Wkly Rep 2022; 71:1526–30.
11. Tenforde MW, Weber ZA, Natarajan K, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults —VISION Network, nine states, September–November 2022. MMWR Morb Mortal Wkly Rep 2022; 71:1616–24.
12. Surie D, DeCuir J, Zhu Y, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated hospitalization among immunocompetent adults aged ≥65 years—IVY Network, 18 states, September 8–November 30, 2022. MMWR Morb Mortal Wkly Rep 2022; 71:1625–30.
13. Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med 2021; 385:187–9.
14. Collier AY, Miller J, Hachmann NP, et al. Immunogenicity of BA.5 bivalent mRNA vaccine boosters. N Engl J Med 2023; 388:565–7.
15. Chemaitelly H, Ayoub HH, Tang P, et al. Immune imprinting and protection against repeat reinfection with SARS-CoV-2. N Engl J Med 2022; 387:1716–8.

Supplementary Material

Supplementary Methods

COVID-19 vaccination rollout in Japan

In Japan, the primary series (doses 1 and 2) rollout started in mid-February 2021, the first booster dose (dose 3) in December 2021, and the second booster dose (dose 4) in late May 2022. The second booster dose was administered exclusively to individuals who were ≥60 years old, had any comorbidities, or were healthcare/long-term care workers. Most individuals received either BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) for all doses, thus recipients of other vaccines were excluded from this report. The primary series followed manufacturer-recommended intervals (21 days for BNT162b2, 28 days for mRNA-1273). For both booster doses, individuals became eligible 5 months after their last dose. For bivalent vaccines, completing the primary series was a prerequisite and individuals became eligible 5 months (until October 2022) or 3 months (after October 2022) after receipt of their previous monovalent vaccine. After BA.4/BA.5-containing bivalent vaccines was approved for use, the choice between BA.1-containing and BA.4/BA.5-containing bivalent vaccines was based on local availability and/or personal preference, but not based on risk status.

Supplementary Table. Demographic and Clinical Characteristics of the Study Participants by Vaccination Status[a]

	Vaccinated (n = 5457)	Unvaccinated (n = 668)
Age in years, n (%)		
16–19	254 (4.7)	39 (5.8)
20–29	1447 (26.5)	252 (37.7)
30–39	1306 (23.9)	184 (27.5)
40–49	1136 (20.8)	100 (15.0)
50–59	822 (15.1)	66 (9.9)
60–69	324 (5.9)	19 (2.8)
70+	168 (3.1)	8 (1.2)
Sex, n (%); missing = 18 (0.3%)		

Male	2961 (54.4)	402 (60.3)
Female	2479 (45.6)	265 (39.7)
Comorbidity,[b] n (%)		
Yes	1341 (24.6)	168 (25.2)
No	4116 (75.4)	500 (74.9)
Occupation, n (%)		
Healthcare/long-term care worker	394 (7.2)	30 (4.5)
Other	5063 (92.8)	638 (95.5)
Mask-wearing in the past 2 weeks; missing = 122 (2.0%)		
Wore at home and outside	365 (6.8)	46 (7.0)
Wore outside at all times	4678 (87.5)	539 (82.4)
Wore only when having conversation	286 (5.4)	58 (8.9)
Almost never wore masks	20 (0.4)	11 (1.7)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol present), n (%); missing = 182 (3.0%)		
Yes	1848 (34.9)	219 (33.8)
No	3448 (65.1)	428 (66.2)

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Among individuals with known vaccination status (n = 6125).

[b] Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.

Paper 6 : VE against symptomatic infection in Japan (BA.1/BA.2 and BA.5)

Arashiro T*, Arima Y, Kuramochi J, et al. Immune escape and waning immunity of COVID-19 monovalent mRNA vaccines against symptomatic infection with BA.1/BA.2 and BA.5 in Japan. **Vaccine.** 2023;S0264-410X(23)01194-5. doi:10.1016/j.vaccine.2023.10.021.

PhD candidate contributions:
Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 3A.

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Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Vaccine		
When was the work published?	October 13, 2023		
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SECTION E

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Date	February 25, 2024

Supervisor Signature	Chris Smith
Date	February 25, 2024

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Immune escape and waning immunity of COVID-19 monovalent mRNA vaccines against symptomatic infection with BA.1/BA.2 and BA.5 in Japan

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ABSTRACT

Background: Repeated emergence of variants with immune escape capacity and waning immunity from vaccination are major concerns for COVID-19. We examined whether the surge in Omicron subvariant BA.5 cases was due to immune escape or waning immunity through vaccine effectiveness (VE) evaluation.
Methods: A test-negative case-control study was conducted in 16 clinics/hospitals during the BA.1/BA.2-dominant and BA.5-dominant periods. VE against symptomatic infection was estimated after adjusting for

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Vaccine effectiveness
SARS-CoV-2 variants

age, sex, comorbidity, occupation, testing frequency, prior infection, close contact history, clinic/hospital, week, and preventive measures. Absolute VE (aVE) was calculated for 2/3/4 doses, compared to the unvaccinated. Relative VE (rVE) was calculated, comparing 3 vs 2 and 4 vs 3 doses.

Results: 13,025 individuals were tested during the BA.1/BA.2-dominant and BA.5-dominant periods with similar baseline characteristics. For BA.1/BA.2, aVE was 52 % (95 %CI:34–66) 14 days-3 months post-dose 2, 42 % (29–52) > 6 months post-dose 2, 71 % (64–77) 14 days-3 months post-dose 3, and 68 % (52–79) 3–6 months post-dose 3. rVE was 49 % (38–57) 14 days-3 months post-dose 3 and 45 % (18–63) 3–6 months post-dose 3. For BA.5, aVE was 56 % (27–73) 3–6 months post-dose 2, 32 % (12–47) > 6 months post-dose 2, 70 % (61–78) 14 days-3 months post-dose 3, 59 % (48–68) 3–6 months post-dose 3, 50 % (29–64) > 6 months post-dose 3, and 74 % (61–83) ≥ 14 days post-dose 4. rVE was 56 % (45–65) 14 days-3 months post-dose 3, 39 % (27–48) 3–6 months post-dose 3, 25 % (-2–45) > 6 months post-dose 3, and 30 % (-6–54) ≥ 14 days post-dose 4.

Conclusions: Booster doses initially provided high protection against BA.5 at a level similar to that against BA.1/BA.2. However, the protection seemed shorter-lasting against BA.5, which likely contributed to the surge. Furthermore, rVE post-dose 4 was low even among recent vaccinees. These results support the introduction of variant-containing vaccines and emphasize the need for vaccines with longer duration of protection.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally [1]. Although COVID-19 mRNA vaccines initially showed high efficacy and effectiveness [2–7], there are concerns due to waning immunity [8–11] and the repeated emergence of variants with immune escape capacity [12,13]. In November 2021, the Omicron variant, which harbors numerous mutations in the spike protein, was first detected in South Africa. Several studies, including our previous study, reported early estimates of vaccine effectiveness (VE) against Omicron (mostly on the earliest subvariant BA.1); results showed low to moderate VE for the mRNA primary series (2 doses) with an mRNA booster dose (dose 3) providing high protection against symptomatic infection shortly after vaccination, although mid- to long-term VE remained in question [14–17]. In mid-2022, a new subvariant BA.5 rapidly spread globally and replaced BA.1/BA.2 [18,19]. As with many other countries, Japan experienced a large BA.5 surge [20,21], becoming a leading country in reported case counts, partially owing to reduced testing in other countries [19]. Although initial *in vitro* neutralization studies suggested further immune escape capacity [22,23], it was unclear whether the surge was owing to the substantial increase in immune escape capacity compared to BA.1/BA.2, waning immunity, or both.

Despite continued need, accurate VE evaluation has become increasingly challenging as much of the global population has already been infected, with differences in proportions with prior infection between the vaccinated and unvaccinated [24]. Also, testing practices have been rapidly changing and varying public health and social measures (PHSM) are implemented both at the individual and population levels [19,25]. Japan provides a uniquely suited population to estimate VE, as a majority of individuals are infection-naïve (infection-induced seroprevalence in Tokyo was 2.8 % before the Omicron-dominant period; 5.7 % at the peak of the BA.1/BA.2 wave; and 26.5 % after the BA.5 wave) [20,26,27]. Also, during the entire study period, mask wearing was required by the government, regardless of vaccination

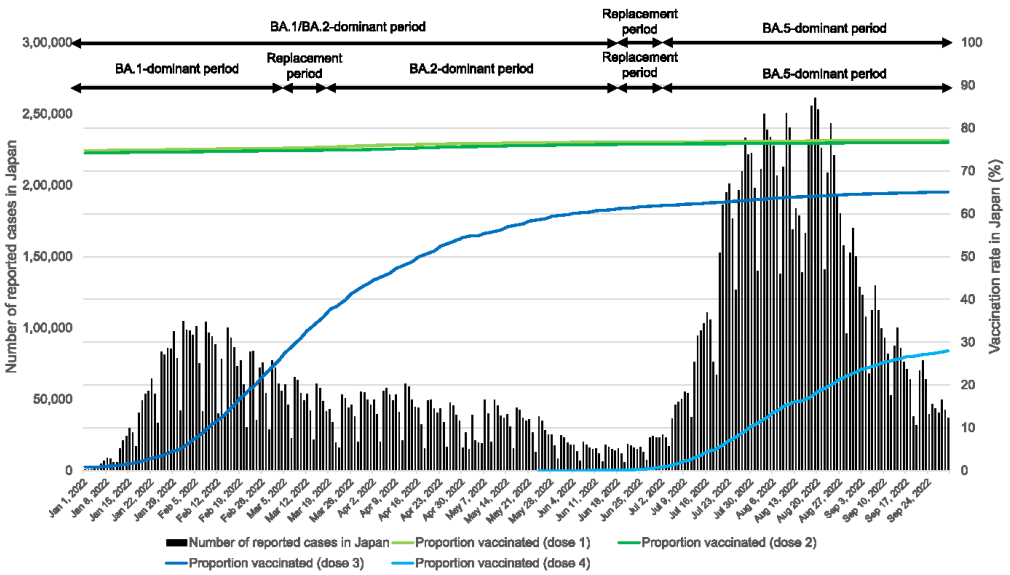

Fig. 1. Number of reported COVID-19 cases since the beginning of the pandemic and proportion of individuals vaccinated in Japan by dose number. (Data sources: Ministry of Health, Labour and Welfare, Japan [https://www.mhlw.go.jp/stf/covid-19/open-data.html] and Digital Agency, Japan [https://info.vrs.digital.go.jp/dashboard]).

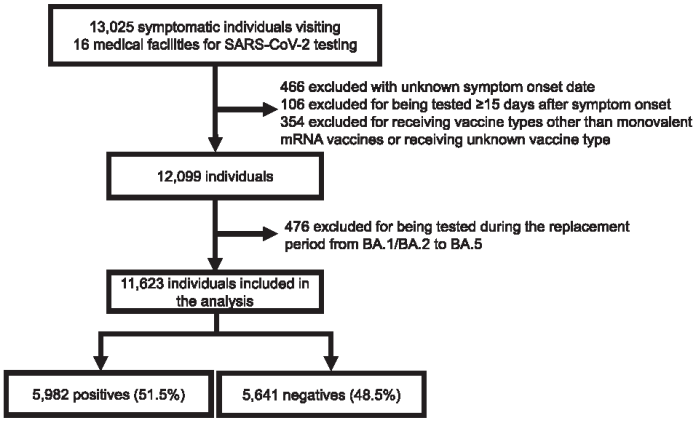

Fig. 2. Flow diagram of the study participants.

status, in indoor public places where physical distancing is not possible [28].

Here we report the results of a multi-center test-negative design case-control study conducted in Japan to evaluate VE against symptomatic SARS-CoV-2 infection during the BA.1/BA.2- and BA.5-dominant periods. We estimated absolute VE (aVE) and relative VE (rVE) of 2 or 3 doses for the BA.1/BA.2-dominant period and 2, 3, or 4 doses for the BA.5-dominant period.

2. Methods

2.1. COVID-19 vaccination rollout in Japan

In Japan, BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), and AZD1222 (AstraZeneca) have been approved for use in the primary series (doses 1 and 2) since mid-February 2021 (Fig. 1) [29]. BNT162b2, mRNA-1273, and NVX-CoV2373 (Novavax) have been approved for use as the first booster dose (dose 3) since December 2021. BNT162b2 and mRNA-1273 have been approved for use as the second booster dose (dose 4) since late May 2022, exclusively for individuals who were ≥60 years, had any comorbidities, or were healthcare/long-term care workers. The majority of individuals received either BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) for all doses, thus recipients of other vaccines were excluded from this report. The primary series followed manufacturer-recommended intervals (21 days for BNT162b2 and 28 days for mRNA-1273). For both booster doses, individuals became eligible 5 months after the previous dose, as of the end of the study period.

2.2. Study design and setting

Our study, Factors Associated with SARS-CoV-2 Infection And The Effectiveness of COVID-19 vaccines (FASCINATE study), is a multi-center case-control study in healthcare facilities in Japan. A general description of the study is published elsewhere [17]. This report includes individuals who visited one of 16 healthcare facilities in an outpatient setting due to COVID-19-like symptom(s) in the Kanto region (Tokyo and 4 surrounding metropolitan prefectures). For this report, individuals tested between January 1, 2022 and September 30, 2022 were included. Based on data from the SARS-CoV-2 genomic surveillance with random sampling, in early January 2022, the case counts rose rapidly owing to the introduction of BA.1, with BA.1 estimated to be responsible for over 90 % of SARS-CoV-2 infections in the Kanto region [30]. In mid-March, BA.2 overtook BA.1 and became dominant. BA.2 was estimated to be responsible for 89 % of SARS-CoV-2 infections in the Kanto region during the week of June 13–19 (epidemiologic week 24) [31], but was rapidly replaced by BA.5. Therefore, we defined January 1 to June 19, 2022 (weeks 1–24) as the BA.1/BA.2-dominant period (Fig. 1). Since the sample size was limited with previous reports suggesting similar VE estimates against BA.1 and BA.2 [32], we did not stratify these periods. Then, since the replacement from BA.2 to BA.5 occurred rapidly between June 20 and July 3, 2022 (weeks 25–26) [31], we defined this period as the replacement period. Finally, by the week of July 4–10 (week 27), BA.5 was estimated to be responsible for 76 % of SARS-CoV-2 infections in the Kanto region (week 28, 84 %; week 30, 96 %; week 32, 99 %) [31]. Therefore, we defined July 4 to September 30, 2022 (weeks 27–39) as the BA.5-dominant period. During the study period, newer subvariants such as BQ.1 and XBB were only sporadically detected in Japan, mostly at ports of entry [33].

2.3. Inclusion and exclusion criteria

The inclusion criterion was all symptomatic individuals aged ≥20 years for the BA.1/BA.2-dominant period and was expanded to individuals aged ≥16 years for some sites for the BA.5-dominant period. We defined symptomatic individuals as individuals with any of the following: fever ≥37.5 °C, malaise, chills, joint pain, headache, runny nose, cough, sore throat, shortness of breath, gastrointestinal symptoms (vomiting, diarrhea, stomachache), and loss of taste/smell. Individuals who did not or could not consent to participate in the study, required immediate lifesaving treatment, or had previously participated in this study during each of the two periods were excluded. At the analysis stage, we also excluded individuals who had unknown symptom onset, were tested ≥15 days after symptom onset, received vaccine types other than monovalent mRNA vaccines, received an unknown vaccine type, or were tested during the replacement period from BA.1/BA.2 to BA.5.

2.4. Classification of exposures and outcome

A paper or web-based (according to the subject's preference) questionnaire was administered before the test results were available to minimize social desirability bias. Vaccination status (number of doses, vaccine manufacturer, and date of last dose) was recorded based on the questionnaire (via a copy of the vaccine record/certificate) and checked for plausibility (e.g., the vaccine doses and dates received were in line with the Japanese rollout schedule). Vaccination status was classified

Table 1
Demographic and clinical characteristics of the study participants.

	All (n = 11,623)	Test positive (n = 5982)	Test negative (n = 5641)
Age in years, n (%)			
16–19	292 (2.5)	200 (3.3)	92 (1.6)
20–29	3439 (29.6)	1714 (28.7)	1725 (30.6)
30–39	3006 (25.9)	1448 (24.2)	1558 (27.6)
40–49	2361 (20.3)	1310 (21.9)	1051 (18.6)
50–59	1542 (13.3)	846 (14.1)	696 (12.3)
60–69	622 (5.4)	332 (5.6)	290 (5.1)
70–79	278 (2.4)	106 (1.8)	172 (3.1)
80+	83 (0.7)	26 (0.4)	57 (1.0)
Sex, n (%); missing = 24 (0.2 %)			
Male	5968 (51.5)	3186 (53.4)	2782 (49.4)
Female	5631 (48.6)	2783 (46.6)	2847 (50.6)
Comorbidity,[a] n (%)			
Yes	2938 (25.3)	1397 (23.4)	1541 (27.3)
No	8685 (74.7)	4585 (76.7)	4100 (72.7)
Occupation, n (%)			
Healthcare/long-term care worker	827 (7.1)	426 (7.1)	401 (7.1)
Other	10,796 (92.9)	5556 (92.9)	5240 (92.9)
Days from onset to SARS-CoV-2 test; exact onset date missing = 20 (0.2 %)[b]	1 (1–2)	1 (1–2)	1 (1–2)
History of close contact, n (%)			
Yes	1286 (11.1)	866 (14.5)	420 (7.5)
No/unknown	10,337 (88.9)	5116 (85.5)	5221 (92.6)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 435 (3.7 %)			
Yes	1834 (16.4)	849 (14.9)	985 (18.0)
No	9354 (83.6)	4866 (85.1)	4488 (82.0)
Past SARS-CoV-2 infection, n (%); missing = 220 (1.9 %)			
Yes	660 (5.8)	176 (3.0)	484 (8.8)
Ancestral strain-dominant period (2020–February 2021)	124 (1.1)	48 (0.8)	76 (1.4)
Ancestral-to-Alpha replacement period (March–May 2021)	54 (0.5)	27 (0.5)	27 (0.5)
Alpha-to-Delta replacement period (June–July 2021)	63 (0.6)	25 (0.4)	38 (0.7)
Delta-dominant period (August–December 2021)	122 (1.1)	32 (0.5)	90 (1.6)
BA.1/BA.2-dominant period (January–June 2022)	241 (2.1)	29 (0.5)	212 (3.8)
BA.5-dominant period (July 2022)	3 (0.0)	0 (0.0)	3 (0.1)
Multiple infections	5 (0.0)	0 (0.0)	5 (0.1)
Period of infection missing	48 (0.4)	15 (0.3)	33 (0.6)
No	10,743 (94.2)	5711 (97.0)	5032 (91.2)
Number of vaccinations received, n (%); missing = 85 (0.7 %)			
0	1566 (13.6)	1015 (17.1)	551 (9.8)
1	103 (0.9)	54 (0.9)	49 (0.9)
2	5182 (44.9)	2617 (44.1)	2565 (45.8)
3	4353 (37.7)	2110 (35.5)	2243 (40.1)
4	334 (2.9)	145 (2.4)	189 (3.4)
Vaccine type, n (%)			
BNT162b2	5217 (52.3)	2635 (53.5)	2582 (51.2)
mRNA-1273	3207 (32.2)	1539 (31.2)	1668 (33.1)
Heterologous mRNA	1548 (15.5)	752 (15.3)	796 (15.8)
Interval between dose 2 and SARS-CoV-2 testing[b]	184 (144–251)	196 (153–271)	174 (136–228)
Interval between dose 3 and SARS-CoV-2 testing[b]	102 (59–142)	115 (72–148)	87 (46–131)
Interval between dose 4 and SARS-CoV-2 testing[b]	27 (15–43)	22 (13–41)	29 (16–44)
Mask-wearing in the past 2 weeks; missing = 239 (2.1 %)			
Wore at home and outside	868 (7.6)	462 (7.9)	406 (7.3)
Wore outside at all times	10,049 (88.3)	5115 (87.4)	4934 (89.2)
Wore only when having conversation	444 (3.9)	261 (4.5)	183 (3.3)
Almost never wore masks	23 (0.2)	14 (0.2)	9 (0.2)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol present), n (%); missing = 568 (4.9 %)			
Yes	3862 (34.9)	2075 (36.5)	1787 (33.2)
No	7193 (65.1)	3604 (63.5)	3589 (66.8)
Eligible for dose 4[c]			
Yes	3902 (33.6)	1892 (31.6)	2010 (35.6)
No	7721 (66.4)	4090 (68.4)	3631 (64.4)

Notes. SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
[a] Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.
[b] Median (interquartile range).
[c] Individuals who either were ≥60 years, had any comorbidities, or were healthcare/long-term care workers.

into 11 categories: (1) not vaccinated, (2) dose 1 or ≤13 days after dose 2 (partially vaccinated), (3) 14 days–3 months (14–90 days) after dose 2, (4) 3–6 months (90–180 days) after dose 2, (5) >6 months (181 days) after dose 2, (6) ≤13 days after dose 3 (first booster dose), (7) 14 days–3 months (14–90 days) after dose 3, (8) 3–6 months (90–180 days) after dose 3, (9) >6 months (181 days) after dose 3, (10) ≤13 days after dose 4 (second booster dose), and (11) ≥14 days after dose 4. SARS-CoV-2 polymerase chain reaction (PCR) was done at each medical facility or commercial company for diagnostic purposes; PCR-positive individuals were considered cases and PCR-negative individuals were controls.

2.5. Data analysis

Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group, sex, presence of any comorbidity, occupation (healthcare/long-term care worker or not), SARS-CoV-2 diagnostic test in the past month, self-reported past SARS-CoV-2 infection (categorized by the period of infection), history of close contact, healthcare facility in which SARS-CoV-2 testing was done, and calendar week. We defined comorbidity as any of the following: hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use. These potential confounders were determined *a priori* [5–11]. VE against symptomatic SARS-CoV-2 infection was estimated using the following equation: VE = (1 - adjusted odds ratio [aOR]) × 100 %. In addition to aVE (VE comparing the vaccinated and unvaccinated), we calculated rVE (VE comparing individuals who have received the most recent eligible booster dose vs those who did not [e.g., VE comparing 3 vs 2 doses and VE comparing 4 doses vs 3 doses]) to evaluate the added effect of each booster dose. In the secondary analysis, we further adjusted the odds ratios (OR) for preventive measures, including mask wearing and high-risk behavior (dining at a restaurant/bar at night with alcohol consumption in a group as a proxy [34]), in an attempt to control for differential exposures between vaccinated and unvaccinated individuals. We also performed sub-analysis by restricting the analysis to individuals who either were ≥65 years or had any comorbidities, who have higher risk of developing severe COVID-19. Finally, although complete case analysis was done in primary/secondary/sub-analyses, multiple imputation by chained equations was performed as a sensitivity analysis. We used the same variables used in the primary analyses to impute missing data and to further calculate aOR and VE. Data analyses were performed using STATA version 17.0.

2.6. Consideration of bias due to co-circulation of influenza and influenza vaccination

Co-circulation of influenza and COVID-19 can result in biased VE estimates as propensity to get vaccinated may be similar for COVID-19 vaccines and influenza vaccines [35]. However, in Japan, unlike in

Table 2
Demographic and clinical characteristics of the study participants during BA.1/BA.2-dominant period and BA.5-dominant period.

BA.1/BA.2-dominant period	All (n = 6163)	Test positive (n = 2670)	Test negative (n = 3493)
Age in years, n (%)			
20–29	1999 (32.4)	896 (33.6)	1103 (31.6)
30–39	1787 (29.0)	714 (26.7)	1073 (30.7)
40–49	1208 (19.6)	587 (22.0)	621 (17.8)
50–59	741 (12.0)	320 (12.0)	421 (12.1)
60–69	293 (4.8)	122 (4.6)	171 (4.9)
70–79	106 (1.7)	27 (1.0)	79 (2.3)
80+	29 (0.5)	4 (0.2)	25 (0.7)
Sex, n (%); missing = 9 (0.1 %)			
Male	3010 (48.9)	1331 (49.9)	1679 (48.2)
Female	3144 (51.1)	1337 (50.1)	1807 (51.8)
Comorbidity,[a] n (%)			
Yes	1508 (24.5)	585 (21.9)	923 (26.4)
No	4655 (75.5)	2085 (78.1)	2570 (73.6)
Occupation, n (%)			
Healthcare/long-term care worker	316 (5.1)	112 (4.2)	204 (5.8)
Other	5847 (94.9)	2558 (95.8)	3289 (94.2)
Days from onset to SARS-CoV-2 test; exact onset date missing = 7 (0.1 %)[b]	1 (1–2)	1 (1–2)	1 (1–3)
History of close contact, n (%)			
Yes	960 (15.6)	629 (23.6)	331 (9.5)
No/unknown	5203 (84.4)	2041 (76.4)	3162 (90.5)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 114 (1.8 %)			
Yes	1032 (17.1)	429 (16.4)	603 (17.6)
No	5017 (82.9)	2187 (83.6)	2830 (82.4)
Past SARS-CoV-2 infection, n (%); missing = 107 (1.7 %)			
Yes	367 (6.1)	100 (3.8)	267 (7.8)
Ancestral strain-dominant period (2020–February 2021)	101 (1.7)	38 (1.4)	63 (1.8)
Ancestral-to-Alpha replacement period (March–May 2021)	39 (0.6)	18 (0.7)	21 (0.6)
Alpha-to-Delta replacement period (June–July 2021)	44 (0.7)	14 (0.5)	30 (0.9)
Delta-dominant period (August–December 2021)	80 (1.3)	20 (0.8)	60 (1.8)
BA.1/BA.2-dominant period (January–June 2022)	67 (1.1)	3 (0.1)	64 (1.9)
BA.5-dominant period (July 2022)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple infections	3 (0.1)	0 (0.0)	3 (0.1)
Period of infection missing	33 (0.5)	7 (0.3)	26 (0.8)
No	5689 (93.9)	2534 (96.2)	3155 (92.2)
Number of vaccinations, n (%); missing = 64 (1.0)			
0	887 (14.5)	516 (19.6)	371 (10.7)
1	59 (1.0)	29 (1.1)	30 (0.9)
2	3756 (61.6)	1684 (63.8)	2072 (59.9)
3	1397 (22.9)	411 (15.6)	976 (28.5)
4	0 (0.0)	0 (0.0)	0 (0.0)
Vaccine type, n (%)			
BNT162b2	2761 (53.0)	1156 (54.4)	1605 (52.0)
mRNA-1273	2069 (39.7)	854 (40.2)	1215 (39.4)
Heterologous mRNA	382 (7.3)	114 (5.4)	268 (8.7)
Interval between dose 2 and SARS-CoV-2 testing[b]	169 (135–201)	174 (140–204)	165 (130–199)
Interval between dose 3 and SARS-CoV-2 testing[b]	50 (25–76)	51 (23–72)	49 (25–78)
Interval between dose 4 and SARS-CoV-2 testing[b]	N/A	N/A	N/A
Mask-wearing in the past 2 weeks; missing = 92 (1.5 %)			
Wore at home and outside	468 (7.7)	218 (8.3)	250 (7.3)
Wore outside at all times	5484 (90.3)	2356 (89.7)	3128 (90.9)
Wore only when having conversation	114 (1.9)	51 (1.9)	63 (1.8)
Almost never wore masks	5 (0.1)	3 (0.1)	2 (0.1)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol present), n (%); missing = 362 (5.9 %)			
Yes	2090 (36.0)	944 (37.8)	1146 (34.7)
No	3711 (64.0)	1556 (62.2)	2155 (65.3)

Table 2 (*continued*)

BA.5-dominant Period	All (n = 5460)	Test positive (n = 3312)	Test negative (n = 2148)
Age in years, n (%)			
16–19	292 (5.4)	200 (6.0)	92 (4.3)
20–29	1440 (26.4)	818 (24.7)	622 (29.0)
30–39	1219 (22.3)	734 (22.2)	485 (22.6)
40–49	1153 (21.1)	723 (21.8)	430 (20.0)
50–59	801 (14.7)	526 (15.9)	275 (12.8)
60–69	329 (6.0)	210 (6.3)	119 (5.5)
70–79	172 (3.2)	79 (2.4)	93 (4.3)
80+	54 (1.0)	22 (0.6)	26 (1.2)
Sex, n (%); missing = 15 (0.3 %)			
Male	2958 (54.3)	1855 (56.2)	1103 (51.5)
Female	2487 (45.7)	1447 (43.8)	1040 (48.5)
Comorbidity,[a] n (%)			
Yes	1430 (26.2)	812 (24.5)	618 (28.8)
No	4030 (73.8)	2500 (75.5)	1530 (71.2)
Occupation, n (%)			
Healthcare/long-term care worker	511 (9.4)	314 (9.5)	197 (9.2)
Other	4949 (90.6)	2998 (90.5)	1951 (90.8)
Days from onset to SARS-CoV-2 test; exact onset date missing = 13 (0.2 %)[b]	1 (1–2)	1 (1–2)	1 (1–2)
History of close contact, n (%)			
Yes	326 (6.0)	237 (7.2)	89 (4.1)
No/unknown	5134 (94.0)	3075 (92.8)	2059 (95.9)
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 321 (5.9 %)			
Yes	802 (15.6)	420 (13.6)	382 (18.7)
No	4337 (84.4)	2679 (86.5)	1658 (81.3)
Past SARS-CoV-2 infection, n (%); missing = 113 (2.1 %)			
Yes	293 (5.5)	76 (2.3)	217 (10.4)
Ancestral strain-dominant period (2020–February 2021)	23 (0.4)	10 (0.3)	13 (0.6)
Ancestral-to-Alpha replacement period (March–May 2021)	15 (0.3)	9 (0.3)	6 (0.3)
Alpha-to-Delta replacement period (June–July 2021)	19 (0.4)	11 (0.3)	8 (0.4)
Delta-dominant period (August–December 2021)	42 (0.8)	12 (0.4)	30 (1.4)
BA.1/BA.2-dominant period (January–June 2022)	174 (3.3)	26 (0.8)	148 (7.1)
BA.5-dominant period (July 2022)	3 (0.1)	0 (0.0)	3 (0.1)
Multiple infections	2 (0.0)	0 (0.0)	2 (0.1)
Period of infection missing	15 (0.3)	8 (0.3)	7 (0.3)
No	5054 (94.5)	3177 (97.7)	1877 (89.6)
Number of vaccinations, n (%); missing = 21 (0.4 %)			
0	679 (12.5)	499 (15.1)	180 (8.4)
1	44 (0.8)	25 (0.8)	19 (0.9)
2	1426 (26.2)	933 (28.3)	493 (23.1)
3	2956 (54.4)	1699 (51.5)	1257 (58.8)
4	334 (6.1)	145 (4.4)	189 (8.8)
Vaccine type, n (%)			
BNT162b2	2456 (51.6)	1479 (52.8)	977 (49.9)
mRNA-1273	1138 (23.9)	685 (24.5)	453 (23.1)
Heterologous mRNA	1166 (24.5)	638 (22.8)	528 (27.0)
Interval between dose 2 and SARS-CoV-2 testing[b]	293 (263–325)	291 (262–321)	298 (263–333)
Interval between dose 3 and SARS-CoV-2 testing[b]	126 (95–155)	128 (100–155)	123 (90–154)
Interval between dose 4 and SARS-CoV-2 testing[b]	27 (15–43)	22 (13–41)	29 (16–44)
Mask-wearing in the past 2 weeks; missing = 147 (2.7 %)			
Wore at home and outside	400 (7.5)	244 (7.6)	156 (7.5)
Wore outside at all times	4565 (85.9)	2759 (85.6)	1806 (86.5)
Wore only when having conversation	330 (6.2)	210 (6.5)	120 (5.7)
Almost never wore masks	18 (0.3)	11 (0.3)	7 (0.3)
High-risk behaviors in the past 2 weeks (went to restaurant/bar at night with alcohol present), n (%); missing = 206 (3.8 %)			
Yes	1772 (33.7)	1131 (35.6)	641 (30.9)
No	3482 (66.3)	2048 (64.4)	1434 (69.1)
Eligible for dose 4[c]			

(*continued on next page*)

Table 2 (*continued*)

BA.5-dominant Period	All (n = 5460)	Test positive (n = 3312)	Test negative (n = 2148)
Yes	2000 (36.6)	1158 (35.0)	842 (39.2)
No	3460 (63.4)	2154 (65.0)	1306 (60.8)

Notes. N/A not available; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

[a] Comorbidities include hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use.

[b] Median (interquartile range).

[c] Individuals who either were ≥60 years, had any comorbidities, or were healthcare/long-term care workers.

Table 3
Time interval between last vaccination and SARS-CoV-2 testing for each vaccination status category during BA.1/BA.2-dominant period and BA.5-dominant period.

Vaccination status	Interval between last vaccination and SARS-CoV-2 testing[a]
BA.1/BA.2-dominant period	
Unvaccinated	N/A
Dose 1 or <13 d after dose 2	34 (8–191)
14 d to 3 mo after dose 2	74 (59–83)
3–6 mo after dose 2	148 (126–165)
>6 mo after dose 2	210 (194–234)
<13 d after dose 3	7 (4–10)
14 d to 3 mo after dose 3	49 (32–68)
3–6 mo after dose 3	108 (98–121)
>6 mo after dose 3	187 (185–188)
BA.5-dominant period	
Unvaccinated	N/A
Dose 1 or <13 d after dose 2	225 (18–337)
14 d to 3 mo after dose 2	52 (38–77)
3–6 mo after dose 2	134 (100–157)
>6 mo after dose 2	300 (274–328)
<13 d after dose 3	7 (5–11)
14 d to 3 mo after dose 3	70 (52–81)
3–6 mo after dose 3	133 (115–152)
>6 mo after dose 3	195 (186–208)
<13 d after dose 4	8 (5–10)
>14 d after dose 4	31 (22–47)

Notes. N/A not available; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

[a] Median (interquartile range).

much of Europe and the U.S., which experienced epidemics at a level similar to the pre-pandemic era in the 2021–2022 season, influenza circulation was extremely low since the beginning of the pandemic until the end of the study period (end of September 2022) in Japan. Therefore, we assumed that the potential bias is negligible.

2.7. Ethics statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval numbers 1332 and 1392). Ethics approval was also sought from medical facilities that required review from on-site committees.

3. Results

3.1. Characteristics of the study participants

A total of 13,025 individuals were enrolled from 16 medical facilities during the study period; 466 were excluded for unknown symptom onset date, 106 were excluded for being tested ≥15 days after symptom onset, and 354 were excluded for receiving vaccine types other than monovalent mRNA vaccines or receiving an unknown vaccine type (Fig. 2). Individuals tested during the replacement period from BA.1/BA.2 to BA.5 were also excluded (n = 476). The final analysis included 11,623 individuals with 5982 (51.5 %) positive cases. The median age (interquartile range [IQR]) was 36 (27–48) years, 5968 (51.5 %) were males, and 2938 (25.3 %) had comorbidities (Table 1). Although data on race/ethnicity were not collected, we expect most study participants to be Asians (Japanese nationals). Median (IQR) time from onset to SARS-CoV-2 testing was 1 (1–2) days; 1286 (11.1 %) had history of close contact; 1834 (16.4 %) reported having undergone SARS-CoV-2 diagnostic testing in the past month. Among those vaccinated at least once, 5217 (52.3 %) received BNT162b2, 3207 (32.2 %) received mRNA-1273, and 1548 (15.5 %) received heterologous mRNA vaccines. The median interval between dose 4 and SARS-CoV-2 testing was 27 days (IQR, 15–43). Compared to participants in the BA.1/BA.2-dominant period, those in the BA.5-dominant period were more likely to be healthcare/long-term care workers (9.4 % vs 5.1 %), less likely to have history of close contact (6.0 % vs 15.6 %), more likely to have been vaccinated three or four times (60.5 % vs 22.9 %), more likely to have received heterologous mRNA vaccines (24.5 % vs 7.3 %) with fewer mRNA-1273 homologous vaccine recipients, had longer median days between the last dose and SARS-CoV-2 testing, and were more likely to wear masks only when having a conversation (6.2 % vs 1.9 %) (Table 2). Also, for each vaccination status category, the median time interval between last vaccination and SARS-CoV-2 testing was slightly longer for the BA.5-dominant period compared to the BA.1/BA.2-dominant period (Table 3). Otherwise, the participants' characteristics were similar between the two periods including age distribution (median age [IQR], 38 [27–49] vs 35 [27–46]).

3.2. Absolute VE by time since COVID-19 vaccination

During the BA.1/BA.2-dominant period, aVE estimates were 52 % (95 % confidence interval [CI], 34–66) 14 days–3 months after dose 2, 50 % (95 % CI, 39–58) 3–6 months after dose 2, and 42 % (95 % CI, 29–52) > 6 months after dose 2 (Fig. 3**A**, Supplementary Table 1). With the first booster dose, aVE recovered with estimates of 71 % (95 % CI, 64–77) 14 days–3 months after dose 3 and 68 % (95 % CI, 52–79) 3–6 months after dose 3.

During the BA.5-dominant period, aVE estimates were 56 % (95 % CI, 27–73) 3–6 months after dose 2 and 32 % (95 % CI, 12–47) > 6 months after dose 2. With the first booster dose, aVE recovered but rapidly waned with estimates of 70 % (95 % CI, 61–78) 14 days–3 months after dose 3, 59 % (95 % CI, 48–68) 3–6 months after dose 3, and 50 % (95 % CI, 29–64) > 6 months after dose 3. With the second booster dose, aVE again recovered with estimates of 74 % (95 % CI, 61–83) ≥ 14 days after dose 4.

3.3. Relative VE by time since COVID-19 vaccination

During the BA.1/BA.2-dominant period, rVE comparing 3 vs 2 doses post-5 months was 49 % (95 % CI, 38–57) 14 days–3 months after dose 3 and 45 % (95 % CI, 18–63) 3–6 months after dose 3 (Fig. 3**B**, Supplementary Table 2).

During the BA.5-dominant period, rVE comparing 3 vs 2 doses post-5 months was 56 % (95 % CI, 45–65) 14 days–3 months after dose 3, 39 % (95 % CI, 27–48) 3–6 months after dose 3, and 25 % (95 % CI, −2–45) > 6 months after dose 3. rVE comparing 4 vs 3 doses post-5 months among individuals eligible for the fourth dose was 30 % (95 % CI, −6–54) ≥ 14 days after dose 4.

3.4. Secondary analysis, sub-analysis, and sensitivity analysis

Secondary analysis was performed with additional adjustments for preventive measures including mask wearing and high-risk behaviors. VE estimates were similar to those in the primary analysis during both

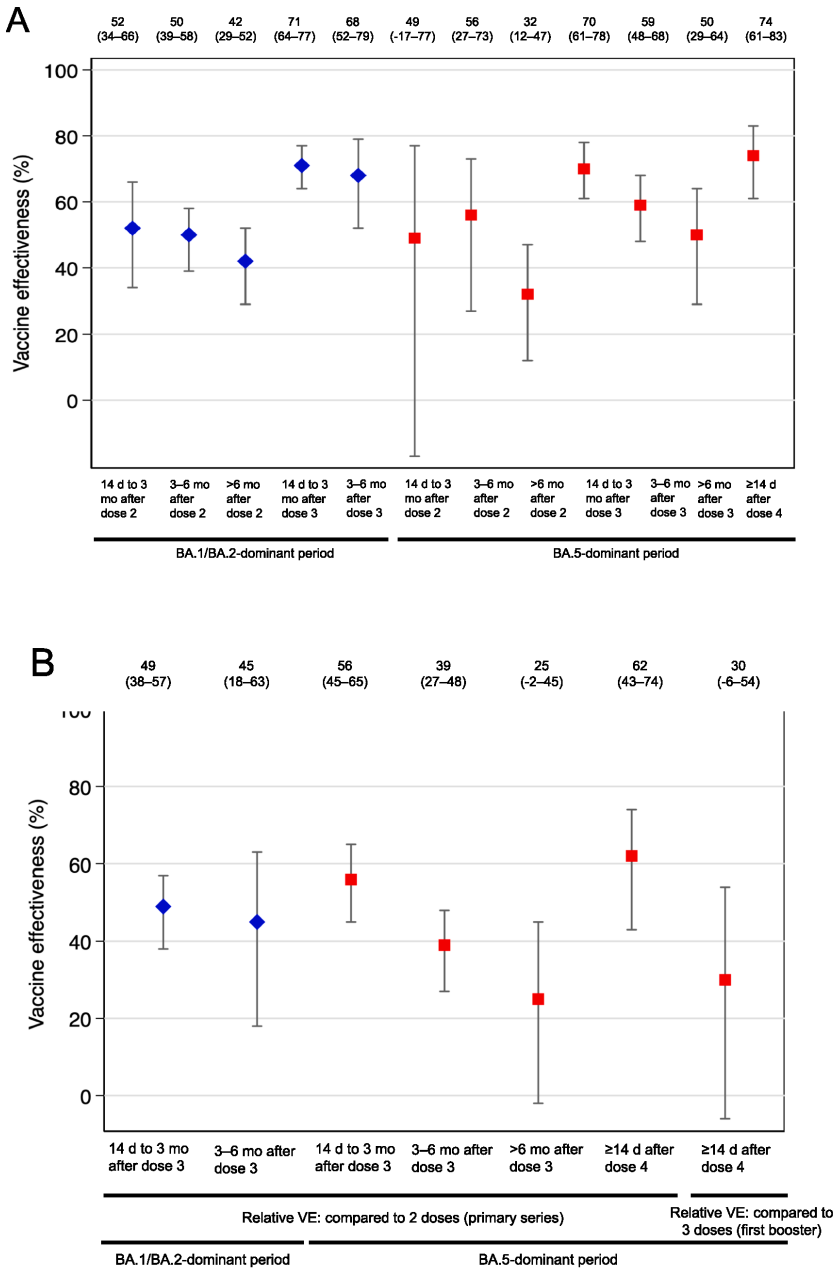

Fig. 3. (A) Absolute effectiveness against symptomatic SARS-CoV-2 infection by period since COVID-19 vaccination compared to unvaccinated individuals and (B) relative vaccine effectiveness against symptomatic SARS-CoV-2 infection by period since COVID-19 vaccination compared to individuals who received 2 or 3 doses of COVID-19 vaccines. Blue diamonds (BA.1/BA.2-dominant period) and red squares (BA.5-dominant period) indicate point estimates and error bars indicate 95 % confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Absolute vaccine effectiveness against symptomatic SARS-CoV-2 by time since vaccination with additional adjustment for preventive measures during the BA.1/BA.2-dominant period and BA.5-dominant period.

Vaccination status	Test positive, n (%)	Test negative, n (%)	Adjusted odds ratios (95 % CI)[a]	Vaccine effectiveness, % (95 % CI)
BA.1/BA.2-dominant period				
Unvaccinated	516 (20.3)	371 (11.3)	1	N/A
Dose 1 or <13 d after dose 2	32 (1.3)	35 (1.1)	0.66 (0.38–1.16)	34 (-16–62)
14 d to 3 mo after dose 2	82 (3.2)	180 (5.5)	0.48 (0.34–0.68)	52 (32–66)
3–6 mo after dose 2	823 (32.4)	1043 (31.6)	0.50 (0.41–0.61)	50 (39–59)
>6 mo after dose 2	683 (26.9)	731 (22.2)	0.57 (0.47–0.70)	43 (30–53)
<13 d after dose 3	63 (2.5)	112 (3.4)	0.33 (0.23–0.48)	67 (52–77)
14 d to 3 mo after dose 3	291 (11.5)	682 (20.7)	0.28 (0.22–0.36)	72 (64–78)
3–6 mo after dose 3	47 (1.9)	144 (4.4)	0.30 (0.20–0.47)	70 (53–80)
>6 mo after dose 3	1 (0.0)	1 (0.0)	0.61 (0.36–10.4)	39 (-940–64)
BA.5-dominant period				
Unvaccinated	499 (17.0)	180 (9.4)	1	N/A
Dose 1 or <13 d after dose 2	28 (1.0)	20 (1.0)	0.43 (0.22–0.86)	57 (14–78)
14 d to 3 mo after dose 2	17 (0.6)	14 (0.7)	0.50 (0.22–1.16)	50 (-16–78)
3–6 mo after dose 2	53 (1.8)	40 (2.1)	0.44 (0.26–0.73)	56 (27–74)
>6 mo after dose 2	713 (24.3)	361 (18.8)	0.69 (0.53–0.90)	31 (10–47)
<13 d after dose 3	17 (0.6)	13 (0.7)	0.36 (0.16–0.80)	64 (20–84)
14 d to 3 mo after dose 3	279 (9.5)	273 (14.3)	0.28 (0.21–0.37)	72 (63–79)
3–6 mo after dose 3	1045 (35.6)	716 (37.4)	0.41 (0.32–0.52)	59 (48–68)
>6 mo after dose 3	152 (5.2)	121 (6.3)	0.48 (0.34–0.69)	52 (31–66)
<13 d after dose 4	34 (1.2)	31 (1.6)	0.26 (0.14–0.51)	74 (49–86)
>14 d after dose 4	101 (3.4)	147 (7.7)	0.25 (0.16–0.38)	75 (62–84)

Notes. CI confidence interval; N/A not available; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
[a] Adjusted for age group, sex, presence of comorbidities, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, calendar week, mask-wearing, and high-risk behaviors in the past two weeks.

Table 5
Absolute vaccine effectiveness against symptomatic SARS-CoV-2 by time since vaccination among individuals with higher risk of developing severe COVID-19 (≥65 years of age or having at least one comorbidity) during BA.1/BA.2-dominant period and BA.5-dominant period.

Vaccination status	**Test positive, n (%)**	**Test negative, n (%)**	**Adjusted odds ratios (95 % CI)[a]**	**Vaccine effectiveness, % (95 % CI)**
BA.1/BA.2-dominant period				
Unvaccinated	103 (17.5)	83 (9.0)	1	N/A
Dose 1 or <13 d after dose 2	5 (0.9)	11 (1.2)	0.53 (0.16–1.72)	47 (-72–84)
14 d to 3 mo after dose 2	20 (3.4)	41 (4.5)	0.64 (0.31–1.30)	36 (-30–69)
3–6 mo after dose 2	173 (29.4)	267 (29.0)	0.47 (0.31–0.72)	53 (27–69)
>6 mo after dose 2	181 (30.8)	213 (23.1)	0.59 (0.39–0.89)	41 (11–61)
<13 d after dose 3	16 (2.7)	34 (3.7)	0.27 (0.12–0.59)	73 (41–88)
14 d to 3 mo after dose 3	72 (12.2)	216 (23.4)	0.27 (0.16–0.43)	73 (57–84)
3–6 mo after dose 3	18 (3.1)	57 (6.2)	0.29 (0.13–0.63)	71 (37–87)
>6 mo after dose 3	0 (0.0)	0 (0.0)	N/A	N/A
BA.5-dominant period				
Unvaccinated	110 (14.2)	48 (8.0)	1	N/A
Dose 1 or <13 d after dose 2	8 (1.0)	7 (1.2)	0.72 (0.21–2.52)	28 (-152–79)
14 d to 3 mo after dose 2	5 (0.7)	6 (1.0)	0.29 (0.08–1.12)	71 (-12–92)
3–6 mo after dose 2	9 (1.2)	8 (1.3)	0.63 (0.19–2.13)	37 (-113–81)
>6 mo after dose 2	137 (17.7)	77 (12.8)	0.77 (0.45–1.30)	23 (-30–65)
<13 d after dose 3	4 (0.5)	4 (0.7)	0.45 (0.09–2.18)	65 (-118–91)
14 d to 3 mo after dose 3	62 (8.0)	66 (11.0)	0.32 (0.18–0.57)	68 (43–72)
3–6 mo after dose 3	298 (38.5)	218 (36.2)	0.48 (0.30–0.78)	52 (22–70)
>6 mo after dose 3	31 (4.0)	34 (5.6)	0.52 (0.26–1.05)	48 (-5–74)
<13 d after dose 4	26 (3.4)	23 (3.8)	0.34 (0.15–0.77)	66 (23–85)
>14 d after dose 4	85 (11.0)	112 (18.6)	0.38 (0.21–0.70)	62 (30–79)

Notes. CI confidence interval; COVID-19 coronavirus disease 2019; N/A not available; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
[a] Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

the BA.1/BA.2-dominant and BA.5-dominant periods for vaccination status categories with sufficient sample size (Table 4). A sub-analysis of individuals who were at higher risk of developing severe COVID-19 also yielded results similar to those observed for the entire study population, although CIs were particularly large due to small sample size (Table 5). There were 85 (0.7 %) participants whose number of COVID-19 vaccinations was missing and 757 (6.5 %) participants whose date of last vaccination was missing. Multiple imputation of missing data yielded similar VE estimates for both the BA.1/BA.2-dominant and BA.5-dominant periods (Table 6).

4. Discussion

In this multi-center test-negative case-control study in Japan, we evaluated VE of 2 or 3 doses for the Omicron subvariant BA.1/BA.2-dominant period and 2, 3, or 4 doses for the BA.5-dominant period.

During the BA.1/BA.2-dominant period, two doses of mRNA vaccines provided moderate protection with only slight waning over 6 months (52–42 %). These estimates were higher than other observational studies; the potential explanation for the difference is discussed previously, including that most of the Japanese population continued to be infection-naïve and adhered to strict mask wearing policy regardless of vaccination status [14–17]. The present study also supported this, with 99.8 % of participants reporting mask wearing with similar VE estimates even after additional adjustment for mask wearing and high-risk behaviors. In agreement with many other observational studies, the first booster dose (dose 3) provided high protection (71 %) against BA.1/BA.2 shortly after vaccination [14–17]. Although various degrees of waning are observed in these studies [14–16], we observed very minimal waning for up to 6 months (71–68 %). In terms of rVE of 3 vs 2 doses, there was a moderate added effect of dose 3 (49 %).

During the BA.5-dominant period, the VE point estimate was slightly lower among individuals who received 2 doses 6 + months earlier albeit

Table 6
Absolute vaccine effectiveness against symptomatic SARS-CoV-2 by time since vaccination with multiple imputation during BA.1/BA.2-dominant period and BA.5-dominant period.

Vaccination status	Adjusted odds ratios (95 % CI)[a]	Vaccine effectiveness, % (95 % CI)
BA.1/BA.2-dominant period		
Unvaccinated	1	N/A
Dose 1 or <13 d after dose 2	0.61 (0.34–1.04)	39 (-4–66)
14 d to 3 mo after dose 2	0.46 (0.33–0.64)	54 (36–67)
3–6 mo after dose 2	0.51 (0.43–0.62)	49 (38–57)
>6 mo after dose 2	0.60 (0.50–0.73)	40 (27–50)
<13 d after dose 3	0.34 (0.24–0.49)	66 (51–76)
14 d to 3 mo after dose 3	0.30 (0.24–0.38)	70 (62–76)
3–6 mo after dose 3	0.32 (0.21–0.49)	68 (51–79)
>6 mo after dose 3	0.68 (0.04–10.3)	32 (-903–96)
BA.5-dominant period		
Unvaccinated	1	N/A
Dose 1 or <13 d after dose 2	0.35 (0.16–0.75)	65 (25–84)
14 d to 3 mo after dose 2	0.47 (0.20–1.07)	53 (-7–80)
3–6 mo after dose 2	0.42 (0.26–0.67)	58 (33–74)
>6 mo after dose 2	0.65 (0.52–0.82)	35 (18–48)
<13 d after dose 3	0.45 (0.24–0.85)	65 (15–76)
14 d to 3 mo after dose 3	0.29 (0.22–0.37)	71 (63–78)
3–6 mo after dose 3	0.40 (0.32–0.49)	60 (51–68)
>6 mo after dose 3	0.47 (0.34–0.65)	53 (35–66)
<13 d after dose 4	0.31 (0.17–0.55)	69 (45–83)
>14 d after dose 4	0.25 (0.17–0.36)	75 (64–83)

Notes. CI confidence interval; N/A not available; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

[a] Adjusted for age group, sex, presence of comorbidities, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

with overlapping CI (BA.5, 32 % vs BA.1/BA.2, 42 %), but this could be due to the longer interval between vaccination and testing in the BA.5-dominant period (BA.5, 300 days vs BA.1/BA.2, 210 days; Table 3). As observed for the BA.1/BA.2-dominant period, dose 3 provided substantial benefit. Notably, VE estimates were similar for BA.1/BA.2 and BA.5 at approximately 70 % among individuals who received a booster dose 14 days to 3 months before, despite a slightly longer interval between vaccination and testing for BA.5 (BA.5, 70 days vs BA.1/BA.2, 49 days). This was in contrast to *in vitro* neutralization studies suggesting further immune escape capacity [22,23], but was in line with epidemiological estimates that showed similar VE estimates against hospitalization/emergency department admission between BA.1/BA.2 and BA.4/BA.5 in the U.S. [36–39]. When we examined the mid- to long-term effect of a booster dose, despite an initial high VE after dose 3, VE waned gradually to 59 % at 3–6 months and 50 % at 6 + months since the first booster dose with a statistical difference between VE at 14 days–3 months vs VE at 6 months ($p = 0.001$). In terms of rVE of 3 vs 2 doses, there was a moderate added effect of dose 3 initially (49 %), but it waned to a low level (25 %) at 6 months. Dose 4 again recovered VE to a high level (75 %). However, in terms of rVE of 4 vs 3 doses, the added protection of dose 4 was low (30 %).

Our observation of similarly high initial VEs with repeated waning after each dose over a span of half a year suggests that the BA.5 surge in Japan was likely due to waning immunity rather than a substantial increase in immune escape capacity (e.g., the one seen for Omicron compared to Delta [17]). In other words, if BA.5 were to have substantially more capacity to escape immunity, then we would have seen lower VE against BA.5 compared to BA.1/BA.2 among individuals who received a booster dose 14 days to 3 months earlier; however, we did not observe this. The speed of waning VE may be faster against BA.5 comparing to BA.1/BA.2, but this could not be definitively confirmed due to the timing of each wave in relation to vaccine rollout (e.g., no data on VE > 6 months after dose 3 for BA.1/BA.2 and longer interval between vaccination and testing within each vaccination status category for BA.5). Finally, rVE against BA.5 soon after dose 4 was low. These collectively support the introduction of variant-containing vaccines. Bivalent vaccines including the ancestral strain and BA.5 have been rolled out but may have suffered from a possibility of immune imprinting (e.g., skewed immune response towards the ancestral strain due to previous exposure through monovalent ancestral vaccines). A monovalent variant-containing vaccine, in theory, would provide a better immune response towards the corresponding variant [40,41]. The short duration of protection remains a concern and is an important avenue for future COVID-19 vaccine development, although many reports indicate that the duration of protection is longer against severe disease compared to mild disease [39]. Based on the final results of initial randomized controlled trials for two mRNA vaccines with very limited waning of VE against symptomatic disease up to 6 months after the primary series during the original strain to Alpha-dominant period [42,43], variant-specific vaccines may provide longer protection against this specific variant.

5. Limitations

This study has several limitations. First, biases inherent in observational studies are possible. Using a detailed questionnaire, we attempted to minimize confounding that is not necessarily accounted for in studies that retrospectively evaluate routine surveillance data. Second, as the vaccine rollout progresses and vaccination rates stabilize, vaccinated and unvaccinated individuals may differ in characteristics other than vaccination status such as prior infection and PHSM. However, as noted above, such biases may be less of an issue in Japan and we adjusted for these factors. Third, as we did not have a system to link test results with vaccination history, we asked participants to refer to their vaccine records/certificates. Among individuals with such data available, 41 % reported carrying their vaccine record; others were asked to refer to their diary/calendar for accuracy. Some reports suggest that self-reports may be a reasonable source of COVID-19 vaccination information for timely VE assessment [44,45]. Fourth, some VE estimates were calculated based on very low numbers, resulting in wide CIs. Fifth, our primary analyses were complete case analyses. However, missing data on vaccination status were minimal and sensitivity analysis with multiple imputation of missing data resulted in similar estimates. Sixth, we were not able to sequence samples from individual COVID-19 cases, thus some misclassification of subvariants may be present, although we expect this influence to be small since the replacement of subvariants happened rapidly. Seventh, the interpretation and comparison of rVE require caution [46]. Finally, we did not assess VE against asymptomatic infection, severe cases, or death.

6. Conclusions

Booster doses initially provided high protection against BA.5 at a level similar to that against BA.1/BA.2. However, the protection seemed shorter-lasting against BA.5, which likely contributed to the surge. Furthermore, rVE post-dose 4 was low even among recent vaccinees. These results support the introduction of variant-containing vaccines and emphasize the need for vaccines with longer duration of protection.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Data availability

Individual-level data of patients included in this manuscript after de-identification are considered sensitive and will not be shared.

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Appendix A. Supplementary material

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References

[1] Coronavirus disease (COVID-19) pandemic. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
[2] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577.
[3] Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389.
[4] Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384(15):1412–3. https://doi.org/10.1056/NEJMoa2101765.
[5] Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021;70(13):495–500. https://doi.org/10.15585/mmwr.mm7013e3.
[6] Pilishvili T, Fleming-Dutra KE, Farrar JL, et al. Interim estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna COVID-19 vaccines among health care personnel - 33 U.S. sites, January-March 2021. MMWR Morb Mortal Wkly Rep 2021;70(20):753–8. https://doi.org/10.15585/mmwr.mm7020e2.
[7] Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ 2021;374:n1943. https://doi.org/10.1136/bmj.n1943.
[8] Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med 2022;386(4):340–50. https://doi.org/10.1056/NEJMoa2115481.
[9] Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021;385(24):e83.
[10] Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med 2021;385(24):e85.
[11] Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021;398(10309):1407–16. https://doi.org/10.1016/S0140-6736(21)02183-8.
[12] Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med 2021;385(2):187–9. https://doi.org/10.1056/NEJMc2104974.
[13] Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021;385(7):585–94. https://doi.org/10.1056/NEJMoa2108891.
[14] Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022;386(16):1532–46. https://doi.org/10.1056/NEJMoa2119451.
[15] Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. JAMA 2022;327(7):639–51. https://doi.org/10.1001/jama.2022.0470.
[16] Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med 2022;28(5):1063–71. https://doi.org/10.1038/s41591-022-01753-y.
[17] Arashiro T, Arima Y, Muraoka H, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). Clin Infect Dis 2022. https://doi.org/10.1093/cid/ciac635.
[18] Tegally H, Moir M, Everatt J, et al. Emergence of SARS-CoV-2 Omicron lineages BA.4 and BA.5 in South Africa. Nat Med 2022;28(9):1785–90. https://doi.org/10.1038/s41591-022-01911-2.
[19] Coronavirus disease (COVID-19) weekly epidemiological update. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[20] Visualizing the data: information on COVID-19 infections. Ministry of Health, Labour and Welfare, Japan. https://covid19.mhlw.go.jp/en/.
[21] Lineage detection in SARS-CoV-2 genomic surveillance [in Japanese]. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/stf/seisakunitsuite/newpage_00061.html.
[22] Cao Y, Yisimayi A, Jian F, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. Nature 2022;608(7923):593–602. https://doi.org/10.1038/s41586-022-04980-y.
[23] Hachmann NP, Miller J, Collier AY, et al. Neutralization escape by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4, and BA.5. N Engl J Med 2022;387(1):86–8. https://doi.org/10.1056/NEJMc2206576.
[24] Bergeri I, Whelan M, Ware H, et al. Global SARS-CoV-2 seroprevalence: a systematic review and meta-analysis of standardized population-based studies from Jan 2020-May 2022. PLoS Med 2022;19(11). https://doi.org/10.1101/2021.12.14.21267791.
[25] Policy responses to the coronavirus pandemic. Our World in Data. https://ourworldindata.org/policy-responses-covid.
[26] Arashiro T, Arai S, Kinoshita R, et al. National seroepidemiological study of COVID-19 after the initial rollout of vaccines: Before and at the peak of the Omicron-dominant period in Japan. Influenza Other Respir Viruses 2023;17(2). https://doi.org/10.1111/irv.13094.
[27] Preliminary results of the seroprevalence study using donor blood [in Japanese]. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/content/10900000/001018624.pdf.
[28] Mask use. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/stf/covid-19/mask.html.
[29] About COVID-19 vaccines [in Japanese]. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_00184.html.
[30] Variant-specific PCR results [in Japanese]. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/content/10900000/000888045.pdf.
[31] Estimated BA.5 prevalence based on data from the SARS-CoV-2 genomic surveillance [in Japanese]. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/content/10900000/000892298.pdf.
[32] COVID-19 vaccine surveillance report: 4 August 2022 (week 31). UK Health Security Agency. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1096327/Vaccine_surveillance_report_week_31_2022.pdf.
[33] About variants of concern: 21st report [in Japanese]. National Institute of Infectious Diseases, Japan. https://www.niid.go.jp/niid/ja/2019-ncov/2551-cepr/11572-sars-cov-2-21.html.
[34] Arashiro T, Arima Y, Muraoka H, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses 2022;16(5):952–61. https://doi.org/10.1111/irv.12992.
[35] Doll MK, Pettigrew SM, Ma J, Verma A. Effects of confounding bias in coronavirus disease 2019 (COVID-19) and influenza vaccine effectiveness test-negative designs due to correlated influenza and COVID-19 vaccination behaviors. Clin Infect Dis 2022;75(1):e564–71. https://doi.org/10.1093/cid/ciac234.
[36] Surie D, Bonnell L, Adams K, et al. Effectiveness of monovalent mRNA vaccines against COVID-19-associated hospitalization among immunocompetent adults during BA.1/BA.2 and BA.4/BA.5 predominant periods of SARS-CoV-2 Omicron variant in the United States - IVY Network, 18 States, December 26, 2021-August 31, 2022. MMWR Morb Mortal Wkly Rep 2022;71(42):1327–34. https://doi.org/10.15585/mmwr.mm7142a3.
[37] Tartof SY, Slezak JM, Puzniak L, et al. Effectiveness and durability of BNT162b2 vaccine against hospital and emergency department admissions due to SARS-CoV-2 omicron sub-lineages BA.1 and BA.2 in a large health system in the USA: a test-negative, case-control study. Lancet. Respir Med 2022. https://doi.org/10.1016/S2213-2600(22)00354-X.
[38] Tartof SY, Slezak JM, Puzniak L, et al. BNT162b2 vaccine effectiveness against SARS-CoV-2 omicron BA.4 and BA.5. Lancet Infect Dis 2022;22(12):1663–5. https://doi.org/10.1016/S1473-3099(22)00692-2.
[39] Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 2022;399(10328):924–44. https://doi.org/10.1016/S0140-6736(22)00152-0.
[40] Collier AY, Miller J, Hachmann NP, et al. Immunogenicity of BA.5 bivalent mRNA vaccine boosters. N Engl J Med 2023;388(6):565–7. https://doi.org/10.1056/NEJMc2213948.
[41] Arashiro T, Arima Y, Kuramochi J, et al. Effectiveness of BA.1- and BA.4/BA.5-containing bivalent COVID-19 mRNA vaccines against symptomatic SARS-CoV-2 infection during the BA.5-dominant period in Japan. Open Forum. Infect Dis 2023;10(6):240. https://doi.org/10.1093/ofid/ofad240.

[42] Thomas SJ, Moreira Jr ED, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385(19):1761–73. https://doi.org/10.1056/NEJMoa2110345.
[43] El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385(19):1774–85. https://doi.org/10.1056/NEJMoa2113017.
[44] Stephenson M, Olson SM, Self WH, et al. Ascertainment of vaccination status by self-report versus source documentation: impact on measuring COVID-19 vaccine effectiveness. Influenza Other Respir Viruses 2022;16(6):1101–11. https://doi.org/10.1111/irv.13023.
[45] Archambault PM, Rosychuk RJ, Audet M, et al. Accuracy of self-reported COVID-19 vaccination status compared with a public health vaccination registry in Québec: observational diagnostic study. JMIR Public Health Surveill 2023;9. https://doi.org/10.2196/44465.
[46] Lewis NM, Murray N, Adams K, et al. Absolute and relative vaccine effectiveness of primary and booster series of COVID-19 vaccines (mRNA and adenovirus vector) against COVID-19 hospitalizations in the United States, December 2021-April 2022. Open Forum Infect Dis 2022;10(1):ofac698. https://doi.org/10.1093/ofid/ofac698.

Supplementary Table 1. Absolute vaccine effectiveness against symptomatic SARS-CoV-2 by time since vaccination during BA.1/BA.2-dominant period and BA.5-dominant period.

Vaccination status	Test positive, n (%)	Test negative, n (%)	Interval between last vaccination and SARS-CoV-2 testing[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
BA.1/BA.2-dominant period					
Unvaccinated	516 (20.3)	371 (11.3)	N/A	1	N/A
Dose 1 or ≤13 d after dose 2	32 (1.3)	35 (1.1)	34 (8–191)	0.58 (0.34–0.99)	42 (1–66)
14 d to 3 mo after dose 2	82 (3.2)	180 (5.5)	74 (59–83)	0.48 (0.34–0.66)	52 (34–66)
3–6 mo after dose 2	823 (32.4)	1,043 (31.6)	148 (126–165)	0.50 (0.42–0.61)	50 (39–58)
>6 mo after dose 2	683 (26.9)	731 (22.2)	210 (194–234)	0.58 (0.48–0.71)	42 (29–52)
≤13 d after dose 3	63 (2.5)	112 (3.4)	7 (4–10)	0.34 (0.23–0.49)	66 (51–77)
14 d to 3 mo after dose 3	291 (11.5)	682 (20.7)	49 (32–68)	0.29 (0.23–0.36)	71 (64–77)
3–6 mo after dose 3	47 (1.9)	144 (4.4)	108 (98–121)	0.32 (0.21–0.48)	68 (52–79)
>6 mo after dose 3	1 (0.0)	1 (0.0)	187 (185–188)	0.59 (0.04–9.98)	41 (-898–96)
BA.5-dominant period					
Unvaccinated	499 (17.0)	180 (9.4)	N/A	1	N/A
Dose 1 or ≤13 d after dose 2	28 (1.0)	20 (1.0)	225 (18–337)	0.46 (0.24–0.91)	54 (-9–74)
14 d to 3 mo after dose 2	17 (0.6)	14 (0.7)	52 (38–77)	0.51 (0.23–1.17)	49 (-17–77)
3–6 mo after dose 2	53 (1.8)	40 (2.1)	134 (100–157)	0.44 (0.27–0.73)	56 (27–73)
>6 mo after dose 2	713 (24.3)	361 (18.8)	300 (274–328)	0.68 (0.53–0.88)	32 (12–47)
≤13 d after dose 3	17 (0.6)	13 (0.7)	7 (5–11)	0.38 (0.17–0.83)	62 (17–83)
14 d to 3 mo after dose 3	279 (9.5)	273 (14.3)	70 (52–81)	0.30 (0.22–0.39)	70 (61–78)
3–6 mo after dose 3	1,045 (35.6)	716 (37.4)	133 (115–152)	0.41 (0.32–0.52)	59 (48–68)
>6 mo after dose 3	152 (5.2)	121 (6.3)	195 (186–208)	0.50 (0.36–0.71)	50 (29–64)
≤13 d after dose 4	34 (1.2)	31 (1.6)	8 (5–10)	0.31 (0.17–0.57)	69 (43–83)
≥14 d after dose 4	101 (3.4)	147 (7.7)	31 (22–47)	0.26 (0.17–0.39)	74 (61–83)

Notes. CI = confidence interval; N/A = not available; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[a] Median (interquartile range). [b] Adjusted for age group, sex, presence of comorbidities, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

Supplementary Table 2. Relative vaccine effectiveness against symptomatic SARS-CoV-2 by time since vaccination during BA.1/BA.2-dominant period and BA.5-dominant period.

Vaccination status	Test positive, n	Test negative, n	Interval between last vaccination and SARS-CoV-2 testing[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
BA.1/BA.2-dominant period (3 doses vs 2 doses)					
>5 mo after dose 2	1,091	1,196	191 (171–217)	1	N/A
≤13 d after dose 3	63	112	7 (4–10)	0.60 (0.43–0.85)	40 (15–57)
14 d to 3 mo after dose 3	291	682	49 (32–68)	0.51 (0.43–0.62)	49 (38–57)
3–6 mo after dose 3	47	144	108 (98–121)	0.55 (0.37–0.82)	45 (18–63)
>6 mo after dose 3	1	1	187 (185–188)	1.05 (0.06–17.5)	-5 (-165–94)
BA.5-dominant period (3 and 4 doses vs 2 doses)					
>5 mo after dose 2	729	374	299 (272–328)	1	N/A
≤13 d after dose 3	17	13	7 (5–11)	0.56 (0.26–1.22)	44 (-22–74)
14 d to 3 mo after dose 3	279	273	70 (52–81)	0.44 (0.35–0.55)	56 (45–65)
3–6 mo after dose 3	1045	716	133 (115–152)	0.61 (0.52–0.73)	39 (27–48)
>6 mo after dose 3	152	121	195 (186–208)	0.75 (0.55–1.02)	25 (-2–45)
≤13 d after dose 4	34	31	8 (5–10)	0.46 (0.25–0.83)	54 (17–75)
≥14 d after dose 4	101	147	31 (22–47)	0.38 (0.26–0.57)	62 (43–74)
BA.5-dominant period (4 doses vs 3 doses)					
>5 mo after dose 3 (eligible population[c])	433	322	171 (159–188)	1	N/A
≤13 d after dose 4	34	31	8 (5–10)	0.80 (0.42–1.50)	20 (-50–58)
≥14 d after dose 4	101	147	31 (22–47)	0.70 (0.46–1.06)	30 (-6–54)

Notes. CI = confidence interval; N/A = not available; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Median (interquartile range).

[b] Adjusted for age group, sex, presence of comorbidities, occupation (healthcare worker or not), SARS-CoV-2 diagnostic test in the past month, past SARS-CoV-2 infection, history of close contact, healthcare facility, and calendar week.

[c] Individuals who either were ≥60 years, had any comorbidities, or were healthcare/long-term care workers.

Paper 7 : VE against severe disease in Japan (Delta/early Omicron)

Arashiro T*, Miwa M, Nakagawa H, et al. COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: a multicenter case-control study (MOTIVATE study). **(**Submitted; ***first and corresponding author)**

PhD candidate contributions:
Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 3D.

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Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
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Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
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If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Vaccine		
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Date	February 25, 2024

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Date	February 25, 2024

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COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: A multicenter case-control study (MOTIVATE study)

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ABSTRACT

Introduction: Since the SARS-CoV-2 Omicron variant became dominant, assessing COVID-19 vaccine effectiveness (VE) against severe disease using hospitalization as an outcome became more challenging due to incidental infections via admission screening and variable admission criteria, resulting in a wide range of estimates. To address this, the World Health Organization (WHO) guidance recommends the use of outcomes that are more specific to severe pneumonia such as oxygen use and mechanical ventilation.
Methods: A case-control study was conducted in 24 hospitals in Japan for the Delta-dominant period (August-November 2021; "Delta") and early Omicron (BA.1/BA.2)-dominant period (January-June 2022; "Omicron"). Detailed chart review/interviews were conducted in January-May 2023. VE was measured using various outcomes including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation (IMV), death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than another condition(s)), and progression from oxygen use to IMV or death among COVID-19 patients.
Results: The analysis included 2125 individuals with respiratory failure (1608 cases [75.7%]; 99.2% of vaccinees received mRNA vaccines). During Delta, 2 doses provided high protection for up to 6 months (oxygen requirement: 95.2% [95% CI:88.7–98.0%] [restricted to "true" severe COVID-19: 95.5% {89.3–98.1%}]; IMV: 99.6% [97.3–99.9%]; fatal: 98.6% [92.3–99.7%]). During Omicron, 3 doses provided high protection for up to 6 months (oxygen requirement: 85.5% [68.8–93.3%] ["true" severe COVID-19: 88.1% {73.6–94.7%}]; IMV: 97.9% [85.9–99.7%]; fatal: 99.6% [95.2–99.97]). There was a trend towards higher VE for more severe and specific outcomes.
Conclusion: Multiple outcomes pointed towards high protection of 2 doses during Delta and 3 doses during Omicron. These results demonstrate the importance of using severe and specific outcomes to accurately measure VE against severe COVID-19, as recommended in WHO guidance in settings of intense transmission as seen during Omicron.

1. Introduction

Several vaccines against coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially showed high efficacy and effectiveness [1–8]. However, concerns have arisen due to waning immunity and the emergence of variants with immune escape capacity [9–16]. Further, since the Omicron variant became dominant globally in early 2022, assessing vaccine effectiveness (VE) against severe disease using hospitalization as a surrogate for severe outcomes has become more challenging [17,18]. Although hospitalization is the most widely used outcome to measure VE against severe disease owing to its ease and clarity in classification, this definition would include hospitalizations unrelated to COVID-19 due to Omicron's high prevalence in the community with an incidental diagnosis of SARS-CoV-2 infection during routine admission screening. Since VE is lower against infection than against severe diseases (i.e. a decoupling of VE against infection and VE against severe disease) [15,17,18], VE against severe disease via hospitalization outcome would be underestimated. Furthermore, criteria for hospitalization have varied over time and by local context. For example, in Japan, all Omicron cases were hospitalized regardless of disease severity when Omicron was initially introduced into the country, and less-burdened prefectures had lower thresholds for hospitalization to ensure case isolation until hospital bed capacities were overwhelmed [19]. These concerns are evident from past studies showing a wide range of VE estimates (30–100% for 2 doses and 50–100% for 3 doses) against severe disease [18]. To address these issues, guidance from the World Health Organization (WHO) proposed the use of outcomes that are more specific to severe pneumonia such as oxygen use and mechanical ventilation [20]. The guidance also recommends using VE against disease progression. However, no study has examined multiple outcomes related to severe pneumonia at the hospital level with detailed medical chart reviews, as such studies are resource-intensive. Therefore, we conducted a hospital-based multicenter case-control study in Japan to measure VE using various outcomes including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation, death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than another condition(s)), and progression from oxygen use to mechanical ventilation or death among COVID-19 patients. We examined these outcomes during the Delta-dominant period and the early Omicron-dominant period (BA.1/BA.2-dominant period).

2. Methods

2.1. COVID-19 vaccination rollout in Japan

In Japan, the primary series (doses 1 and 2) rollout started in mid-February 2021, the first booster dose (dose 3) in December 2021, and the second booster dose (dose 4) in late May 2022 [21]. For the first

[1] These authors contributed equally.

booster dose, individuals became eligible 5 months after their last dose. The second booster dose was administered exclusively to individuals who were ≥ 60 years old, had any comorbidities, or were healthcare/long-term care workers and excluded from this report. Vaccines from multiple manufacturers are approved in Japan, but a great majority of those used were BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) (99.9% for primary series; no published data for the third dose) [22]. The primary series followed manufacturer-recommended intervals (21 days for BNT162b2, 28 days for mRNA-1273).

2.2. Study design and setting

Our study, Moderate-to-severe disease requiring Oxygen Therapy, Intubation, and Ventilation And The Effectiveness of COVID-19 vaccines (MOTIVATE study), is a multicenter case-control study in acute care hospitals in Japan to estimate the real-world effectiveness of COVID-19 vaccines against severe disease. Participating healthcare facilities screened all routinely admitted patients with COVID-19 and other causes of respiratory failure. Although this study was mainly a retrospective chart review, when data were missing from the chart, patients or their family members were contacted by phone to fill in the information. This report includes patients hospitalized in 24 hospitals in 9 of Japan's 47 prefectures between 1 August 2021 and 30 June 2022.

2.3. Inclusion and exclusion criteria

The inclusion criterion was patients aged ≥ 16 years who were hospitalized with respiratory failure (i.e. requiring oxygen therapy). Patients were excluded for the following reasons: unknown symptom onset date; admission ≥ 15 days after onset; onset during hospitalization; tested either ≥ 8 days before or ≥ 15 days after onset; tested ≥ 15 days before or ≥ 15 days after admission; currently on home oxygen therapy or home mechanical ventilation; started oxygen therapy ≥ 15 days before or ≥ 15 days after admission; started invasive mechanical ventilation ≥ 15 days before or ≥ 20 days after admission; past SARS-CoV-2 infection ≥ 3 months before admission; and immunodeficiency or current use of immunosuppressants. The rationale for including patients tested up to 7 days before onset and excluding those tested earlier is that patients may have been tested on routine asymptomatic screening, but the likelihood of testing positive is lower ≥ 8 days before onset. Also, the rationale for including patients who were tested up to 14 days before admission and excluding those who were tested ≥ 15 days before admission is that it takes from a few days to 2 weeks from symptom onset for patients to develop severe disease, and these patients may be tested right after onset and later hospitalized. Finally, the rationale for including patients tested up to 14 days after the onset of illness is that viral load as measured by PCR continues to be high for severe cases in the second week of illness and would likely continue to be positive if the cases are true COVID-19 cases.

2.4. Classification of exposures and outcome

Vaccination status (number of doses, date of last vaccination, and [if available] vaccine manufacturer) was recorded from the medical charts and checked for plausibility. If unavailable, patients or their family members were contacted by phone and asked to refer to their vaccine records/certificates. Vaccination status was classified into 8 categories: (1) not vaccinated, (2) ≤ 13 days after dose 1, (3) ≥ 14 days after dose 1 or ≤ 13 days after dose 2 (partially vaccinated), (4) 14 days–6 months (14–180 days) after dose 2, (5) > 6 months (181 days) after dose 2, (6) ≤ 13 days after dose 3 (booster dose), (7) 14 days–6 months (14–180 days) after dose 3, and (8) > 6 months (181 days) after dose 3.

Regardless of test type, patients who tested positive before or after admission based on the above inclusion and exclusion criteria were defined as cases; patients who tested negative before or after admission based on the above criteria were defined as controls.

To measure VE, we used various severe outcomes including disease requiring oxygen therapy, disease requiring invasive mechanical ventilation, death, outcome restricting to "true" severe COVID-19 (where oxygen requirement is due to COVID-19 rather than other differential diagnoses), and progression from oxygen use to mechanical ventilation or death. "True" severe COVID-19 outcome was based on the judgment of the treating physicians (record on the chart), trained nurse or pharmacist responsible for chart review, as well as the primary investigator (final judgment). For controls, we included all patients who required oxygen for the measurement of VE against all severe outcomes (thus, it is not strictly a test-negative design).

The chart review was conducted between January and May 2023 to ensure that at least 6 months had passed since participants were hospitalized to allow for sufficient time to reach the final discharge outcome for participants.

2.5. Definition of Delta- and Omicron-dominant periods and non-epidemic period

Based on data from variant-specific PCR that can detect the L452R mutation, which is present in the Delta variant but absent in the Alpha and Omicron variants, by 1 August 2021, the Delta variant was estimated to be responsible for over 90% of SARS-CoV-2 infections in Japan, replacing the Alpha variant [23]. Therefore, we defined 1 August to 30 November 2021 as the Delta-dominant period. By the beginning of December 2021, the number of hospitalized cases decreased substantially. This low level lasted until the end of December 2021 [24]. Therefore, we defined 1–31 December 2021 as the non-epidemic period. Based on data from SARS-CoV-2 genomic surveillance with systematic sampling, in early January 2022, the case counts rose rapidly owing to the introduction of BA.1, with BA.1 estimated to be responsible for over 80% of SARS-CoV-2 infections [25]. In mid-March, BA.2 overtook BA.1 and became dominant. BA.2 was estimated to be responsible for 80% of SARS-CoV-2 infections in the Kanto region during the week of 20–26 June (epidemiologic week 25), but was rapidly replaced by BA.5 [26]. Therefore, we defined 1 January to 30 June 2022 as the early Omicron-dominant period (BA.1/BA.2-dominant period). Since the sample size was limited with previous reports suggesting similar VE estimates against BA.1 and BA.2 [27], we did not stratify these periods.

2.6. Sample size

The sample size was determined by the number of patients admitted to participating hospitals during the study period. However, based on *a priori* sample size calculations (assuming a 1:1 ratio between cases and controls, expected COVID-19 vaccine coverage of 80%, and 90% VE, 89 patients are needed in each group for the precision of a lower CI boundary of 10%), we considered that our design would allow for adequately precise VE estimates.

2.7. Data analysis

Patient characteristics were described overall and by case/control status. A severe disease risk score was developed to be incorporated as a covariate. Based on published reports [28,29], we assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, pregnancy while hospitalized, or overweight; the points were added up to calculate the risk score for each patient.

Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group (categorical), sex, risk score categories (0, 1, 2, 3–4, 5+; categorical), hospitalization in the past year (either the admitting hospital or another

Table 1
Diagnoses of control group patients during the respective Delta- and early Omicron (BA.1/BA.2)-dominant periods.[a]

Diagnosis	Delta-dominant period, n (%)	Early Omicron (BA.1/BA.2)-dominant period, n (%)
Pneumonia[b]	74 (40.7)	107 (38.4)
Heart failure	51 (28.0)	76 (27.2)
Aspiration pneumonia	27 (14.8)	65 (23.3)
Interstitial pneumonia exacerbation	18 (9.9)	28 (10.0)
Chronic obstructive pulmonary disease exacerbation	4 (2.2)	9 (3.2)
Pneumonia (due to *Streptococcus pneumoniae*)	2 (1.1)	8 (2.9)
Lung cancer	1 (0.6)	2 (0.7)
Influenza[c]	0 (0.0)	0 (0.0)
Other	17 (9.3)	21 (7.5)

[a] Multiple diagnoses are possible for each patient.
[b] Not due to COVID-19, aspiration, or *Streptococcus pneumoniae*.
[c] Tested positive since onset.

hospital), smoking history, prefecture of the admitting hospital, and calendar week of hospitalization (biweekly).

To estimate VE against progression from oxygen use to mechanical ventilation or death among COVID-19 patients, additional adjustments were made for use of antivirals, monoclonal antibody therapy, steroids, anti-inflammatory drugs (tocilizumab or baricitinib), anticoagulation, and proning. These potential confounders were determined *a priori* based on published reports [8,9,15,17]. VE was estimated using the following equation: VE = (1 − adjusted odds ratio [aOR]) × 100%, including VE against disease progression [30]. Data analyses were performed using STATA version 17.0.

2.8. Consideration of bias due to co-circulation of influenza/influenza vaccination and Streptococcus pneumoniae pneumonia/pneumococcal vaccination

Co-circulation of influenza and COVID-19 can result in biased VE estimates as propensity to get vaccinated may be similar for COVID-19 vaccines and influenza vaccines [31]. In theory, the same concern applies to *Streptococcus pneumoniae* pneumonia and pneumococcal vaccination. However, no influenza was diagnosed since symptom onset for any of the study participants (Table 1). Indeed, unlike in much of Europe and the U.S., which experienced epidemics in the 2021–2022 season at a level similar to the pre-pandemic era, influenza circulation was extremely low since the beginning of the pandemic until the end of the study period (end of June 2022) in Japan [32]. Also, invasive pneumococcal disease was less common during COVID-19 [33], suggesting that the circulation of *Streptococcus pneumoniae* was low. Therefore, we assumed that this potential bias was negligible.

2.9. Ethics statement

The ethics committee of the National Institute of Infectious Diseases approved our study (approval numbers 1454, 1527). Ethics approval was also sought from medical facilities that required review from on-site committees. Although the main design of this study was a retrospective chart review with a waiver of informed consent, patients or their family members were contacted by phone to fill in any missing data on the chart. In this case, their consent was obtained verbally.

3. Results

3.1. Characteristics of the study participants

A total of 2417 individuals were enrolled from 24 hospitals in 9 prefectures. After excluding 292 patients based on exclusion criteria, the final analysis included 2125 patients (1608 cases [75.7%]): 1116 for the

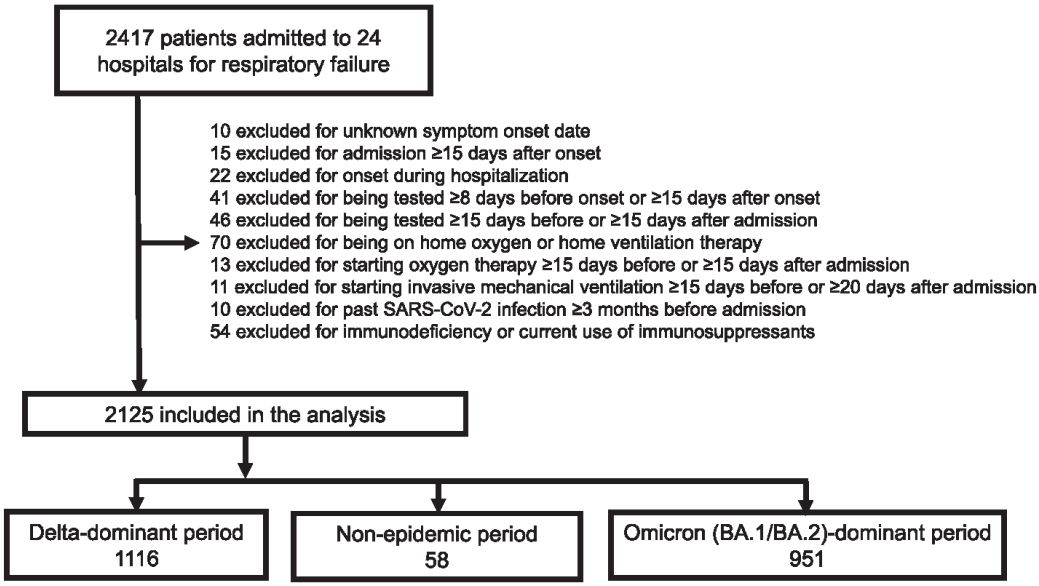

Fig. 1. Flow diagram of the study participants.

Table 2
Demographic and clinical characteristics of the study participants during the Delta- and early Omicron (BA.1/BA.2)-dominant periods.

(A) Delta-dominant period

	All (n = 1116)	Test positive (n = 934)	Test negative (n = 182)
Median age in years[a]	55 (45–69)	52 (43–61)	79 (71–86)
Age in years, n (%)			
16–19	0 (0.0)	0 (0.0)	0 (0.0)
20–29	49 (4.4)	46 (4.9)	3 (1.7)
30–39	118 (10.6)	117 (12.5)	1 (0.6)
40–49	227 (20.3)	219 (43.5)	8 (4.4)
50–59	309 (27.7)	302 (32.3)	7 (3.9)
60–69	139 (12.5)	117 (12.5)	22 (12.1)
70–79	139 (12.5)	85 (9.1)	54 (29.7)
80–89	101 (9.1)	31 (3.3)	70 (38.5)
>90	34 (3.1)	17 (1.8)	17 (9.3)
Sex, n (%)			
Male	787 (70.5)	672 (72.0)	115 (63.2)
Female	329 (29.5)	262 (28.1)	67 (36.8)
Pregnancy at hospitalization, n (%)			
No	1111 (99.6)	929 (99.5)	182 (100.0)
Yes	5 (0.5)	5 (0.5)	0 (0.0)
Comorbidities, n (%)			
Cardiovascular disease	381 (34.1)	269 (28.8)	112 (61.5)
Diabetes mellitus	231 (20.7)	184 (19.7)	47 (25.8)
Dyslipidemia	148 (13.3)	112 (12.0)	36 (19.8)
Chronic kidney disease	64 (5.7)	39 (4.2)	25 (13.7)
Chronic liver disease	28 (2.5)	17 (1.8)	11 (6.0)
Chronic obstructive pulmonary disease	43 (3.9)	28 (3.0)	15 (8.2)
Cancer	98 (8.8)	56 (6.0)	42 (23.1)
Dementia	47 (4.2)	12 (1.3)	35 (19.2)
Depression/schizophrenia	66 (5.9)	55 (5.9)	11 (6.0)
Stroke	48 (4.3)	21 (2.3)	27 (14.8)
Down syndrome	1 (0.1)	0 (0.0)	1 (0.0)
Body mass index			
<25	734 (65.8)	562 (60.2)	172 (94.5)
25–29 (overweight)	219 (19.6)	213 (22.8)	6 (3.3)
>30 (obese)	163 (14.6)	159 (17.0)	4 (2.2)
Severe disease risk score[b]			
0	316 (28.3)	294 (31.5)	22 (12.1)
1	245 (21.9)	213 (22.8)	32 (17.6)
2	221 (19.8)	177 (19.0)	44 (24.2)
3	144 (12.9)	112 (12.0)	32 (17.6)
4	90 (8.1)	70 (7.5)	20 (11.0)
5	50 (4.5)	36 (3.9)	14 (7.7)
>6	50 (4.5)	32 (3.4)	18 (9.9)
Hospitalization in the past year, n (%)			
No	1017 (91.1)	890 (95.3)	127 (69.8)
Yes	99 (8.9)	44 (4.7)	55 (30.2)
Smoking, n (%)			
Never-smoker	481 (43.1)	415 (44.4)	66 (36.3)
Past smoker	328 (29.4)	261 (27.9)	67 (36.8)
Current smoker	191 (17.1)	166 (17.8)	25 (13.7)
Unknown	116 (10.4)	92 (9.9)	24 (13.2)
Number of COVID-19 vaccinations received, n (%)			
None	808 (72.4)	770 (82.4)	38 (20.9)
One	129 (11.6)	116 (12.4)	13 (7.1)
Two	179 (16.0)	48 (5.1)	131 (72.0)
Three	0 (0.0)	0 (0.0)	0 (0.0)
Vaccine type, n (%)[c]			
BNT162b2	144 (82.3)	90 (78.9)	54 (88.5)
mRNA-1273	27 (15.4)	21 (18.4)	6 (9.8)

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Table 2 (*continued*)

(A) Delta-dominant period			
	All (n = 1116)	Test positive (n = 934)	Test negative (n = 182)
AZD1222	2 (1.1)	2 (1.8)	0 (0.0)
mRNA heterologous	1 (0.6)	0 (0.0)	1 (1.6)
Other	1 (0.6)	1 (0.9)	0 (0.0)
Interval from symptom onset to hospitalization (days)	7 (3–9)	7 (5–9)	0 (0–3)
SARS-CoV-2 testing type			
Nucleic acid amplification test	867 (77.7)	734 (78.6)	133 (73.1)
Rapid antigen detection kit	79 (7.1)	74 (7.9)	5 (2.8)
Quantitative antigen test	91 (8.2)	66 (7.1)	25 (13.7)
Unknown	79 (7.1)	60 (6.4)	19 (10.4)
(B) Early Omicron-dominant period			
	All (n = 951)	Test positive (n = 672)	Test negative (n = 279)
Median age in years[a]	79 (69–86)	77 (65–85)	81 (74–87)
Age in years, n (%)			
16–19	4 (0.4)	2 (0.3)	2 (0.7)
20–29	6 (0.6)	4 (0.6)	2 (0.7)
30–39	10 (1.1)	9 (1.3)	1 (0.4)
40–49	26 (2.7)	22 (3.3)	4 (1.4)
50–59	89 (9.4)	73 (10.9)	16 (5.7)
60–69	113 (11.9)	92 (13.7)	21 (7.5)
70–79	257 (27.0)	176 (26.2)	81 (29.0)
80–89	304 (32.0)	201 (29.9)	103 (36.9)
>90	142 (14.9)	93 (13.8)	49 (17.6)
Sex, n (%)			
Male	598 (62.9)	430 (64.0)	168 (60.2)
Female	353 (37.1)	242 (36.0)	111 (39.8)
Pregnancy at hospitalization, n (%)			
No	951 (100.0)	672 (100.0)	279 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Comorbidities, n (%)			
Cardiovascular disease	596 (62.7)	418 (62.2)	178 (63.8)
Diabetes mellitus	293 (30.8)	215 (32.0)	78 (28.0)
Dyslipidemia	166 (17.5)	109 (16.2)	57 (20.4)
Chronic kidney disease	128 (13.5)	88 (13.1)	40 (14.3)
Chronic liver disease	36 (3.8)	22 (3.3)	14 (5.0)
Chronic obstructive pulmonary disease	90 (9.5)	63 (9.4)	27 (9.7)
Cancer	165 (17.4)	111 (16.5)	54 (19.4)
Dementia	184 (19.4)	116 (17.3)	68 (24.4)
Depression/schizophrenia	50 (5.3)	36 (5.4)	14 (5.0)
Stroke	160 (16.8)	103 (15.3)	57 (20.4)
Down syndrome	1 (0.1)	1 (0.2)	0 (0.0)
Body mass index			
<25	793 (83.4)	528 (78.6)	265 (95.0)
25–29 (overweight)	98 (10.3)	90 (13.4)	8 (2.9)
>30 (obese)	60 (6.3)	54 (8.0)	6 (2.2)
Severe disease risk score[b]			
0	104 (10.9)	74 (11.0)	30 (10.8)
1	168 (17.7)	113 (16.8)	55 (19.7)
2	180 (18.9)	131 (19.5)	49 (17.6)
3	162 (17.0)	118 (17.6)	44 (15.8)
4	135 (14.2)	94 (14.0)	41 (14.7)
5	120 (12.6)	89 (13.2)	31 (11.1)
>6	82 (8.6)	53 (7.9)	29 (10.4)
Hospitalization in the past year, n (%)			
No	816 (85.8)	590 (87.8)	226 (81.0)
Yes	135 (14.2)	82 (12.2)	53 (19.0)
Smoking, n (%)			
Never-smoker	395 (41.5)	252 (37.5)	143 (51.3)
Past smoker	318 (33.4)	233 (34.7)	85 (30.5)

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Table 2 (*continued*)

(B) Early Omicron-dominant period			
	All (n = 951)	Test positive (n = 672)	Test negative (n = 279)
Current smoker	90 (9.5)	61 (9.1)	29 (10.4)
Unknown	148 (15.6)	126 (18.8)	22 (7.9)
Number of COVID-19 vaccinations received, n (%)			
None	227 (23.9)	202 (30.1)	25 (9.0)
One	11 (1.2)	9 (1.3)	2 (0.7)
Two	471 (49.5)	357 (53.1)	114 (40.9)
Three	242 (25.5)	104 (15.5)	138 (49.5)
Vaccine type, n (%)[c]			
BNT162b2	321 (87.5)	237 (89.1)	84 (83.2)
mRNA-1273	19 (5.2)	14 (5.3)	5 (5.0)
AZD1222	1 (0.3)	1 (0.4)	0 (0.0)
mRNA heterologous	26 (7.1)	14 (5.3)	12 (11.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Interval from symptom onset to hospitalization (days)	2 (0–6)	3 (1–7)	0 (0–2)
SARS-CoV-2 testing type			
Nucleic acid amplification test	633 (66.6)	410 (61.0)	223 (79.9)
Rapid antigen detection kit	111 (11.7)	106 (15.8)	5 (1.8)
Quantitative antigen test	79 (8.3)	65 (9.7)	14 (5.0)
Unknown	128 (13.5)	91 (13.5)	37 (13.3)

[a] Median (interquartile range).
[b] The following points were added up for each patient: assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, pregnancy while hospitalized, or overweight.
[c] Among individuals with known vaccine type.

Delta-dominant period, 58 for the non-epidemic period, and 951 for the early Omicron-dominant period (Fig. 1). The data from the non-epidemic period are excluded from the further analyses. The median age (interquartile range [IQR]) was 55 (45–69) for the Delta-dominant period and 79 (69–86) for the early Omicron-dominant period. Eight hundred (71.7%) for the Delta-dominant period and 847 (89.1%) for the Omicron-dominant period had at least one risk factor for severe COVID-19 (Table 2). The diagnoses of control groups are described in Table 1. Among vaccinees with known vaccine type, 538/542 (99.2%) received mRNA vaccines (BNT162b2, mRNA-1273, or mRNA heterologous) and 465/542 (85.8%) received BNT162b2 as it was approved first and mainly used for healthcare workers, the elderly, and individuals with comorbidities (Table 2). The number of patients included in estimating each VE is shown in Table 3.

Table 3
Number of patients included in each vaccine effectiveness (VE) estimate.[a]

Diagnosis	Case-patients,n	Control patients,n
VE against severe COVID-19 requiring oxygen therapy		
Delta	911	157
Omicron	574	205
VE against severe COVID-19 requiring invasive mechanical ventilation		
Delta	293	157
Omicron	138	205
VE against fatal COVID-19		
Delta	94	157
Omicron	90	205
VE against severe COVID-19 restricting to patients with respiratory failure due to COVID-19		
Delta	900	157
Omicron	516	205

[a] Note that for controls, all patients who required oxygen were included for the measurement of VE against all severe outcomes (thus the number of patients are the same for Delta and Omicron, respectively).

3.2. Vaccine effectiveness against COVID-19 requiring oxygen therapy, COVID-19 requiring mechanical ventilation, and fatal COVID-19

During the Delta-dominant period, VE estimates for 14 days–6 months after dose 2 were 95.2% (95% confidence interval [CI]: 88.7–98.0%) against COVID-19 requiring oxygen therapy (Table 4**A**, Fig. 2), 99.6% (95% CI: 97.3–99.9%) against COVID-19 requiring invasive mechanical ventilation (Table 5**A**), and 98.6% (95% CI: 92.3–99.7%) against fatal COVID-19 (Table 6**A**).

During the early Omicron-dominant period, VE estimates for > 6 months after dose 2 were 47.9% (95% CI: −2.1–73.4%) against COVID-19 requiring oxygen therapy (Table 4**B**), 82.7% (95% CI: 37.1–95.3%) against COVID-19 requiring invasive mechanical ventilation (Table 5**B**), and 59.5% (95% CI: −41.9–88.4%) against fatal COVID-19 (Table 6**B**). VE estimates for 14 days–6 months after dose 3 (first booster dose) were 85.5% (95% CI: 68.8–93.3%) against COVID-19 requiring oxygen therapy (Table 4**B**), 97.9% (95% CI: 85.9–99.7%) against COVID-19 requiring invasive mechanical ventilation (Table 5**B**), and 99.6% (95% CI: 95.2–99.97%) against fatal COVID-19 (Table 6**B**).

3.3. Vaccine effectiveness against "true" severe COVID-19 where oxygen requirement was due to COVID-19 rather than another differential diagnosis(es)

We estimated VE by excluding COVID-19 patients whose oxygen requirement was not due to COVID-19 or who likely had oxygen requirements from COVID-19 as well as another condition(s) (i.e. when it was difficult to distinguish whether oxygen requirement was due to one or the other). Such cases were present for 13/934 (1.4%) cases during the Delta-dominant period and 69/672 (10.3%) during the early Omicron-dominant period (Table 7).

During the Delta-dominant period, the resulting VE estimate for 14 days–6 months after dose 2 was 95.5% (95% CI: 89.3–98.1%) (Table 8**A**). During the early Omicron-dominant period, VE estimates were 50.2% (95% CI: 1.1–75.0%) for > 6 months after dose 2 and 88.1%

Table 4
Vaccine effectiveness against severe COVID-19 requiring oxygen therapy during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	770	38	N/A	1	N/A
Within 13 days of dose 1	67	4	9 (7–11)	0.430 (0.104–1.786)	57.0 (-78.6–89.6)
14 days after dose 1 or within 13 days of dose 2	41	27	15 (10–21)	0.044 (0.017–0.110)	95.6 (89.0–98.3)
14 days to 6 months after dose 2	33	87	76 (47–117)	0.048 (0.020–0.113)	95.2 (88.7–98.0)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	202	25	N/A	1	N/A
Within 13 days of dose 1	1	0	7 (7–7)	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	6	2	220 (100–243)	0.213 (0.032–1.409)	78.7 (-40.9–96.8)
14 days to 6 months after dose 2	76	22	155 (123–172)	0.630 (0.263–1.509)	37.0 (-50.9–73.7)
>6 months after dose 2	202	47	218 (204–235)	0.521 (0.266–1.021)	47.9 (-2.1–73.4)
Within 13 days of dose 3	36	16	6 (3–9)	0.271 (0.104–0.706)	72.9 (29.4–89.6)
14 days to 6 months after dose 3	51	93	67 (34–104)	0.145 (0.067–0.312)	85.5 (68.8–93.3)
>6 months after dose 3	0	0	N/A	N/A	N/A

Abbreviations: CI, confidence interval; N/A, not applicable.
[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score category (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).

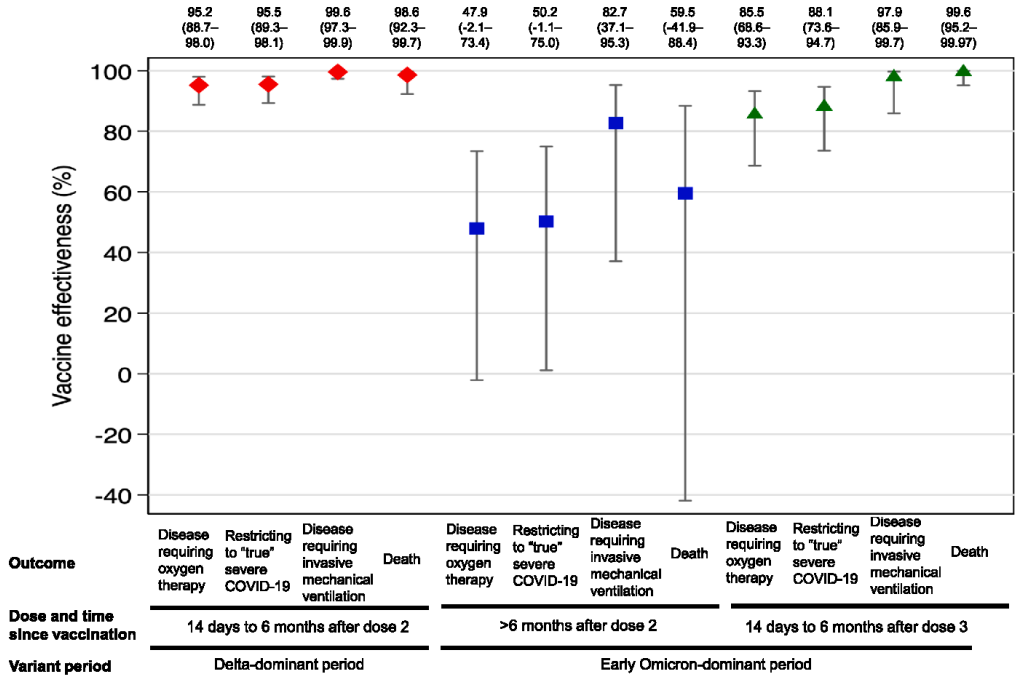

Fig. 2. Vaccine effectiveness against various severe outcomes during the Delta-dominant period (red diamonds) and early Omicron (BA.1/BA.2)-dominant periods (blue squares for 2 doses and green triangles for 3 doses), all compared to unvaccinated individuals. Red diamonds, blue squares, and green triangles indicate point estimates and error bars indicate 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 5
Vaccine effectiveness against severe COVID-19 requiring invasive mechanical ventilation during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	257	38	N/A	1	N/A
Within 13 days of dose 1	22	4	9 (7–10)	0.810 (0.093–7.048)	19.0 (-604.8–90.7)
14 days after dose 1 or within 13 days of dose 2	9	27	11 (7–24)	0.009 (0.002–0.055)	99.1 (94.5–99.8)
14 days to 6 months after dose 2	5	87	83 (49–123)	0.004 (0.001–0.027)	99.6 (97.3–99.9)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	63	25	N/A	1	N/A
Within 13 days of dose 1	1	0	7 (7–7)	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	1	2	53 (12–146)	0.065 (0.004–1.161)	93.5 (-16.1–99.6)
14 days to 6 months after dose 2	20	22	149 (123–168)	0.263 (0.053–1.306)	73.7 (-30.6–94.7)
>6 months after dose 2	37	47	215 (201–237)	0.173 (0.047–0.629)	82.7 (37.1–95.3)
Within 13 days of dose 3	11	16	5 (3–9)	0.315 (0.067–1.471)	68.5 (-47.1–93.3)
14 days to 6 months after dose 3	5	93	64 (27–102)	0.021 (0.003–0.141)	97.9 (85.9–99.7)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

Table 6
Vaccine effectiveness against fatal COVID-19 during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	77	38	N/A	1	N/A
Within 13 days of dose 1	9	4	9 (7–11)	0.712 (0.069–7.358)	28.8 (-635.8–93.1)
14 days after dose 1 or within 13 days of dose 2	3	27	10 (7–38)	0.006 (0.000–0.073)	99.4 (92.7–99.96)
14 days to 6 months after dose 2	5	87	83 (47–123)	0.014 (0.003–0.077)	98.6 (92.3–99.7)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	37	25	N/A	1	N/A
Within 13 days of dose 1	0	0	N/A	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	1	2	53 (12–218)	0.343 (0.001–1.409)	65.7 (-40.9–99.9)
14 days to 6 months after dose 2	10	22	139 (99–164)	0.569 (0.103–3.134)	43.1 (-213.4–89.7)
>6 months after dose 2	30	47	216 (205–244)	0.405 (0.116–1.419)	59.5 (-41.9–88.4)
Within 13 days of dose 3	10	16	4 (2–8)	0.142 (0.027–0.747)	85.8 (25.3–97.3)
14 days to 6 months after dose 3	2	93	64 (28–104)	0.004 (0.000–0.048)	99.6 (95.2–99.97)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

(95% CI: 73.6–94.7%) for 14 days–6 months after dose 3 (Table 8**B**).

3.4. Vaccine effectiveness against progression from oxygen use to mechanical ventilation or death among COVID-19 patients

We finally estimated VE against progression from oxygen use to mechanical ventilation or death among COVID-19 patients. During the Delta-dominant period, the resulting VE estimate for 14 days–6 months after dose 2 was 90.5% (95% CI: 65.4–97.4%) (Table 9**A**). During the early Omicron-dominant period, VE estimates were 45.9% (95% CI: −4.0–71.9%) for > 6 months after dose 2 and 65.5% (95% CI: −73.3–93.1%) for 14 days–6 months after dose 3 (Table 9**B**).

Table 7
Differential diagnosis in patients whose oxygen requirement was not or not solely due to COVID-19[a].

Diagnosis	Delta-dominant period, n (%)	Early Omicron (BA.1/BA.2)-dominant period, n (%)
Aspiration pneumonia	3 (23.1)	18 (26.1)
Heart failure[b]	4 (30.8)	12 (17.4)
Pneumonia (etiology other than COVID-19)	0 (0.0)	10 (14.5)
Cancer [c]	1 (7.7)	2 (2.9)
Other respiratory disease	3 (23.1)	4 (5.8)
Other[d]	2 (15.4)	23 (33.3)

[a] Primary diagnosis for oxygen requirement ascertained based on disease course and test results including CT scan.
[b] Includes pulmonary edema due to acute kidney injury on chronic kidney disease.
[c] Includes non-lung cancer resulting in pulmonary effusion.
[d] Includes non-pulmonary causes of oxygen requirement including altered mental status due to stroke.

4. Discussion

In this multicenter case-control study in Japan, we evaluated COVID-19 VE against various severe outcomes for 2 doses during the Delta-dominant period and 2 or 3 doses during the Omicron-dominant period. During the Delta-dominant period, in agreement with other observational studies [9,15,17], 2 doses provided very high (over 95%) protection for up to 6 months (oxygen requirement: 95.2% [restricted to "true" severe COVID-19: 95.5%]; invasive mechanical ventilation: 99.6%; fatal: 98.6%). During the Omicron-dominant period, 2 doses provided variable moderate-to-high (50–85%) protection after 6 months depending on outcome severity (oxygen requirement: 47.9% [restricted to "true" severe COVID-19: 50.2%]; invasive mechanical ventilation: 82.7%; fatal: 59.5% [some with wide CI]). However, the first booster (3 doses total) again provided very high protection for up to 6 months (oxygen requirement: 85.5% [restricted to "true" severe COVID-19: 88.1%]; invasive mechanical ventilation: 97.9%; fatal: 99.6%). There was a consistent trend towards higher VE for more severe and specific outcomes during the Delta-dominant period for 2 doses and during the Omicron-dominant period for 2 or 3 doses (Fig. 2). This concurs with a study in the U.K., which is the only study, to our knowledge, that looked at varying severity in detail [17]. However, the study used hospital-coded data, which can still result in contamination of incidental SARS-CoV-2 infection. The authors noted that "a study where data are collected prospectively on cases using reporting forms or detailed case note review could avoid this misclassification bias, but is much more challenging to do". We addressed their concern by conducting a detailed chart review. Since our first outcome was on COVID-19 requiring oxygen therapy, which is already a specific outcome for severe pneumonia, we did not see a large difference when restricting to "true" severe COVID-19. The difference may have been larger if we had used hospital admission (regardless of oxygen use) as the main outcome. Notably, 2 doses provided high (85%) protection after 6 months against invasive mechanical ventilation use even against Omicron, which may explain the relatively low incidence of COVID-19 requiring mechanical ventilation despite high case counts during the Omicron-dominant period [24,34,35]. Overall, our report supports previous reports where VE against severe disease is sustained for at least 6 months despite lower/waning effectiveness against symptomatic infection during Omicron [18].

Finally, we examined VE against progression from oxygen use to mechanical ventilation; the estimates were high (90.5% after 2 doses) during the Delta-dominant period, but moderate (45.9% for > 6 months after dose 2; 65.5% for 14 days–6 months after dose 3) during the Omicron-dominant period, with wide confidence intervals. Although WHO guidance recommends measuring VE against disease progression [20] and VE can be estimated through analysis of COVID-19 cases only (i.e. non-COVID-19 controls are not required), the concept may be harder to interpret or communicate.

5. Limitations

This study has several limitations. First, biases, confounding, and

Table 8
Vaccine effectiveness against severe COVID-19 requiring oxygen therapy during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination, restricting to patients with respiratory failure due to COVID-19.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	764	38	N/A	1	N/A
Within 13 days of dose 1	67	4	9 (7–11)	0.436 (0.107–1.784)	56.4 (-78.4–89.3)
14 days after dose 1 or within 13 days of dose 2	40	27	15 (10–21)	0.045 (0.018–0.113)	95.5 (88.7–98.2)
14 days to 6 months after dose 2	29	87	79 (46–118)	0.045 (0.019–0.107)	95.5 (89.3–98.1)
>6 months after dose 2	0	1	222 (222–222)	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	189	25	N/A	1	N/A
Within 13 days of dose 1	0	0	N/A	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	4	2	220 (53–242)	0.088 (0.012–0.639)	91.2 (36.1–98.8)
14 days to 6 months after dose 2	67	22	155 (125–171)	0.589 (0.241–1.439)	41.1 (-43.9–75.9)
>6 months after dose 2	185	47	218 (204–235)	0.498 (0.250–0.989)	50.2 (1.1–75.0)
Within 13 days of dose 3	30	16	6 (4–9)	0.259 (0.098–0.688)	74.1 (31.2–90.2)
14 days to 6 months after dose 3	41	93	67 (34–104)	0.119 (0.053–0.264)	88.1 (73.6–94.7)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

Table 9
Vaccine effectiveness against disease progression to intubation and/or death during the Delta- and early Omicron (BA.1/BA.2)-dominant periods by time since vaccination among individuals with severe COVID-19 requiring oxygen therapy.

(A) Delta-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	280	488	N/A	1	N/A
Within 13 days of dose 1	24	42	9 (7–11)	0.676 (0.318–1.437)	32.4 (-43.7–68.2)
14 days after dose 1 or within 13 days of dose 2	9	32	18 (15–21)	0.364 (0.124–1.066)	63.6 (-6.6–87.6)
14 days to 6 months after dose 2	7	26	58 (47–85)	0.095 (0.026–0.346)	90.5 (65.4–97.4)
>6 months after dose 2	0	0	N/A	N/A	N/A

(B) Early Omicron-dominant period

Vaccination status	Case-patients,n	Control patients,n	Last vaccination to admission, days[a]	Adjusted odds ratios (95% CI)[b]	Vaccine effectiveness, % (95% CI)
Unvaccinated	82	119	N/A	1	N/A
Within 13 days of dose 1	1	0	7 (7–7)	N/A	N/A
14 days after dose 1 or within 13 days of dose 2	2	4	232 (218–244)	0.445 (0.060–3.295)	55.5 (-229.5–94.0)
14 days to 6 months after dose 2	25	51	157 (130–173)	0.791 (0.338–1.852)	20.9 (-85.2–66.2)
>6 months after dose 2	52	148	219 (204–234)	0.541 (0.281–1.040)	45.9 (-4.0–71.9)
Within 13 days of dose 3	18	17	7 (3–9)	1.321 (0.441–3.956)	−32.1 (-295.6–55.9)
14 days to 6 months after dose 3	5	45	71 (40–104)	0.345 (0.069–1.733)	65.5 (-73.3–93.1)
>6 months after dose 3	0	0	N/A	N/A	N/A

[a] Median (interquartile range).
[b] Adjusted for age group, sex, risk score categories (0, 1, 2, 3–4, 5 +), hospitalization in the past year (either the admitting hospital or another hospital), smoking history, prefecture of admitting hospital, and calendar week of hospitalization (biweekly).
Abbreviations: CI, confidence interval; N/A, not applicable.

misclassifications inherent in observational studies are possible. However, using specific and severe outcomes, we aimed to minimize the inclusion of incidental SARS-CoV-2 positive cases. Second, the current hospital-based case-control study was not strictly a test-negative design as controls include all patients who required oxygen even for severe outcomes such as mechanical ventilation use and death. However, individuals who require oxygen therapy are likely to seek care regardless of SARS-CoV-2 infection or vaccination status due to shortness of breath and other manifestations, resulting in the same advantage of control for healthcare-seeking behavior. Third, wide CIs for some estimates warrant careful interpretation of point estimates and the small sample size in some multivariable models resulted in possible sparse data bias. However, even when the VE was very high (e.g. two doses against severe COVID-19 requiring invasive mechanical ventilation during the Delta-dominant period), adjusted OR and crude OR were fairly similar (crude OR: 0.008 [95% CI: 0.003–0.022]; adjusted OR: 0.004 [95% CI: 0.006–0.027]) and the qualitative conclusion remains similar. Fourth, our analysis was a complete case analysis in relation to vaccination history; 220/2067 (10.6%) had no record of the last vaccination date and thus were excluded from the VE estimates although VE by vaccine dose yielded similar estimates (data not shown), and this missing proportion is less than observed in data-linkage studies [9]. Another variable with missing data was smoking status, in which unknown smoking status was included as one category. There were no other variables with missing data included in the model. Fifth, vaccine type was not always recorded in the charts, though almost all individuals with known vaccine type (99.2%) received mRNA vaccines. Sixth, we could not classify individual COVID-19 cases as infected with the Omicron or Delta variant. However, since there was a non-epidemic period between these two periods, misclassification was likely minimal. Finally, our VE estimates were short- to mid-term and we did not assess the effectiveness of Omicron-containing bivalent vaccines.

6. Conclusions

In this multicenter case-control study in Japan, VE of 2 doses of COVID-19 was high against Delta and moderate to high against Omicron for multiple severe outcomes. With a booster (third) dose, VE recovered to a high level against Omicron for multiple severe outcomes. There was a consistent trend towards higher VE for more severe and specific outcomes during the Delta-dominant period for 2 doses and during the Omicron-dominant period for 2 or 3 doses. These results demonstrate the usefulness of severe and specific outcomes to accurately measure VE, as recommended in WHO guidance in the setting of intense transmission as seen during Omicron.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Takeshi Arashiro is an unpaid consultant for the World Health

Organization. The other authors declare no conflicts of interest.

Data availability

Individual-level data of patients included in this manuscript after de-identification are considered sensitive and will not be shared. The study methods and statistical analyses are all described in detail in the Methods and throughout the manuscript.

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References

[1] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577.
[2] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389.
[3] Thomas SJ, Moreira Jr ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385(19):1761–73. https://doi.org/10.1056/NEJMoa2110345.
[4] El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385(19):1774–85. https://doi.org/10.1056/NEJMoa2113017.
[5] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384(15):1412–3. https://doi.org/10.1056/NEJMoa2101765.
[6] Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021; 70(13): 495–500. 10.15585/mmwr.mm7013e3.
[7] Pilishvili T, Fleming-Dutra KE, Farrar JL, Gierke R, Mohr NM, Talan DA, et al. Interim estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna COVID-19 vaccines among health care personnel - 33 U.S. sites, January-March 2021. MMWR Morb Mortal Wkly Rep 2021; 70(20): 753–8. 10.15585/mmwr.mm7020e2.
[8] Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ 2021;374:n1943. https://doi.org/10.1136/bmj.n1943.
[9] Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med 2022;386(4):340–50. https://doi.org/10.1056/NEJMoa2115481.
[10] Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021;385(24):e83.
[11] Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med 2021;385(24):e85.
[12] Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021;398(10309):1407–16. https://doi.org/10.1016/S0140-6736(21)02183-8.
[13] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022;386(16):1532–46. https://doi.org/10.1056/NEJMoa2119451.
[14] Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. JAMA 2022;327(7):639–51. https://doi.org/10.1001/jama.2022.0470.
[15] Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med 2022;28(5):1063–71. https://doi.org/10.1038/s41591-022-01753-y.
[16] Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Coronavirus disease 19 (COVID-19) vaccine effectiveness against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during Delta-dominant and Omicron-dominant periods in Japan: a multicenter prospective case-control study (Factors Associated with SARS-CoV-2 Infection and the Effectiveness of COVID-19 Vaccines Study). Clin Infect Dis 2023;76(3):e108–15. https://doi.org/10.1093/cid/ciac635.
[17] Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation, a test negative case-control study. Nat Commun 2022;13(1):5736. https://doi.org/10.1038/s41467-022-33378-7.
[18] International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health; World Health Organization; Coalition for Epidemic Preparedness Innovations. Results of COVID-19 vaccine effectiveness studies: an ongoing systematic review. [cited 10 October 2023]. Available from: https://view-hub.org/sites/default/files/2023-06/COVID19%20VE%20Studies_Forest%20Plots_Omicron.pdf.
[19] Ministry of Health, Labour and Welfare, Japan. Hospitalization, discharge, and handling of close contacts on aircraft for cases infected with B.1.1.529 (Omicron) [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/content/000860731.pdf.
[20] World Health Organization. Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination: second addendum to Evaluation of COVID-19 vaccine effectiveness: interim guidance. [cited 10 October 2023]. Available from: https://apps.who.int/iris/handle/10665/363344.
[21] Ministry of Health, Labour and Welfare, Japan. About COVID-19 vaccines [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_00184.html.
[22] Cabinet Public Affairs Office, Cabinet Secretariat. COVID-19 vaccines [in Japanese]. [cited 10 October 2023]. Available from: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html.
[23] Kobayashi Y, Arashiro T, Otsuka M, Tsuchihashi Y, Takahashi T, Arima Y, et al. Replacement of SARS-CoV-2 strains with variants carrying N501Y and L452R mutations in Japan: an epidemiological surveillance assessment. Western Pac Surveill Response J 2022;13(3):1–10. https://doi.org/10.5365/wpsar.2022.13.3.943.
[24] National Institute of Infectious Diseases, Japan. COVID-19 surveillance weekly report [in Japanese]. [cited 10 October 2023]. Available from: https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10754-2021-41-10-11-10-17-10-19.html.
[25] Ministry of Health, Labour and Welfare, Japan. Variant-specific PCR results [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/content/10900000/000892298.pdf.
[26] Ministry of Health, Labour and Welfare, Japan. Estimated subvariant prevalence via SARS-CoV-2 genomic surveillance using specimen from commercial company [in Japanese]. [cited 10 October 2023]. Available from: https://www.mhlw.go.jp/content/10900000/001039363.pdf.
[27] UK Health Security Agency. COVID-19 vaccine surveillance report: 4 August 2022 (week 31). [cited 10 October 2023]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1096327/Vaccine_surveillance_report_week_31_2022.pdf.
[28] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584(7821):430–6. https://doi.org/10.1038/s41586-020-2521-4.
[29] Clift AK, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 2020;371:m3731. https://doi.org/10.1136/bmj.m3731.
[30] Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ 2022;376:e069761.
[31] Doll MK, Pettigrew SM, Ma J, Verma A. Effects of confounding bias in coronavirus disease 2019 (COVID-19) and influenza vaccine effectiveness test-negative designs due to correlated influenza and COVID-19 vaccination behaviors. Clin Infect Dis 2022;75(1):e564–71. https://doi.org/10.1093/cid/ciac234.
[32] National Institute of Infectious Diseases, Japan. Influenza activity compared to past 10 years [in Japanese]. [cited 10 October 2023]. Available from: https://www.niid.go.jp/niid/ja/flu-m/813-idse/map/130-flu-10year.html.
[33] National Institute of Infectious Diseases, Japan. Notifications of invasive pneumococcal disease, 2014 week 1 to 2021 week 35 [in Japanese]. [cited 10 October 2023]. Available from: https://www.niid.go.jp/niid/ja/pneumococcal-m/pneumococcal-idwrs/10779-ipd-211126.html.
[34] NPO Japan ECMOnet. Summary situation of COVID-19 severe cases. [cited 10 October 2023]. Available from: https://crisis.ecmonet.jp.
[35] Ministry of Health, Labour and Welfare, Japan. Visualizing the data: information on COVID-19 infections [in Japanese]. [cited 10 October 2023]. Available from: https://covid19.mhlw.go.jp/en/.

Paper 8: Risk factors and VE against symptomatic infection in the Philippines

Arashiro T*, et al. Socio-behavioral factors associated with SARS-CoV-2 infection and COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines: a prospective case-control study (FASCINATE-P study). **(**under review; ***first and corresponding author)**

PhD candidate contributions:
Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objectives 1B and 3B.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

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First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	WHO WPRO Western Pacific Surveillance and Response journal
Please list the paper's authors in the intended authorship order:	Takeshi Arashiro, Regina Pascua Berba, Joy Potenciano Calayo, Marie Kris, Reby Marie Garcia, Shuichi Suzuki, Cecile Dungog, Jonathan Rivera, Greco Mark Malijan, Kristal An Agrupis, Mary Jane Salazar, Mary Ann Salazar,

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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualization (main), design (main), recruitment of participating healthcare facilities (sub), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported research nurses), data analysis (main), writing – original draft (main), funding acquisition (main: WISE, WHO; support: AMED, MHLW)

SECTION E

Student Signature	Takeshi Arashiro
Date	April 5, 2024

Supervisor Signature	Chris Smith
Date	April 6, 2024

Original research

Socio-behavioural factors associated with SARS-CoV-2 infection and COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines: a prospective case-control study (FASCINATE-P study)

Short title: Factors associated with SARS-CoV-2 infection in the Philippines

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ABSTRACT

Objective: We examined socio-behavioral factors associated with SARS-CoV-2 infection and estimated COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines, as such studies are limited in low- and middle-income countries, especially from Southeast Asia.

Methods: A case-control study was conducted in 2 hospitals in Manila, Philippines in March 2022 to June 2023. Socio-behavioural factors and vaccination history were interviewed. PCR-positive individuals were cases, while PCR-negative individuals were controls. Adjusted odds ratios (aOR) were calculated to examine associations between socio-behavioural factors/vaccination and SARS-CoV-2 infection.

Results: The analysis included 2489 individuals (574 positives [23.1%]; median age [interquartile range] 35 [27–51] years). Although education and household income were not associated with infection, being a health-care worker (HCW) was (aOR 1.45 [95% CI 1.03–2.06]). The odds of infection were higher among individuals who attended gatherings of five+ people compared to smaller gatherings (aOR 2.58 [95% CI 1.14–5.83]) and individuals who attended gatherings that lasted 2+ hours compared to shorter gatherings (aOR 1.75 [95% CI 0.95–3.22]). Absolute VE comparing vaccinated versus unvaccinated was not estimated due to high risk of bias. Moderate relative VE (rVE) for the first booster (32%) and the second booster (48%) were observed (both with wide CI), albeit with waning trend after half a year.

Discussion: Higher odds of infection among HCWs emphasize the importance of infection prevention and control measures. Moderate rVE with waning reiterates the need for more efficacious vaccines against symptomatic infection caused by circulating variants and with longer duration of protection.

INTRODUCTION

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally.[1] Before the COVID-19 vaccines were developed and widely rolled out, various public health and social measures (PHSMs) were the only countermeasures to prevent the spread of SARS-CoV-2 and thus were implemented as obligations or strong recommendations in each country.[2] Some of these PHSMs included lockdowns, mask mandates, and border closures. There have been many studies in various countries to evaluate the behavioural and social factors associated with SARS-CoV-2 infection to inform decision-making related to such PHSMs.[3–5] However, such evidence is scarce in low- and middle-income countries (LMICs). Furthermore, once safe and effective vaccines have been rolled out, there was a need to monitor the real-world effectiveness of the vaccines (vaccine effectiveness; VE), given concerns due to waning immunity and the emergence of variants with immune escape capacity.[6–14] There have been numerous studies to evaluate VE, mostly from high-income countries (HICs), but the evidence is very limited in LMICs, especially from Southeast Asia.[15] However, it would be valuable for more LMICs to conduct VE studies for several reasons, including: (1) evaluation of vaccines that are mainly distributed in LMICs, (2) confirmation that the vaccines remain active through distribution networks (e.g. no cold chain breach), (3) considerably different cumulative infection burdens among countries (e.g. individuals with prior infection are protected against subsequent infection/disease), (4) substantial variation in PHSMs and policies/risk communication activities among countries, (5) vaccine confidence within and among surrounding countries, and (6) capacity building to

conduct operational research to inform public health response for COVID-19 as well as future epidemics and pandemics.

In Japan, several authors from the present report evaluated behavioural factors associated with SARS-CoV-2 infection, many of which were in line with the local policy/risk communication implemented, and estimated VE against symptomatic infection.[5,14,16–18] We used the same design (multi-centre case-control study) to examine (1) Behavioural factors associated with SARS-CoV-2 infection and (2) COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines as a companion study.

METHODS

COVID-19 epidemiology and vaccination rollout in the Philippines

The epidemic curve of reported COVID-19 cases and vaccination rollout in the Philippines are illustrated together with the study period in **Fig. 1**. In the Philippines, the primary series (1 dose for Janssen and 2 doses for all other vaccine types) rollout started on 1 March 2021.[19] The first booster dose rollout started on 16 November 2021 among health-care workers (HCWs), on 22 November 2021 among senior citizens and immunocompromised persons, and on 3 December 2021 among all adults aged 18 years or above. The second booster dose rollout started on 25 April 2022 among HCWs and individuals who were ≥60 years old, and on 27 July 2022 among individuals who were ≥50 years old as well as individuals aged 18–49 years with comorbidities. The primary series followed manufacturer-recommended intervals. During the study period, Omicron subvariant B.1.1.529 are XBB.1.5 were reported to be dominant.[20]

Study design and setting

Our study, Factors Associated with SARS-CoV-2 INfection And The Effectiveness of COVID-19 vaccines in the Philippines (FASCINATE-P study), is a multi-centre case-control study in health-care facilities with two objectives: (1) to elucidate behavioural and demographic risk factors associated with SARS-CoV-2 infection and (2) to estimate the real-world effectiveness of COVID-19 vaccines against symptomatic infection. This study was conducted at Philippine General Hospital and San Lazaro Hospital in Manila, which had outpatient clinics that routinely tested individuals using polymerase chain reaction (PCR) for clinical diagnostic purposes and were functioning as some of the main COVID-19 response sites in the country.[21,22] For this report, individuals who were tested between 22 March 2022 and 16 June 2023 were included. We followed the same design as the one conducted in Japan and published previously.[5,14,16–18]

Inclusion and exclusion criteria

The inclusion criterion was all symptomatic individuals aged ≥18 years who were tested for SARS-CoV-2. We defined symptomatic individuals as individuals with any of the following: fever ≥37.5°C, malaise, chills, joint pain, headache, runny nose, cough, sore throat, shortness of breath, gastrointestinal symptoms (vomiting, diarrhoea, or stomach-ache), and loss of taste/smell. Individuals who did not or could not consent to participate in the study, individuals who required immediate lifesaving treatment, and individuals who had previously participated in this study were excluded. At the analysis stage, we excluded individuals with unknown symptom onset or who were tested ≥15 days after symptom onset.

Classification of exposures and outcome

Trained research nurses administered an oral interview before PCR results were available to avoid social desirability bias, where individuals who tested positive were

less likely to report potentially high-risk behaviours or more likely to report vaccination status. The interview included general information (e.g. sociodemographic factors), symptoms in the past two weeks, preventive measures such as mask wearing in the past two weeks, history of close contact in the past two weeks, history of work/school/travel in the past two weeks, behaviours such as social gatherings in the past two weeks, and COVID-19 vaccination status. To ascertain vaccination status (number of doses, vaccine manufacturer, and date of each dose), we asked participants to present their vaccination cards. Vaccination status was classified into 15 categories: (1) not vaccinated, (2) dose 1 or ≤13 days after dose 2 (partially vaccinated), (3) 14 days–3 months (14–90 days) after dose 2, (4) 3–6 months (90–180 days) after dose 2, (5) 6–9 months (181–270 days) after dose 2, (6) 9–12 months (271–360 days) after dose 2, (7) >12 months (361 days) after dose 2, (8) ≤13 days after first booster dose, (9) 14 days–3 months (14–90 days) after first booster dose, (10) 3–6 months (90–180 days) after first booster dose, (11) >6 months (181 days) after first booster dose, (12) ≤13 days after second booster dose, (13) 14 days–3 months (14–90 days) after second booster dose, (14) 3–6 months (90–180 days) after second booster dose, and (15) >6 months (181 days) after second booster dose.

SARS-CoV-2 PCR was done at each medical facility for diagnostic purposes; PCR-positive individuals were considered cases and PCR-negative individuals were controls.

Sample size calculation

For risk factor analysis, assuming 10% positivity (based on data when the study was planned), 30–50% of controls having the exposures of interest, a two-tailed significance level of 5%, and 80% power, enrolment of approximately 70–80 cases

and 700–800 controls were needed to detect a minimal odds ratio of 2. For VE estimates, assuming 10% positivity, expected vaccine coverage of 30%, and 90% VE (based on data from the ancestral strain when the study was planned), 207 cases and 1864 controls are needed for the precision of the lower confidence interval (CI) boundary of 10%. We planned to continue enrolment even after reaching this target to allow for sub-analysis and continued assessment of factors that may be time-varying.

Data analysis

Participant characteristics and vaccination status were described.

For risk factor analysis, individuals with a history of close contact were excluded because an infection, if confirmed, is most likely due to this specific contact rather than exposures asked about in the questionnaire. Logistic regression to identify associations between behavioural risk factors and SARS-CoV-2 infection was conducted adjusting for age, sex, presence of comorbidities, prior SARS-CoV-2 infection, week of testing (biweekly), study site, and vaccination status by dosage. These potential confounders were determined *a priori* based on published reports.[5]

For VE evaluation, to reduce confounding by various socioeconomic factors and priority of vaccination that can be confounders, we restricted the analyses to HCWs, older adults, and individuals with comorbidities (who were also eligible for the fourth dose). Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age, sex, presence of comorbidities, history of close contact, SARS-CoV-2 testing in the past month, prior SARS-CoV-2 infection, education, work/school, going out to eat/drink in the evening/night without alcohol, week of testing (biweekly), study site. These potential confounders were also determined *a priori* based on published reports.[14] VE against

symptomatic SARS-CoV-2 infection was estimated using the following equation: VE = (1 - adjusted odds ratio [aOR]) × 100%. In addition to absolute VE (aVE; VE comparing the vaccinated and unvaccinated), we planned to calculate relative VE (rVE; VE comparing individuals who received a booster of interest vs. individuals who only received the previous dose 3+ months earlier [e.g. VE comparing 3 vs 2 doses and VE comparing 4 doses vs 3 doses]) to evaluate the added effect of the booster.

Data analyses were performed using STATA version 18.0.

Choice of controls in risk factor analysis

We considered that the behavioural and demographic traits among cases and controls would be most similar as they were sourced from those presenting to the same medical facilities for testing (e.g. health-seeking behaviours). Also, if controls were infected with other viruses due to similar exposures, the odds ratio for SARS-CoV-2 infection would be an underestimate of the true association. In other words, our design would detect differences in the magnitude of a particular risk factor or risk factors that would be specific to COVID-19. In fact, even though many respiratory pathogens (influenza virus, *Streptococcus pneumoniae*, etc.) were circulating at extremely low levels during the early phase of the pandemic, likely due to social and public health measures, SARS-CoV-2 epidemics occurred repeatedly. This suggests that SARS-CoV-2 has unique features that allow it to circulate even under strict PHSMs. Please see the Supplementary Methods of our previous report[5] for further detailed rationale.

RESULTS

Characteristics of the study participants

A total of 2691 symptomatic individuals were enrolled from 2 hospitals during the study period; we excluded 11 due to unknown symptom onset and 191 due to being tested ≥15 days after symptom onset (**Fig. 2**). The final analysis included 2489 individuals with 574 (23.1%) positive cases. The median age (interquartile range [IQR]) was 35 (27–51) years, 892 were males (35.8%), 877 (35.2%) had comorbidities, and 1743 (70.1%) were working (**Table 1**). Although data on race/ethnicity were not collected, 2486 (99.9%; 3 missing) were Filipinos, so we expect most study participants to be Asians. All participants answered that they wore a mask when going out. Most had received COVID-19 vaccines (2246; 90.2%). Among the vaccinees, most had their vaccination cards (2123; 94.5%). Among the vaccinees for the primary series, 39% received AstraZeneca, 37% received Sinovac, 11% received Pfizer, 7% received Moderna, and 6% received other types. Among the vaccinees for booster doses, over 90% received mRNA vaccines.

Association between socio-behavioural factors and SARS-CoV-2 infection

After excluding individuals with a history of close contact, 2,088 individuals were included in this analysis. No apparent association was observed between SARS-CoV-2 infection and socioeconomic factors such as cohabitation status, education, or household income (**Table 2**). On the other hand, having work or school, specifically being a HCW, was associated with SARS-CoV-2 infection (adjusted odds ratio [aOR] 1.83 [95% CI 1.09–3.07]; aOR 1.45 [95% CI 1.03–2.06], respectively). We also looked at various behaviours in the past two weeks. No apparent association was observed between SARS-CoV-2 infection and various social gatherings with food or drinks. However, among those who attended social gatherings, the odds of infection were higher among individuals who attended gatherings of five or more people compared to those who attended smaller

gatherings (aOR 2.58 [95% CI 1.14–5.83]) and individuals who attended gatherings that lasted 2 hours or longer compared to individuals who attended shorter gatherings (aOR 1.75 [95% CI 0.95–3.22]). The odds of infection were not higher among those who ordered takeout, used food delivery services, and ate out by oneself, all compared to those who did not (**Table 2**). Other behaviours unrelated to food or drink were also not apparently associated with SARS-CoV-2 infection, except that the odds of infection were slightly higher among those who reported having gone to the gym (aOR 1.53 [95% CI 0.94–2.49]) or to karaoke (aOR 1.74 [95% CI 0.81–3.86]).

Association between COVID-19 vaccination (by doses and period since vaccination) and SARS-CoV-2 infection

After restricting to HCWs, older adults, and individuals with comorbidities, 1,890 individuals were included in this analysis. As for the comparison between vaccinated and unvaccinated, there were inconsistent odds of infection depending on the vaccination category. As for the comparison between the first booster and 3 months after the primary series, there was a moderate effect 14 days to 3 months after the booster dose (rVE 32% [95% CI -120–79]), but VE seems to wane after half a year (rVE -8% [95% CI -72–33]). Comparison between the second booster and 3 months after the first booster showed a similar trend of moderate effect for the short term (rVE 48% [95% CI -23–78]) with waning protection.

DISCUSSION

In this multi-centre case-control study in the Philippines, we investigated the association between various socio-behavioural factors and SARS-CoV-2 infection. We also examined the association between COVID-19 vaccination and SARS-CoV-2

symptomatic infection. By following the same design as a similar study conducted by some of the authors in Japan, we aimed to look at country-specific differences in factors associated with SARS-CoV-2 infection.[5]

First, there was no apparent association between socioeconomic factors such as cohabitation status, education, or household income and SARS-CoV-2 infection, suggesting that SARS-CoV-2 has spread regardless of socioeconomic status. However, working, especially in the health-care environment, had higher odds of SARS-CoV-2 infection compared to others. This was also observed in other countries early in the pandemic.[23] With proper personal protective equipment (PPE) and infection prevention and control measures in the health-care setting, the risk of occupational exposure should be minimized, as this trend was not observed in Japan, where strict infection prevention and control measures were in place.[5,24] Policies should also make sure that adequate supplies of PPE are available to protect those on the frontline. We next examined various behaviours that may be associated with SARS-CoV-2 infection. Among those who attended social gatherings, the odds of infection were higher among individuals who attended gatherings of five or more people compared to smaller gatherings and individuals who attended for 2 hours or longer compared to shorter gatherings. Although not statistically significant, going to the gym or karaoke were associated with higher odds of infection, while other behaviours such as ordering takeout, using food delivery services, and eating out by oneself were not associated with infection. These findings were reassuring, made sense, and were in line with findings from Japan and highlighted the nature of this pathogen where transmission can occur efficiently in specific situations.[5,25]

We next examined the association between COVID-19 vaccination and SARS-CoV-2 infection in an attempt to estimate COVID-19 VE against symptomatic infection. As for the comparison between vaccinated and unvaccinated, there were inconsistent odds of infection depending on the vaccination category. We did include various covariates to adjust for in the multivariable analysis, but we suspected that the risk of residual bias was high, and therefore, aVE was not presented. One bias that could have caused this is that, due to a substantial delay in ethics approval, the enrolment started after a large Omicron wave in early 2022, when the majority of the unvaccinated were already/recently infected without being ascertained, resulting in a protective effect at a level higher than that from vaccination several months before. Also, vaccination cards were required to be presented in some stores and restaurants, which can potentially underestimate VE.[18] This is in line with a few reports from other countries where negative effectiveness was observed.[26–28] On the other hand, moderate rVE for the first booster (32%) and the second booster (48%) against symptomatic SARS-CoV-2 infection were observed (both were not statistically significant due to the small sample size). However, these effects seemingly have waned after half a year. These findings were consistent with the Japanese study and studies from other countries and reiterate the need for vaccines that are more efficacious against symptomatic infection caused by circulating variants and with a longer duration of protection.

Limitations

This study had several limitations. First, biases inherent in observational studies are possible. Using a detailed questionnaire, we attempted to minimize confounding that is not necessarily accounted for in studies that retrospectively evaluate routine surveillance data, but unmeasured and residual confounding could have occurred.

However, specifically, as explained above, the association between vaccination and SARS-CoV-2 infection has likely suffered from residual bias with most unvaccinated individuals being infected, and thus aVE was not presented. Second, for the risk factor analyses, controls may have been infected with other viruses due to similar exposures, which can underestimate the odds ratio (see **Methods** for details). Third, identified risk factors may be country-, region-, culture-, and population-specific and time-dependent due to changes in COVID-19-related policies and behaviours. Also, ascertainment of past infection was likely suboptimal, and this could have protected "truly high-risk groups" from getting infected during the study period. Specifically, our study population had a large proportion of HCWs, thus the risk factor analyses may not be generalizable to the overall population in the Philippines. Fourth, our primary analyses were complete case analyses. However, due to the prospective nature of the study with thorough interviews, the amount of missing data was minimal, as shown in **Table 1**. Finally, some estimates were calculated based on very low numbers, resulting in wide CIs.

Conclusions

In this case-control study in the Philippines, working or going to school, especially in the health-care environment, had higher odds of SARS-CoV-2 infection compared to others, suggesting the importance of infection prevention and control measures in the health-care setting. Also, attending social gatherings with five or more people or longer duration was associated with SARS-CoV-2 infection. Although COVID-19 vaccine effectiveness comparing vaccinated versus unvaccinated was not able to be estimated due to the high risk of bias, moderate rVE against symptomatic SARS-CoV-2 infection was observed, albeit with a waning trend after half a year.

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Conflicts of interest

Authors declare no conflicts of interest.

Ethics statement

Ethics approval was obtained from each participating hospital. Before the interview, written informed consent was obtained from each participant.

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Author Contributions

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Drafting of the manuscript: Takeshi Arashiro

Critical revision of the manuscript for important intellectual content and final approval of the manuscript: All authors

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REFERENCES

1. Coronavirus disease (COVID-19) pandemic. Geneva: World Health Organization; 2023. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019, accessed 5 November 2023.
2. Measuring the effectiveness and impact of public health and social measures. Geneva: World Health Organization; 2023. Available from: https://covid19.who.int/measures, accessed 5 November 2023.
3. Fisher KA, Tenforde MW, Feldstein LR, Lindsell CJ, Shapiro NI, Files DC, et al. Community and close contact exposures associated with COVID-19 Among symptomatic adults ≥18 years in 11 outpatient health care facilities - United States, July 2020. MMWR Morb Mortal Wkly Rep. 2020;69(36):1258–64. doi:10.15585/mmwr.mm6936a5 pmid:32915165
4. Galmiche S, Charmet T, Schaeffer L, Paireau J, Grant R, Chény O, et al. Exposures associated with SARS-CoV-2 infection in France: A nationwide online case-control study. Lancet Reg Health Eur. 2021;7:100148. doi:10.1016/j.lanepe.2021.100148 pmid:34124709
5. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses. 2022;16(5):952–61. doi:10.1111/irv.12992 pmid:35470969
6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15. doi:10.1056/NEJMoa2034577 pmid:33301246

371 7. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and
372 safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med.
373 2021;384(5):403–16. doi:10.1056/NEJMoa2035389 pmid:33378609
374 8. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.
375 Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-
376 CoV-2: an interim analysis of four randomised controlled trials in Brazil, South
377 Africa, and the UK. Lancet. 2021;397(10269):99–111. doi:10.1016/S0140-
378 6736(20)32661-1 pmid:33306989
379 9. Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al.
380 Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med.
381 2021;385(10):875–84. doi:10.1056/NEJMoa2107715 pmid:34233097
382 10. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al.
383 Duration of protection against mild and severe disease by Covid-19 vaccines. N
384 Engl J Med. 2022;386(4):340–50. doi:10.1056/NEJMoa2115481 pmid:35021002
385 11. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM,
386 et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in
387 Qatar. N Engl J Med. 2021;385(24):e83. doi:10.1056/NEJMoa2114114
388 pmid:34614327
389 12. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-
390 19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med.
391 2022;386(16):1532–46. doi:10.1056/NEJMoa2119451 pmid:35249272
392 13. Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al.
393 Association between 3 doses of mRNA COVID-19 vaccine and symptomatic
394 infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA.
395 2022;327(7):639–51. doi:10.1001/jama.2022.0470 pmid:35060999

14. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Coronavirus disease 19 (COVID-19) vaccine effectiveness against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during Delta-dominant and Omicron-dominant periods in Japan: a multicenter prospective case-control study (Factors Associated with SARS-CoV-2 Infection and the Effectiveness of COVID-19 vaccines study). Clin Infect Dis. 2023;76(3):e108–15. doi:10.1093/cid/ciac635 pmid:35918782

15. VIEW-hub: COVID-19 data, vaccine effectiveness studies. Baltimore (MD): International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health; 2023. Available from: https://view-hub.org/covid-19/effectiveness-studies, accessed 5 November 2023.

16. Arashiro T, Arima Y, Kuramochi J, Muraoka H, Sato A, Chubachi K, et al. Immune escape and waning immunity of COVID-19 monovalent mRNA vaccines against symptomatic infection with BA.1/BA.2 and BA.5 in Japan. Vaccine. 2023;41(47):6969–79. doi:10.1016/j.vaccine.2023.10.021 pmid:37839947

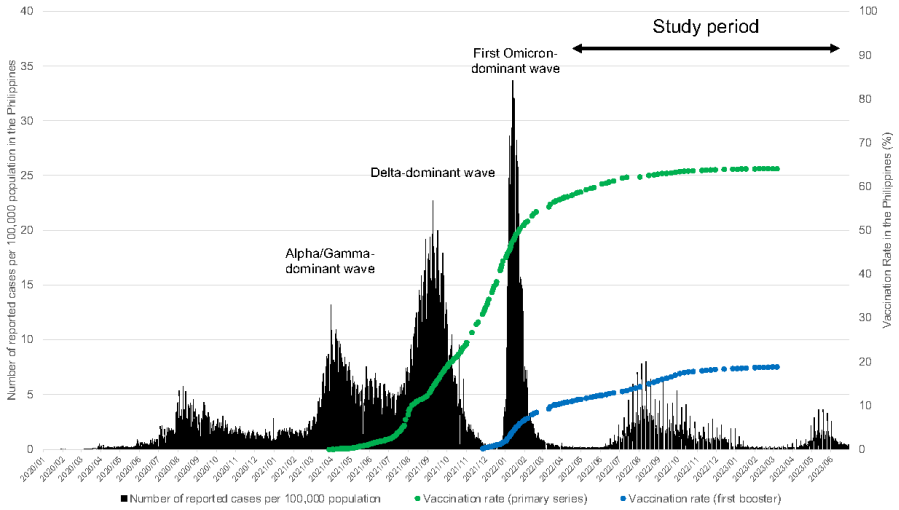
17. Arashiro T, Arima Y, Kuramochi J, Muraoka H, Sato A, Chubachi K, et al. Effectiveness of BA.1- and BA.4/BA.5-containing bivalent COVID-19 mRNA vaccines against symptomatic SARS-CoV-2 infection during the BA.5-dominant period in Japan. Open Forum Infect Dis. 2023;10(6):ofad240. doi:10.1093/ofid/ofad240 pmid:37351451

18. Arashiro T, Arima Y, Kuramochi J, Muraoka H, Sato A, Chubachi K, et al. Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. Euro Surveill. 2023;28(4):2300034. doi:10.2807/1560-7917.ES.2023.28.4.2300034 pmid:36700869

421 19. Updates on COVID-19 vaccines. Manila: Department of Health, Philippines;
422 2023. Available from: https://doh.gov.ph/vaccines, accessed 5 November 2023.
423 20. hCoV-19 variants dashboard. Munich: GISAID; 2023. Available from:
424 https://gisaid.org/hcov-19-variants-dashboard/, accessed 5 November 2023.
425 21. Salva EP, Villarama JB, Lopez EB, Sayo AR, Villanueva AMG, Edwards T, et al.
426 Epidemiological and clinical characteristics of patients with suspected COVID-19
427 admitted in Metro Manila, Philippines. Trop Med Health. 2020;48(1):51.
428 doi:10.1186/s41182-020-00241-8 pmid:34686216
429 22. Malundo AFG, Abad CLR, Salamat MSS, Sandejas JCM, Planta JEG, Poblete
430 JB, et al. Clinical characteristics of patients with asymptomatic and symptomatic
431 COVID-19 admitted to a tertiary referral centre in the Philippines. IJID Reg.
432 2022;2:204–11. doi:10.1016/j.ijregi.2022.02.002 pmid:35721425
433 23. Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, et al. Risk of
434 COVID-19 among front-line health-care workers and the general community: a
435 prospective cohort study. Lancet Public Health. 2020;5(9):e475–83.
436 doi:10.1016/S2468-2667(20)30164-X pmid:32745512
437 24. Tanaka A, Yamamoto S, Miyo K, Mizoue T, Maeda K, Sugiura W, et al.
438 Seroprevalence of antibodies against SARS-CoV-2 in a large national hospital
439 and affiliated facility in Tokyo, Japan. J Infect. 2021;82(4):e1–3.
440 doi:10.1016/j.jinf.2021.01.010 pmid:33524423
441 25. Furuse Y, Sando E, Tsuchiya N, Miyahara R, Yasuda I, Ko YK, et al. Clusters of
442 coronavirus disease in communities, Japan, January–April 2020. Emerg Infect
443 Dis. 2020;26(9):2176–9. doi:10.3201/eid2609.202272 pmid:32521222
444 26. Bodner K, Irvine MA, Kwong JC, Mishra S. Observed negative vaccine
445 effectiveness could be the canary in the coal mine for biases in observational

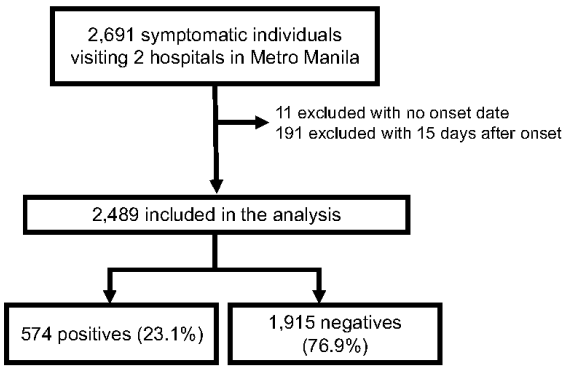
446 COVID-19 studies. Int J Infect Dis. 2023;131:111–4.
447 doi:10.1016/j.ijid.2023.03.022 pmid:36990200
448 27. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg H-D, Krause TG, Mølbak
449 K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron
450 or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273
451 vaccination series: a Danish cohort study. medRxiv 2021.
452 doi:10.1101/2021.12.20.21267966
453 28. Buchan SA, Chung H, Brown KA, Austin PC, Fell DB, Gubbay JB, et al.
454 Estimated effectiveness of COVID-19 vaccines against Omicron or Delta
455 symptomatic infection and severe outcomes. JAMA Netw Open.
456 2022;5(9):e2232760. doi:10.1001/jamanetworkopen.2022.32760 pmid:36136332
457

Fig. 1. Number of reported COVID-19 cases since the beginning of the pandemic and COVID-19 vaccination rate with primary series and first booster in the Philippines



The data are likely underestimated due to reporting constraints, testing/reporting intensity varied substantially over time, and COVID-19 vaccination data are up to 9 March 2023.
Source: Our World in Data [https://ourworldindata.org].

Fig. 2. Flow diagram of the study participants.



468 **Table 1.** Demographic and clinical characteristics of the study participants

Characteristic	All (*n* = 2489)	Test positive (*n* = 574)	Test negative (*n* = 1915)
Age in years, n (%)[a]	35 (27–51)	32 (26–43)	37 (28–52)
18–19	50 (2.0)	16 (2.8)	34 (1.8)
20–29	830 (33.4)	239 (41.6)	591 (30.8)
30–39	594 (23.9)	158 (27.5)	436 (22.8)
40–49	352 (14.1)	69 (12.0)	283 (14.8)
50–59	359 (14.4)	62 (10.8)	297 (15.5)
60–69	194 (7.8)	24 (4.2)	170 (8.9)
70–79	98 (3.9)	6 (1.1)	92 (4.8)
80–89	12 (0.5)	0 (0.0)	12 (0.6)
Sex, *n* (%)			
Male	892 (35.8)	178 (31.0)	714 (37.3)
Female	1597 (64.2)	396 (69.0)	1201 (62.7)
Educational attainment, *n* (%)			
Master's and above	158 (6.4)	51 (8.9)	107 (5.6)
College	1570 (63.1)	458 (79.8)	1112 (58.1)
Vocational	128 (5.1)	18 (3.1)	110 (5.7)
Secondary/high school	526 (21.1)	41 (7.1)	485 (25.3)
Primary/elementary	107 (4.3)	6 (1.1)	101 (5.3)
Comorbidity,[b] *n* (%)			
Yes	877 (35.2)	126 (22.0)	751 (39.2)
No	1612 (64.8)	448 (78.1)	1164 (60.8)
Occupation, *n* (%)			
Health-care worker	1207 (48.5)	400 (69.7)	807 (42.1)
Other	1282 (51.5)	174 (30.3)	1108 (57.9)
Smoking, *n* (%); missing = 7 (0.3%)			
Never-smoker	2042 (82.3)	520 (90.8)	1522 (79.7)
Past smoker	346 (13.9)	35 (6.1)	311 (16.3)
Current smoker	94 (3.8)	18 (3.1)	76 (4.0)
Days from onset to SARS-CoV-2 test	3 (2–5)	2 (2–3)	3 (2–6)
History of close contact, *n* (%)			
Yes	401 (16.1)	149 (26.0)	252 (13.2)
No/unknown	2088 (83.9)	425 (74.0)	1663 (86.8)
SARS-CoV-2 diagnostic test in the past month, *n* (%); missing = 1 (0.0%)			
Yes	599 (22.5)	94 (16.4)	465 (24.3)
No	1929 (77.5)	480 (83.6)	1449 (75.7)
Past SARS-CoV-2 infection, *n* (%)			
No	1801 (72.4)	395 (68.8)	1406 (73.4)
Once	627 (25.2)	164 (28.6)	463 (24.2)
Twice	57 (2.3)	13 (2.3)	44 (2.3)
Three times	4 (0.2)	2 (0.4)	2 (0.1)
Vaccination card carriage, *n* (%)			
Yes	2123 (94.5)	532 (94.7)	1591 (94.5)
No	123 (5.5)	30 (5.3)	93 (5.5)
Number of COVID-19 vaccinations received, *n* (%)			
None	243 (9.8)	12 (2.1)	231 (12.1)
Once (except for Ad26.COV2.S[c])	15 (0.6)	2 (0.4)	13 (0.7)
Twice or received Ad26.COV2.S	682 (27.4)	76 (13.2)	606 (31.6)
First booster received	820 (32.9)	232 (40.4)	588 (30.7)
Second booster received	729 (29.3)	252 (43.9)	477 (24.9)
Vaccine type (primary series), *n* (%)			
AZD1222 (AstraZeneca)	868 (38.6)	265 (47.2)	603 (35.8)
CoronaVac (SinoVac)	828 (36.9)	187 (33.3)	641 (38.1)
BNT162b2 (Pfizer)	249 (11.1)	46 (8.2)	203 (12.1)
mRNA-1273 (Moderna)	159 (7.1)	40 (7.1)	119 (7.1)
Ad26.COV2.S (Janssen/J&J)	50 (2.2)	6 (1.3)	44 (2.6)

Sputnik V (Gameleya)	41 (1.8)	7 (1.3)	34 (2.0)
BBIBP-CorV (Sinopharm)	7 (0.3)	0 (0.0)	7 (0.4)
BBV152 (Bharat BioTech)	1 (0.0)	0 (0.0)	1 (0.1)
Unknown	1 (0.0)	1 (0.2)	0 (0.0)
Heterologous	42 (1.9)	10 (1.8)	32 (1.9)
Vaccine type (first booster), *n* (%)			
BNT162b2 (Pfizer)	1149 (74.2)	381 (78.7)	768 (72.1)
mRNA-1273 (Moderna)	250 (16.1)	67 (13.8)	183 (17.2)
AZD1222 (AstraZeneca)	109 (7.0)	26 (5.4)	83 (7.8)
CoronaVac (SinoVac)	39 (2.5)	10 (2.1)	29 (2.7)
Ad26.COV2.S (Janssen/J&J)	1 (0.1)	0 (0.0)	1 (0.1)
Sputnik V (Gameleya)	1 (0.1)	0 (0.0)	1 (0.1)
Vaccine type (second booster), *n* (%)			
BNT162b2 (Pfizer)	407 (55.8)	141 (56.0)	266 (55.8)
mRNA-1273 (Moderna)	315 (43.2)	111 (44.1)	204 (42.8)
AZD1222 (AstraZeneca)	6 (0.8)	0 (0.0)	6 (1.3)
Sputnik V (Gameleya)	1 (0.1)	0 (0.0)	1 (0.2)

[a] Median (interquartile range).

[b] Comorbidities (self-reported) include hypertension, heart disease, diabetes mellitus, kidney disease, asthma, chronic obstructive pulmonary disease, obesity, cancer, immunodeficiency, and immunosuppressant use.

[c] Primary series is one dose, whereas other vaccine types are two doses

474 **Table 2.** Association between social/behavioural factors and SARS-CoV-2 infection in the Philippines

Social/behavioural factors	Test positive, *n* (%)	Test negative, *n* (%)	Crude odds ratios (95% CI)	Adjusted odds ratios (95% CI)[a]
Cohabitation				
Living by oneself	87 (28.9)	214 (71.1)	1	1
Living with family	244 (16.1)	1276 (84.0)	0.47 (0.35–0.63)	0.86 (0.61–1.24)
Living with people other than family	94 (35.2)	173 (64.8)	1.34 (0.94–1.90)	1.12 (0.74–1.70)
Education				
Primary/elementary	6 (5.6)	101 (94.4)	1	1
Secondary/high school	38 (7.4)	475 (92.6)	1.35 (0.55–3.27)	0.89 (0.34–2.34)
Vocational	16 (13.7)	101 (86.3)	6.22 (2.71–14.31)	1.30 (0.48–3.50)
College	343 (27.0)	928 (73.0)	6.39 (2.45–16.65)	1.12 (0.35–3.54)
Post-graduate/Master's/PhD	22 (27.5)	58 (72.5)	2.67 (1.00–7.09)	1.20 (0.39–3.71)
Monthly household income				
Unemployed and no income	5 (2.9)	166 (97.1)	1	1
<10 000 PHP (<176.5 USD)	17 (6.1)	261 (93.9)	2.16 (0.78–5.97)	0.93 (0.25–3.51)
10 000–<50 000 PHP (176.5–882.6 USD)	169 (18.4)	748 (81.6)	7.50 (3.03–18.54)	1.08 (0.29–3.97)
50 000–<80 000 PHP (882.6–1412.2 USD)	150 (34.1)	290 (65.9)	17.17 (6.90–42.71)	1.31 (0.34–5.06)
>80 000 PHP (>1412.2 USD)	78 (34.8)	146 (65.2)	17.74 (6.99–45.00)	1.39 (0.35–5.47)
Work or school				
No work/school	49 (6.7)	682 (93.3)	1	1
Have work/school	376 (27.7)	978 (72.2)	5.35 (3.91–7.32)	1.83 (1.09–3.07)
Health-care workers				
Not health-care workers	153 (12.7)	1055 (87.3)	1	1
Health-care workers	272 (30.9)	608 (69.1)	3.08 (2.47–3.85)	1.45 (1.03–2.06)
Going out to eat/drink in the daytime with alcohol				
No	422 (20.4)	1646 (79.6)	1	1
Yes	3 (15.0)	17 (85.0)	0.69 (0.20–2.36)	0.36 (0.09–1.38)
Going out to eat/drink in the evening/night with alcohol				
No	393 (19.9)	1585 (80.1)	1	1
Yes	32 (29.1)	78 (70.9)	1.65 (1.08–2.53)	1.24 (0.74–2.06)
Going out to eat/drink in the daytime without alcohol				
No	259 (16.4)	1322 (83.6)	1	1
Yes	166 (32.7)	259 (16.4)	2.48 (1.98–3.12)	0.90 (0.64–1.25)
Going out to eat/drink in the evening/night without alcohol				
No	296 (17.3)	1421 (82.8)	1	1

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Yes	129 (34.8)	296 (17.2)	2.56 (2.00–3.28)	1.31 (0.94–1.82)
Going out to café				
No	346 (19.5)	1425 (80.5)	1	1
Yes	79 (24.9)	238 (75.1)	1.37 (1.03–1.81)	0.97 (0.69–1.35)
Max. number of people attended the gatherings with food/drinks including oneself				
<5 people	65 (22.9)	219 (77.1)	1	1
≥5 people	15 (44.1)	19 (55.9)	2.66 (1.28–5.53)	2.58 (1.14–5.83)
Max. time spent at the gatherings with food/drinks attended including oneself				
<2 hours	27 (17.7)	126 (82.4)	1	1
≥2 hours	53 (32.3)	111 (67.7)	2.23 (1.31–3.78)	1.75 (0.95–3.22)
Ordering takeout				
No	290 (21.3)	1075 (78.8)	1	1
One	13 (22.8)	44 (77.2)	1.10 (0.58–2.06)	1.12 (0.52–2.39)
Twice	59 (21.0)	222 (79.0)	0.99 (0.72–1.35)	1.14 (0.78–1.67)
Three times or more	63 (16.4)	322 (83.6)	0.72 (0.54–0.98)	0.98 (0.68–1.40)
Food delivery				
No	215 (15.3)	1187 (84.6)	1	1
One	5 (9.8)	46 (90.2)	0.60 (0.24–1.53)	0.34 (0.12–0.93)
Twice	35 (27.6)	92 (72.4)	2.10 (1.39–3.18)	1.10 (0.67–1.80)
Three times or more	170 (33.5)	338 (66.5)	2.78 (2.20–3.51)	1.18 (0.85–1.62)
Eating out by oneself				
No	410 (20.6)	1579 (79.4)	1	1
Yes	15 (15.2)	84 (84.9)	0.69 (0.39–1.20)	0.81 (0.43–1.53)
Going to mall				
No	148 (14.4)	878 (85.6)	1	1
Yes	277 (26.1)	785 (73.9)	2.09 (1.68-2.61)	1.07 (0.80-1.42)
Going to gym				
No	390 (19.8)	1578 (80.2)	1	1
Yes	35 (29.2)	85 (70.8)	1.67 (1.11-2.51)	1.53 (0.94-2.49)
Going to karaoke				
No	411 (20.1)	1635 (79.9)	1	1
Yes	14 (33.3)	28 (66.7)	1.99 (1.03-3.81)	1.76 (0.81-3.86)
Going to church				
No	308 (22.4)	1069 (77.6)	1	1
Yes	117 (16.5)	594 (83.5)	0.68 (0.54-0.86)	0.89 (0.66-1.20)

475 [a] Adjusted for age, sex, comorbidities, prior infection, week of testing, study site, vaccine by dosage.

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Table 3. Association between COVID-19 vaccination (by doses and time since vaccination) and SARS-CoV-2 infection in the Philippines

Vaccination status	Test positive	Test negative	Crude odds ratios (95% CI)[a]	Adjusted odds ratios (95% CI)[a]	VE % (95% CI)
Comparison between vaccinated and unvaccinated					
Unvaccinated	11	171	1	1	N/A
Dose 1 or ≤13 d after primary series	2	11	2.83 (0.56–14.36)	2.08 (0.35–12.4)	Not calculated[b]
14 d to 3 mo after primary series	0	12	N/A	N/A	Not calculated[b]
3–6 mo after primary series	2	42	0.74 (0.16–3.47)	0.69 (0.13–3.59)	Not calculated[b]
6–9 mo after primary series	6	73	1.28 (0.46–3.59)	0.78 (0.25–2.42)	Not calculated[b]
9–12 mo after primary series	17	114	2.32 (1.05–5.13)	2.57 (1.06–6.19)	Not calculated[b]
>12 mo after primary series	29	157	2.87 (1.39–5.94)	1.43 (0.59–3.50)	Not calculated[b]
≤13 d after first booster	0	0	N/A	N/A	Not calculated[b]
14 d to 3 mo after first booster	5	23	3.38 (1.08–10.60)	0.96 (0.25–3.64)	Not calculated[b]
3–6 mo after first booster	12	69	2.70 (1.14–6.42)	1.07 (0.38–3.02)	Not calculated[b]
>6 mo after first booster	160	348	7.15 (3.78–13.52)	1.57 (0.66–3.72)	Not calculated[b]
≤13 d after second booster	2	3	10.36 (1.57–68.6)	2.94 (0.35–24.55)	Not calculated[b]
14 d to 3 mo after second booster	8	31	4.01 (1.49–10.77)	0.77 (0.24–2.50)	Not calculated[b]
3–6 mo after second booster	78	153	7.93 (4.06–15.45)	1.46 (0.59–3.59)	Not calculated[b]
>6 mo after second booster	121	230	8.18 (4.28–15.64)	2.05 (0.83–5.09)	
Comparison between the first booster and 3 months after primary series					
>3 mo after primary series	54	386	1	1	N/A
≤13 d after first booster	0	0	N/A	N/A	N/A
14 d to 3 mo after first booster	5	23	1.55 (0.57–4.26)	0.68 (0.21–2.20)	32 (-120–79)
3–6 mo after first booster	12	69	1.24 (0.63–2.44)	0.73 (0.33–1.60)	27 (-60–67)
>6 mo after first booster	160	348	3.29 (2.34–4.62)	1.08 (0.67–1.72)	-8 (-72–33)
Comparison between the second booster and 3 months after the first booster					
>3 mo after first booster	172	417	1	1	N/A
≤13 d after second booster	2	3	1.62 (0.27–9.76)	1.96 (0.27–14.0)	Too few
14 d to 3 mo after second booster	8	31	0.63 (0.28–1.39)	0.52 (0.22–1.23)	48 (-23–78)
3–6 mo after second booster	78	153	1.24 (0.89–1.71)	0.98 (0.66–1.43)	2 (-43–34)
>6 mo after second booster	121	230	1.28 (0.96–1.69)	1.34 (0.94–1.91)	-34 (-91–6)

VE, vaccine effectiveness; CI, confidence interval

[a] Adjusted for age, sex, comorbidities, history of close contact, SARS-CoV-2 testing in the past month, prior infection, education, work/school, going out to eat/drink in the evening/night without alcohol, week of testing, study site.

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Factors associated with SARS-CoV-2 infection in the Philippines

[b] not calculated due to high risk of bias

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Paper 9: VE against severe disease in the Philippines

Arashiro T*, et al. Factors associated with COVID-19 in-hospital death and COVID-19 vaccine effectiveness against COVID-19 hospitalization in the Philippines during pre-Omicron and Omicron period: a descriptive and case-control study (MOTIVATE-P study) **(**Under internal clearance; ***first and corresponding author)**

PhD candidate contributions:
Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is the result of Objective 3E.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The Lancet Regional Health - Western Pacific
Please list the paper's authors in the intended authorship order:	Takeshi Arashiro, Rontgene Solante, Ana Ria Sayo, Reby Marie Garcia, Marie Kris, Shuichi Suzuki, Greco Mark Malijan, Mary Jane Salazar, Mary Ann Salazar, Grace Devota Go, Edna Miranda, Michelle Carandang-Cuvin, Joy

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Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualization (main), design (main), recruitment of participating healthcare facilities (sub), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported research nurses), data analysis (main), writing – original draft (main), funding acquisition (main: WISE, WHO; support: AMED)

SECTION E

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Date	May 11, 2024

Supervisor Signature	Chris Smith
Date	May 15, 2024

Factors associated with COVID-19 in-hospital death and COVID-19 vaccine effectiveness against COVID-19 hospitalization in the Philippines during pre-Omicron and Omicron period: a case-control study (MOTIVATE-P study)

Running title: COVID-19 in-hospital death and vaccine effectiveness in the Philippines

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121 **Keywords:** severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus

122 disease (COVID-19); epidemiological study; vaccine effectiveness; SARS-CoV-2 variants;

123 Philippines

Abstract (250/250 words)

Background: COVID-19 vaccine effectiveness studies against severe disease are limited in low- and middle-income countries, especially in Southeast Asia.

Methods: A descriptive and case-control study was done in the Philippines during the pre-Omicron and Omicron periods. Factors associated with in-hospital death were elucidated. After restricting to patients >50 years of age, VEs were estimated for various severe hospitalization outcomes.

Findings: The analysis included 1782 COVID-19 patients for description (366 [20.5%] in-hospital death) and 1059 patients for VE estimate (869 [82.1%] cases; among vaccinees, 49–57% inactivated vaccines, 28–32% viral vector vaccines, 10–20% mRNA vaccines). Older age, with tuberculosis (aOR 2.45 [95%CI 1.69–3.57]), with HIV (aOR 3.30 [95%CI 2.03–5.37]), and current smokers (aOR 2.65 [95%CI 1.72–4.10]) were some factors associated with in-hospital death. In pre-Omicron, 2 doses provided high protection for a median of 2 months (hospitalization: 85.4% [95%CI 35.9–96.7%], oxygen requirement: 91.0% [95%CI 49.4–98.4%]; IMV: 97.0% [95%CI: 65.7–99.7%]; death: 96.5% [95%CI: 67.1–99.6%]). During Omicron, 2 doses provided mid-high protection for a median of 6–9 months (hospitalization: 70.2% [95%CI 27.0–87.8%], oxygen requirement: 71.4% [95%CI 29.3–88.4%]; IMV: 72.7% [95%CI: -11.6–93.3%]; death: 58.9% [95%CI: -82.8–90.8%]).

Interpretation: VEs of 2 doses against severe COVID-19 outcomes were consistently high for 6 months during both pre-Omicron and Omicron periods in the setting where approximately half of the vaccinees received inactivated vaccines as primary series. Our findings will inform/defend policies in LMICs, where many rolled out inactivated vaccines but with scarce real-world data.

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Research in context

Evidence before this study

There have been numerous studies to evaluate VE, mostly from high-income countries (HICs), but the evidence is very limited in low and middle-income countries (LMICs). The International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health is conducting a weekly living systematic review together with the World Health Organization and Coalition for Epidemic Preparedness Innovations. As of late May 2024, they have identified 592 studies that met their criteria. Among these, there were 214 studies from the European Region and 257 studies from the Region of the Americas. In contrast, there were 53 studies from the Western Pacific Region. Among these, there is one from lower-middle-income countries, where the Philippines is currently categorized. This study was done in the Philippines, but was a household transmission study nested in phase 2/3 efficacy study of the adjuvanted recombinant protein-based COVID-19 vaccine SCB-2019. As a reference, there were 10 studies from the South-East Asia Region, 7 studies from the African Region, and 30 studies from the East Mediterranean Region. These show clear disparities in the amount of COVID-19 vaccine effectiveness studies despite the difference in the types of vaccines distributed for primary series (inactivated vaccines in LMICs vs mRNA vaccines in high-income countries) and population distribution. Also, specifically for inactivated vaccines, there are variable VE against hospitalization outcomes and data against the Omicron variant is especially limited.

Added value of this study

We first identified multiple factors associated with in-hospital death, some of which may be unique to the situation in LMICs including comorbidities such as tuberculosis and HIV. VEs of 2 doses against various severe COVID-19 outcomes were consistently high for 6 months during both pre-Omicron and Omicron periods in the setting where approximately half of the

vaccinees received inactivated vaccines as primary series. Our findings may be of use to LMICs, where many rolled out inactivated vaccines but with scarce real-world data, and may inform/defend policy.

Implications of all the available evidence

Numerous pieces of evidence collectively support the efficacy and effectiveness of primary series COVID-19 vaccines, including both mRNA and inactivated vaccines, to protect against severe disease. However, additional studies will be important to further inform and defend vaccination policies in various settings, especially in the context of LMICs. Another important challenge will be to conduct such studies in a timely manner for future health emergencies.

Main text (3122 words)

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally.[1] Once the COVID-19 vaccines were rolled out based on trial results,[2-7] there was a need to monitor the real-world effectiveness of the vaccines (vaccine effectiveness; VE), given concerns due to waning immunity and the emergence of variants with immune escape capacity.[8-12] There have been numerous studies to evaluate VE, mostly from high-income countries (HICs), but the evidence is very limited in low and middle-income countries (LMICs). This is especially true for Southeast Asia (specifically, the Western Pacific Region) and Africa.[13] It was considered valuable for more LMICs, especially LICs and lower-middle-income countries, to conduct VE studies for several reasons, including: (1) evaluation of vaccines that are mainly distributed in these countries, (2) confirmation that the vaccines remain active through distribution networks (e.g., no cold chain breach), (3) considerably different cumulative infection burdens among countries (e.g., individuals with prior infection are protected against subsequent infection/disease), (4) substantial variation in PHSMs and policies/risk communication activities among countries, (5) vaccine confidence within and among surrounding countries, and (6) capacity building to conduct operational research to inform public health response for COVID-19 as well as future epidemics and pandemics. Also, specifically for inactivated vaccines, which were widely rolled out in LMICs, there were highly variable VE against hospitalization outcomes reported from previous reports and data against the Omicron variant is especially limited.[13-14] This variability in hospitalization outcomes may be due to varying criteria for hospitalization and incidental diagnosis of SARS-CoV-2 infection during routine admission screening.[15-16] This can potentially result in lower VE estimates against severe disease due to generally lower VE against infection than

209 against severe disease.[13,15,16] Therefore, we initiated a study to describe patients hospitalized
210 with COVID-19 and to evaluate COVID-19 vaccine effectiveness against hospitalization in
211 the Philippines during pre-Omicron and Omicron periods using various outcomes, including
212 more severe and specific outcomes such as oxygen use and invasive mechanical ventilation
213 use.

Methods

COVID-19 epidemiology and vaccination rollout in the Philippines

The epidemic curve of reported COVID-19 cases and vaccination rollout in the Philippines are illustrated together with the study period between 1 March 2021 (when the COVID-19 vaccination rollout started in the Philippines) and 31 March 2023 (before Omicron subvariant XBB became dominant) in **Figure 1**. In the Philippines, the primary series (1 dose for Janssen and two doses for all other vaccine types) rollout started on 1 March 2021.[17] The first booster dose rollout began on 16 November 2021 among healthcare workers (HCWs), on 22 November 2021 among senior citizens and immunocompromised persons, and on 3 December 2021 among all adults aged 18 years or above. The second booster dose rollout started on 25 April 2022 among HCWs and individuals who were ≥60 years old and on 27 July 2022 among individuals who were ≥50 years old and individuals aged 18-49 years with comorbidities. The primary series followed manufacturer-recommended intervals. Based on the genomic surveillance data, the Omicron variant started to be detected in the Philippines and quickly replaced the Delta variant in November 2021.[18] Therefore, we defined 1 March 2021 to 31 October 2021 as the pre-Omicron (Alpha, Gamma, Delta) period and 1 November 2021 to 31 March 2023 as the Omicron period.

Study design and setting

Our study, Moderate-to-severe disease requiring Oxygen Therapy, Intubation, and Ventilation And The Effectiveness of COVID-19 vaccines in the Philippines (MOTIVATE-P study), is a single-center study at San Lazaro Hospital (SLH) in Manila to describe characteristics and outcomes of COVID-19 patients requiring hospitalization and estimate the real-world effectiveness of COVID-19 vaccines against severe disease. SLH routinely admitted patients with COVID-19 and pneumonia caused by other pathogens and routinely

tested individuals admitted using polymerase chain reaction (PCR) for clinical diagnostic and screening purposes.[19] It has also been functioning as one of the main COVID-19 response sites in the country. We followed the same design as the study conducted and published previously by some of the authors in Japan.[15] Data were collected via a review of medical charts and other relevant hospital documents by trained research nurses. To ensure the quality of data entry, ten charts were randomly selected soon after the initiation of the study, entered by two different nurses, and checked for data entry consistency.

Inclusion and exclusion criteria

The inclusion criteria were SARS-CoV-2-positive hospitalized patients and SARS-CoV-2-negative hospitalized pneumonia patients. Pneumonia caused by tuberculosis was not included as the clinical presentation would be different from the one caused by COVID-19 pneumonia or common bacterial pneumonia with acute onset. Patients were excluded for the following reasons: onset during hospitalization; tested ≥15 days before or ≥15 days after admission; and unknown test date. Additionally, for the VE analysis, patients were further excluded for the following reasons: being <50 years of age, past SARS-CoV-2 infection, and (for controls) diagnosis of pneumococcal pneumonia or influenza. The rationale for including patients who were tested up to 14 days before admission and excluding those who were tested ≥15 days before admission is that it takes from a few days to 2 weeks from symptom onset for patients to develop severe disease, and these patients may be tested right after onset and later hospitalized. The rationale for restricting to individuals <50 years of age was to aim for better internal validity among most at risk of severe COVID-19, and because people aged 50 years and above were eligible for the second booster. This, we considered, would allow us to reduce confounding through different socioeconomic factors and vaccine prioritization. Finally, co-circulation of influenza and COVID-19 can result in biased VE estimates as the

propensity to get vaccinated may be similar for COVID-19 and influenza vaccines.[20] In theory, the same concern applies to *Streptococcus pneumoniae* pneumonia and pneumococcal vaccination. Therefore, we excluded patients with pneumococcal pneumonia or influenza.

Classification of exposures and outcome for the vaccine effectiveness analysis

Vaccination status (number of doses, vaccine type [e.g., manufacturer], and vaccination dates) was recorded from the case investigation form (which was mandatory to be completed when conducting SARS-CoV-2 testing during the study period and generally filled out by referencing the vaccination card), the medical charts, and other relevant hospital documents and checked for plausibility. Vaccination status was first classified by doses. Also, to assess the duration of protection, the status was classified into 11 categories by time since vaccination: (1) not vaccinated, (2) ≤13 days after dose 1, (3) ≥14 days after dose 1 or ≤13 days after dose 2 (partially vaccinated; (2) and (3) were combined for Omicron period due to small sample sizes in these categories), (4) 14 days–6 months (14–180 days) after dose 2, (5) >6 months (181 days) after dose 2, (6) ≤13 days after dose 3 (first booster dose), (7) 14 days–6 months (14–180 days) after dose 3, (8) >6 months (181 days) after dose 3, (9) ≤13 days after dose 4 (second booster dose), (10) 14 days–6 months (14–180 days) after dose 4, (11) >6 months (181 days) after dose 4.

Patients who tested positive before or after admission based on the above inclusion and exclusion criteria were defined as cases; patients who tested negative before or after admission based on the above criteria were defined as controls.

To measure VE, we used various severe outcomes, including all COVID-19 hospitalizations, disease requiring oxygen therapy, disease requiring invasive mechanical ventilation, death, outcome restricting to “true” severe COVID-19 (where oxygen requirement is due to COVID-19 rather than other differential diagnoses), and progression from oxygen use to

mechanical ventilation or death. “True” severe COVID-19 outcome was based on the judgment of the treating physicians (chart record) and trained nurses responsible for chart review. The chart review was conducted between June 2023 and May 2024 to ensure that at least 6 months had passed since participants were hospitalized to allow for sufficient time to reach the final discharge outcome for participants.

Data description and analysis

First, characteristics of SARS-CoV-2-positive hospitalized patients were described overall and by pre-Omicron and Omicron periods. Logistic regression was used to estimate odds ratios for in-hospital death. The model was adjusted for age group (categorical), sex, risk score categories (0, 1, 2, 3-4, 5+; categorical [elaborated later]), calendar week of hospitalization (biweekly), and vaccine doses (except for the factor of interest). The risk score for severe disease developed in a study published by some of the authors in Japan was incorporated as a covariate.[15,21,22] Here, we assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, tuberculosis, immunocompromised condition (HIV infection or other immunodeficiency, or immunosuppressant use), pregnancy while hospitalized, or overweight; the points were added up to calculate the risk score for each patient.

Second, for the VE analysis, patient characteristics were described overall and by case/control status. Then, logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age group (categorical), sex, risk score categories (0, 1, 2, 3-4, 5+; categorical), smoking history, and

calendar week of hospitalization (biweekly). These potential confounders were determined *a priori* based on published reports.[10,15] VE was estimated using the following equation: VE = (1 – adjusted odds ratio [aOR]) × 100%. Data analyses were performed using STATA version 18.0.

Ethics statement

Ethics approval was obtained from San Lazaro Hospital. Informed consent was deemed unnecessary due to the retrospective nature of the study.

Results

The study participants

A total of 1800 SARS-CoV-2-positive hospitalized patients and 637 SARS-CoV-2-negative hospitalized pneumonia patients were initially included. For the description of SARS-CoV-2 hospitalization, after excluding 18 patients based on exclusion criteria, the final analysis included 1782 patients: 1342 for the pre-Omicron period and 440 for the Omicron period (**Figure 2**). For the cases of VE analysis, after further excluding 913 patients based on exclusion criteria, the final analysis included 869 patients: 750 for the pre-Omicron period and 119 for the Omicron period. For the controls of VE analysis, after excluding 447 patients based on exclusion criteria, the final analysis included 190 patients: 55 for the pre-Omicron period and 135 for the Omicron period.

Description of SARS-CoV-2-positive hospitalized patients

The median age (interquartile range [IQR]) was 53 (37–66) for the pre-Omicron period and 33 (24–54) for the Omicron period (**Table 1**). Most individuals had at least one risk factor for severe COVID-19 (1078 [80.3%] for the pre-Omicron period and 315 [71.6%] for the Omicron period). The majority of individuals received oxygen therapy (1299 [72.9%]), and some received invasive mechanical ventilation (263 [14.8%]). Most individuals improved and discharged (1074 [80.0%] for the pre-Omicron period and 320 [72.7%] for the Omicron period) (**Table 1**). However, in-hospital death occurred in 252 (18.8%) for the pre-Omicron period and 114 (25.9%) for the Omicron period.

Factors associated with in-hospital death among SARS-CoV-2-positive hospitalized patients

Among hospitalized cases, older age was associated with in-hospital death in an incremental manner (compared to individuals who were in their 20s; adjusted odds ratio [aOR] for 40s:

2.03 [95% confidence interval {CI} 1.11–3.71]; aOR for 50s: 2.01 [95% CI 1.10–3.65]; aOR for 60s: 2.94 [95% CI 1.10–3.65]; aOR for 70s: 4.54 [95% CI 2.43–8.46]; aOR for 80: 4.96 [95% CI 2.43–10.1]; aOR for <10 years of age: 0.31 [95% CI 0.10–0.97]) (**Table 1**). Other factors associated with in-hospital death included male sex (aOR 1.60 [95% CI 1.17–2.17]), with chronic kidney disease as comorbidity (aOR 4.39 [95% CI 1.52–12.67]), with tuberculosis as comorbidity (aOR 2.45 [95% CI 1.69–3.57]), with HIV infection as comorbidity (aOR 3.30 [95% CI 2.03–5.37]), hospitalization in the past year (aOR 3.38 [95% CI 2.01–5.67]), and current smoker (aOR 2.65 [95% CI 1.72–4.10]) (**Table 1**).

Baseline characteristics for the vaccine effectiveness analysis

The median age (interquartile range [IQR]) was 64 (57–71) for the pre-Omicron period and 64 (57–72) for the Omicron period and it was similar between cases and controls (**Table 2**). Most individuals had at least one risk factor for severe COVID-19 (716 [88.9%] for the pre-Omicron period and 228 [89.8%] for the Omicron period). During the pre-Omicron period, 118 (56.7%) received CoronaVac (SinoVac), 43 (20.7%) received AZD1222 (AstraZeneca), 24 (11.5%) received Ad26.COV2.S (Janssen/J&J), 10 (4.8%) received BNT162b2 (Pfizer), 7 (3.4%) received mRNA-1273 (Moderna), and 2 (1.0%) received Sputnik V (Gameleya) with 4 (1.9%) unknown vaccine type (**Table 2**). During the Omicron period, as primary series, 72 (49.3%) received CoronaVac (SinoVac), 23 (15.3%) received AZD1222 (AstraZeneca), 18 (12.3%) received BNT162b2 (Pfizer), 18 (12.3%) received Ad26.COV2.S (Janssen/J&J), 10 (6.9%) received mRNA-1273 (Moderna), 1 (0.7%) received Sputnik V (Gameleya), and 1 (0.7%) received BBIBP-CorV (Sinopharm) with 3 (2.1%) unknown vaccine type (**Table 2**). As a first booster, 14 (48.3%) received BNT162b2 (Pfizer), 6 (20.7%) received AZD1222 (AstraZeneca), and 5 (17.2%) received mRNA-1273 (Moderna) with 4 (13.8%) unknown

vaccine type. As a second booster, 3 (75.0%) received BNT162b2 (Pfizer) and 1 (25.0%) received mRNA-1273 (Moderna) (none with unknown vaccine type).

Vaccine effectiveness against all COVID-19 hospitalization, COVID-19 requiring oxygen therapy, COVID-19 requiring mechanical ventilation, and fatal COVID-19

During the pre-Omicron period, VE estimates for 2 doses were 85.4% (95%CI 35.9–96.7%) against all COVID-19 hospitalization, 91.0% (95%CI 49.4–98.4%) against COVID-19 requiring oxygen therapy, 97.0% (95% CI: 65.7–99.7%) against COVID-19 requiring invasive mechanical ventilation, and 96.5% (95% CI: 67.1–99.6%) against fatal COVID-19 (**Table 3**). During the Omicron period, VE estimates for 2 doses were 70.2% (95%CI 27.0–87.8%) against all COVID-19 hospitalization, 71.4% (95%CI 29.3–88.4%) against COVID-19 requiring oxygen therapy, 72.7% (95% CI: -11.6–93.3%) against COVID-19 requiring invasive mechanical ventilation, and 58.9% (95% CI: -82.8–90.8%) against fatal COVID-19 (**Table 3**). During the Omicron period, some individuals received 3 or 4 doses, but the confidence intervals were very wide due to the small sample size. Similarly, we attempted to estimate VE by time since vaccination, but failed to estimate some, and even if we could, the confidence intervals were wide (**Supplementary Table 1**).

Discussion

In this descriptive and case-control study in the Philippines, we described the characteristics and outcomes of COVID-19 patients requiring hospitalization and estimated the real-world effectiveness of COVID-19 vaccines against severe disease during pre-Omicron and Omicron periods.

Among SARS-CoV-2-positive hospitalized patients, in-hospital death occurred in 20.5%, which was in line with what was observed in the systematic review/meta-analysis published early in the pandemic,[23] although variable hospitalization criteria among countries and hospitals warrant caution in interpretation. We found several factors associated with in-hospital death, including increasing age, male sex (aOR 1.60), CKD (aOR 4.39), tuberculosis (aOR 2.45), with HIV (aOR 3.30), hospitalization in the past year (aOR 3.38), and current smokers (aOR 2.65). All these are in line with previous reports,[21,22,24-26] although these findings were new in LMICs in the Western Pacific Region and Southeast Asia.

Next, in the VE analysis, during the pre-Omicron period, over half (56.7%) of the vaccinees received CoronaVac, 32.2% received viral vector vaccines, and 8.2% received mRNA vaccines (**Table 2**). With these vaccine types, 2 doses provided high (85–97%) protection for a range of severe COVID-19 outcomes during the pre-Omicron (Alpha, Gamma, Delta) period for the approximate median interval since the last vaccination of 2 months (all hospitalization: 85.4%, oxygen requirement: 91.0% [restricted to "true" severe COVID-19: 90.9%]; invasive mechanical ventilation: 97.0%; fatal: 96.5%) (**Table 3**). These findings were in agreement with other observational studies.[13] including studies that assessed inactivated vaccines such as CoronaVac.[14] Also, the trend towards higher VE for more severe and specific outcomes was observed.[15,16]

During the Omicron period, approximately half (49.3%) of the primary series vaccinees received CoronaVac, 27.6% received viral vector vaccines, and 19.2% received mRNA

vaccines (**Table 2**). For boosters, the majority received either mRNA or viral vector vaccines (only mRNA vaccines for the second booster doses). Here, 2 doses also provided variable moderate-to-high (59–77%) protection (all hospitalization: 70.2%, oxygen requirement: 71.4% [restricted to "true" severe COVID-19: 76.9%]; invasive mechanical ventilation: 72.7%; fatal: 58.9% [some with wide CI]) (**Table 2**). Numerically lower VE against more severe outcomes such as mechanical ventilation and death may be due to a longer period since the last vaccination (median interval of approximately 9 months vs. 6 months) in addition to small sample sizes. Unfortunately, we could not estimate VE for booster doses, VE by vaccine type (e.g., manufacturers), and VE by time since vaccination in detail due to sample size limitation.

Limitations

This study has several limitations. First, biases, confounding, and misclassifications inherent in observational studies are possible. However, using specific and severe outcomes, we aimed to minimize the inclusion of incidental SARS-CoV-2 positive cases which could occur as admission screening was in place at the time of the study. Second, the current hospital-based case-control study was not strictly a test-negative design as controls included all patients who required oxygen even for severe outcomes such as mechanical ventilation use and death. However, individuals who require oxygen therapy are likely to seek care regardless of SARS-CoV-2 infection or vaccination status due to shortness of breath and other manifestations, resulting in the same advantage of control for healthcare-seeking behavior. Third, the present study was a single-center study, and thus, the results may not be generalizable to the whole country. Fourth, wide CIs for some estimates warrant careful interpretation of point estimates and the small sample size in some multivariable models resulted in possible sparse data bias. Fifth, our analysis was a complete case analysis with more missing data during the pre-

Omicron period, as the first version of the case investigation form for SARS-CoV-2 testing used during this period did not include vaccination information. However, it is possible that these patients with missing data were unvaccinated (being early in the course of the vaccination rollout) and we obtained very similar VE estimates for various outcomes when we treated missing as unvaccinated (data not shown). Also, this missing proportion is comparable to data-linkage studies.[27] Sixth, we could not classify individual COVID-19 cases as infected with the pre-Omicron or Delta variant. Finally, our VE estimates were short- to mid-term.

Conclusions

In this descriptive and case-control study in the Philippines, we identified increasing age, male sex, certain comorbidities (CKD, tuberculosis, and HIV), hospitalization in the past year, and current smokers as factors associated with in-hospital death among hospitalized COVID-19 patients. Also, VE estimates against severe COVID-19 requiring hospitalization, oxygen, mechanical ventilation, and death were high for 6 months during both pre-Omicron and Omicron periods in the setting where over half of the vaccinees receiving inactivated vaccines as primary series. Our findings will inform policies in lower-middle and low-income countries where many rolled out inactivated vaccines but with scarce real-world data.

Conflicts of interest

Authors declare no conflicts of interest.

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476 **References**

477 1. Coronavirus disease (COVID-19) pandemic *[Internet]*. World Health Organization;
478 2024. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-
479 2019. Accessed May 10, 2024.
480 2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA
481 Covid-19 vaccine. *N Engl J Med.* 2020;383(27):2603–15.
482 https://doi.org/10.1056/NEJMoa2034577.
483 3. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-
484 CoV-2 vaccine. *N Engl J Med.* 2021;384(5):403–16.
485 https://doi.org/10.1056/NEJMoa2035389.
486 4. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2
487 mRNA Covid-19 vaccine through 6 months. *N Engl J Med.* 2021;385(19):1761–73.
488 https://doi.org/10.1056/NEJMoa2110345.
489 5. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Adnerson EJ, et al.
490 Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N*
491 *Engl J Med.* 2021;385(19):1774–85. https://doi.org/10.1056/NEJMoa2113017.
492 6. Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on
493 Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA.*
494 2021;326(1):35-45. https://doi.org/10.1001/jama.2021.8565.
495 7. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated
496 whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind,
497 randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296):213-
498 222. https://doi.org/10.1016/S0140-6736(21)01429-X.

8. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med.* 2021;385(24):e83. https://doi.org/10.1056/NEJMoa2114114.
9. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet.* 2021;398(10309):1407–16. https://doi.org/10.1016/S0140-6736(21)02183-8.
10. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med.* 2022;386(16):1532–46. https://doi.org/10.1056/NEJMoa2119451.
11. Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. *JAMA.* 2022;327(7):639–51. https://doi.org/10.1001/jama.2022.0470.
12. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Coronavirus disease 19 (COVID-19) vaccine effectiveness against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during Delta-dominant and Omicron-dominant periods in Japan: a multicenter prospective case-control study (FASCINATE Study). *Clin Infect Dis.* 2023;76(3):e108–15. https://doi.org/10.1093/cid/ciac635.
13. VIEW-hub: COVID-19 data, vaccine effectiveness studies *[Internet]*. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health; 2024. Available from: https://view-hub.org/covid-19/effectiveness-studies. Accessed May 10, 2024.
14. Law M, Ho SSH, Tsang GKC, et al. Efficacy and effectiveness of inactivated vaccines against symptomatic COVID-19, severe COVID-19, and COVID-19 clinical outcomes in

524 the general population: a systematic review and meta-analysis. *Lancet Reg Health West*
525 *Pac.* https://doi.org/10.1016/j.lanwpc.2023.100788.
526 15. Arashiro T, Miwa M, Nakagawa H, et al. COVID-19 vaccine effectiveness against
527 severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death
528 in Japan: A multicenter case-control study (MOTIVATE study). *Vaccine*.
529 2024;42(3):677-688. https://doi.org/10.1016/j.vaccine.2023.12.033.
530 16. Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19
531 vaccines against Omicron and Delta hospitalisation, a test negative case-control study.
532 *Nat Commun.* 2022;13(1):5736. https://doi.org/10.1038/s41467-022-33378-7.
533 17. Updates on COVID-19 vaccines *[Internet]*. Department of Health, Philippines; 2023.
534 Available from: https://doh.gov.ph/vaccines. Accessed May 10, 2024.
535 18. hCoV-19 variants dashboard *[Internet]*. GISAID; 2023. Available from:
536 https://gisaid.org/hcov-19-variants-dashboard/. Accessed May 10, 2024.
537 19. Salva EP, Villarama JB, Lopez EB, et al. Epidemiological and clinical characteristics of
538 patients with suspected COVID-19 admitted in Metro Manila, Philippines. *Trop Med*
539 *Health.* 2020;48(1):51. https://doi.org/10.1186/s41182-020-00241-8.
540 20. Doll MK, Pettigrew SM, Ma J, Verma A. Effects of Confounding Bias in Coronavirus
541 Disease 2019 (COVID-19) and Influenza Vaccine Effectiveness Test-Negative Designs
542 Due to Correlated Influenza and COVID-19 Vaccination Behaviors. *Clin Infect Dis.*
543 2022;75(1):e564-e571. https://doi.org/10.1093/cid/ciac234.
544 21. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-
545 related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436.
546 https://doi.org/10.1038/s41586-020-2521-4.
547 22. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID)
548 for risk of hospital admission and mortality from coronavirus 19 in adults: national

549 derivation and validation cohort study. *BMJ.* 2020;371:m3731.
550 https://doi.org/10.1136/bmj.m373.
551 23. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review
552 and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis.* 2021;21(1):855.
553 https://doi.org/10.1186/s12879-021-06536-3.
554 24. Western Cape Department of Health in collaboration with the National Institute for
555 Communicable Diseases, South Africa. Risk Factors for Coronavirus Disease 2019
556 (COVID-19) Death in a Population Cohort Study from the Western Cape Province,
557 South Africa. *Clin Infect Dis.* 2021;73(7):e2005-e2015.
558 https://doi.org/10.1093/cid/ciaa1198.
559 25. Bertagnolio S, Thwin SS, Silva R, et al. Clinical features of, and risk factors for, severe
560 or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data
561 from the WHO Global Clinical Platform of COVID-19. *Lancet HIV.* 2022;9(7):e486-
562 e495. https://doi.org/10.1016/S2352-3018(22)00097-2.
563 26. Patanavanich R, Siripoon T, Amponnavarat S, Glantz SA. Active Smokers Are at Higher
564 Risk of COVID-19 Death: A Systematic Review and Meta-analysis. *Nicotine Tob Res.*
565 2023;25(2):177-184. https://doi.org/10.1093/ntr/ntac085.
566 27. Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe
567 disease by Covid-19 vaccines. *N Engl J Med.* 2022;386(4):340–50.
568 https://doi.org/10.1056/NEJMoa2115481.

Figure 1. Epidemic curves of the number of reported COVID-19 cases and vaccine rollout in the Philippines. The data are likely underestimated due to reporting constraints, testing/reporting intensity varied substantially over time, and COVID-19 vaccination data are up to 9 March 2023. Source: Our World in Data [https://ourworldindata.org].

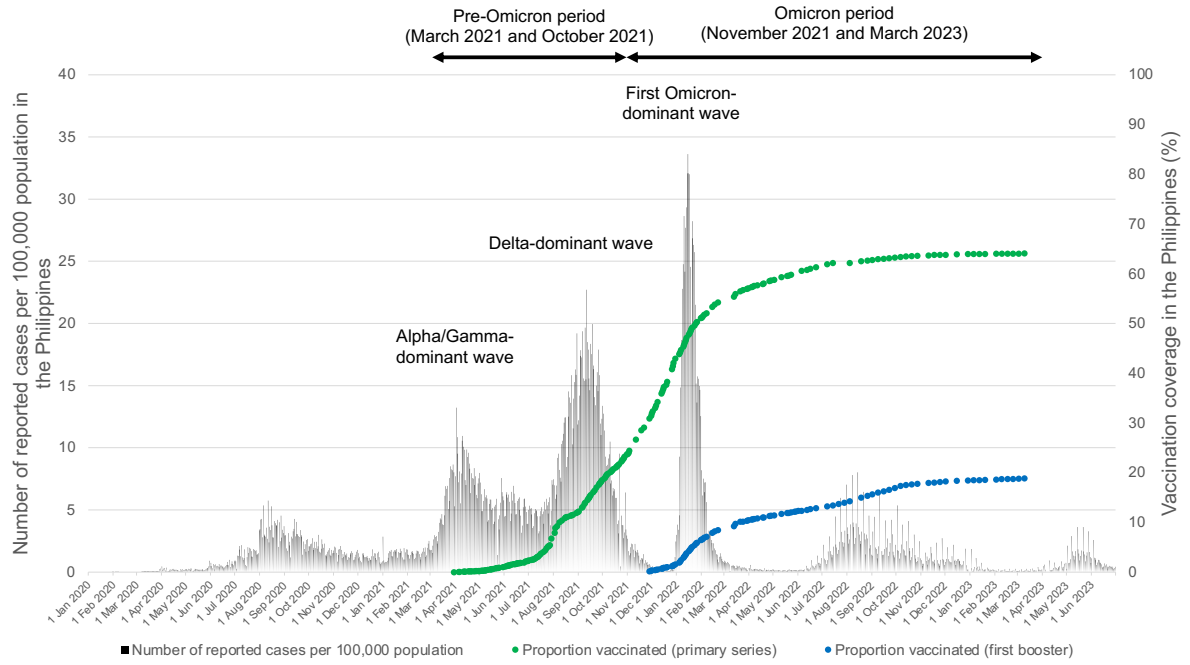
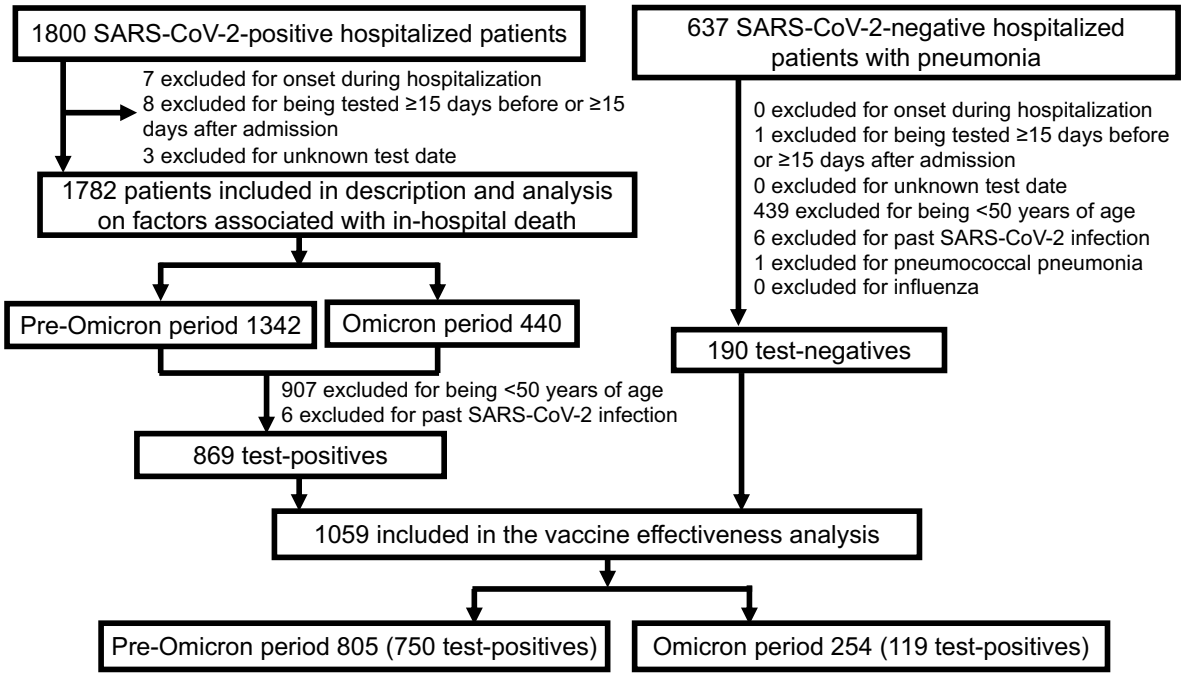


Figure 2. Flow diagram of the study participants.



576 **Table 1.** Demographic and clinical characteristics of hospitalized COVID-19 cases and factors associated with in-hospital death during the

577 pre-Omicron (Alpha, Gamma, Delta) and Omicron periods in San Lazaro Hospital, Philippines

	All (n = 1,782)	Pre-Omicron (n = 1,342)	Omicron (n = 440)	Adjusted odds ratios for in-hospital death (95% CI)[a]
Median age in years[b]	49 (32–64)	53 (37−66)	33 (24–54)	N/A
Age in years, n (%)				
0-9	81 (4.6)	30 (2.2)	51 (11.6)	0.31 (0.10–0.97)
10–19	74 (4.2)	37 (2.8)	37 (8.4)	0.92 (0.38–2.26)
20–29	194 (10.9)	109 (8.1)	85 (19.3)	1
30–39	311 (17.5)	212 (15.8)	99 (22.5)	1.53 (0.87–2.71)
40–49	247 (13.9)	201 (15.0)	46 (10.5)	2.03 (1.11–3.71)
50–59	296 (16.6)	252 (18.8)	44 (10.0)	2.01 (1.10–3.65)
60–69	308 (17.3)	273 (20.3)	35 (8.0)	2.94 (1.63–5.32)
70–79	179 (10.0)	155 (11.6)	24 (5.5)	4.54 (2.43–8.46)
80–89	82 (4.6)	67 (5.0)	15 (3.4)	4.96 (2.43–10.14)
≥90	10 (0.6)	6 (0.5)	4 (0.9)	5.16 (0.92–28.9)
Sex, n (%)				
Female	698 (39.2)	556 (41.4)	142 (32.3)	1
Male	1,084 (60.8)	786 (58.6)	298 (67.7)	1.60 (1.17–2.17)
Pregnancy at hospitalization among female, n (%)				
No	677 (97.0)	545 (98.0)	132 (93.0)	1
Yes	21 (3.0)	11 (2.0)	10 (7.0)	Could not be estimated
Healthcare worker, n (%)				
No	1,673 (93.9)	1,250 (93.1)	423 (96.1)	1
Yes	109 (6.1)	92 (6.9)	17 (3.9)	0.25 (0.07–0.85)
Comorbidities, n (%)[c]				
Cardiovascular disease	759 (42.6)	671 (50.0)	88 (20.0)	0.83 (0.60–1.17)
Diabetes mellitus	371 (20.8)	325 (24.2)	46 (10.5)	1.18 (0.82–1.68)
Dyslipidemia	56 (3.1)	49 (3.7)	7 (1.6)	0.88 (0.38–2.03)
Chronic kidney disease	20 (1.1)	14 (1.0)	6 (1.4)	4.39 (1.52–12.67)

Chronic liver disease	4 (0.2)	2 (0.2)	2 (0.5)	3.44 (0.43–27.8)
Chronic obstructive pulmonary disease	15 (0.8)	9 (0.7)	6 (1.4)	0.55 (0.13–2.29)
Cancer	20 (1.1)	13 (1.0)	7 (1.6)	2.36 (0.79–7.06)
Dementia	7 (0.4)	5 (0.4)	2 (0.5)	Could not be estimated
Depression/schizophrenia	3 (0.2)	3 (0.2)	0 (0.0)	6.64 (0.37–120.0)
Stroke	44 (2.5)	32 (2.4)	12 (2.7)	1.30 (0.62–2.74)
Down syndrome	2 (0.1)	0 (0.0)	2 (0.5)	Could not be estimated
Tuberculosis	306 (17.2)	128 (9.5)	178 (40.5)	2.45 (1.69–3.57)
HIV infection	162 (9.1)	43 (3.2)	119 (27.1)	3.30 (2.03–5.37)
Immunodeficiency without HIV	1 (0.1)	0 (0.0)	1 (0.2)	Could not be estimated
Immunosuppressant use	2 (0.1)	0 (0.0)	2 (0.5)	4.47 (0.24–84.0)
Body mass index, n (%) (among individuals over 18 years of age with data available)				
<25	819 (55.8)	560 (48.4)	259 (83.3)	1
25–29 (overweight)	393 (26.8)	359 (31.0)	34 (10.9)	0.90 (0.61–1.32)
≥30 (obese)	257 (17.5)	230 (20.6)	18 (5.8)	0.72 (0.44–1.18)
Hospitalization in the past year, n (%)				
No	1,680 (94.3)	1,290 (96.1)	390 (88.6)	1
Yes	102 (5.7)	52 (3.9)	50 (11.4)	3.38 (2.01–5.67)
Past SARS-CoV-2 infection, n (%)				
None	1,746 (97.9)	1,330 (99.1)	416 (94.6)	1
Once	35 (2.0)	11 (0.8)	24 (5.5)	0.40 (0.11–1.52)
Twice	1 (0.1)	1 (0.1)	0 (0.0)	Could not be estimated
Smoking, n (%)				
Never-smoker	995 (55.8)	828 (61.7)	167 (38.0)	1
Past smoker	177 (9.9)	131 (9.8)	46 (10.5)	1.56 (0.98–2.48)
Current smoker	205 (11.5)	126 (9.4)	79 (18.0)	2.65 (1.72–4.10)
Underage	166 (9.3)	73 (5.4)	93 (21.1)	N/A
Unknown	239 (13.4)	184 (13.7)	55 (12.5)	N/A
Number of COVID-19 vaccinations received[d], n (%); missing 310 (17.4%)				
None	865 (58.8)	687 (66.2)	178 (41.0)	Refer to VE evaluation later
One	147 (10.0)	124 (12.0)	23 (5.3)	Refer to VE evaluation later
Two	410 (27.9)	226 (21.8)	184 (42.4)	Refer to VE evaluation later

Three	44 (3.0)	1 (0.1)	43 (9.9)	Refer to VE evaluation later
Four	6 (0.4)	0 (0.0)	6 (1.4)	Refer to VE evaluation later
Symptoms, n (%)				
Fever above 37.5℃	1,230 (69.0)	985 (73.4)	245 (55.7)	N/A
Malaise	626 (35.1)	515 (38.4)	111 (25.2)	N/A
Chills	82 (4.6)	57 (4.3)	25 (5.7)	N/A
Joint and body ache	228 (12.8)	178 (13.3)	50 (11.4)	N/A
Headache	243 (13.6)	191 (14.2)	52 (11.8)	N/A
Runny nose	347 (19.5)	287 (21.4)	60 (13.6)	N/A
Cough	1,339 (75.4)	1,061 (79.1)	278 (63.2)	N/A
Sore throat	224 (12.6)	194 (14.5)	30 (6.8)	N/A
Shortness of breath	934 (52.4)	742 (55.3)	192 (43.6)	N/A
Vomiting, diarrhea, stomachache	355 (19.9)	235 (17.5)	120 (27.3)	N/A
Loss of taste or smell	172 (9.7)	170 (12.7)	2 (0.5)	N/A
Oxygen or invasive mechanical ventilation use, n (%)				
No oxygen	483 (27.1)	330 (24.6)	153 (34.8)	N/A
Oxygen only	1,036 (58.1)	838 (62.4)	198 (45.0)	N/A
Invasive mechanical ventilation use	263 (14.8)	174 (13.0)	89 (20.2)	N/A
Outcome, n (%)				
Improved and discharged	1,394 (78.2)	1,074 (80.0)	320 (72.7)	N/A
Improved and transferred	3 (0.2)	1 (0.1)	2 (0.5)	N/A
Stable and transferred	6 (0.3)	6 (0.5)	0 (0.0)	N/A
Worsened and transferred	2 (0.1)	1 (0.1)	1 (0.2)	N/A
In-hospital death	366 (20.5)	252 (18.8)	114 (25.9)	N/A
Discharge against medical advice	11 (0.6)	8 (0.6)	3 (0.7)	N/A
Hospitalization length (days)[b]	10 (6–14)	10 (7–14)	9 (4–15)	N/A
Oxygen use length (days)[b]	6 (3–10)	7 (3–11)	4 (1–9)	N/A
Ventilation use length (days)[b]	1 (2–7)	2 (1–8)	2 (1–5)	N/A

[a] Adjusted for age group, sex, risk score category (0, 1, 2, 3-4, 5+), calendar week of hospitalization (biweekly), and vaccine doses (except for the factor of interest); estimated only for baseline characteristics before infection

[b] Median (interquartile range). [c] Odds ratio compared to not having each condition as a reference

[d] Since the primary series is one dose for Ad26.COV2.S (Janssen/J&J), patients who received one dose of this vaccine are included in the two-dose category.

Abbreviations: CI, confidence interval; N/A, not applicable.

583 **Table 2.** Demographic and clinical characteristics of individuals included in the vaccine effectiveness estimates during the pre-Omicron

584 (Alpha, Gamma, Delta) period and the Omicron period in San Lazaro Hospital, Philippines

	All (n = 805)	Test positive (n = 750)	Test negative (n = 55)
Pre-Omicron (Alpha, Gamma, Delta) period			
Median age in years[a]	64 (57–71)	64 (57–71)	66 (58–74)
Age in years, n (%)			
50–59	266 (33.0)	250 (33.3)	16 (29.1)
60–69	288 (35.8)	272 (36.3)	16 (29.1)
70–79	173 (21.5)	155 (20.7)	18 (32.7)
80–89	72 (8.9)	67 (8.9)	5 (9.1)
≥90	6 (0.8)	6 (0.8)	0 (0.0)
Sex, n (%)			
Male	432 (53.7)	402 (53.6)	30 (54.6)
Female	373 (46.3)	348 (46.4)	25 (45.5)
Pregnancy at hospitalization, n (%)			
No	804 (99.9)	749 (99.9)	55 (100.0)
Yes	1 (0.1)	1 (0.1)	0 (0.0)
Comorbidities, n (%)			
Cardiovascular disease	549 (68.2)	510 (68.0)	39 (70.9)
Diabetes mellitus	280 (34.8)	259 (34.5)	21 (38.2)
Dyslipidemia	38 (4.7)	38 (5.1)	0 (0.0)
Chronic kidney disease	13 (1.6)	10 (1.3)	3 (5.5)
Chronic liver disease	2 (0.3)	2 (0.3)	0 (0.0)
Chronic obstructive pulmonary disease	10 (1.2)	9 (1.2)	1 (1.8)
Cancer	10 (1.2)	9 (1.2)	1 (1.8)
Dementia	6 (0.8)	5 (0.7)	1 (1.8)
Depression/schizophrenia	2 (0.3)	2 (0.3)	0 (0.0)
Stroke	32 (4.0)	27 (3.6)	5 (9.1)
Down syndrome	0 (0.0)	0 (0.0)	0 (0.0)

Tuberculosis	73 (9.1)	60 (8.0)	13 (2.7)
HIV infection	8 (1.0)	7 (0.9)	1 (1.8)
Immunodeficiency without HIV	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressant use	0 (0.0)	0 (0.0)	0 (0.0)
Body mass index, n (%)			
<25	376 (52.4)	348 (52.0)	28 (57.1)
25–29 (overweight)	218 (30.4)	208 (31.1)	10 (20.4)
≥30 (obese)	124 (17.3)	113 (16.9)	11 (22.5)
Severe disease risk score[b], n (%)			
0	89 (11.1)	84 (11.2)	5 (9.1)
1	225 (28.0)	212 (28.3)	13 (23.6)
2	152 (18.9)	143 (19.1)	9 (16.4)
3	166 (20.6)	154 (20.5)	12 (21.8)
≥4	173 (21.5)	157 (20.9)	16 (29.1)
Hospitalization in the past year, n (%)			
No	778 (96.7)	730 (97.3)	48 (87.3)
Yes	27 (3.4)	20 (2.7)	7 (12.7)
Smoking, n (%)			
Never-smoker	514 (63.9)	482 (64.3)	32 (58.2)
Past smoker	102 (12.7)	93 (12.4)	9 (16.4)
Current smoker	81 (10.7)	70 (9.3)	11 (20.0)
Unknown	108 (13.4)	105 (14.0)	3 (5.5)
Number of COVID-19 vaccinations received[c], n (%); missing 204 (25.3%)			
None	393 (65.4)	361 (64.5)	32 (78.1)
One	77 (12.8)	75 (13.4)	2 (4.9)
Two	131 (21.8)	124 (22.1)	7 (17.1)
Three	0 (0.0)	0 (0.0)	0 (0.0)
Vaccine type (primary series), n (%)[d]			
CoronaVac (SinoVac)	118 (56.7)	113 (56.8)	5 (55.6)
AZD1222 (AstraZeneca)	43 (20.7)	40 (20.1)	3 (33.3)
Ad26.COV2.S (Janssen/J&J)	24 (11.5)	23 (11.6)	1 (11.1)
BNT162b2 (Pfizer)	10 (4.8)	10 (5.0)	0 (0.0)

mRNA-1273 (Moderna)	7 (3.4)	7 (3.5)	0 (0.0)
Sputnik V (Gameleya)	2 (1.0)	2 (1.0)	0 (0.0)
Unknown	4 (1.9)	4 (2.0)	0 (0.0)
SARS-CoV-2 testing type, n (%)			
Nucleic acid amplification test	782 (97.1)	729 (97.2)	53 (96.4)
Rapid antigen detection kit	20 (2.5)	18 (2.4)	2 (3.6)
Unknown	3 (0.4)	3 (0.4)	0 (0.0)
the Omicron period			
	All (n = 254)	Test positive (n = 119)	Test negative (n = 135)
Median age in years[a]	64 (57–72)	64 (57–73)	63 (57–71)
Age in years, n (%)			
50–59	94 (37.0)	43 (36.1)	51 (37.8)
60–69	79 (31.1)	35 (29.4)	44 (32.6)
70–79	45 (17.7)	23 (19.3)	22 (16.3)
80–89	29 (11.4)	14 (11.8)	15 (11.1)
≥90	7 (2.8)	4 (3.4)	3 (2.2)
Sex, n (%)			
Male	161 (63.4)	74 (62.2)	87 (64.4)
Female	93 (36.6)	45 (37.8)	48 (35.6)
Pregnancy at hospitalization, n (%)			
No	254 (100.0)	119 (100.0)	135 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Comorbidities, n (%)			
Cardiovascular disease	118 (46.5)	64 (53.8)	54 (40.0)
Diabetes mellitus	64 (25.2)	35 (29.4)	29 (21.5)
Dyslipidemia	4 (1.6)	4 (3.4)	0 (0.0)
Chronic kidney disease	8 (3.2)	4 (3.4)	4 (3.0)
Chronic liver disease	0 (0.0)	0 (0.0)	0 (0.0)
Chronic obstructive pulmonary disease	16 (6.3)	5 (4.2)	11 (8.2)
Cancer	8 (3.2)	5 (4.2)	3 (2.2)
Dementia	3 (1.2)	2 (1.7)	1 (0.7)

Depression/schizophrenia	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	16 (6.3)	10 (8.3)	6 (4.4)
Down syndrome	1 (0.4)	0 (0.0)	1 (0.7)
Tuberculosis	125 (49.2)	46 (38.7)	79 (58.5)
HIV infection	8 (3.2)	3 (2.5)	5 (3.7)
Immunodeficiency without HIV	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressant use	0 (0.0)	0 (0.0)	0 (0.0)
Body mass index, n (%)			
<25	178 (79.8)	78 (76.5)	100 (82.6)
25–29 (overweight)	28 (12.6)	17 (16.7)	11 (9.1)
≥30 (obese)	17 (7.6)	7 (6.9)	10 (8.3)
Severe disease risk score[b], n (%)			
0	26 (10.2)	16 (13.5)	10 (7.4)
1	86 (33.9)	30 (25.2)	56 (41.5)
2	61 (24.0)	28 (23.5)	33 (24.4)
3	41 (16.1)	26 (21.9)	15 (11.1)
≥4	40 (15.8)	19 (16.0)	21 (15.6)
Hospitalization in the past year, n (%)			
No	237 (93.3)	111 (93.3)	126 (93.3)
Yes	17 (6.7)	8 (6.7)	9 (6.7)
Smoking, n (%)			
Never-smoker	109 (42.9)	55 (46.2)	54 (40.0)
Past smoker	42 (16.5)	23 (19.3)	19 (14.1)
Current smoker	72 (28.4)	25 (21.0)	47 (34.8)
Unknown	31 (12.2)	16 (13.5)	15 (11.1)
Number of COVID-19 vaccinations received, n (%)[c]; missing 4 (1.6%)			
None	104 (41.6)	54 (45.8)	50 (37.9)
One	7 (2.8)	4 (3.4)	3 (2.3)
Two	110 (44.0)	45 (38.1)	65 (49.2)
Three	25 (10.0)	13 (11.0)	12 (9.1)
Four	4 (1.6)	2 (1.7)	2 (1.5)
Vaccine type (primary series), n (%)[d]			

CoronaVac (SinoVac)	72 (49.3)	35 (54.7)	37 (45.1)
AZD1222 (AstraZeneca)	23 (15.8)	9 (14.1)	14 (17.1)
BNT162b2 (Pfizer)	18 (12.3)	7 (10.9)	11 (13.4)
Ad26.COV2.S (Janssen/J&J)	18 (12.3)	7 (10.9)	11 (13.4)
mRNA-1273 (Moderna)	10 (6.9)	4 (6.3)	6 (7.3)
Sputnik V (Gameleya)	1 (0.7)	1 (1.6)	0 (0.0)
BBIBP-CorV (Sinopharm)	1 (0.7)	0 (0.0)	1 (1.2)
Unknown	3 (2.1)	1 (1.6)	2 (2.4)
Vaccine type (first booster), n (%)[d]			
BNT162b2 (Pfizer)	14 (48.3)	9 (60.0)	5 (35.7)
AZD1222 (AstraZeneca)	6 (20.7)	3 (20.0)	3 (21.4)
mRNA-1273 (Moderna)	5 (17.2)	2 (13.3)	3 (21.4)
Unknown	4 (13.8)	1 (6.7)	3 (21.4)
Vaccine type (second booster), n (%)[d]			
BNT162b2 (Pfizer)	3 (75.0)	2 (100.0)	1 (50.0)
mRNA-1273 (Moderna)	1 (25.0)	0 (0.0)	1 (50.0)
SARS-CoV-2 testing type, n (%)			
Nucleic acid amplification test	241 (94.9)	111 (93.3)	130 (96.3)
Rapid antigen detection kit	9 (3.5)	5 (4.2)	4 (3.0)
Unknown	4 (1.6)	3 (2.5)	1 (0.7)

[a] Median (interquartile range).
[b] The following points were added up for each patient: assigned 2 points for the presence of either diabetes mellitus, chronic kidney disease, dementia, Down syndrome, or obesity and assigned 1 point for the presence of cardiovascular disease (including hypertension), dyslipidemia, chronic liver disease, chronic obstructive pulmonary disease, cancer, depression/schizophrenia, stroke, pregnancy while hospitalized, or overweight.
[c] Since the primary series is one dose for Ad26.COV2.S (Janssen/J&J), patients who received one dose of this vaccine are included in the two-dose category.
[d] Among individuals with known vaccine type; one dose of Johnson and Johnson/Janssen was counted as two doses (as the primary series requires only one dose)

592 **Table 3.** Vaccine effectiveness against various COVID-19 hospitalization outcomes by the number of doses received during the pre-

593 Omicron (Alpha, Gamma, Delta) and Omicron periods in San Lazaro Hospital, Philippines

Vaccination status[a]	Case-patients, n	Control patients, n	Last vaccination to admission, days[b]	Adjusted odds ratios (95% CI)[c]	Vaccine effectiveness, % (95% CI)[d]
Pre-Omicron: all COVID-19 hospitalization					
Unvaccinated	361	32	N/A	1	N/A
One dose	75	2	19 (12–31)	1.800 (0.356–9.098)	N/A
Two doses	124	7	65 (34–108)	0.146 (0.033–0.641)	85.4 (35.9–96.7)
Pre-Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	318	32	N/A	1	N/A
One dose	57	2	20 (13–30)	1.430 (0.260–7.873)	N/A
Two doses	95	7	64 (38–104)	0.090 (0.016–0.506)	91.0 (49.4–98.4)
Pre-Omicron: COVID-19 requiring oxygen therapy, restricting to patients with respiratory failure due to COVID-19					
Unvaccinated	314	32	N/A	1	N/A
One dose	57	2	20 (13–30)	1.440 (0.261–7.929)	N/A
Two doses	95	7	64 (38–104)	0.091 (0.016–0.511)	90.9 (48.9–98.4)
Pre-Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	80	32	N/A	1	N/A
One dose	6	2	19 (11–31)	0.188 (0.140–2.541)	N/A
Two doses	13	7	59 (36–110)	0.030 (0.003–0.343)	97.0 (65.7–99.7)
Pre-Omicron: fatal COVID-19					
Unvaccinated	114	32	N/A	1	N/A
One dose	7	2	14 (11–30)	0.707 (0.073–6.821)	N/A
Two doses	19	7	60 (28–106)	0.035 (0.004–0.329)	96.5 (67.1–99.6)
Omicron: all COVID-19 hospitalization					

Unvaccinated	54	50	N/A	1	N/A
One dose	4	3	76 (36–213)	0.930 (0.101–8.592)	N/A
Two doses	45	65	172 (142–294)	0.298 (0.122–0.730)	70.2 (27.0–87.8)
Three doses	13	12	84 (28–281)	1.402 (0.337–5.837)	N/A
Four doses	2	2	Could not be estimated		
Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	53	50	N/A	1	N/A
One dose	3	3	102 (50–213)	0.661 (0.062–7.063)	N/A
Two doses	31	65	177 (148–359)	0.286 (0.116–0.707)	71.4 (29.3–88.4)
Three doses	5	12	197 (75–321)	0.752 (0.155–3.650)	N/A
Four doses	0	2	Could not be estimated		
Omicron: COVID-19 requiring oxygen therapy, restricting to patients with respiratory failure due to COVID-19					
Unvaccinated	51	50	N/A	1	N/A
One dose	3	3	102 (50–213)	0.636 (0.058–6.945)	N/A
Two doses	29	65	182 (149–362)	0.231 (0.090–0.595)	76.9 (40.5–91.0)
Three doses	5	12	197 (75–321)	0.690 (0.140–3.388)	N/A
Four doses	0	2	Could not be estimated		
Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	19	50	N/A	1	N/A
One dose	2	3	158 (76–227)	9.725 (0.232–408.111)	N/A
Two doses	7	65	269 (149–473)	0.273 (0.067–1.116)	72.7 (-11.6–93.3)
Three doses	1	12	93 (75–197)	0.427 (0.028–6.631)	N/A
Four doses	0	2	Could not be estimated		
Omicron: fatal COVID-19					
Unvaccinated	20	50	N/A	Could not be estimated	
One dose	1	3	213 (50–240)	Could not be estimated	
Two doses	11	65	265 (153–456)	0.411 (0.092–1.828)	58.9 (-82.8–90.8)

Three doses	1	12	93 (75–197)	0.126 (0.009–1.868)	87.4 (-86.8–99.1)
Four doses	0	2	Could not be estimated		

[a] Since the primary series is one dose for Ad26.COV2.S (Janssen/J&J), patients who received one dose of this vaccine are included in the two-dose category.
[b] Median (interquartile range); among individuals with available vaccination dates
[c] Adjusted for age group, sex, risk score category (0, 1, 2, 3-4, 5+), smoking history, and calendar week of hospitalization (biweekly).
[d] Effectiveness estimates are provided when the confidence intervals are ±100%
Abbreviations: CI, confidence interval; N/A, not applicable.

599 **Supplementary Table 1.** Vaccine effectiveness against various COVID-19 hospitalization outcomes by time since vaccination during the

600 pre-Omicron (Alpha, Gamma, Delta) and Omicron periods in San Lazaro Hospital, Philippines

Vaccination status[a]	Case-patients, n	Control patients, n	Last vaccination to admission, days[b]	Adjusted odds ratios (95% CI)[c]	Vaccine effectiveness, % (95% CI)[d]
Pre-Omicron: all COVID-19 hospitalization					
Unvaccinated	361	32	N/A	1	N/A
Within 13 days of dose 1	24	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	57	3	25 (16–38)	0.511 (0.112–2.318)	N/A
14 days to 6 months after dose 2	103	4	73 (40–110)	0.222 (0.043–1.150)	77.8 (-15.0–95.7)
>6 months after dose 2	1	1	191 (190–192)	0.014 (0.0002–1.030)	98.6 (-3.0–99.98)
Pre-Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	318	32	N/A	1	N/A
Within 13 days of dose 1	16	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	44	3	24 (15–34)	0.423 (0.086–2.077)	N/A
14 days to 6 months after dose 2	81	4	67 (41–104)	0.207 (0.040–1.083)	79.3 (-8.3–96)
>6 months after dose 2	1	1	191 (190–192)	0.015 (0.0002–1.042)	98.5 (-4.2–99.98)
Pre-Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	80	32	N/A	1	N/A
Within 13 days of dose 1	3	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	5	3	19 (11–31)	0.024 (0.001–0.427)	97.6 (57.3–99.9)
14 days to 6 months after dose 2	9	4	67 (49–110)	0.077 (0.005–1.107)	92.3 (-10.7–99.5)

>6 months after dose 2	0	1	Could not be estimated		
Pre-Omicron: fatal COVID-19					
Unvaccinated	114	32	N/A	1	N/A
Within 13 days of dose 1	4	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	6	3	14 (10–30)	0.071 (0.006–0.774)	92.9 (22.6–99.4)
14 days to 6 months after dose 2	15	4	67 (50–106)	0.066 (0.006–0.758)	93.4 (24.2–99.4)
>6 months after dose 2	0	1	Could not be estimated		
Omicron: all COVID-19 hospitalization					
Unvaccinated	54	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	4	2	76 (36–213)	1.852 (0.325–10.555)	N/A
14 days to 6 months after dose 2	19	9	144 (116–163)	1.955 (0.810–4.720)	N/A
>6 months after dose 2	10	16	319 (240–475)	0.579 (0.240–1.393)	42.1 (-39.3–76)
Within 13 days of dose 3	1	0	Could not be estimated		
14 days to 6 months after dose 3	2	2	46 (26–78)	0.926 (0.126–6.824)	N/A
>6 months after dose 3	3	1	301 (239–321)	2.778 (0.280–27.585)	N/A
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	1	1	53 (31–75)	0.926 (0.056–15.202)	N/A
>6 months after dose 4	0	0	Could not be estimated		
Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	53	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	3	2	102 (50–213)	1.100 (0.080–15.142)	N/A
14 days to 6 months after dose 2	13	9	148 (136–164)	0.642 (0.111–3.711)	N/A
>6 months after dose 2	6	16	359 (265–487)	0.273 (0.044–1.688)	72.7 (-68.8–95.6)
Within 13 days of dose 3	0	0	Could not be estimated		
14 days to 6 months after dose 3	0	2	Could not be estimated		
>6 months after dose 3	3	1	Could not be estimated		
Within 13 days of dose 4	0	0	Could not be estimated		

14 days to 6 months after dose 4	0	1	Could not be estimated		
>6 months after dose 4	0	0	Could not be estimated		
Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	19	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	2	2	158 (76–227)	20.994 (0.356-1237.956)	N/A
14 days to 6 months after dose 2	3	9	144 (129–158)	0.881 (0.071–10.875)	N/A
>6 months after dose 2	2	16	421 (294–516)	1.131 (0.060–21.283)	N/A
Within 13 days of dose 3	0	0	Could not be estimated		
14 days to 6 months after dose 3	0	2	Could not be estimated		
>6 months after dose 3	1	1	Could not be estimated		
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	0	1	Could not be estimated		
>6 months after dose 4	0	0	Could not be estimated		
Omicron: fatal COVID-19					
Unvaccinated	20	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	1	2	Could not be estimated		
14 days to 6 months after dose 2	5	9	148 (141–164)	193.205 (0.822–45422.870)	N/A
>6 months after dose 2	3	16	385 (270–516)	0.814 (0.011–62.734)	N/A
Within 13 days of dose 3	0	0	Could not be estimated		
14 days to 6 months after dose 3	0	2	Could not be estimated		
>6 months after dose 3	1	1	Could not be estimated		
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	0	1	Could not be estimated		
>6 months after dose 4	0	0	Could not be estimated		

[a] Since the primary series is one dose for Ad26.COV2.S (Janssen/J&J), patients who received one dose of this vaccine are included in the two-dose category.
[b] Median (interquartile range); among individuals with available vaccination dates
[c] Adjusted for age group, sex, risk score category (0, 1, 2, 3-4, 5+), smoking history, and calendar week of hospitalization (biweekly).
[d] Effectiveness estimates are provided when the confidence intervals are ±100%
Abbreviations: CI, confidence interval; N/A, not applicable.

606 **Table 4.** Vaccine effectiveness against various COVID-19 hospitalization outcomes by the number of doses received during the pre-Omicron (Alpha,

607 Gamma, Delta) and Omicron periods in San Lazaro Hospital, Philippines

Vaccination status[a]	Case-patients, n	Control patients, n	Last vaccination to admission, days[b]	Adjusted odds ratios (95% CI)[c]	Vaccine effectiveness, % (95% CI)[d]
Pre-Omicron: all COVID-19 hospitalization					
Unvaccinated	361	32	N/A	1	N/A
One dose	75	2	19 (12–31)	1.800 (0.356–9.098)	N/A
Two doses	124	7	65 (34–108)	0.146 (0.033–0.641)	85.4 (35.9–96.7)
Pre-Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	318	32	N/A	1	N/A
One dose	57	2	20 (13–30)	1.430 (0.260–7.873)	N/A
Two doses	95	7	64 (38–104)	0.090 (0.016–0.506)	91.0 (49.4–98.4)
Pre-Omicron: COVID-19 requiring oxygen therapy, restricting to patients with respiratory failure due to COVID-19					
Unvaccinated	314	32	N/A	1	N/A
One dose	57	2	20 (13–30)	1.440 (0.261–7.929)	N/A
Two doses	95	7	64 (38–104)	0.091 (0.016–0.511)	90.9 (48.9–98.4)
Pre-Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	80	32	N/A	1	N/A
One dose	6	2	19 (11–31)	0.188 (0.140–2.541)	N/A
Two doses	13	7	59 (36–110)	0.030 (0.003–0.343)	97.0 (65.7–99.7)
Pre-Omicron: fatal COVID-19					
Unvaccinated	114	32	N/A	1	N/A
One dose	7	2	14 (11–30)	0.707 (0.073–6.821)	N/A
Two doses	19	7	60 (28–106)	0.035 (0.004–0.329)	96.5 (67.1–99.6)
Omicron: all COVID-19 hospitalization					
Unvaccinated	54	50	N/A	1	N/A
One dose	4	3	76 (36–213)	0.930 (0.101–8.592)	N/A
Two doses	45	65	172 (142–294)	0.298 (0.122–0.730)	70.2 (27.0–87.8)
Three doses	13	12	84 (28–281)	1.402 (0.337–5.837)	N/A
Four doses	2	2	Could not be estimated		
Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	53	50	N/A	1	N/A

One dose	3	3	102 (50–213)	0.661 (0.062–7.063)	N/A
Two doses	31	65	177 (148–359)	0.286 (0.116–0.707)	71.4 (29.3–88.4)
Three doses	5	12	197 (75–321)	0.752 (0.155–3.650)	N/A
Four doses	0	2	Could not be estimated		
Omicron: COVID-19 requiring oxygen therapy, restricting to patients with respiratory failure due to COVID-19					
Unvaccinated	51	50	N/A	1	N/A
One dose	3	3	102 (50–213)	0.636 (0.058–6.945)	N/A
Two doses	29	65	182 (149–362)	0.231 (0.090–0.595)	76.9 (40.5–91.0)
Three doses	5	12	197 (75–321)	0.690 (0.140–3.388)	N/A
Four doses	0	2	Could not be estimated		
Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	19	50	N/A	1	N/A
One dose	2	3	158 (76–227)	9.725 (0.232–408.111)	N/A
Two doses	7	65	269 (149–473)	0.273 (0.067–1.116)	72.7 (-11.6–93.3)
Three doses	1	12	93 (75–197)	0.427 (0.028–6.631)	N/A
Four doses	0	2	Could not be estimated		
Omicron: fatal COVID-19					
Unvaccinated	20	50	N/A	Could not be estimated	
One dose	1	3	213 (50–240)	Could not be estimated	
Two doses	11	65	265 (153–456)	0.411 (0.092–1.828)	58.9 (-82.8–90.8)
Three doses	1	12	93 (75–197)	0.126 (0.009–1.868)	87.4 (-86.8–99.1)
Four doses	0	2	Could not be estimated		

608 [a] Since the primary series is one dose for Ad26.COV2.S (Janssen/J&J), patients who received one dose of this vaccine are included in the two-dose category.

609 [b] Median (interquartile range); among individuals with available vaccination dates

610 [c] Adjusted for age group, sex, risk score category (0, 1, 2, 3-4, 5+), smoking history, and calendar week of hospitalization (biweekly).

611 [d] Effectiveness estimates are provided when the confidence intervals are ±100%

612 Abbreviations: CI, confidence interval; N/A, not applicable.

Supplementary Table 1. Vaccine effectiveness against various COVID-19 hospitalization outcomes by time since vaccination during the pre-Omicron (Alpha, Gamma, Delta) and Omicron periods in San Lazaro Hospital, Philippines

Vaccination status[a]	Case-patients, n	Control patients, n	Last vaccination to admission, days[b]	Adjusted odds ratios (95% CI)[c]	Vaccine effectiveness, % (95% CI)[d]
Pre-Omicron: all COVID-19 hospitalization					
Unvaccinated	361	32	N/A	1	N/A
Within 13 days of dose 1	24	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	57	3	25 (16–38)	0.511 (0.112–2.318)	N/A
14 days to 6 months after dose 2	103	4	73 (40–110)	0.222 (0.043–1.150)	77.8 (-15.0–95.7)
>6 months after dose 2	1	1	191 (190–192)	0.014 (0.0002–1.030)	98.6 (-3.0–99.98)
Pre-Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	318	32	N/A	1	N/A
Within 13 days of dose 1	16	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	44	3	24 (15–34)	0.423 (0.086–2.077)	N/A
14 days to 6 months after dose 2	81	4	67 (41–104)	0.207 (0.040–1.083)	79.3 (-8.3–96)
>6 months after dose 2	1	1	191 (190–192)	0.015 (0.0002–1.042)	98.5 (-4.2–99.98)
Pre-Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	80	32	N/A	1	N/A
Within 13 days of dose 1	3	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	5	3	19 (11–31)	0.024 (0.001–0.427)	97.6 (57.3–99.9)
14 days to 6 months after dose 2	9	4	67 (49–110)	0.077 (0.005–1.107)	92.3 (-10.7–99.5)
>6 months after dose 2	0	1	Could not be estimated		
Pre-Omicron: fatal COVID-19					
Unvaccinated	114	32	N/A	1	N/A
Within 13 days of dose 1	4	0	Could not be estimated		
14 days after dose 1 or within 13 days of dose 2	6	3	14 (10–30)	0.071 (0.006–0.774)	92.9 (22.6–99.4)
14 days to 6 months after dose 2	15	4	67 (50–106)	0.066 (0.006–0.758)	93.4 (24.2–99.4)
>6 months after dose 2	0	1	Could not be estimated		

Omicron: all COVID-19 hospitalization					
Unvaccinated	54	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	4	2	76 (36–213)	1.852 (0.325–10.555)	N/A
14 days to 6 months after dose 2	19	9	144 (116–163)	1.955 (0.810–4.720)	N/A
>6 months after dose 2	10	16	319 (240–475)	0.579 (0.240–1.393)	42.1 (-39.3–76)
Within 13 days of dose 3	1	0	Could not be estimated		
14 days to 6 months after dose 3	2	2	46 (26–78)	0.926 (0.126–6.824)	N/A
>6 months after dose 3	3	1	301 (239–321)	2.778 (0.280–27.585)	N/A
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	1	1	53 (31–75)	0.926 (0.056–15.202)	N/A
>6 months after dose 4	0	0	Could not be estimated		
Omicron: COVID-19 requiring oxygen therapy					
Unvaccinated	53	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	3	2	102 (50–213)	1.100 (0.080–15.142)	N/A
14 days to 6 months after dose 2	13	9	148 (136–164)	0.642 (0.111–3.711)	N/A
>6 months after dose 2	6	16	359 (265–487)	0.273 (0.044–1.688)	72.7 (-68.8–95.6)
Within 13 days of dose 3	0	0	Could not be estimated		
14 days to 6 months after dose 3	0	2	Could not be estimated		
>6 months after dose 3	3	1	Could not be estimated		
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	0	1	Could not be estimated		
>6 months after dose 4	0	0	Could not be estimated		
Omicron: COVID-19 requiring invasive mechanical ventilation					
Unvaccinated	19	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	2	2	158 (76–227)	20.994 (0.356-1237.956)	N/A
14 days to 6 months after dose 2	3	9	144 (129–158)	0.881 (0.071–10.875)	N/A
>6 months after dose 2	2	16	421 (294–516)	1.131 (0.060–21.283)	N/A
Within 13 days of dose 3	0	0	Could not be estimated		
14 days to 6 months after dose 3	0	2	Could not be estimated		
>6 months after dose 3	1	1	Could not be estimated		
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	0	1	Could not be estimated		
>6 months after dose 4	0	0	Could not be estimated		
Omicron: fatal COVID-19					
Unvaccinated	20	50	N/A	1	N/A
Dose 1 or within 13 days of dose 2	1	2	Could not be estimated		

14 days to 6 months after dose 2	5	9	148 (141–164)	193.205 (0.822–45422.870)	N/A
>6 months after dose 2	3	16	385 (270–516)	0.814 (0.011–62.734)	N/A
Within 13 days of dose 3	0	0	Could not be estimated		
14 days to 6 months after dose 3	0	2	Could not be estimated		
>6 months after dose 3	1	1	Could not be estimated		
Within 13 days of dose 4	0	0	Could not be estimated		
14 days to 6 months after dose 4	0	1	Could not be estimated		
>6 months after dose 4	0	0	Could not be estimated		

615 [a] Since the primary series is one dose for Ad26.COV2.S (Janssen/J&J), patients who received one dose of this vaccine are included in the two-dose category.

616 [b] Median (interquartile range); among individuals with available vaccination dates

617 [c] Adjusted for age group, sex, risk score category (0, 1, 2, 3-4, 5+), smoking history, and calendar week of hospitalization (biweekly).

618 [d] Effectiveness estimates are provided when the confidence intervals are ±100%

619 Abbreviations: CI, confidence interval; N/A, not applicable.

Paper 10: Lessons Learnt in Japan and the Philippines

Arashiro T[*], et al. Experience in conducting COVID-19 vaccine effectiveness studies in response to the COVID-19 pandemic in Japan and the Philippines: lessons for future epidemics and potential pandemics (Under WHO internal clearance; [*]**first and corresponding author)**

PhD candidate contributions:
Conceptualization (main), design (main), recruitment of participating healthcare facilities (main), data acquisition (development of data collection scheme, development of questionnaire: main; actual questionnaire collection: supported healthcare facility staff), data analysis (main), writing – original draft (main), funding acquisition (main: WISE; support: AMED, MHLW)

The paper is based on Objective 3C as well as one of critical overarching discussion and scientific and public Health contributions of this PhD.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2100510	**Title**	Dr
First Name(s)	Takeshi		
Surname/Family Name	Arashiro		
Thesis Title	Factors associated with SARS-CoV-2 infection and effectiveness of COVID-19 vaccines in Japan and the Philippines		
Primary Supervisor	Chris Smith		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	WHO WPRO Western Pacific Surveillance and Response journal
Please list the paper's authors in the intended authorship order:	Takeshi Arashiro, Regina Pascua Berba, Joy Potenciano Calayo, Rontgene Solante, Shuichi Suzuki, Jinho Shin, Motoi Suzuki, Martin Hibberd, Koya Ariyoshi, Chris Smith

Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualization (main), design (main), interpretation (main), writing – original draft (main), funding acquisition (main: WISE, WHO; support: AMED, MHLW)

SECTION E

Student Signature	Takeshi Arashiro
Date	April 5, 2024

Supervisor Signature	Chris Smith
Date	April 6, 2024

Experience in conducting COVID-19 vaccine effectiveness studies in response to the COVID-19 pandemic in Japan and the Philippines: lessons for future epidemics and potential pandemics

ABSTRACT

Problem: Once COVID-19 vaccines were rolled out, there was a need to monitor real-world vaccine effectiveness (VE) to accumulate evidence to inform policy and risk communication. This was especially true in Japan and the Philippines, given historical issues that affected vaccine confidence.

Context: Neither country had public health surveillance that can be enhanced to evaluate VE or readily available national vaccination databases.

Action: Study groups to assess VE against symptomatic infection and VE against severe disease were formed with multiple health-care facilities in each country.

Outcome: In Japan, multiple study reports were published in Japanese on the website of the National Institute of Infectious Diseases and presented at the national government's advisory board. There was nationwide media coverage, which facilitated transparency and provided confidence to the government and the general public in the vaccination program. In the Philippines, there was a substantial delay to align with various stakeholders and institutional review board (IRB) approval, but the studies were successfully initiated and completed.

Discussion: There were four main challenges in conducting our studies: (1) finding health-care facilities for data collection, (2) obtaining exposure (vaccination) data, (3) epidemiological biases/confounders, (4) informing policy/risk communication in a timely manner. Preparedness during inter-emergency/epidemic/pandemic period to rapidly evaluate interventions such as vaccination is critical and should include the

following considerations: (1) establishment/maintenance of prospective data collection platforms, ideally under public health surveillance (if not, clinical research networks or linked databases), (2) uniform and practical protocols with consideration of biases/confounders and (3) communication with stakeholders including IRBs.

PROBLEM

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally. Once vaccines were rolled out, there was a need to monitor the real-world vaccine effectiveness (VE) to accumulate evidence in order to inform policy and risk communication.[1] This became more apparent as there was early unblinding of randomized controlled trials,[2] together with evidence of waning immunity and the emergence of variants with immune escape properties.[3,4] Although the World Health Organization (WHO) guidance does not recommend all countries to conduct VE studies due to methodological complexity and susceptibility to biases,[5] it was considered valuable for Japan and the Philippines to conduct VE studies for several reasons: (1) vaccine confidence within the country and among surrounding countries (especially given historical issues that affected vaccine confidence: human papillomavirus/influenza vaccines in Japan[6,7] and dengue vaccine in the Philippines[8]), (2) new vaccine technologies, such as mRNA vaccines and viral vector vaccines, were rolled out to the broad population for the first time and the effect may vary by population subgroups, (3) substantial variation in public health and social measures implemented among countries (which may affect the VE estimates[9]), and (4) considerably different cumulative infection burdens among countries (as individuals with prior infection are at least partially protected against subsequent infection/disease). VE studies in low and middle-income countries (LMICs) were considered particularly informative for the following reasons: (1) evaluation of vaccines that are mainly distributed in LMICs as part of public health response measures, (2) confirmation that the vaccines remain active through distribution networks (e.g. no cold chain breach as temperature control is especially important

for vaccines such as mRNA vaccines), and (3) capacity building to conduct operational research to inform various public health responses for COVID-19 as well as future epidemics and pandemics.

The lead investigator (TA), together with other authors and collaborators, established health-care facility-based study groups in Japan and the Philippines to assess VE against symptomatic infection (FASCINATE study) and severe disease (MOTIVATE study).[9–13] This report describes the experience of planning, establishing, and executing these VE studies during the COVID-19 pandemic.

CONTEXT

Similar to other countries, COVID-19 affected Japan and the Philippines substantially. The epidemic curve of reported COVID-19 cases and vaccination rollout with select study milestones in each country are illustrated in **Fig. 1**. In Japan, the primary series rollout started in mid-February 2021, with the first booster dose in December 2021, the second booster dose in May 2022, and the third booster dose (bivalent vaccines) in September 2022. The second booster dose was administered exclusively to individuals who were ≥60 years old, had any comorbidities, or were health-care/long-term care workers. The majority of vaccines administered were vaccines manufactured by Pfizer-BioNTech and Moderna (99.9% for the primary series).

In the Philippines, the primary series rollout started in March 2021. The first booster dose rollout started in November 2021 among health-care workers (HCWs), senior citizens, and immunocompromised persons, and expanded to adults aged ≥18 years in December 2021. The second booster dose rollout started in April 2022 among HCWs and individuals who were ≥60 years old, and in July 2022 among

individuals who were ≥50 years old and individuals aged 18–49 years with comorbidities. In the FASCINATE study, among the vaccinees for the primary series, 39% received AstraZeneca, 37% received Sinovac, 18% received Pfizer-BioNTech or Moderna, and 6% received other types. For booster doses, over 90% received vaccines by Pfizer-BioNTech or Moderna.

Neither country had public health surveillance (e.g., influenza-like illness [ILI] or severe acute respiratory infection [SARI] surveillance) that can be rapidly enhanced to evaluate VE or readily available national databases on exposure data (vaccination records) and outcome data (symptomatic infection/severe disease data). Therefore, we set up prospective studies together with health-care facilities in both countries.

ACTION

Study groups to assess VE against symptomatic infection (FASCINATE study groups) were formed in each country. Mild symptomatic infection was the outcome of choice as it was the endpoint of the trials. Health-care facilities that could participate in the studies were recruited and the studies were initiated in each country. Healthcare facilities which were routinely testing for SARS-CoV-2 among symptomatic individuals in various age range in outpatient setting were chosen to be recruited. The FASCINATE study also aimed to elucidate socio-behavioural factors associated with SARS-CoV-2 infection. Next, as there was emerging evidence suggesting that VE wanes against mild symptomatic infection and is also less effective in the setting of Omicron, resulting in target product profile shifting to severe disease, there was an increasing need to evaluate VE against severe disease. Therefore, in both countries, additional study groups were formed (MOTIVATE study

groups) and the studies were initiated. For MOTIVATE study groups, healthcare facilities which were routinely admitting individuals with COVID-19 as well as pneumonia due to other etiology (e.g., bacterial pneumonia). We examined VE against various severe outcomes including oxygen use, invasive mechanical ventilation use, and death. We also collected data on whether the medical intervention, such as oxygen use, was due to COVID-19 or other diseases among those who tested positive for SARS-CoV-2.

OUTCOME

In Japan, as a result of the study, multiple study reports were published in Japanese on the website of the National Institute of Infectious Diseases (NIID) and presented at the national government's advisory board to inform policy and risk communication (**Fig. 1**). Since NIID is part of the Ministry of Health, Labour and Welfare (MHLW) in Japan, clearance from MHLW was obtained before publication. Every time we published the findings, they were disseminated via multiple nationwide news media, providing confidence to the government and the general public in the vaccination programme. This continued until the transition to the endemic phase in May 2023. In the Philippines, due to a substantial delay in the initiation of the study, the report became available in November 2023 for the FASCINATE (outpatient) study and March 2024 for the MOTIVATE (inpatient) study.

DISCUSSION

We faced many challenges in both countries (**Table 1**). Here we highlight four main challenges. The first challenge was difficulty in identifying health-care facilities willing to cooperate in the study. Health-care workers were working tirelessly around the

clock to respond to the pandemic and thus, any additional work for them was often not possible. In Japan, the lead investigator contacted the health-care facilities directly to seek cooperation. Finally, 16 clinics/hospitals for the FASCINATE study and 29 hospitals for the MOTIVATE study agreed to join. Specifically, for the MOTIVATE study in Japan, NIID and ECMOnet (a non-profit organization formed by critical care physicians) successfully collaborated to identify health-care facilities.[13] In the Philippines, the FASCINATE study was conducted in two hospitals while the MOTIVATE study was a single-centre study.

The second challenge was that there was no national database of vaccination records. Therefore, such data were collected at each health-care facility (using either a vaccination card, medical chart, or [if neither was available] self-report[14]). However, collecting accurate vaccination history can be resource-intensive as described in this report. This was a disadvantage compared to a few other countries, such as the United Kingdom of Great Britain and Northern Ireland, where such data were readily available. However, we saw this as an opportunity to assess VE in an accurate manner by prospectively collecting data that were not readily available and by being able to set a clear clinical case definition to reduce bias caused by unclear definitions. Specifically, for the FASCINATE study, we collected past behavioural data such as attending social gatherings that can potentially be associated with both exposure (likelihood of vaccination or change in behaviour given vaccination) and outcome (likelihood of infection). In fact, the FASCINATE study also aimed to elucidate socio-behavioural factors associated with SARS-CoV-2 infection, which turned out to be important in adjusting for potential biases.[9] For the MOTIVATE study, we collected data on whether the medical intervention, such as oxygen use, was due to COVID-19 or other diseases among those who tested positive for SARS-

CoV-2[13] since incidental infection found at the time of hospital admission with unrelated conditions was an issue in using a database to conduct VE studies.[15]

The third challenge was that of evolving epidemiological biases and confounders (**Table 2**). Due to the prospective nature of the study, we were able to mitigate the majority of these, but the risk of residual bias was considered high in the Philippines study results. Some reasons for this included most unvaccinated individuals likely being infected prior to study initiation (which was immediately after the first Omicron surge), which likely afforded better protection compared to vaccination several months earlier; and differential sociodemographic and risk behaviour status between the vaccinated and the unvaccinated.

The final challenge was the timeline. There was a substantial delay in study initiation in the Philippines. What took time was the alignment with various stakeholders and institutional review board (IRB) approval. Following IRB approval, a memorandum of agreement as well as a non-disclosure agreement needed to be signed and validated by the hospital legal department with apostille required. Recruitment was also a challenge as the investigation finally started right after the large surge of Omicron. In Japan, we were able to initiate the study and publish reports in a relatively timely manner to inform policy/risk communication. However, it was not always possible to respond to the rapidly evolving policy/communication needs, especially on VE against severe disease.

For future epidemics and pandemics, preparedness during the inter-epidemic/inter-pandemic periods will be critical so that interventions such as vaccination can be rapidly evaluated when such health emergencies occur. Based on our experience, we summarized three main lessons learnt. First is the importance of establishing and maintaining platforms to rapidly evaluate interventions such as

vaccination. These would be ideally incorporated into public health surveillance (e.g., ILI or SARI surveillance) and done via prospective data collection with clear clinical case definition. This is to ensure clear case definition and collection of essential information such as relevant potential confounders. If this is infeasible, means of clinical research networks such as ISARIC and/or a unified database that can link exposure and outcome data (as well as genomic characterization of infections) can be considered. Setting up these platforms and monitoring epidemics such as seasonal influenza and RSV infection during the inter-emergency/pandemic period in advance is critical as these can rapidly be translated to utilize in newly-emerging respiratory infections with pandemic potential. The second lesson is the usefulness of uniform and practical protocols with careful and agile consideration of biases and confounders to conduct clinical research based on policy/risk communication needs, which would also allow for cross-comparison of studies. A guidance document on VE studies was published by WHO,[5,15] but it was generic in nature. Therefore, some of the authors at the WHO Regional Office for the Western Pacific prepared a practical protocol, which was used as a basis for a VE study in Viet Nam. The third lesson is the value of communication with all potential stakeholders including the institutional review board during the inter-emergency/epidemic/pandemic period to pre-approve generic clinical study protocols which can then be expedited when health emergency occurs.

During health emergencies, responding to the event itself is the priority, and conducting operational studies may seem less important. However, evidence-based decision-making is key to successful response, and such studies are exactly what inform health emergency response.

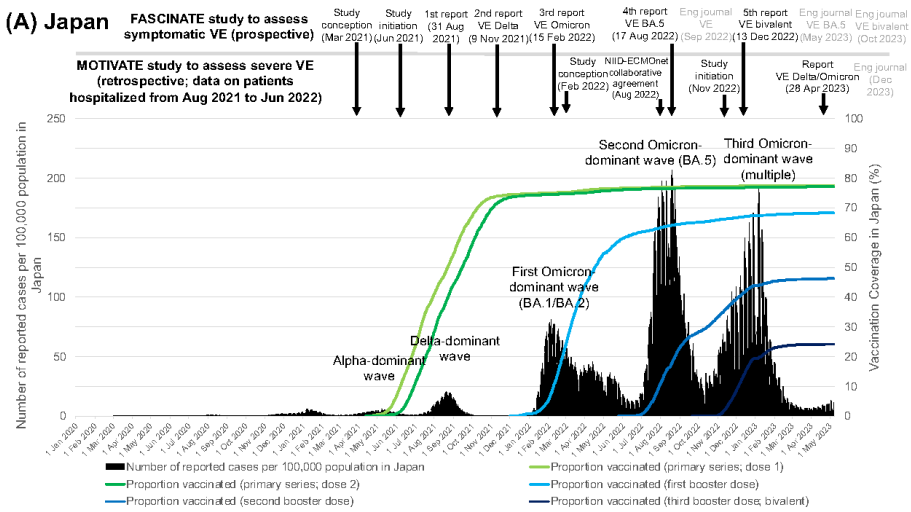
REFERENCES

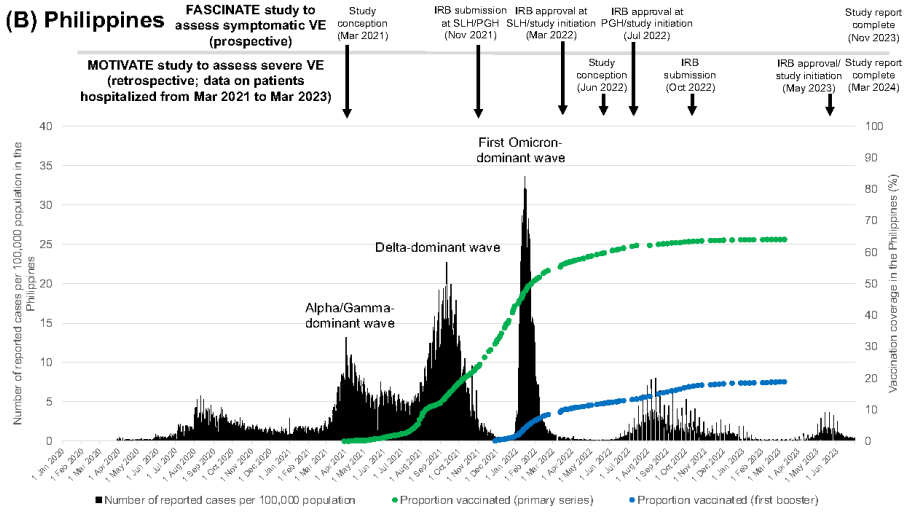
1. COVID-19 vaccine effectiveness. Geneva: World Health Organization; 2024. Available from: https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/covid-19-vaccine-effectiveness-and-impact, accessed 1 January 2024.
2. COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: ethical considerations. Geneva: World Health Organization; 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Policy-brief-Vaccine-trial-design-2021.1, accessed 1 January 2024.
3. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med. 2022;386(4):340–50. doi:10.1056/NEJMoa2115481 pmid:35021002
4. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med. 202;386(16):1532–46. doi:10.1056/NEJMoa2119451 pmid:35249272
5. Evaluation of COVID-19 vaccine effectiveness: interim guidance. Geneva: World Health Organization; 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1, accessed 1 January 2024.
6. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med. 2001;344(12):889–96. doi:10.1056/NEJM200103223441204 pmid:11259722

7. Simms KT, Hanley SJB, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. Lancet Public Health. 2020;5(4):e223–34. doi:10.1016/S2468-2667(20)30010-4 pmid:32057317
8. Larson HJ, Hartigan-Go K, de Figueiredo A. Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. Hum Vaccin Immunother. 2019;15(3):625–7. doi:10.1080/21645515.2018.1522468 pmid:30309284
9. Arashiro T, Arima Y, Kuramochi J, Muraoka H, Sato A, Chubachi K, et al. Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. Euro Surveill. 2023;28(4):2300034. doi:10.2807/1560-7917.ES.2023.28.4.2300034 pmid:36700869
10. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, et al. Coronavirus disease 19 (COVID-19) vaccine effectiveness against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during Delta-dominant and Omicron-dominant periods in Japan: a multicenter prospective case-control study (FASCINATE study). Clin Infect Dis. 2023;76(3):e108–15. doi:10.1093/cid/ciac635 pmid:35918782
11. Arashiro T, Arima Y, Kuramochi J, Muraoka H, Sato A, Chubachi K, et al. Effectiveness of BA.1- and BA.4/BA. 5-containing bivalent COVID-19 mRNA vaccines against symptomatic SARS-CoV-2 infection during the BA.5-dominant period in Japan. Open Forum Infect Dis. 2023;10(6):ofad240. doi:10.1093/ofid/ofad240 pmid:37351451
12. Arashiro T, Arima Y, Kuramochi J, Muraoka H, Sato A, Chubachi K, et al. Immune escape and waning immunity of COVID-19 monovalent mRNA vaccines

252 against symptomatic infection with BA.1/BA.2 and BA.5 in Japan. Vaccine.
253 2023;41(47):6969–79. doi:10.1016/j.vaccine.2023.10.021 pmid:37839947
254 13. Arashiro T, Miwa M, Nakagawa H, Takamatsu J, Oba K, Fujimi S, et al. COVID-
255 19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy,
256 invasive mechanical ventilation, and death in Japan: a multicenter case-control
257 study (MOTIVATE study). Vaccine. 2023:S0264-410X(23)01480-9.
258 doi:10.1016/j.vaccine.2023.12.033 pmid:38114409
259 14. Stephenson M, Olson SM, Self WH, Ginde AA, Mohr NM, Gaglani M, et al.
260 Ascertainment of vaccination status by self-report versus source documentation:
261 Impact on measuring COVID-19 vaccine effectiveness. Influenza Other Respir
262 Viruses. 2022;16(6):1101–11. doi:10.1111/irv.13023 pmid:35818721
263 15. Evaluation of COVID-19 vaccine effectiveness in a changing landscape of
264 COVID-19 epidemiology and vaccination second addendum to evaluation of
265 COVID-19 vaccine effectiveness: interim guidance. Geneva: World Health
266 Organization; 2022. Available from: https://www.who.int/publications/i/item/WHO-
267 2019-nCoV-vaccine_effectiveness-VE_evaluations-2022.1, accessed 1 January
268 2024.

Fig. 1. Epidemic curves of the number of reported COVID-19 cases and vaccine rollout with study milestones in (A) Japan and (B) the Philippines





Sources:
Japan: Ministry of Health, Labour and Welfare, Japan [https://www.mhlw.go.jp/stf/covid-19/open-data.html] and Digital Agency, Japan [https://info.vrs.digital.go.jp/dashboard]
Philippines: Our World in Data [https://ourworldindata.org].
Note that the data are likely underestimated due to reporting constraints, testing/reporting intensity varied substantially over time, and COVID-19 vaccination data for the Philippines are up to 9 March 2023.

280 **Table 1.** Implementation challenges in conducting vaccine effectiveness (VE) studies during the COVID-19 pandemic based on

281 experience in Japan and the Philippines

Implementation challenges	Solutions/mitigations (checkmark (✓) for the ones used and arrowhead (➢) for suggestions for future studies)	Countries
Recruitment of health-care facilities	✓ Search for health-care facilities where testing is done frequently and both COVID-19 as well as other respiratory infection patients are admitted frequently ✓ Convey the public health value of the research ✓ Collaborate with existing clinical networks ✓ Design the study in a way that the burden of health-care facilities is minimal ➢ Establishing a unified database that can link vaccination records and outcomes may minimize/eliminate the need to do this	Both (especially Japan)
Unavailability of vaccination record database	✓ Refer to either vaccination card or medical chart (if neither is available, self-report) ➢ Establish a unified database for vaccination records	Both
Epidemiological biases and confounders (see below for specific list)	✓ Be careful and agile in consideration of biases and confounders ➢ Ensure clear case definition and collection of essential information such as relevant potential confounders (best done as prospective study by ideally incorporating into public health surveillance such as influenza-like illness [ILI] or severe acute respiratory infection [SARI] surveillance) ➢ Prepare uniform and practical protocols, which can rapidly be adopted if a health emergency occurs ➢ See below for specific solutions/mitigations for each bias or confounder	Both
Timeline	✓ Communicate with various stakeholders including institutional review board secretariat/members regularly	Both (especially the Philippines)

	➢	Establish/maintain of platforms such as clinical research networks and unified databases during inter-emergency/epidemic/pandemic period	
	➢	Conduct studies as public health activities rather than research (if feasible under local circumstances)	
	➢	Append VE evaluation component to existing public health surveillance such as ILI or SARI surveillance	
	➢	Prepare uniform and practical protocols, which can be pre-approved and then rapidly adopted when a health emergency occurs	
	➢	Establish a mechanism to publish and disseminate study results rapidly	
Maintaining motivation of health-care facilities	✓	Periodically communicate and publish findings to acknowledge contributions	Japan
Infection prevention and control measures in health-care facilities	✓	Show evidence that the virus can be inactivated on paper after several days	Both
	✓	Design the study in a way that the burden of health-care facilities is minimal	
Human resources	✓	Support from medical students who are eager to gain research experience	
	➢	Establish ways to build surge capacity	
Funding	✓	Publishing multiple reports resulted in further funding (Japan)	Both
	✓	World Health Organization provided funding (the Philippines)	

283 **Table 2.** Biases and how to approach them in conducting vaccine effectiveness (VE) studies during the COVID-19 pandemic

284 based on experience in Japan and the Philippines

Epidemiological biases and confounders	**Problem**	**Approach to reduce biases/confounders (checkmark (✓) for the ones used and arrowhead (➢) for suggestions for future studies)**
Potential confounding factors known in the beginning of the study	Potential confounding factors include age, sex, race/ethnicity, socioeconomic status, occupation, chronic medical conditions, close contact history, onset date, and priority groups for vaccination	✓ Adjust for confounders
Diagnostic bias	Health workers more likely to test certain population such as unvaccinated individuals or individuals at high-risk of severe COVID-19	✓ Ask health workers to not decide who to test based on vaccination or other status ✓ Use specific case definition for study inclusion
Misclassification of the outcome	False positives and false negatives	✓ Use PCR that has high sensitivity and specificity ✓ Use more specific and severe outcomes ✓ Restrict to individuals with symptom onset within two weeks or less
Misclassification of the exposure	Wrong vaccination data	✓ Ascertain vaccination history with vaccine card/certificate ➢ Establish unified database that can link vaccination record and outcomes such as hospitalizations
Prior infection	• Prior infection may partially protect against subsequent infection, resulting in underestimate of VE • Individuals with known prior SARS-CoV-2 infection are less likely to get vaccinated	✓ Adjust for prior infection ➢ Perform sensitivity analysis excluding those with prior SARS-CoV-2 infection ➢ Under-ascertainment of prior infection results in residual bias (although exploratory, use of infection-specific serology may help to mitigate this)
Spurious waning	An ever-increasing pool of unvaccinated individuals become immune through infection, resulting in a progressively increasing underestimate of VE, giving the appearance of waning	➢ Conduct the study in a short period of time before the epidemic peak ➢ Enrol only those without prior infection
Vaccination certificate/passport policy (for domestic purposes)	Vaccination passport to allow vaccinated individuals to engage in high-risk behaviours such as going to restaurants and bars, while keeping unvaccinated individuals from such activities, resulting in underestimate of VE (or even negative VE)	✓ Adjust for risk behaviour status

Differential risk behaviour based on vaccine status	Vaccinated individuals are more likely to engage in high-risk behaviours such as going to restaurants and bars as they feel protected, resulting in underestimate of VE (or even negative VE)	✓	Adjust for risk behaviour status
Incidental infection among individuals hospitalized with unrelated conditions	If SARS-CoV-2 testing at hospital admission is done for individuals without COVID-19-like symptoms in the setting of high transmission, this will result in underestimate of VE (given lower VE against infection compared to hospitalization)	✓	Use of more specific and severe outcomes such as oxygen use, mechanical ventilation use, or ideally restrict to individuals who are hospitalized specifically for COVID-19
Care seeking and testing behaviour/changing testing strategies	• Vaccinated persons are less likely to seek care/testing for COVID-19-like illness due to perception of protection, resulting in overestimate of VE • Changing testing strategies (e.g. after Omicron, testing became less frequent in many countries)	✓ ➢	Breakthrough infection is common enough that individuals should be encouraged to get tested even after vaccination Make sure testing strategy remains stable (such as by prospective study design)
Bias due to co-circulation of influenza, RSV, or *Streptococcus pneumoniae* and COVID-19	Co-circulation of influenza, RSV, or *Streptococcus pneumoniae* and COVID-19 can result in biased VE estimates as propensity to get vaccinated may be similar for COVID-19 vaccines and influenza/pneumococcal vaccines	✓	Exclude influenza/RSV/*Streptococcus pneumoniae* *pneumoniae* cases or adjust for influenza vaccination/pneumococcal vaccination status
Other residual confounder/biases	Other potential residual confounder/biases	➢	Restrict the study population to special population such as health-care workers whose sociodemographic factors are similar between the vaccinated and unvaccinated

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Results not in the manuscripts

Most results are compiled into papers. However, some are independent results that are not included in the papers. This section describes these results.

Triangulation with exploratory controls (part of objective 1)

The questionnaire was disseminated starting on February 12, 2022, and 300 individuals eligible to participate answered the questionnaire within 3 days. After excluding two individuals who had symptoms or who tested positive for SARS-CoV-2 within 14 days, 298 individuals were included in the analysis as exploratory controls. As for the test-positive and test-negative individuals, individuals who were tested in calendar week 5−8 of 2022 (January 31−February 20; two weeks before and after the data collection for exploratory control) were extracted; as a result, 400 test-positives and 337 test-negatives were included for this analysis. Among all 1035 participants, the median age (interquartile range [IQR]) was 37 (28−48) years, 504 were males (48.7%), and 252 (24.4%) had comorbidities. Overall, the TND comparison (comparison between test-positive and test-negative) did not yield higher odds, unlike the report during the Alpha to Delta replacement period. In contrast, in the CC-positive comparison (comparison between test-positive and exploratory control), some factors were associated with SARS-CoV-2 infection, including attending social gathering once (aOR 4.29 [95% CI 2.21–8.31]; note dose dependency was not observed), attending social gatherings without alcohol (aOR 1.85 [95% CI 1.14–3.01]), attending social gatherings with alcohol (aOR 1.45 [95% CI 0.99–2.12]), attending social gatherings at restaurants/bars (aOR 1.65 [95% CI 1.17–2.32]), attending social gathering in the evening/night (aOR 1.55 [95% CI 1.07–2.24]), and attending gatherings of five or more people (aOR 2.36 [95% CI 1.11–4.99]), all compared to those who did not attend gatherings. Also, unlike the report during the Alpha to Delta replacement period, going to work or school was associated with infection (aOR 6.23 [95% CI 3.72–10.45]), with increasing frequency of teleworking/attending online classes being associated with protection. It is counter-intuitive, but residing in an urban location (aOR 0.39 [95% CI 0.26–0.59]) or visiting an urban location (aOR 0.39 [95% CI 0.25–0.63]) were associated with protection, compared to never visiting an urban location. Also, in CC-negative comparison (comparison between test-negative and exploratory control), some factors were associated with SARS-CoV-2 infection including having a conversation at a close distance (aOR 1.53 [95% CI 1.08–2.16]), attending social gathering twice (aOR 1.91 [95% CI 1.05–3.48]), attending social gatherings without alcohol (aOR 2.35 [95% CI 1.43–3.87]), attending social gatherings with alcohol (aOR 1.45 [95% CI 0.97–2.16]), attending social gatherings at restaurants/bars (aOR 1.65 [95% CI 1.23–2.54]), attending social gathering during daytime only (aOR

2.10 [95% CI 1.25–3.50]), attending social gathering in the evening/night (aOR 1.53 [95% CI 1.03–2.27]), and attending gatherings of five or more people (aOR 2.42 [95% CI 1.10–5.32]), all compared to those who did not attend gatherings. Going to work or school was also associated with infection (aOR 3.44 [95% CI 2.15–5.49]), with teleworking/attending online classes almost all the time being associated with protection (aOR 0.41 [95% CI 0.19–0.90]). Similar to the CC-positive comparison, residing in an urban location (aOR 0.21 [95% CI 0.14–0.33]) or visiting an urban location (aOR 0.21 [95% CI 0.13–0.35]) were associated with protection, compared to never visiting an urban location. There are several points to note regarding the results. First, data collection was done during the first peak of the early Omicron wave, and there was widespread community spread of SARS-CoV-2, where there were various occasions of getting infected (unlike during the Alpha to Delta replacement period where the viruses were circulating in more limited population engaging in high-risk population even under the state of emergency policy in effect). Also, there may have been other respiratory viruses that were circulating at higher levels during the early Omicron. These may have resulted in the TND comparison (comparison between test-positive and test-negative) not yielding higher odds, unlike the report during the Alpha to Delta replacement period when the controls may not have necessarily been infected with other respiratory pathogens. In contrast, many factors were associated with infection in the CC-positive comparison but not in the TND comparison. This indicates the potential usefulness of the exploratory control. However, there were some results that seem to be counter-intuitive, including residing or visiting an urban location being associated with protection from infection. One possible explanation is that individuals who take online surveys may be more likely to visit urban locations compared to those who get tested and are found to be positive at healthcare facilities (e.g., those who take online surveys may do self-testing, etc.), individuals. Overall, as explained in the "*Note on case-control studies with test-negative design*" in the method section, the choice of control is always a challenge in case-control studies. Thus, careful interpretation is necessary as there may be a higher likelihood of residual bias by not being able to control for healthcare seeking.

Table 1. Demographic and clinical characteristics of the study participants

	All (n = 1035)	Test-positive (n = 400)	Test-negative (n = 337)	Community control (n = 298)
Median age in years	37 (28–48)	40 (29–49)	35 (28–47)	35 (27–46)
Age in years, n (%)				
20-29	326 (31.5)	103 (25.8)	105 (31.2)	118 (39.6)
30-39	278 (26.9)	94 (23.5)	110 (32.6)	74 (24.8)
40-49	225 (21.7)	110 (27.5)	55 (16.3)	60 (20.1)
50-59	129 (12.5)	56 (14.0)	43 (12.8)	30 (10.1)
60+	77 (7.4)	37 (9.3)	24 (7.1)	16 (5.4)
Sex, n (%); missing = 1 (0.1%)				
Male	504 (48.7)	200 (50.0)	154 (45.8)	150 (50.3)
Female	530 (51.3)	200 (50.0)	182 (54.2)	148 (49.7)
Educational attainment, n (%); missing = 10 (1.0%)				
Middle school or less	24 (2.3)	12 (3.1)	7 (2.1)	5 (1.7)
High school	236 (23.0)	92 (23.4)	92 (27.6)	52 (17.5)
Junior college/technical college	210 (20.5)	99 (25.1)	68 (20.4)	43 (14.3)
Undergraduate or graduate school	555 (54.2)	191 (48.5)	166 (49.9)	198 (66.4)
Place of residence, n (%); missing = 8 (0.8%)				
Home	1,011 (98.4)	390 (98.2)	328 (98.8)	293 (98.3)
Hospital or long-term care facility	2 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)
Dormitory or other	14 (1.4)	6 (1.5)	3 (0.9)	5 (1.7)
Comorbidities, n (%)				
No	783 (75.6)	299 (74.8)	234 (69.4)	250 (83.9)
Yes	252 (24.4)	101 (25.3)	103 (30.6)	48 (16.1)
Smoking, n (%)				
Never-smoker	572 (55.3)	209 (52.3)	174 (51.6)	189 (63.4)
Past smoker	240 (23.2)	107 (26.8)	82 (24.3)	51 (17.1)
Current smoker	223 (21.6)	84 (21.0)	81 (24.0)	58 (19.5)
Days from onset to SARS-CoV-2 test*				
	1 (1–3)	2 (1–3)	1 (1–3)	N/A
SARS-CoV-2 diagnostic test in the past month, n (%); missing = 14				

No	846 (82.9)	331 (84.4)	265 (80.1)	250 (83.9)
Yes	175 (17.1)	61 (15.6)	66 (19.9)	48 (16.1)
Past SARS-CoV-2 infection, n (%)				
No	1009 (97.5)	394 (98.5)	323 (95.9)	292 (98.0)
Yes	26 (2.5)	6 (1.5)	14 (4.2)	6 (2.0)
Number of COVID-19 vaccinations received, n (%); missing = 15				
None	135 (13.2)	59 (15.1)	29 (8.8)	47 (15.8)
One	11 (1.1)	4 (1.0)	3 (0.9)	4 (1.3)
Two	817 (80.1)	314 (80.3)	277 (83.7)	226 (75.8)
Three	57 (5.6)	14 (3.6)	22 (6.7)	21 (7.1)

*Median (interquartile range)

Table 2. Association of SARS-CoV-2 infection with various activities/situations

	Test-positive, n (%)	Test-negative, n (%)	Community control, n (%)	TND: Crude odds ratio (95% CI)	TND: Adjusted odds ratio (95% CI)†	CC positive: Crude odds ratio (95% CI)	CC positive: Adjusted odds ratio (95% CI)†	CC negative: Crude odds ratio (95% CI)	CC negative: Adjusted odds ratio (95% CI)†
Having a conversation at a close distance (within arm's reach)									
No	265 (66.3)	199 (59.1)	202 (67.8)	1	1	1	1	1	1
Yes	135 (33.8)	138 (41.0)	96 (32.2)	0.73 (0.54–0.99)	0.79 (0.57–1.11)	1.07 (0.78–1.48)	1.14 (0.82–1.60)	1.46 (1.05–2.02)	1.53 (1.08–2.16)
Closed spaces with poor ventilation/air exchange									
No	358 (89.5)	300 (89.0)	274 (92.0)	1	1	1	1	1	1
Yes	42 (10.5)	37 (11.0)	24 (8.1)	0.95 (0.60–1.52)	0.99 (0.59–1.66)	1.34 (0.79–2.27)	1.43 (0.83–2.48)	1.41 (0.82–2.41)	1.26 (0.70–2.23)
Large gatherings that involve eating and/or drinking for an extended period of time									
No	384 (96.0)	321 (95.3)	282 (94.6)	1	1	1	1	1	1
Yes	16 (4.0)	16 (4.8)	16 (5.4)	0.84 (0.41–1.70)	0.72 (0.33–1.55)	0.73 (0.36–1.49)	0.84 (0.40–1.77)	0.88 (0.43–1.79)	1.05 (0.49–2.25)
Crowded places									
No	328 (82.0)	272 (80.7)	236 (79.2)	1	1	1	1	1	1
Yes	72 (18.0)	65 (19.3)	62 (20.8)	0.92 (0.63–1.33)	0.86 (0.57–1.31)	0.84 (0.57–1.22)	0.84 (0.56–1.25)	0.91 (0.62–1.34)	0.89 (0.58–1.36)
Cohabitation in small living quarters									
No	380 (95.0)	321 (95.3)	281 (94.3)	1	1	1	1	1	1
Yes	20 (5.0)	16 (4.8)	17 (5.7)	1.06 (0.54–2.07)	1.13 (0.54–2.37)	0.87 (0.45–1.69)	0.93 (0.46–1.87)	0.82 (0.41–1.66)	0.93 (0.44–1.97)
Frequency of social gatherings attended that involved eating/drinking									
0 (did not attend)	201 (54.8)	169 (53.1)	186 (62.6)	1	1	1	1	1	1

1	57 (15.5)	49 (15.4)	13 (4.4)	0.98 (0.63–1.51)	0.97 (0.60–1.58)	4.06 (2.15–7.65)	4.29 (2.21–8.31)	4.15 (2.17–7.91)	4.63 (2.36–9.08)
2	36 (9.8)	35 (11.0)	23 (7.7)	0.86 (0.52–1.44)	0.95 (0.54–1.68)	1.45 (0.83–2.54)	1.73 (0.96–3.10)	1.67 (0.95–2.95)	1.91 (1.05–3.48)
≥3	73 (19.9)	65 (20.4)	75 (25.3)	0.94 (0.64–1.40)	0.97 (0.62–1.52)	0.90 (0.62–1.32)	1.01 (0.68–1.51)	0.95 (0.64–1.41)	1.11 (0.72–1.69)
Presence or absence of alcohol in social gatherings that involved eating/drinking									
Did not attend	201 (54.8)	169 (53.1)	186 (62.8)	1	1	1	1	1	1
No alcohol	67 (18.3)	63 (19.8)	34 (11.5)	0.89 (0.60–1.33)	0.93 (0.59–1.47)	1.82 (1.15–2.88)	1.85 (1.14–3.01)	2.04 (1.28–3.25)	2.35 (1.43–3.87)
With alcohol	99 (27.0)	86 (27.0)	76 (25.7)	0.97 (0.68–1.38)	0.99 (0.67–1.48)	1.21 (0.84–1.73)	1.45 (0.99–2.12)	1.25 (0.86–1.81)	1.45 (0.97–2.16)
Location of social gatherings attended that involved eating/drinking									
Did not go out to eat	201 (54.8)	169 (53.1)	186 (62.6)	1	1	1	1	1	1
Only at home	16 (4.4)	16 (5.0)	7 (2.4)	0.84 (0.41–1.73)	1.01 (0.43–2.39)	2.12 (0.85–5.26)	2.08 (0.79–5.49)	2.52 (1.01–6.26)	2.97 (1.15–7.67)
Restaurants/bars[‡]	149 (40.6)	132 (41.5)	95 (32.0)	0.95 (0.70–1.30)	0.97 (0.68–1.38)	1.45 (1.05–2.01)	1.65 (1.17–2.32)	1.53 (1.09–2.14)	1.77 (1.23–2.54)
Outdoors/parks[§]	1 (0.3)	1 (0.3)	9 (3.0)	0.84 (0.05–13.54)	0.70 (0.40–12.39)	0.10 (0.01–0.82)	0.11 (0.01–0.99)	0.12 (0.02–0.98)	0.09 (0.01–0.85)
Time of day of social gatherings attended that involved eating/drinking									
Did not go out to eat	201 (54.8)	169 (53.1)	186 (62.6)	1	1	1	1	1	1
Daytime only	52 (14.2)	53 (16.7)	32 (10.7)	0.82 (0.53–1.27)	0.78 (0.48–1.27)	1.50 (0.93–2.44)	1.58 (0.94–2.63)	1.82 (1.12–2.96)	2.10 (1.25–3.50)
Evening/night	114 (31.1)	96 (30.2)	79 (26.6)	1.00 (0.71–1.40)	1.09 (0.73–1.61)	1.34 (0.94–1.89)	1.55 (1.07–2.24)	1.34 (0.93–1.92)	1.53 (1.03–2.27)
Visiting a cafe with others									
No	263 (76.0)	219 (72.8)	215 (72.4)	1	1	1	1	1	1
Yes	83 (24.0)	82 (27.2)	82 (27.6)	0.84 (0.59–1.20)	0.77 (0.51–1.15)	0.83 (0.58–1.18)	0.93 (0.64–1.36)	0.98 (0.69–1.41)	1.02 (0.69–1.50)

Ordering takeout									
No	233 (67.0)	177 (59.0)	190 (64.0)	1	1	1	1	1	1
Yes	115 (33.1)	123 (41.0)	107 (36.0)	0.71 (0.52–0.98)	0.75 (0.52–1.07)	0.88 (0.63–1.21)	0.78 (0.55–1.10)	1.23 (0.89–1.72)	1.18 (0.83–1.67)
Food delivery									
No	271 (78.1)	225 (73.8)	222 (74.8)	1	1	1	1	1	1
Yes	76 (21.9)	80 (26.2)	75 (25.3)	0.79 (0.55–1.13)	0.64 (0.42–0.97)	0.83 (0.58–1.20)	0.93 (0.63–1.38)	1.05 (0.73–1.52)	1.08 (0.73–1.59)
Eating out by oneself									
No	230 (66.1)	219 (71.3)	175 (58.9)	1	1	1	1	1	1
Yes	118 (33.9)	88 (28.7)	122 (41.1)	1.28 (0.92–1.78)	1.06 (0.72–1.54)	0.74 (0.53–1.01)	0.80 (0.57–1.13)	0.58 (0.41–0.81)	0.67 (0.47–0.96)
Maximum number of people attended including oneself									
Did not go out to eat/drink or to a cafe	174 (51.5)	137 (48.6)	166 (55.9)	1	1	1	1	1	1
<5 people	140 (41.4)	126 (44.7)	118 (39.7)	0.88 (0.63–1.22)	0.86 (0.59–1.27)	1.13 (0.82–1.57)	1.25 (0.89–1.76)	1.29 (0.92–1.81)	1.45 (1.01–2.10)
≥5 people	24 (7.1)	19 (6.7)	13 (4.4)	0.99 (0.52–1.89)	1.03 (0.50–2.12)	1.76 (0.87–3.57)	2.36 (1.11–4.99)	1.77 (0.84–3.71)	2.42 (1.10–5.32)
Maximum time spent									
Did not go out to eat/drink or to a cafe	174 (51.9)	137 (48.8)	166 (55.9)	1	1	1	1	1	1
<2 hours	72 (21.5)	76 (27.1)	51 (17.2)	0.75 (0.50–1.10)	0.71 (0.46–1.11)	1.35 (0.89–2.04)	1.43 (0.92–2.21)	1.81 (1.18–2.75)	1.90 (1.21–2.98)
≥2 hours	89 (26.6)	68 (24.2)	80 (26.9)	1.03 (0.70–1.52)	1.08 (0.68–1.70)	1.06 (0.73–1.54)	1.25 (0.84–1.85)	1.03 (0.69–1.53)	1.26 (0.82–1.94)

[†]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, past SARS-CoV-2 infection, health-care facility, and calendar week.

[‡]Individuals may or may not have history of gathering at home.

[§]Individuals may or may not have history of gathering at home, restaurants, and bars.

Table 3. Association of SARS-CoV-2 infection with behaviors other than going out to eat/drink

	Test-positive, n (%)	Test-negative, n (%)	Community control, n (%)	TND: Crude odds ratio (95% CI)	TND: Adjusted odds ratio (95% CI)†	CC positive: Crude odds ratio (95% CI)	CC positive: Adjusted odds ratio (95% CI)†	CC negative: Crude odds ratio (95% CI)	CC negative: Adjusted odds ratio (95% CI)†
Indoor events/gathering‡									
No	313 (92.6)	285 (95.0)	271 (91.3)	1	1	1	1	1	1
Yes	25 (7.4)	15 (5.0)	26 (8.8)	1.52 (0.78–2.94)	1.35 (0.67–2.74)	0.83 (0.47–1.48)	0.88 (0.48–1.61)	0.55 (0.28–1.06)	0.57 (0.28–1.15)
Outdoor events/gathering‡									
No	314 (94.6)	285 (94.4)	272 (91.6)	1	1	1	1	1	1
Yes	18 (5.4)	17 (5.6)	25 (8.4)	0.96 (0.49–1.90)	1.06 (0.51–2.21)	0.62 (0.33–1.17)	0.73 (0.38–1.42)	0.65 (0.34–1.23)	0.70 (0.35–1.39)
Department stores and shopping malls									
No	157 (46.0)	117 (38.4)	132 (44.4)	1	1	1	1	1	1
Yes	184 (54.0)	188 (61.6)	165 (55.6)	0.73 (0.53–1.00)	0.93 (0.66–1.32)	0.94 (0.69–1.28)	0.91 (0.65–1.26)	1.29 (0.93–1.78)	1.16 (0.82–1.65)
Karaoke with others									
No	332 (96.5)	293 (95.4)	278 (93.6)	1	1	1	1	1	1
Yes	12 (3.5)	14 (4.6)	19 (6.4)	0.76 (0.34–1.66)	0.55 (0.24–1.27)	0.53 (0.25–1.11)	0.56 (0.26–1.22)	0.70 (0.34–1.42)	0.82 (0.39–1.75)
Gym									
No	303 (87.8)	282 (91.8)	268 (90.2)	1	1	1	1	1	1
Yes	42 (12.2)	25 (8.1)	29 (9.8)	1.56 (0.93–2.63)	1.42 (0.81–2.52)	1.28 (0.78–2.11)	1.37 (0.81–2.31)	0.82 (0.47–1.43)	0.97 (0.53–1.77)
Work/school									

No	36 (9.7)	45 (13.8)	81 (27.2)	1	1	1	1	1	1
Yes	334 (90.3)	281 (86.2)	217 (72.8)	1.49 (0.93–2.37)	1.54 (0.88–2.72)	3.46 (2.26–5.31)	6.23 (3.72–10.45)	2.33 (1.55–3.50)	3.44 (2.15–5.49)
Work/school full-time[§]									
Part-time	45 (13.5)	46 (16.4)	35 (16.1)	1	1	1	1	1	1
Full-time	288 (86.5)	234 (83.6)	182 (83.9)	1.26 (0.81–1.96)	1.29 (0.77–2.16)	1.23 (0.76–1.99)	1.51 (0.89–2.59)	0.98 (0.61–1.58)	1.27 (0.74–2.19)
Use trains to commute[§]									
No	150 (45.9)	166 (60.4)	71 (32.7)	1	1	1	1	1	1
Yes	177 (54.1)	109 (39.6)	146 (67.3)	1.80 (1.30–2.49)	1.30 (0.84–2.01)	0.57 (0.40–0.82)	0.68 (0.46–1.01)	0.32 (0.22–0.46)	0.29 (0.19–0.45)
Frequency of teleworking/attending online classes[§,¶]									
0%	181 (64.4)	157 (68.9)	87 (47.8)	1	1	1	1	1	1
25%	39 (13.9)	23 (10.1)	35 (19.2)	1.47 (0.84–2.57)	1.35 (0.71–2.55)	0.54 (0.32–0.90)	0.66 (0.37–1.16)	0.36 (0.20–0.66)	0.43 (0.23–0.84)
50%	17 (6.1)	18 (7.9)	18 (9.9)	0.82 (0.41–1.64)	0.68 (0.31–1.49)	0.45 (0.22–0.92)	0.55 (0.26–1.17)	0.55 (0.27–1.12)	0.77 (0.36–1.65)
75%	13 (4.6)	16 (7.0)	20 (11.0)	0.70 (0.33–1.51)	0.51 (0.22–1.49)	0.31 (0.15–0.66)	0.37 (0.17–0.83)	0.44 (0.22–0.90)	0.62 (0.29–1.32)
Almost 100%	31 (11.0)	14 (6.1)	22 (12.1)	1.92 (0.99–3.74)	1.36 (0.64–2.90)	0.68 (0.37–1.24)	0.72 (0.37–1.38)	0.35 (0.17–0.72)	0.41 (0.19–0.90)
Residing/visiting an urban location[#]									
Never	131 (35.9)	157 (49.2)	48 (16.1)	1	1	1	1	1	1
Residing an urban location	151 (41.4)	110 (34.5)	165 (55.4)	1.65 (1.17–2.31)	1.21 (0.62–2.36)	0.34 (0.23–0.50)	0.39 (0.26–0.59)	0.20 (0.14–0.31)	0.21 (0.14–0.33)
Visiting an urban location	83 (22.7)	52 (16.3)	85 (28.5)	1.91 (1.26–2.90)	1.09 (0.64–1.88)	0.36 (0.23–0.56)	0.39 (0.25–0.63)	0.19 (0.12–0.30)	0.21 (0.13–0.35)
Travel									

No travel	334 (95.7)	291 (96.4)	276 (92.6)	1	1	1	1	1	1
Business travel	6 (1.7)	4 (1.3)	6 (2.0)	1.31 (0.37–4.68)	1.52 (0.38–6.07)	0.83 (0.26–2.59)	0.90 (0.27–2.98)	0.63 (0.18–2.26)	0.21 (0.14–0.33)
Non-business travel	9 (2.5)	7 (2.3)	16 (5.4)	1.12 (0.41–3.05)	1.10 (0.35–3.41)	0.46 (0.20–1.07)	0.49 (0.21–1.16)	0.41 (0.17–1.02)	0.21 (0.13–0.35)

[†]Adjusted for age group, sex, presence of comorbidities, educational attainment, place of residence, past SARS-CoV-2 infection, health-care facility, and calendar week.

[‡]Gatherings include events, social groups, school extracurricular activities, etc.

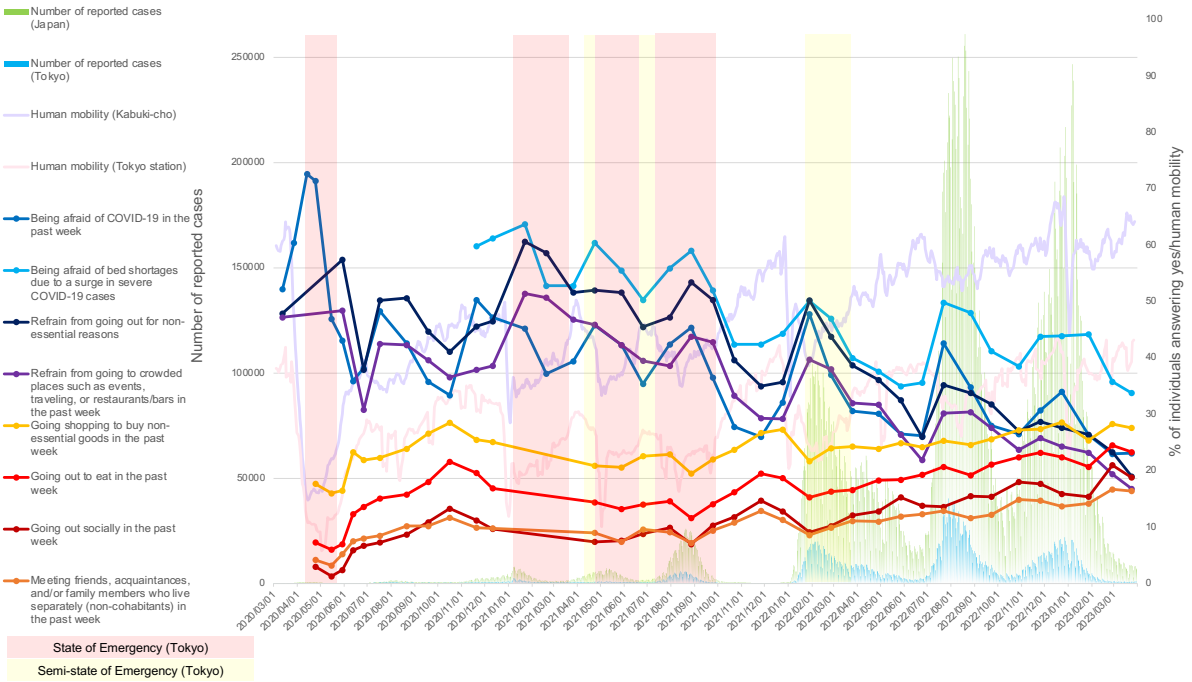
[§]Restricted to individuals with work and/or school.

[¶]Restricted to individuals who work full-time.

[#]Surrounding areas of city centers/major train stations.

Description of temporal changes in anxiety and high-risk behaviors (part of objective 2)

This was a retrospective analysis of an online serial cross-sectional survey on life during the COVID-19 pandemic conducted by a marketing research company. A description of temporal changes in anxiety and high-risk behaviors was presented monthly to the COVID-19 Advisory Board (organized by the Ministry of Health, Labour and Welfare, Japan) in Japanese as below (translated to English):



The number of reported cases is shown in blue for Tokyo and green for Japan. Daily mobility data for Tokyo station and Kabuki Cho, a famous nightlife district in Japan, are shown in pale purple and pink. Cool colors such as blue and purple indicate anxiety. The upward trend for these colors means an increase in anxiety. Warm colors such as red, orange, and brown indicate behaviors in the past week. The upward trend for these colors implies an increase in high-risk behaviors. Within each line graph, the survey was done when there was a dot. Therefore, it is important to note that some questions are not asked in some surveys (e.g., questions related to behaviors were not asked between January and March 2021).

Focusing on the past several waves (as all questions are constantly asked after the fourth wave in the spring of 2021), during our fifth wave, or Delta wave in the summer of 2021 when Japan and Tokyo hosted the Olympic/Paralympic games, anxiety went up in late July 2021 as the reported cases increased, but some behavior indicators continued to increase in this July survey. One month later, as the cases grew (late August survey), the behavior finally went down. So, there was a gap in the

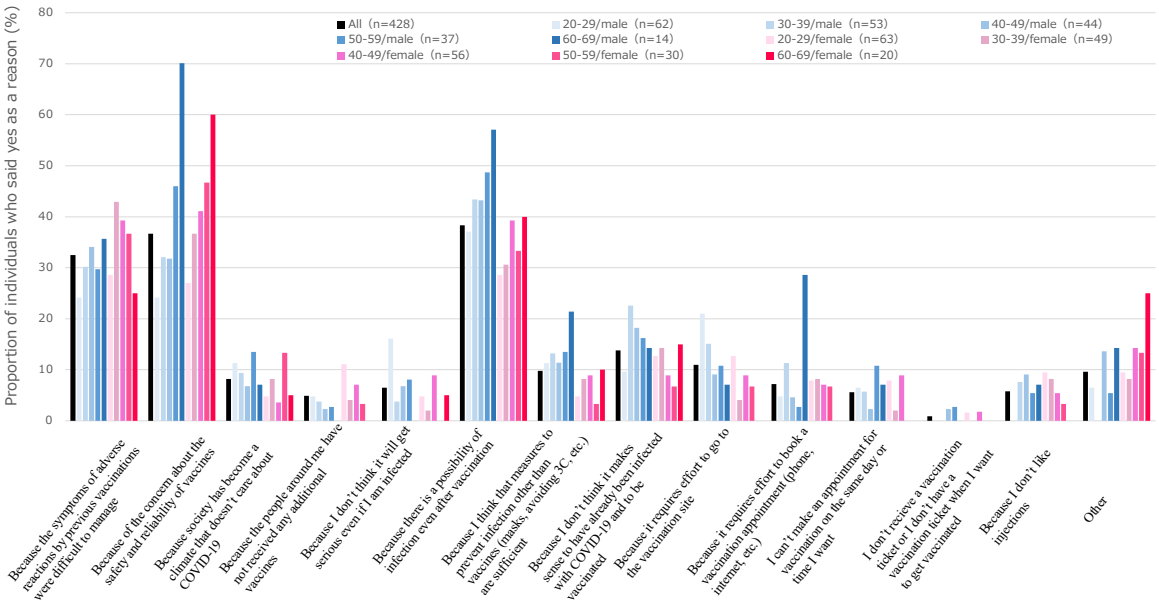
increase in anxiety and decrease in risk behaviors, suggesting that people may have been afraid of COVID-19, but this was not enough to alter their behaviors. This Delta wave ended up being the worst regarding the burden of severe cases for us. During 6th wave, an increase in anxiety happened at the same time with reduced high-risk behaviors.

Interestingly, however, the increase in anxiety about hospital bed shortages was less than in the previous wave. Finally, during the 7th and 8th waves, although there was an increase in anxiety, we continued to see some behavior indicators go up. Overall, since the first Omicron wave in early 2022, there was an increase in anxieties following an increase in reported cases. Still, the behaviors are constantly increasing, suggesting that individuals are afraid, but this did not translate much into the behavior change. There are limitations, including the ecological nature. Still, these suggest potential usefulness as early indicators of COVID-19 epidemic trends to complement traditional surveillance parameters such as case counts and support the importance of a pluralistic approach in surveillance. In future health emergencies, such indicators may be obtained on a weekly basis as done for other surveillance indicators to be more useful in real life as these anxieties and behaviors are upstream of infection (i.e., potentially one of the earliest indicators).

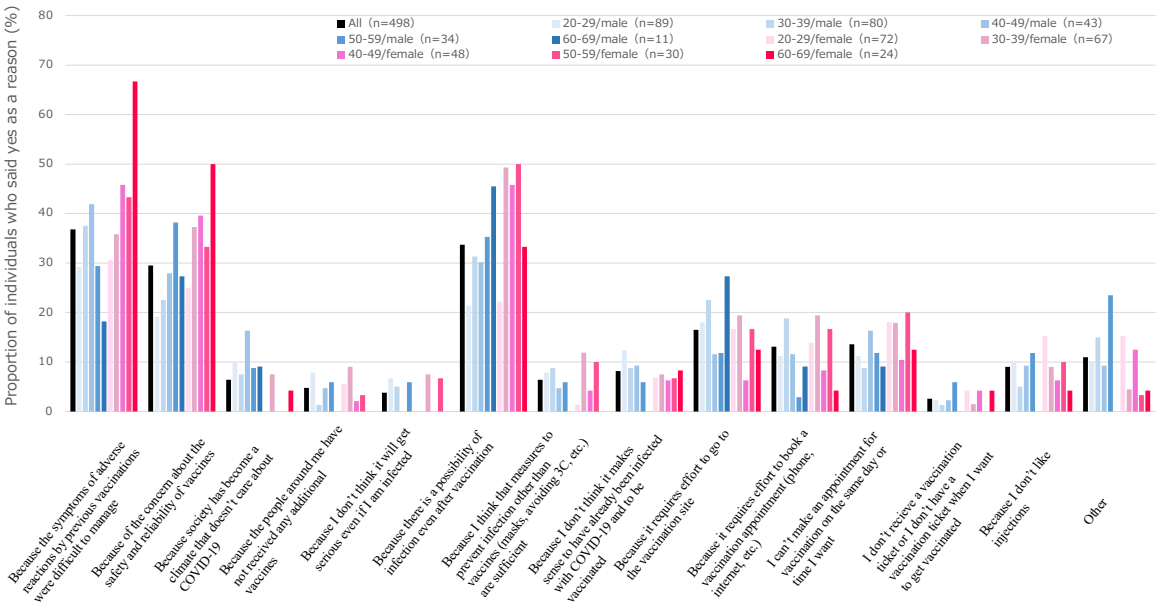
Description of intention to receive COVID-19 booster vaccines (part of objective 2)

This was also a retrospective analysis of an online serial cross-sectional survey on life during the COVID-19 pandemic conducted by a marketing research company between July and September 2022. The importance of booster doses (third or fourth) has been suggested for COVID-19 vaccines due to waning immunity and the emergence of variants, but booster vaccination coverage was stagnating in Japan. Therefore, this analysis examined why some individuals may not have the intention or are unsure of getting booster doses to contribute to future policy and risk communication. The reasons were described for the overall population and by age group (20s to 60s) and sex. The analysis was presented at the COVID-19 Advisory Board (organized by the Ministry of Health, Labour and Welfare, Japan) in Japanese as below (translated to English):

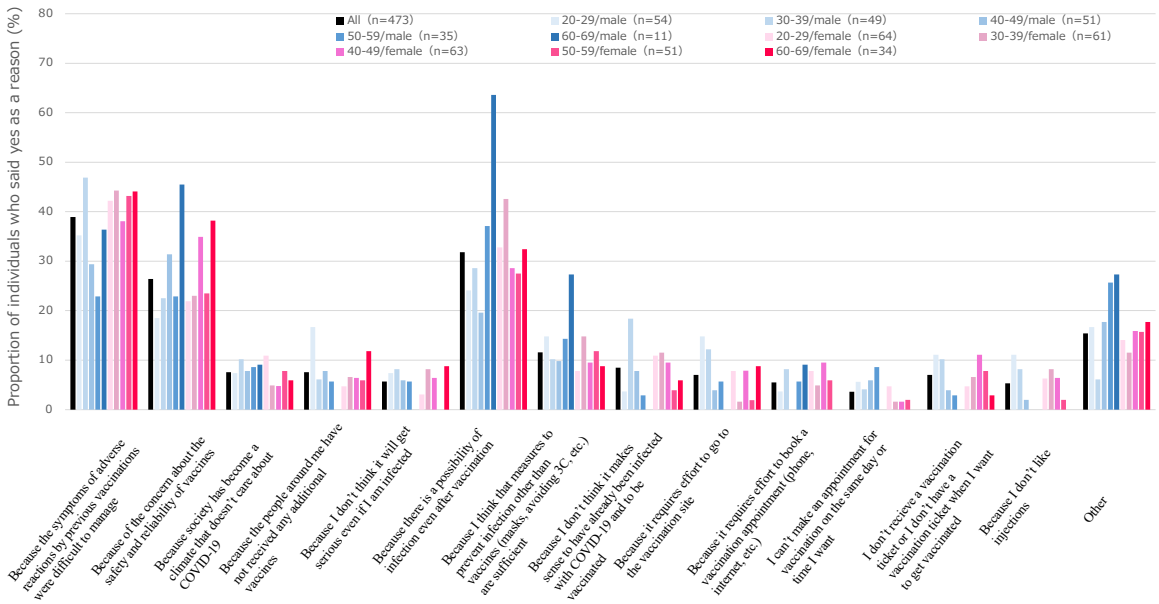
Reasons for those who do not intend to receive the third dose



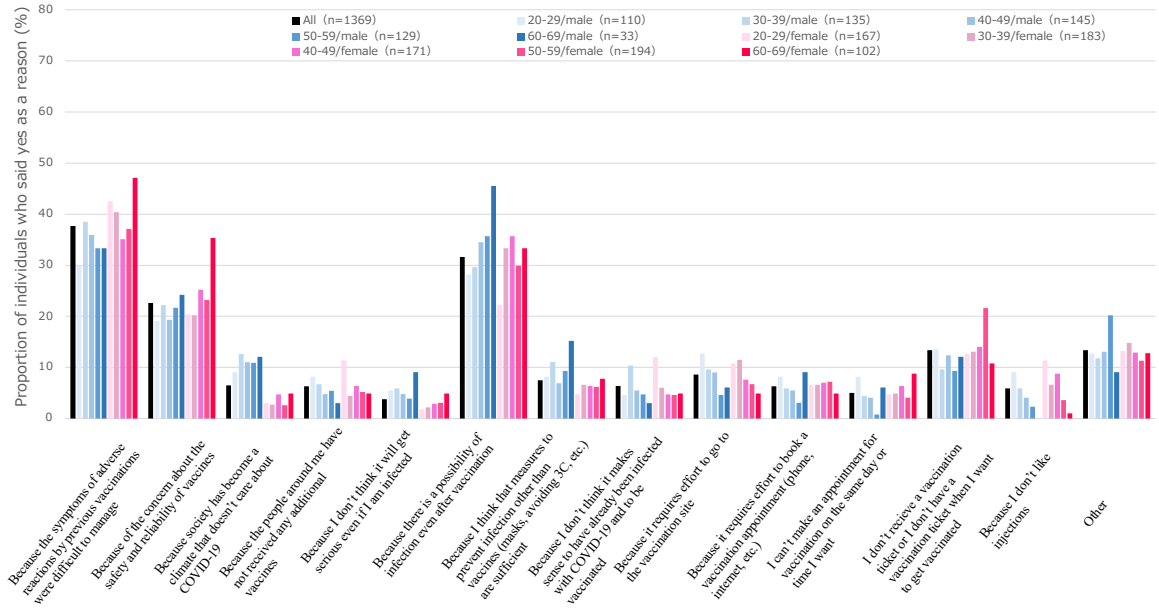
Reasons for being unsure to receive the third dose



Reasons for those who do not intend to receive the fourth dose



Reasons for being unsure to receive the fourth dose



Many people raised concerns about adverse reactions, safety, and reliability as the reasons for not receiving or being unsure about receiving the booster doses. This suggested the continued importance of communicating information about the risks and benefits of vaccines. There were a few, but a certain degree of people answered that the effort required to get vaccinated is one obstacle to receiving booster doses, which is also a critical implementation consideration.

Generic Protocol/Guidance on COVID-19 VE Studies For the Western Pacific Region

Generic protocol/guidance was prepared as part of Objective 3C and provided in the appendices section.

Overarching Discussion and Scientific and Public Health Contributions of this PhD

Evolving background

This thesis studied social and behavioral risk factors associated with SARS-CoV-2 infection and evaluated COVID-19 vaccine effectiveness (VE) against symptomatic infection as well as severe disease in Japan and the Philippines as the entire world dynamically progressed through different phases of the COVID-19 pandemic and the transition to the endemic state. Specifically, the PhD study data period covered mainly from March 2021 (when the cases infected with the new variant B.1.1.7first detected in the U.K. [later named Alpha] were increasing in Japan) to May 2023 (when the pandemic was declared to be over by WHO and Japan also shifted to the endemic policy as the surveillance shifted from notifications of all cases from sentinel surveillance to monitor trends and levels similar to seasonal influenza) [97-99].

The transmission of SARS-CoV-2 has been occurring through a complex interplay of public health and social measures (non-pharmaceutical interventions), high-risk behaviors, social background, past infection, and vaccination. I needed to be agile and adapt to rapidly evolving situations in an attempt to contribute to policies and risk communication in a timely manner.

Behavioral factors associated with SARS-COV-2 infection before widespread rollout of vaccines in Japan

In early 2021, when the studies in this PhD were initially conceptualized, the relative contribution of public health and social measures (non-pharmaceutical interventions), compared to COVID-19 vaccines, was still large. COVID-19 vaccines were starting to be approved and introduced then, but their rollout was limited to healthcare workers [100]. With new, more transmissible variants such as Alpha and Delta variants emerging, there was a need to communicate the behavioral factors associated with SARS-CoV-2 infection quickly. I compiled early preliminary results from the pilot study that suggested social gatherings with food/drinks, which was published in Japan in July 2021 by the COVID-19 National Advisory Board [101]. It was also presented at the COVID-19 Advisory Committee on the Basic Action Policy to provide evidence on the semi-state of emergency in Japan [102]. I wrote a report with further comprehensive analyses that was published on the NIID website in Japanese in October 2021. This was then updated in English and published in a peer-reviewed journal in April 2022 (**Paper 1**) [103-104]. The paper identified multiple behavioral factors associated with

SARS-CoV-2 infection, many of which were in line with the policy/risk communication implemented in Japan. The results also suggested a plausible explanation for the low burden of COVID-19 in Japan relative to other countries with uniquely strict restrictions imposed upon bars/restaurants.

During the Omicron-dominant period at a later time point, a triangulation approach using exploratory community/populational control (as opposed to test-negative control) in assessing the behavioral risk factors was explored. The results suggested that some risk factors may be changing over time during different phases of the pandemic and indicate the importance of continuous monitoring of risk factors. The results also suggested the potential usefulness of such control groups, especially where test-positives and test-negatives with respiratory symptoms may share the same risk factors. However, careful assessment bias arising from not being able to control for sociodemographic backgrounds (which could be partially controlled for with test-negative design) will be essential. For future pandemics and epidemics, it will always be critical to understand socio-behavioral factors associated with infection, especially before vaccines are developed and reliance on public health and social measures is needed. In order to do so, it is important to continue to explore various epidemiological methods and tools to evaluate risk factors. This was one particularly novel and unique contribution of this PhD.

Temporal changes in anxiety and high-risk behaviors during the pandemic in Japan

As specific behavioral factors associated with SARS-CoV-2 infection were identified, I thought it would be important to find a way to monitor temporal changes in anxiety and high-risk behaviors to see if they are useful as an early indicator of COVID-19 epidemic trends (since such high-risk behaviors would come upstream of infection [i.e., can potentially detect rise in cases as early as the length of incubation period]). Fortunately, there was an online serial cross-sectional survey on life during the COVID-19 pandemic conducted by a marketing research company since the beginning of the pandemic. Since this is a retrospective analysis, I had no control over the specific questions included. However, high-risk behaviors identified in the risk factor analysis, such as going out to eat, going out socially, or going out to crowds, were captured constantly. Also, the strength of utilizing this survey was that it was not specifically intended to measure high-risk behavior. Therefore, the social desirability bias was considered minimal (e.g., asking whether one took high-risk behavior would result in most individuals answering “no”). This was included in the COVID-19 National Advisory Board meeting material in September 2021 and continued monthly until March 2023 [105]. Overall, there was a descriptive trend of earlier peaking of behaviors compared to the number of

reported cases. In future pandemics, it may be more beneficial to monitor anxiety and high-risk behaviors on a weekly basis.

Evaluation of COVID-19 vaccine effectiveness against symptomatic infection in Japan (Alpha to early-Omicron)

As the vaccine was being rolled out, it was necessary to monitor its effectiveness in the real world. I initially provided evidence on the Alpha to Delta-dominant period in August 2021 in Japan. The data showed high effectiveness against symptomatic infection, similar to other countries [106]. This was the first report on the effectiveness of the vaccine in Japan, and it provided reassurance to the policy to continue rolling out the vaccine. It was also used for risk communication via media reports. However, the emergence of new variants and the potential waning of vaccine-induced immunity further complicated the situation. Therefore, I collected and analyzed additional data to examine the effectiveness during the Delta-dominant period and published a Japanese report on the NIID website in November 2021, which showed that the VE against symptomatic infection was still very high, around 90% [107]. With the emergence of Omicron with high immune escape capacity *in vitro*, I quickly published a Japanese report on the NIID website in February 2022 to show that the booster dose recovers VE against symptomatic infection with Omicron [108]. These VE estimates during the Delta-dominant and the early Omicron (BA.1/BA.2)-dominant periods were published in a peer-reviewed journal in April 2022 (**Paper 3**) [109]. In doing this study, I also paid particular attention to the influence of high-risk behaviors on VE estimates (**Paper 4**) [110]. Specifically, two of the factors identified as related to the risk of SARS-CoV-2 infection (namely, mask-wearing and high-risk behaviors) were included in the VE analysis to provide more accurate VE estimates in Japan. I did not see a large difference in COVID-19 VE estimates in Japan before and after adjusting for behaviors. This is expected because the Japanese government did not introduce policies differentially targeting the vaccinated and unvaccinated, and our incorporation of high-risk behaviors and mask-wearing as covariates strengthened our observational findings. I also did an exploratory secondary analysis to estimate VEs of 2-dose mRNA vaccine recipients among those who did or did not engage in high-risk behaviors (dining at restaurants/bars at night with alcohol consumption in a group was used as a proxy) compared with unvaccinated individuals who did not engage in high-risk behaviors during the BA.1/BA.2-dominant period, assuming a hypothetical scenario of domestic vaccine passport introduction. The resulting VE estimate was significantly lower among vaccinees with high-risk behaviors (36%; 95% confidence interval (CI): 14–53) than among vaccinees with no high-risk behaviors (56%; 95% CI: 41–67; $p < 0.001$), indicating that VE can be underestimated by 20% via

vaccine passport introduction. Including such behavioral factors is a novel and unique contribution of this PhD and this will inform future epidemics and pandemics as infectious diseases are attracting the attention of the public and influencing behaviors. More observational studies utilize existing data sources, which may not always contain the information necessary for the appropriate analysis.

Social and behavioral factors associated with no intention to receive COVID-19 vaccines among the general public in Japan

Next, as the vaccines were rolled out towards the end of 2021, it became apparent that the COVID-19 vaccination coverage rate (VCR) plateaued at a bit less than 80% in Japan. There was also an active anti-vaccination movement, primarily via social networking services. Therefore, I used the above-mentioned marketing research data to examine socio-behavioral factors associated with the lack of intent to receive COVID-19 vaccines to inform policies to improve vaccination coverage (**Paper 2**) [111]. The study revealed that persons in Japan who did not intend to receive COVID-19 vaccines after the widespread rollout were less likely than others to engage in preventive measures or to be afraid of getting infected or infecting others. They were also not less likely to engage in potentially high-risk behaviors, suggesting similar or higher exposure risks. Therefore, individuals without vaccination intent perceived themselves to be low risk, although their behavior proves otherwise. This is also an important contribution of this PhD to rapidly identify potentially modifiable factors associated with vaccination to inform policies and risk communications to improve VCR. Similarly, the first booster VCR plateaued at a bit less than 70% and the VCR for the second booster was even lower. Therefore, the reasons for some individuals not having the intention or being unsure of getting booster doses were described to contribute further to policy and risk communication. This identified some key reasons individuals may be reluctant to get booster doses (adverse events, breakthrough infection, and some due to the effort required to get the vaccines). This type of simple description will rapidly inform policies and risk communication on who and how to target vaccination campaigns.

Evaluation of COVID-19 vaccine effectiveness against symptomatic infection in Japan (BA.5): immune escape and waning immunity

Going back to the VE against symptomatic infection, even though we showed that the booster doses provided high VE in the early Omicron (BA.1/BA.2)-dominant period in early 2022, we continued to see more waves of reported COVID-19 cases. Specifically, in Japan, there was a large BA.5 surge (second Omicron surge) in the summer to fall of 2022, becoming a leading country in reported case counts, partially owing to reduced testing in other countries. Although initial *in vitro* neutralization

studies suggested further immune escape capacity, it was unclear whether the surge was due to the substantial increase in immune escape capacity of BA.5 compared to BA.1/BA.2, waning immunity, or both. Therefore, I tested this and published it on the NIID website in Japanese in August 2022, which was then published in a peer-reviewed journal in October 2022 (**Paper 6**) [112-113]. Data showed that the booster doses initially provided high protection against BA.5 at a level similar to that against BA.1/BA.2. However, the protection seemed shorter-lasting against BA.5, which likely contributed to the surge. This epidemiological study uniquely allowed us to make an important differentiation between immune escape and waning immunity.

Evaluation of COVID-19 vaccine effectiveness against symptomatic infection in Japan (BA.5): bivalent vaccines

The emergence of Omicron with high immune escape capacity supported the introduction of variant-containing vaccines. Indeed, bivalent vaccines containing mRNA coding for the ancestral strain and Omicron subvariant BA.1 or BA.4/BA.5 were developed and rapidly approved in late 2022. Since these bivalent vaccines were approved based on *in vitro* and animal model data, quality real-world epidemiological data were urgently needed to assess their real-world VE. Therefore, I estimated the VE of bivalent vaccines and published it on the NIID website in Japanese in December 2022, which was then published in a peer-reviewed journal in May 2023 (**Paper 5**) [114-115]. The data showed that the VE of BA.1-containing bivalent COVID-19 vaccines was 65%, and that of BA.4/BA.5-containing bivalent vaccines was 76% during the BA.5-dominant period, both against symptomatic infection. Although bivalent VE was high, the bivalent vaccine was not superior to the monovalent vaccine. In fact, VE was lower than that observed for the monovalent primary series against the ancestral strain, Alpha, and Delta variants (85%–95%), which was in line with immune imprinting against the ancestral strain, which supported the use of monovalent variant vaccines in the future as done for XBB.1.5 COVID-19 vaccine. This epidemiological study was important globally, as Japan provided a uniquely suited population to estimate VE, as over two-thirds of the population were still considered infection-naïve based on a nationwide seroprevalence study among blood donors and with a relatively stable testing strategy with high case-ascertainment then (other countries had difficulty estimating absolute VE due to scarcity of infection-naïve individuals as outlined in the next paragraph and the paper was selected to be one of "editor's choice" articles). Also, this study explored the aOR of SARS-CoV-2 infection by influenza vaccination status as a negative control exposure (during the period with extremely low influenza activity in Japan) to assess the risk of bias. The results of aOR

0.95 (95% CI, 0.79–1.13) indicated no association between influenza vaccination and SARS-CoV-2 testing, suggesting a low risk of bias.

Evaluation of COVID-19 vaccine effectiveness against symptomatic infection in Japan: absolute and relative vaccine effectiveness

As we progress through the pandemic, the increase in the proportion of individuals vaccinated and the depletion of naïve unvaccinated individuals (those who were not vaccinated had a higher chance of getting infected) made it increasingly challenging to estimate VEs even in Japan. One way to alleviate this was to calculate relative VE (rVE). rVE compares individuals who have received the most recent eligible booster dose vs. those who did not (e.g., VE comparing three vs. 2 doses and VE comparing four doses vs. three doses), while absolute VE (aVE; or simply "VE" for previous contexts) compares the vaccinated and unvaccinated. I had been calculating both aVE and rVE since the report of early Omicron (**Paper 3**). This rVE did have some issues where it was challenging to communicate and tended to have lower estimates as the comparator group had some levels of protection from previous vaccinations (although technically, this rVE is estimated for influenza vaccines yearly). Also, there was an evolvingly complex immune history due to multiple vaccinations and infections, making collecting accurate vaccination history increasingly challenging. Finally, it became clear that VE against symptomatic infection wanes after half a year to a year, and it was infeasible to vaccinate all individuals (including individuals with low risk of severe disease). Due to these constraints, the bivalent VE was the last estimate done against symptomatic infection.

Evaluation of COVID-19 vaccine effectiveness against severe disease in Japan

In the meantime, the above-increasing challenges and the emerging evidence suggest that VE wanes against mild symptomatic infection and is also less effective in the Omicron setting. This resulted in the target product profile shifting to severe disease with an increasing need to evaluate VE against severe disease [81-82]. Therefore, VE against severe COVID-19 was also evaluated in hospitals that admit severe COVID-19 cases in Japan (**Paper 7**) [116]. I started planning this in February 2022 with the emergence of the Omicron variant, but it was challenging recruiting hospitals to participate (similar to when initiating the study to evaluate risk factors and VE against symptomatic infection). Therefore, I contacted the investigator of ECMONet (a non-profit organization formed by critical care physicians) to seek support in recruiting hospitals to participate, as they were surveillance activities of severe COVID-19 cases requiring mechanical ventilation in Japan. With their support, it was possible to recruit 24 acute care hospitals in Kanto (Tokyo and surrounding prefectures) and Kansai (Osaka

and surrounding prefectures). After less than a year of planning, the data collection was finally started in early 2023. Due to the retrospective nature, I focused on the Delta-dominant and the early Omicron (BA.1/BA.2)-dominant periods to provide evidence on the initial vaccination rollout campaign up to the provision of the first booster. I recruited research nurses to collect data via chart review and contact the patients and their families for their vaccination history pre-hospitalization via phone calls. In conducting studies, I collected data on whether medical interventions, such as oxygen use, were due to COVID-19 or other diseases among those who tested positive for SARS-CoV-2 since incidental infection found at the time of hospital admission with unrelated conditions was an issue in using a database to conduct VE studies. The study showed that multiple outcomes pointed towards high protection of two doses during the Delta-dominant period and three doses during the early Omicron-dominant period. This provided additional evidence to support Japan's initial rollout of COVID-19 vaccines. Furthermore, these results demonstrate the importance of using severe and specific outcomes to accurately measure VE against severe COVID-19, as recommended in WHO guidance in settings of intense transmission, as seen during Omicron. This is an important and unique contribution of this PhD, which will inform VE estimates of any infectious disease with epidemic/seasonal or pandemic potential.

Social and behavioral risk factor analysis and evaluation of COVID-19 vaccine effectiveness against symptomatic infection in the Philippines

In the Philippines, as discussed in **Paper 10** [117], ethics and alignment with internal stakeholders proved challenging for outpatient and inpatient studies. The study to assess socio-behavioral risk factors and VE against symptomatic infection was planned in March 2021. However, the study was finally approved to start in one hospital in March 2022 and the other in July 2022 (**Paper 8**) [118]. Due to the substantial delay, the enrolment started after a large Omicron wave in January to February 2022, when the majority of the unvaccinated were likely already/recently infected without being ascertained (due to less testing), resulting in a protective effect higher than that from vaccination several months before. However, some important findings were noted in the risk factor analysis. Unlike in the Japanese study, working, especially in the healthcare environment, had a higher risk of infection. This emphasizes the need for proper infection prevention and control measures. Among those who attended social gatherings, the odds of infection were higher among individuals who attended gatherings of five or more people compared to smaller gatherings and individuals who attended for 2 hours or longer compared to shorter gatherings. These findings were in line with findings from Japan and highlighted the nature of this pathogen, where transmission can occur

efficiently in specific situations. As for the VE estimates, I did include various covariates to adjust for in the multivariable analysis. However, the risk of residual bias may have been high (as partly explained above), and therefore, aVE was not presented. In contrast, moderate rVE for the first booster (32%) and the second booster (48%) against symptomatic SARS-CoV-2 infection were observed (both were not statistically significant due to the small sample size). However, these effects seemingly have waned after half a year. These findings were consistent with the Japanese study and studies from other countries and reiterated the need for vaccines that are more efficacious against symptomatic infection caused by circulating variants and with a longer duration of protection. Future research may also focus on quantitative bias analysis/modeling to further understand how negative VE estimates could have arisen and how to mitigate these biases to get more accurate estimates, especially in the setting of complex immune history from multiple vaccination and infection episodes [119]. Also, appropriate reporting/communication of negative VE estimates, which can happen (and did occur in this project as well as in other countries, including developed countries [119]) even after careful planning and execution, will be important to avoid misinformation/disinformation.

Evaluation of COVID-19 vaccine effectiveness against severe disease in the Philippines

The study to assess VE against severe infection in the Philippines was conceived in June 2022, but the study was finally approved to start in one hospital in May 2023 for the same reasons as above (**Paper 9**) [120]. Even after the COVID-19 pandemic has shifted to epidemics, for inactivated vaccines, which were widely rolled out in LMICs, there were variable VE against hospitalization outcomes and data against the Omicron variant is especially limited. VEs of 2 doses against various severe COVID-19 outcomes were consistently high for 6 months during both pre-Omicron and Omicron periods in the setting where approximately half of the vaccinees received inactivated vaccines as primary series. Also, there were multiple factors associated with in-hospital death, some of which are unique to the situation in LMICs, including comorbidities such as tuberculosis and HIV. Our findings may be of use to LMICs, where many rolled out inactivated vaccines but with scarce real-world data, and may inform/defend policy. As observed in the study in Japan, the usefulness of using severe and specific outcomes to accurately measure VE against severe COVID-19 was re-confirmed.

Major strengths and limitations of the PhD projects

Overall, there are several strengths of the PhD projects. First, as stated at the beginning of this section, the rapidly evolving situation of the COVID-19 pandemic was a unique challenge that this PhD faced, but I was able to be agile and adapt to the situations in an attempt to contribute to policies and risk

communication in a timely manner. Second, relationships with the collaborators needed to be built from scratch by the student (except for San Lazaro Hospital, where Nagasaki University had a research collaboration office), which was challenging, especially during the pandemic, and consumed much time. However, it supported me to develop interpersonal skills related to research activities. Third, due to the prospective nature (for the outpatient study) and manual nature (for both the outpatient and inpatient studies), I was able to control for various biases/confounders such as high-risk behavior and incidental SARS-CoV-2 infection due to admission screening, which was unique to the pandemic situation (or situation for epidemics of high interest).

Although specific limitations of each project/manuscript are provided in each manuscript, there are some overall limitations. First, although some countries started to utilize existing health databases during the COVID-19 pandemic, both Japan and the Philippines did not have such readily available databases. However, this allowed me to consider many factors that are not routinely collected and was able to produce some robust data, which informed both from policy/risk communication aspects as well as scientific/methodological aspects. Second, since all studies are observational in nature, there are biases and confounders inherent to these. I did consider various factors and adjusted as appropriate as outlined in the strength. Finally, due to sample size limitations, some quantitative estimates provided were with wide CIs and thus careful interpretation is necessary.

Lessons learnt and conclusion

With numerous lessons learned via implementing operational research in an attempt to inform policies and risk communication (some outlined above), I have compiled a lessons learnt paper **(Paper 10)** [117]. I identified four main challenges in conducting the studies: (1) finding healthcare facilities for data collection, (2) linking exposure (vaccination) and outcome (infection/ disease) data, (3) epidemiological biases/confounders, (4) informing policy/risk communication in a timely manner. I also identified three recommendations based on lessons learnt: (1) establishment/maintenance of platforms such as clinical research networks and unified databases, (2) uniform and practical protocols with careful consideration of biases/confounders and (3) communication with stakeholders, including IRBs. In both Japan and the Philippines, primary data collection was necessary as existing databases were not sufficient to achieve most of the objectives. The shift from a prospective collection of relatively small-sized data to the use of available big data is becoming a trend in many parts of the world. High precision may be achieved through this transition, but we also need to remember that existing big data cannot always achieve high accuracy. Therefore, there needs to be a mechanism to

ensure high accuracy (e.g., by utilizing sentinel sites to provide more detailed prospective data to validate findings from large-scale retrospective analyses).

For future epidemics and pandemics, preparedness during the inter-epidemic/inter-pandemic periods to rapidly evaluate public health interventions such as non-pharmaceutical interventions and vaccines will be critical. The proper and timely dissemination of results to inform policies and risk communication will also be necessary. Although this pandemic may have affected LMICs to a lesser degree compared to HICs due to the risk of severe disease being skewed towards older adults, the next health emergencies may affect younger age groups. Also, societies in LMICs will also age and the number and proportion of individuals who are older, who generally have a higher risk of severe infectious diseases, will increase. In such case s, conducting operational research in not only HICs but also in LMICs will be critical. In terms of health economics perspectives, VE studies, preferably in a local setting, will also be necessary as one of the parameters in cost-effectiveness analysis. As we face increasing epidemic and pandemic threats, this PhD informs some novel epidemiological theories and methods to consider and mitigate biases and confounders under the high attention of society and the general public through real-world data analyses and how we can build capacities to conduct high-quality operational research rapidly, efficiently, and sustainably for policy and risk communication in developed countries such as Japan and LMICs such as the Philippines.

Academic and Public Health Activities during the PhD enrollment period

- LSTHM MSc modules
  - Statistics for Epidemiology and Population Health, Extended Epidemiology, Statistical Methods in Epidemiology, Advanced Statistical Methods in Epidemiology
- Epidemiologist/research scientist at the National Institute of Infectious Diseases (NIID), Japan (July 2020-April 2023)
  - The position helped facilitate the implementation of the study in Japan and the Philippines as a national organization in Japan since the project has public health significance nationally and globally (although I solely led the conception, design, setting up, data collection/analysis, report/manuscript writing).
  - Other related activities
    - Involved in national surveillance activities of infectious diseases in Japan (notifiable diseases; focus on rare diseases, respiratory infectious diseases such as influenza and COVID-19)
    - Surveillance officer and secretariat for Infectious Diseases Weekly Report (IDWR), an official infectious disease surveillance publication by NIID and the Ministry of Health, Labour and Welfare, Japan
    - Secretariat for Infectious Agent Surveillance Report (IASR), an official public health journal by NIID and the Ministry of Health, Labour and Welfare, Japan
    - Planned and implemented the national COVID-19 seroprevalence study in Japan and provided technical assistance to the antibody/serology laboratory team
    - Co-led the public health investigation to study epidemiological, virological, and serological characteristics of COVID-19 vaccine breakthrough infection
    - Direct hiring/line manager for staff on VE-related projects, including five research staff/nurses (three in Japan, two in the Philippines) and three part-time medical students
    - Developed risk assessment of SARS-CoV-2 variants at the national level as a core working group member
    - Assisted in the implementation of the next genome sequencing of SARS-CoV-2 in Mongolia
    - Participated in enhanced surveillance and response activities related to infectious diseases during the Tokyo 2020 Olympic and Paralympic Games
- Part-time unpaid consultant at WHO (May 2022-April 2023; Agreement for Performance of Work between WHO and Nagasaki University)
  - Implementation of the VE study in the Philippines

    - Development of the protocol for VE studies to be implemented in the Western Pacific Region
    - Providing technical assistance to Member States and WHO Country Offices in planning and implementing VE studies
- Medical Manager at Sanofi Vaccines (formally Sanofi Pasteur), Japan (May 2023-Present)
    - Medical lead mainly in charge of (1) RSV/nirsevimab and other early development products to prevent RSV infection, (2) influenza/high-dose influenza vaccine, and (3) pneumococcal disease/pneumococcal candidate vaccine (assigned additional areas including chlamydia, acne, Extraintestinal pathogenic E. coli; also supporting all other products)
    - Peri-launch (before and after product approval and launch) medical activities for nirsevimab and high-dose influenza vaccine
    - Independently planning, defining, and executing/implementing country medical strategies by effectively working with local and global internal stakeholders
    - Leading multiple burden of disease studies using large healthcare databases (RSV in children and influenza in older adults); supporting the burden of disease studies done by external researchers and cost-effectiveness analyses; planning real-world effectiveness/impact studies as well as post-licensure commitment studies
    - Contributing to the overall country business plans from medical, epidemiological, and other technical perspectives in a neutral position by working collaboratively with other various internal stakeholders, including commercial (marketing and sales), public affairs, and market access under strict compliance
    - Engaging with key external stakeholders, including national and international experts in various fields and government officers, to exchange scientific information and to obtain critical insights and actionable intelligence to drive decision-making at both local and global levels
    - Supporting human resources activities, including CV screening, interviewing, and giving webinars to recruiters and potential candidates
    - Presented scientific data on multiple external occasions, including domestic and international medical congresses and meetings with government officers and academic society committee members
    - Providing scientific and medical training to medical and non-medical internal stakeholders
    - Proactively contributing to building a new way of working to prioritize and efficiently allocate resources and build teamwork for robust outcomes
    - Reviewing promotional and non-promotional materials from medical, epidemiological, and other technical perspective in a neutral, compliant, and ethical manner
- Peer-reviewed journal articles that are not part of PhD that were published or submitted during PhD enrollment:

1. **Arashiro T*,** et al. The burden of seasonal influenza and its potential complications among older Japanese adults: a real-world database study. (Under peer review)
2. **Arashiro T*,** et al. Inpatient Burden of Respiratory Syncytial Virus Infection and Influenza in Children Younger than 5 years in Japan, 2011-2022: A database study. (Under peer review) **(*corresponding author)**
3. **Arashiro T*,** et al. Usefulness of a pluralistic approach in sentinel surveillance: seasonal influenza activity based on case counts per sentinel site in the National Epidemiological Surveillance of Infectious Diseases Program and test counts, case counts, and test positivity from the National Hospital Organization. **Jpn J Infect Dis.** 2024. doi: 10.7883/yoken.JJID.2023.368.
4. Arima Y, Yuuki T, Takahara O, Shimbashi R, **Arashiro T,** et al. Pathogens detected from patients with acute respiratory infections negative for SARS-CoV-2, Saitama, Japan, 2020. **Western Pac Surveill Response J.** 2024. doi: 10.5365/wpsar.2024.15.1.1135.
5. Miyamoto S, Nishiyama T, Ueno A, et al. Infectious virus shedding duration reflects secretory IgA antibody response latency after SARS-CoV-2 infection. **Proc Natl Acad Sci U S A.** 2023;120(52):e2314808120. doi:10.1073/pnas.2314808120
6. Kasamatsu A, Otsuka M, Takahashi T, et al. Epidemiology of syphilis among female sex workers and pregnant women during a period of increasing syphilis among women in Japan, 2019-2021. **Sex Transm Infect.** 2024;100(1):55-56. Published 2024 Jan 17. doi:10.1136/sextrans-2023-055934
7. Kinoshita R, **Arashiro T,** et al. Infection-Induced SARS-CoV-2 Seroprevalence among Blood Donors, Japan, 2022. **Emerg Infect Dis.** 2023;29(9):1868-1871. doi:10.3201/eid2909.230365
8. Kasamatsu A, Kanou K, Fukusumi M, Arima Y, Omori S, Nakamura H, Sato T, Serizawa Y, Takeda A, Fujikura H, Ikenoue C, Nishiki S, Fujiya Y, **Arashiro T,** et al. Epidemiologic trends and distributions of imported infectious diseases among travelers to Japan before and during the COVID-19 pandemic, 2016 to 2021: a descriptive study. **J Epidemiol.** 2023;10.2188/jea.JE20230025. doi:10.2188/jea.JE20230025
9. Kasamatsu A, Takahashi T, Arima Y, Otsuka M, **Arashiro T,** et al. Unprecedented increase in syphilis cases among heterosexual men and women in Japan, 2021-2022. **Sex Health.** 2023;20(4):370-372. doi:10.1071/SH23031
10. Miyamoto S, Kuroda Y, Kanno T, Ueno A, Shiwa-Sudo N, Iwata-Yoshikawa N, Sakai Y, Nagata N, **Arashiro T,** et al. Saturation time of exposure interval for cross-neutralization response to SARS-CoV-2: Implications for vaccine dose interval. **iScience.** 2023;26(5):106694. doi:10.1016/j.isci.2023.106694.
11. Shimbashi R, Shiino T, Ainai A, Moriyama S, Arai S, Morino S, Takanashi S, **Arashiro T,** et al. Specific COVID-19 risk behaviors and the preventive effect of personal protective

equipment among healthcare workers in Japan. **Glob Health Med.** 2023; doi: 10.35772/ghm.2022.01060.

12. **Arashiro T,** et al. National seroepidemiological study of COVID-19 after the initial rollout of vaccines: Before and at the peak of the Omicron-dominant period in Japan. **Influenza Other Respir Viruses.** 2023. doi: 10.1111/irv.13094.
13. Miyamoto S, **Arashiro T[*],** et al. Non-Omicron breakthrough infection with higher viral load and longer vaccination-infection interval improves SARS-CoV-2 BA.4/5 neutralization. **iScience.** 2023 Feb 17;26(2):105969. doi: 10.1016/j.isci.2023.105969. **([*]co-first author)**
14. Hirata Y, Iida S, **Arashiro T,** et al. Impact of the COVID-19 pandemic on pathological autopsy practices in Japan. **Pathol Int.** 2023 Jan 4. doi: 10.1111/pin.13306.
15. Kobayashi Y, **Arashiro T,** et al. Replacement of SARS-CoV-2 strains with variants carrying N501Y and L452R mutations in Japan: an epidemiological surveillance assessment. **Western Pac Surveill Response J.** 2022. doi: 10.5365/wpsar.2022.13.3.943.
16. Ko YK, Kinoshita R, Yamauchi M, Otani K, Kamigaki T, Kasuya K, Yoneoka D, Arima Y, Kobayashi Y, **Arashiro T,** et al. Impact of the Coming-of-Age Day and ceremony on the risk of SARS-CoV-2 transmission in Japan: A natural-experimental study based on national surveillance data. **Influenza Other Respir Viruses.** 2022 Nov;16(6):1026-1032. doi: 10.1111/irv.13027.
17. Moriyama Y, Ishikane M, Ueno M, Matsunaga A, Ishizaka Y, **Arashiro T,** et al. A case report of breakthrough infection with the SARS-CoV-2 delta variant and household transmission: Role of vaccination, anti-spike IgG and neutralizing activity. **J Infect Chemother.** 2022 Jul;28(7):962-964. doi: 10.1016/j.jiac.2022.02.003.
18. Takahashi K, Ishikane M, Ujiie M, Iwamoto N, Okumura N, Sato T, Nagashima M, Moriya A, Suzuki M, Hojo M, Kanno T, Saito S, Miyamoto S, Ainai A, Tobiume M, **Arashiro T,** et al. Duration of Infectious Virus Shedding by SARS-CoV-2 Omicron Variant-Infected Vaccinees. **Emerg Infect Dis.** 2022 May;28(5):998-1001. doi: 10.3201/eid2805.220197.
19. Miyamoto S, **Arashiro T[*],** et al. Vaccination-infection interval determines cross-neutralization potency to SARS-CoV-2 Omicron after breakthrough infection by other variants. **Med (N Y).** 2022 Apr 8;3(4):249-261.e4. doi: 10.1016/j.medj.2022.02.006. **([*]co-first author)**

Conclusions

This thesis studied social and behavioral risk factors associated with SARS-CoV-2 infection and evaluated COVID-19 vaccine effectiveness (VE) against symptomatic infection as well as severe disease in Japan and the Philippines as the entire world dynamically progressed through different phases of the COVID-19 pandemic and the transition to the endemic state. Before the widespread rollout of COVID-19 vaccines, multiple behavioral factors associated with SARS-CoV-2 infection were identified, and these were used in risk communication in Japan. Some of these factors, together with anxiety, were monitored over time, together with the number of reported cases in Japan. A triangulation approach using community controls (in addition to test-positive and test-negative individuals) to assess the behavioral risk factors was explored and showed the potential usefulness of using such control groups. For the VE analyses, multiple VE estimates were published in Japan. The prospective approach in estimating VE against symptomatic infection enabled exploration of the influence of preventive measures such as mask-wearing and high-risk behaviors on estimates of COVID-19 VE. Social and behavioral factors associated with no intention to receive COVID-19 vaccines were also identified to inform on vaccination policy further. With the increasing importance of evaluating VE against severe disease, this was also evaluated in hospitals that admit severe COVID-19 cases in each country. Through detailed data collection on medical interventions, such as oxygen use and mechanical ventilation, the importance of using severe and specific outcomes to accurately measure VE against severe COVID-19 was shown. Additionally, in collaboration with the World Health Organization Western Pacific Regional Office, a practical protocol to implement COVID-19 VE studies was developed for the planning and/or implementation of such studies in other countries. Finally, to inform future health emergencies, epidemics, and potential pandemics, the challenges and lessons learned from setting up and executing operational research to evaluate public health interventions, including non-pharmaceutical interventions and vaccines, were summarized.

References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Accessed March 31, 2024. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Johns Hopkins University. Coronavirus resource center. Accessed March 31, 2024. https://coronavirus.jhu.edu/map.html
3. Arashiro T, Furukawa K, Nakamura A. COVID-19 in 2 Persons with Mild Upper Respiratory Tract Symptoms on a Cruise Ship, Japan. Emerg Infect Dis. 2020;26(6):1345-1348. doi:10.3201/eid2606.200452
4. Wiegele PN, Kabar I, Kerschke L, et al. Symptom Diary-Based Analysis of Disease Course among Patients with Mild Coronavirus Disease, Germany, 2020. Emerg Infect Dis. 2021;27(5):1353-1361. doi:10.3201/eid2705.204507
5. World Health Organization. End-to-end integration of SARS-CoV-2 and influenza sentinel surveillance: revised interim guidance. Accessed March 31, 2024. https://www.who.int/publications/i/item/WHO-2019-nCoV-Integrated_sentinel_surveillance-2022.1
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
7. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-436. doi:10.1038/s41586-020-2521-4
8. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81(2):e16-e25. doi:10.1016/j.jinf.2020.04.021
9. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543-558. doi:10.1038/s41569-020-0413-9
10. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ. 2021;374:n1648. doi:10.1136/bmj.n1648
11. Arashiro T, Nakamura S, Asami T, et al. SARS-CoV-2 and Legionella co-infection in a person returning from a Nile cruise. J Travel Med. 2020;27(3):taaa053. doi:10.1093/jtm/taaa053
12. World Health Organization. Global technical consultation report on proposed terminology for pathogens that transmit through the air? Accessed August 11, 2024. https://www.who.int/publications/m/item/global-technical-consultation-report-on-proposed-terminology-for-pathogens-that-transmit-through-the-air
13. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-1567. doi:10.1056/NEJMc2004973
14. Fears AC, Klimstra WB, Duprex P, et al. Persistence of Severe Acute Respiratory Syndrome

Coronavirus 2 in Aerosol Suspensions. Emerg Infect Dis. 2020;26(9):2168-2171. doi:10.3201/eid2609.201806
15. Duval D, Palmer JC, Tudge I, et al. Long distance airborne transmission of SARS-CoV-2: rapid systematic review. BMJ. 2022;377:e068743. doi:10.1136/bmj-2021-068743
16. World Health Organization. Roadmap to improve and ensure good indoor ventilation in the context of COVID-19. Accessed March 31, 2024. https://www.who.int/publications/i/item/9789240021280
17. Onakpoya IJ, Heneghan CJ, Spencer EA, et al. Viral cultures for assessing fomite transmission of SARS-CoV-2: a systematic review and meta-analysis. J Hosp Infect. 2022;130:63-94. doi:10.1016/j.jhin.2022.09.007
18. The United States Centers for Disease Control and Prevention. Science Brief: SARS-CoV-2 and Surface (Fomite) Transmission for Indoor Community Environments. Accessed March 31, 2024. https://stacks.cdc.gov/view/cdc/104762
19. Wu Y, Kang L, Guo Z, Liu J, Liu M, Liang W. Incubation Period of COVID-19 Caused by Unique SARS-CoV-2 Strains: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(8):e2228008. doi:10.1001/jamanetworkopen.2022.28008
20. Du Z, Liu C, Wang L, et al. Shorter serial intervals and incubation periods in SARS-CoV-2 variants than the SARS-CoV-2 ancestral strain. J Travel Med. 2022;29(6):taac052. doi:10.1093/jtm/taac052
21. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). Nat Commun. 2021;12(1):267. doi:10.1038/s41467-020-20568-4
22. Takahashi K, Ishikane M, Ujiie M, et al. Duration of Infectious Virus Shedding by SARS-CoV-2 Omicron Variant-Infected Vaccinees. Emerg Infect Dis. 2022;28(5):998-1001. doi:10.3201/eid2805.220197
23. Ministry of Health, Labour and Welfare, Japan. Information on health and medical consultation. 2020. Accessed March 31, 2024. https://www.mhlw.go.jp/stf/covid-19/kenkou-iryousoudan_00006.html
24. Cabinet Secretariat, Japan. Avoid the three Cs. [In Japanese] Accessed March 31, 2024. https://www.kantei.go.jp/jp/content/000061868.pdf
25. World Health Organization. Considerations for implementing and adjusting public health and social measures in the context of COVID-19. 2021. Accessed March 31, 2024. https://www.who.int/publications/i/item/considerations-in-adjusting-public-health-and-social-measures-in-the-context-of-covid-19-interim-guidance
26. Government of Japan. Avoiding the Three Cs: A Key to Preventing the Spread of COVID-19. Accessed March 31, 2024. https://www.japan.go.jp/kizuna/2020/avoiding_the_three_cs.html
27. Oshitani H; Expert Members of The National COVID-19 Cluster Taskforce at The Ministry of Health, Labour and Welfare, Japan. Cluster-Based Approach to Coronavirus Disease 2019

(COVID-19) Response in Japan, from February to April 2020. Jpn J Infect Dis. 2020;73(6):491-493. doi:10.7883/yoken.JJID.2020.363
28. Furuse Y, Sando E, Tsuchiya N, et al. Clusters of coronavirus disease in communities, Japan, January-April 2020. Emerg Infect Dis. 2020;26(9):2176–2179. doi:10.3201/eid2609.202272
29. Tokyo Metropolitan Government. Number and proportion increase of cases with unknown contact history. Accessed March 31, 2024. https://catalog.data.metro.tokyo.lg.jp/dataset/t000010d2000000471
30. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20:533–534. doi:10.1016/S1473-3099(20)30120-1
31. Our World in Data. Coronavirus pandemic (COVID-19). March 31, 2024. https://ourworldindata.org/coronavirus#explore-the-global-situation
32. Nguyen LH, Drew DA, Graham MS, et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health. 2020;5(9):e475–e483. doi:10.1016/S2468-2667(20)30164-X
33. Ng OT, Marimuthu K, Koh V, et al. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. Lancet Infect Dis. 2021;21(3):333–343. doi:10.1016/S1473-3099(20)30833-1
34. Doung-Ngern P, Suphanchaimat R, Panjangampatthana A, et al. Case-control study of use of personal protective measures and risk for SARS-CoV 2 infection, Thailand. Emerg Infect Dis. 2020;26(11):2607–2616. doi:10.3201/eid2611.203003
35. Fisher KA, Tenforde MW, Feldstein LR, et al. Community and close contact exposures associated with COVID-19 among symptomatic adults ≥18 years in 11 outpatient health care facilities - United States, July 2020. MMWR Morb Mortal Wkly Rep. 2020;69(36):1258–1264. doi:10.15585/mmwr.mm6936a5
36. Fisher KA, Olson SM, Tenforde MW, et al. Telework before illness onset among symptomatic adults aged ≥18 years with and without COVID-19 in 11 outpatient health care facilities - United States, July 2020. MMWR Morb Mortal Wkly Rep. 2020;69(44):1648–1653. doi:10.15585/mmwr.mm6944a4
37. Galmiche S, Charmet T, Schaeffer L, et al. Exposures associated with SARS-CoV-2 infection in France: A nationwide online case-control study. Lancet Reg Health Eur. 2021;7:100148. doi:10.1016/j.lanepe.2021.100148
38. Munch PK, Espenhain L, Hansen CH, Müller L, Krause TG, Ethelberg S. Societal activities associated with SARS-CoV-2 infection: a case-control study in Denmark, November 2020. Epidemiol Infect. 2021;150:e9. doi:10.1017/S0950268821002478
39. Speaker SL, Doherty CM, Pfoh E, et al. Social Behaviors Associated With a Positive COVID-19 Test Result. Cureus. 2021;13(2):e13064. doi:10.7759/cureus.13064
40. Leite A, Leão T, Soares P, et al. A Case-Control Study of Contextual Factors for SARS-CoV-2 Transmission. Front Public Health. 2021;9:772782. doi:10.3389/fpubh.2021.772782

41. Cajar MD, Tan FCC, Boisen MK, et al. Behavioral factors associated with SARS-CoV-2 infection. BMJ Open. 2022;12(6):e056393. doi:10.1136/bmjopen-2021-056393
42. Pritchard E, Jones J, Vihta KD, et al. Monitoring populations at increased risk for SARS-CoV-2 infection in the community using population-level demographic and behavioural surveillance. Lancet Reg Health Eur. 2022;13:100282. doi:10.1016/j.lanepe.2021.100282
43. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–2615. doi:10.1056/NEJMoa2034577
44. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;385(19):1761-1773. doi:10.1056/NEJMoa2110345
45. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2020;10.1056/NEJMoa2035389. doi:10.1056/NEJMoa2035389
46. El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021;385(19):1774-1785. doi:10.1056/NEJMoa2113017
47. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2020;S0140-6736(20)32661-1. doi:10.1016/S0140-6736(20)32661-1
48. Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;385(25):2348-2360. doi:10.1056/NEJMoa2105290
49. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. COVID Vaccines Study Explorer. Accessed March 31, 2024. https://view-hub.org/vaccine/covid/effectiveness-studies
50. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412–1423. doi:10.1056/NEJMoa2101765
51. Public Health England. PHE monitoring of the early impact and effectiveness of COVID-19 vaccination in England. Accessed March 31, 2024. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/968977/COVID-19_vaccine_effectiveness_surveillance_report_February_2021.pdf
52. Pilishvili T, Fleming-Dutra KE, Farrar JL, et al. Interim estimates of vaccine effectiveness of Pfizer-BioNTech and Moderna COVID-19 vaccines among health care personnel - 33 U.S. sites, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(20):753–758. doi:10.15585/mmwr.mm7020e2
53. Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S.

locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(13):495–500. doi:10.15585/mmwr.mm7013e3

54. Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021;374:n1943. doi:10.1136/bmj.n1943
55. Nunes B, Rodrigues AP, Kislaya I, et al. mRNA vaccine effectiveness against COVID-19-related hospitalisations and deaths in older adults: a cohort study based on data linkage of national health registries in Portugal, February to August 2021. Euro Surveill. 2021;26(38):2100833. doi:10.2807/1560-7917.ES.2021.26.38.2100833
56. Ranzani OT, Hitchings MDT, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ. 2021;374:n2015. doi:10.1136/bmj.n2015
57. Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med. 2021;385(10):875–884. doi:10.1056/NEJMoa2107715
58. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med. 2021;385(24):e85. doi:10.1056/NEJMoa2114228
59. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med. 2021;385(24):e83. doi:10.1056/NEJMoa2114114
60. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021;398(10309):1407–1416. doi:10.1016/S0140-6736(21)02183-8
61. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance - VISION Network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(7):255-263. doi:10.15585/mmwr.mm7107e2
62. Horne EMF, Hulme WJ, Keogh RH, et al. Waning effectiveness of BNT162b2 and ChAdOx1 covid-19 vaccines over six months since second dose: OpenSAFELY cohort study using linked electronic health records. BMJ. 2022;378:e071249. doi:10.1136/bmj-2022-071249
63. Ferdinands JM, Rao S, Dixon BE, et al. Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study. BMJ. 2022;379:e072141. doi:10.1136/bmj-2022-072141
64. Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med. 2021;385(2):187–189. doi:10.1056/NEJMc2104974
65. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med. 2021;385(7):585–594. doi:10.1056/NEJMoa2108891

66. Grannis SJ, Rowley EA, Ong TC, et al. Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19-Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance - Nine States, June-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(37):1291-1293. doi:10.15585/mmwr.mm7037e2
67. Thiruvengadam R, Awasthi A, Medigeshi G, et al. Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: a test-negative, case-control study and a mechanistic study of post-vaccination immune responses. Lancet Infect Dis. 2022;22(4):473-482. doi:10.1016/S1473-3099(21)00680-0
68. Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. N Engl J Med. 2022;386(5):494-496. doi:10.1056/NEJMc2119270
69. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med. 2022;386(16):1532–1546. doi:10.1056/NEJMoa2119451
70. Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants. JAMA. 2022;327(7):639-651. doi:10.1001/jama.2022.0470
71. Buchan SA, Chung H, Brown KA, et al. Estimated Effectiveness of COVID-19 Vaccines Against Omicron or Delta Symptomatic Infection and Severe Outcomes. JAMA Netw Open. 2022;5(9):e2232760. doi:10.1001/jamanetworkopen.2022.32760
72. Suah JL, Tng BH, Tok PSK, et al. Real-world effectiveness of homologous and heterologous BNT162b2, CoronaVac, and AZD1222 booster vaccination against Delta and Omicron SARS-CoV-2 infection. Emerg Microbes Infect. 2022;11(1):1343-1345. doi:10.1080/22221751.2022.2072773
73. Low EV, Tok PSK, Husin M, et al. Assessment of Heterologous and Homologous Boosting With Inactivated COVID-19 Vaccine at 3 Months Compared With Homologous Boosting of BNT162b2 at 6 Months. JAMA Netw Open. 2022;5(8):e2226046. doi:10.1001/jamanetworkopen.2022.26046
74. Lim AH, Ab Rahman N, Ong SM, et al. Evaluation of BNT162b2 vaccine effectiveness in Malaysia: test negative case-control study. Vaccine. 2022;40(39):5675-5682. doi:10.1016/j.vaccine.2022.08.032
75. Toh TH, Qi YY, Yong SM, et al. Effectiveness of vero cell inactivated vaccine against severe acute respiratory infections (SARI) in Sibu, Malaysia: A retrospective test-negative design. Hum Vaccin Immunother. 2023;19(1):2167438. doi:10.1080/21645515.2023.2167438
76. Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 among hospitalized adults aged ≥65 Years - United States, January-March 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):674–679. doi:10.15585/mmwr.mm7018e1

77. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med. 2022;10.1038/s41591-022-01753-y. doi:10.1038/s41591-022-01753-y
78. Hyams C, Marlow R, Maseko Z, et al. Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study. Lancet Infect Dis. 2021;21(11):1539–1548. doi:10.1016/S1473-3099(21)00330-3
79. Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation, a test negative case-control study. Nat Commun. 2022;13(1):5736. doi:10.1038/s41467-022-33378-7
80. UK Health Security Agency. COVID-19 vaccine surveillance reports. Accessed March 31, 2024. https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports
81. World Health Organization. WHO Target Product Profiles for COVID-19 Vaccines. Revised version April 2022. Accessed March 31, 2024. https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines
82. World Health Organization. WHO Target Product Profiles for COVID-19 Vaccines. Version 3 - 29 April 2020. Accessed March 31, 2024. https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf
83. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine. 2013;31(17):2165–2168. doi:10.1016/j.vaccine.2013.02.053
84. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev Vaccines. 2014;13(12):1571–1591. doi:10.1586/14760584.2014.966695
85. Dean NE, Hogan JW, Schnitzer ME. Covid-19 vaccine effectiveness and the test-negative design. N Engl J Med. 2021;385(15):1431–1433. doi:10.1056/NEJMe2113151
86. Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls CMJE, Pearce N. A test-negative design with additional population controls can be used to rapidly study causes of the SARS-CoV-2 epidemic. Epidemiology. 2020;31(6):836–843. doi:10.1097/EDE.0000000000001251
87. Arashiro T, Arai S, Kinoshita R, et al. National seroepidemiological study of COVID-19 after the initial rollout of vaccines: Before and at the peak of the Omicron-dominant period in Japan. Influenza Other Respir Viruses. 2023;17(2):e13094. doi:10.1111/irv.13094
88. Kinoshita R, Arashiro T, Kitamura N, et al. Infection-Induced SARS-CoV-2 Seroprevalence among Blood Donors, Japan, 2022. Emerg Infect Dis. 2023;29(9):1868-1871. doi:10.3201/eid2909.230365
89. Nomura S, Eguchi A, Yoneoka D, et al. Reasons for being unsure or unwilling regarding intention to take COVID-19 vaccine among Japanese people: A large cross-sectional national survey. Lancet Reg Health West Pac. 2021;14:100223. doi:10.1016/j.lanwpc.2021.100223

90. Yoda T, Katsuyama H. Willingness to receive COVID-19 vaccination in Japan. Vaccines. 2021;9(1):48. doi:10.3390/vaccines9010048
91. Machida M, Nakamura I, Kojima T, et al. Acceptance of a COVID-19 vaccine in Japan during the COVID-19 pandemic. Vaccines. 2021;9(3):210. doi:10.3390/vaccines9030210
92. Okubo R, Yoshioka T, Ohfuji S, Matsuo T, Tabuchi T. COVID-19 vaccine hesitancy and its associated factors in Japan. Vaccines. 2021;9(6):662. doi:10.3390/vaccines9060662
93. World Health Organization. Evaluation of COVID-19 vaccine effectiveness. Accessed March 31, 2024. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1
94. World Health Organization. Guidance on conducting vaccine effectiveness evaluations in the setting of new SARS-CoV-2 variants: interim guidance, 22 July 2021. Addendum to Evaluation of COVID-19 vaccine effectiveness. 2021. Accessed March 31, 2024. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-variants-2021.1
95. World Health Organization. Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination. Second addendum to Evaluation of COVID-19 vaccine effectiveness: Interim guidance. Accessed March 31, 2024. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-VE_evaluations-2022.1
96. Doll MK, Pettigrew SM, Ma J, Verma A. Effects of Confounding Bias in Coronavirus Disease 2019 (COVID-19) and Influenza Vaccine Effectiveness Test-Negative Designs Due to Correlated Influenza and COVID-19 Vaccination Behaviors. Clin Infect Dis. 2022;75(1):e564-e571. doi:10.1093/cid/ciac234
97. Outbreak.info. Japan Variant Report. Accessed March 31, 2024. https://outbreak.info/location-reports?loc=JPN&pango=B.1.1.7&selected=B.1.1.7
98. World Health Organization. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. Accessed March 31, 2024. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic
99. Ministry of Health, Labour and Welfare, Japan. Response to COVID 19 (Novel Coronavirus) after the classification change. Accessed March 31, 2024. https://www.mhlw.go.jp/stf/covid-19/kenkou-iryousoudan_00006.html
100. NHK. Who gets vaccine priority?. Accessed March 31, 2024. https://www3.nhk.or.jp/nhkworld/en/news/backstories/1547/
101. Ministry of Health, Labour and Welfare, Japan. The COVID-19 National Advisory Board meeting material: Preliminary report on pilot study to evaluate behavioral risk factors associated with SARS-CoV-2 infection. Accessed March 31, 2024.

https://www.mhlw.go.jp/content/10900000/000807662.pdf
102. Cabinet Secretariat, Japan. The COVID-19 Advisory Committee on the Basic Action Policy meeting material: Preliminary report on pilot study to evaluate behavioral risk factors associated with SARS-CoV-2 infection. Accessed March 31, 2024. https://www.cas.go.jp/jp/seisaku/ful/taisakusuisin/taisyo/dai11/gijishidai.pdf
103. Arashiro T, et al. Preliminary report on case-control study to evaluate behavioral risk factors associated with SARS-CoV-2 infection. National Institute of Infectious Diseases, Japan [in Japanese]. 2021. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10692-covid19-59.html
104. Arashiro T, Arima Y, Muraoka H, et al. Behavioral factors associated with SARS-CoV-2 infection in Japan. Influenza Other Respir Viruses. 2022;16(5):952-961. doi:10.1111/irv.12992
105. Ministry of Health, Labour and Welfare, Japan. The COVID-19 National Advisory Board meeting material: Description of temporal changes in anxiety and high-risk behaviors. Accessed March 31, 2024. https://www.mhlw.go.jp/content/10900000/000836418.pdf
106. Arashiro T, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (first report). National Institute of Infectious Diseases, Japan [in Japanese]. Accessed March 31, 2024. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10614-covid19-55.html
107. Arashiro T, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (second report): vaccine effectiveness during Delta variant-dominant period. National Institute of Infectious Diseases, Japan [in Japanese]. Accessed March 31, 2024. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10757-covid19-61.html
108. Arashiro T, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (third report): vaccine effectiveness during Omicron variant-dominant period. National Institute of Infectious Diseases, Japan [in Japanese]. Accessed March 31, 2024. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10966-covid19-71.html
109. Arashiro T, Arima Y, Muraoka H, et al. Coronavirus Disease 19 (COVID-19) Vaccine Effectiveness Against Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection During Delta-Dominant and Omicron-Dominant Periods in Japan: A Multicenter Prospective Case-control Study (FASCINATE Study). Clin Infect Dis. 2023;76(3):e108-e115. doi:10.1093/cid/ciac635
110. Arashiro T, Arima Y, Kuramochi J, et al. Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. Euro Surveill. 2023;28(4):2300034. doi:10.2807/1560-7917.ES.2023.28.4.2300034
111. Arashiro T, Arima Y, Stucky A, et al. Social and Behavioral Factors Associated with Lack of Intent to Receive COVID-19 Vaccine, Japan. Emerg Infect Dis. 2022;28(9):1909-1910. doi:10.3201/eid2809.220300
112. Arashiro T, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (fourth report): vaccine effectiveness during BA.5-dominant period. National

Institute of Infectious Diseases, Japan [in Japanese]. Accessed March 31, 2024. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/11405-covid19-999.html

113. Arashiro T, Arima Y, Kuramochi J, et al. Immune escape and waning immunity of COVID-19 monovalent mRNA vaccines against symptomatic infection with BA.1/BA.2 and BA.5 in Japan. Vaccine. 2023;41(47):6969-6979. doi:10.1016/j.vaccine.2023.10.021
114. Arashiro T, et al. Preliminary report on case-control study to evaluate COVID-19 vaccine effectiveness (fifth report): bivalent vaccine effectiveness. National Institute of Infectious Diseases, Japan [in Japanese]. Accessed March 31, 2024. https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/11688-covid19-9999.html
115. Arashiro T, Arima Y, Kuramochi J, et al. Effectiveness of BA.1- and BA.4/BA. 5-Containing Bivalent COVID-19 mRNA Vaccines Against Symptomatic SARS-CoV-2 Infection During the BA.5-Dominant Period in Japan. Open Forum Infect Dis. 2023;10(6):ofad240. doi:10.1093/ofid/ofad240
116. Arashiro T, Miwa M, Nakagawa H, et al. COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: A multicenter case-control study (MOTIVATE study). Vaccine. 2024;42(3):677-688. doi:10.1016/j.vaccine.2023.12.033
117. Arashiro T, Berba RP, Calayo JP, et al. Lessons from COVID-19 vaccine effectiveness studies conducted in response to the COVID-19 pandemic in Japan and the Philippines (Under review)
118. Arashiro T, Berba RP, Calayo JP, et al. Socio-behavioral factors associated with SARS-CoV-2 infection and COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines: a prospective case-control study (FASCINATE-P study). (Under review)
119. Bodner K, Irvine MA, Kwong JC, Mishra S. Observed negative vaccine effectiveness could be the canary in the coal mine for biases in observational COVID-19 studies. Int J Infect Dis. 2023;131:111-114. doi:10.1016/j.ijid.2023.03.022
120. Arashiro T, et al. COVID-19 vaccine effectiveness against severe COVID-19 requiring hospitalization, oxygen therapy, invasive mechanical ventilation, and death in the Philippines: a case-control study (MOTIVATE-P study). (Under internal clearance)

Appendices

Evaluation of COVID-19 Vaccine Effectiveness: A Practical Protocol (starting from next page)

Evaluation of COVID-19 Vaccine Effectiveness: A Practical Protocol

Western Pacific Regional Office, World Health Organization

April 2023

World Health Organization
Western Pacific Region

Table of Contents

Glossary

AZD1222	COVID-19 vaccine developed by AstraZeneca/Oxford University
BNT162b2	COVID-19 vaccine developed by Pfizer/BioNTech
CoronaVac	COVID-19 vaccine developed by SinoVac
COVID-19	Coronavirus disease 2019
ILI	Influenza-like illness
mRNA-1273	COVID-19 vaccine developed by Moderna/NIAID
PCR	Polymerase chain reaction
PGH	Philippine General Hospital, the Philippines
PHSM	Public Health and Social Measures
RCT	Randomized controlled trial
RT-PCR	Reverse-transcription polymerase chain reaction
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VE	Vaccine effectiveness
WHO	World Health Organization
WPRO	WHO Western Pacific Regional Office

Background, Purpose, and Intended Audience

Background

As COVID-19 vaccination programs are being rolled out, countries are encouraged to conduct real-world vaccine effectiveness studies, especially in the context of the emergence of new variants and waning immunity. Especially, it would be valuable for more LMICs to conduct VE studies for several reasons, including: (1) evaluation of vaccines that are mainly distributed in these countries, such as CoronaVac, (2) confirmation that there is no cold chain breach, (3) considerably different cumulative burdens among countries (e.g., individuals with prior infection are protected against next infection/disease), (4) substantial variation in public health and social measures and policies/risk communication activities among countries, (5) vaccine confidence within and among surrounding countries, and (6) capacity building to conduct operational research to inform public health response in LMICs for COVID-19 pandemics and for future epidemics and pandemics. In implementing VE studies, close guidance is needed to ensure the efficient implementation of quality studies. Standard World Health Organization (WHO) guidance is available regarding the evaluation of COVID-19 vaccine effectiveness [1-3]. However, this guidance is generic in nature; more concrete and specific guidance and protocols/manuals are required to implement these studies, such as one using a test-negative design.

Purpose

The purpose of this protocol is to provide step-by-step guide to implement COVID-19 vaccine effectiveness studies using test-negative design, which is the method recommended by the WHO [1]. The protocol is written mainly for the setting where primary data collection is necessary, but some countries may have existing databases on SARS-CoV-2 testing and/or vaccination records, in which case they may adopt the protocol to utilize these existing databases. Theoretical details are not included to keep this protocol simple, concise, and practical; please refer to the WHO guidance for these [1-3].

Intended Audience

- Technical officials who are involved in the evaluation of COVID-19 vaccine effectiveness and COVID-19 vaccine-related policy/risk communication
- Investigators at national institutes and universities who are planning for COVID-19 vaccine effectiveness studies

If the country is planning or implementing observational studies to measure vaccine effectiveness for the first time, it is recommended to consult WHO WPRO, the WHO country office focal point, or a regional expert.

Key Steps in Study Implementation

1. Understanding study objectives
2. Choice of the study sites, sample size calculation, and ethical considerations
3. Measuring the outcomes of interest and assessing COVID-19 vaccination status
4. Considerations of biases and confounders with choice of covariates
5. Initiation of the study and pilot description of data
6. Interim analysis
7. Translating the results to inform policies and risk communication

Study Objectives

The primary objective is to estimate VE by time since vaccination in a specific variant-dominant period (e.g., Delta-dominant period, Omicron-dominant period)

The secondary objective is to estimate VE by

- Vaccine product
- Number of booster dose(s)
- Age group (e.g., children, young adults, elderly)
- The group that is at high risk for severe disease (e.g., elderly and individuals with comorbidities)

These can be achieved mainly for symptomatic infection and severe disease (e.g., hospitalization). See "Measuring the COVID-19 Outcomes of Interest and Assessing COVID-19 Vaccination Status" for details.

Choice of the Study Sites, Sample Size Calculation, and Ethical Considerations

Choosing the study sites

It would be most efficient if existing sentinel sites for influenza-like illness (ILI) surveillance and severe acute respiratory infection (SARI) surveillance systems could be utilized. If there is no such system within the country, study sites should be selected based on where SARS-CoV-2 testing is done routinely and cooperation of local investigators and stakeholders is expected. The number of study sites to be recruited would depend on the expected sample size (see below) and how many tests are done at each site.

Sample size calculation

There is a simple tool prepared by WHO HQ to calculate the sample size needed to achieve specific precision (i.e., 95% CI): https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement_tool-2021.1.

Since matching is not used here, we can have differing numbers of cases and controls. However, it would be ideal to have some cases and controls that are enrolled from the same facilities.

As an example, assuming 10% positivity, expected COVID-19 vaccine coverage of 30%, and 90% vaccine effectiveness, 207 cases and 1864 controls are needed for the precision of the lower confidence interval (CI) boundary of 10%.

Considering potential missing data, the difference in exposure probabilities, multivariable analyses/sub-analyses, and evaluation of vaccine effectiveness in various settings (vaccine types, waning immunity, different public health and social measures, variants, etc.), it would be ideal to continue enrollment for the duration of the study period even after reaching this initial target, given approval from ethics committee.

Ethical Considerations

Depending on the country's regulations and legal requirements, the country may conduct VE studies as part of public health activities. There may or may not be a need to go through a research ethics committee review. If the studies cannot be conducted as public health activities, they will need to go through a research ethics committee review as operational research activities.

Measuring the COVID-19 Outcomes of Interest and Assessing COVID-19 Vaccination Status

Outcomes of Interest

Ascertainment of cases (test-positive) and controls (test-negative) should ideally be done via RT-PCR. If rapid antigen tests are partially used, it is good to perform sensitivity analysis excluding individuals tested with rapid antigen tests. Another way to avoid bias arising from antigen test use is to exclude individuals who tested negative with antigen tests. This is because rapid antigen tests have lower sensitivity compared to RT-PCR, which means that false negatives are possible, resulting in outcome misclassification.

COVID-19 vaccine effectiveness can be measured against:

- Infection (i.e., including asymptomatic cases)
- Symptomatic infection
- Severe disease (e.g., hospitalization, requiring oxygen, intubated/ventilated, etc.)
- Death

This protocol will focus on VE against symptomatic infection and VE against severe disease as these are important and the most feasible outcomes to be measured.

VE against infection is generally reserved for cohort study (which is out of the scope of this document) as reason for testing of asymptomatic individuals varies substantially, which makes it hard to control for biases.

Vaccination Status

The following information regarding vaccination history is important to estimate VE:

- Dose number
- Vaccination date (record the latest vaccination date if challenging to collect all dates)
- Vaccine product

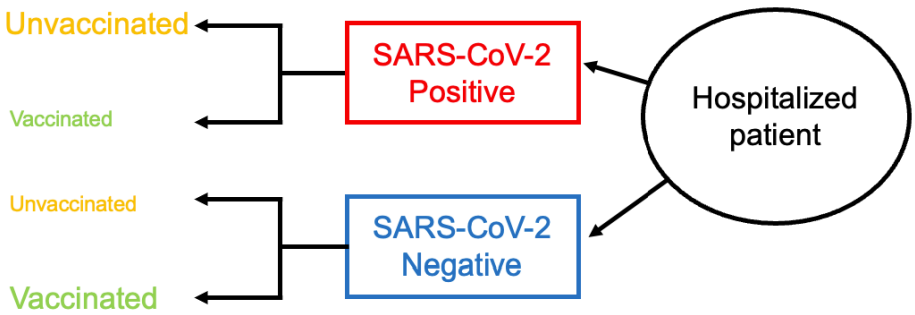
Vaccination status can be confirmed via the following sources:

- Vaccination registry
- Vaccination card
- Self-report

Although ideally, the first two should be used to confirm vaccination history, this may not always be possible. If so, self-reported history should be checked for plausibility (e.g., rollout timing/prioritization). The vaccination card needs to be checked for validity (e.g., fake vaccination cards may be used especially in the countries implementing policies to relax PHSM among the vaccinees). The vaccination registry may not be timely or complete as well (e.g., the booster dose may be separately recorded even for the same individual; classifying individuals who are not in the vaccination registry as unvaccinated can result in exposure misclassification).

Brief Introduction to a Test-negative Case-control Study

There are several study designs that can be used to measure vaccine efficacy or effectiveness. A randomized controlled trial (RCT) is a gold standard for evaluating the effect of a vaccine (called vaccine effectiveness). RCTs were done for COVID-19 vaccines before they were widely rolled out. However, after the rollout of vaccines, it is usually unethical to randomize and allocate some individuals with a placebo. Therefore, observational studies are necessary to evaluate vaccine effectiveness post-licensure, especially in the setting of waning immunity and the emergence of immune-escaping variants. There are several designs to do this.
A cohort study is one design, but since the severe outcome is relatively rare for COVID-19 and there is a need to follow up with individuals who are vaccinated and unvaccinated and compare the incidence rate, it is difficult to do so. Also, healthcare-seeking may be different between the vaccinees and non-vaccinees (those who are vaccinated may get tested less due to perception of protection or conversely, those who are not vaccinated may have less access to testing. Therefore, the current protocol focuses on test-negative case-control study, which is recommended by the WHO. Although there are some important limitations, including selection bias, a test-negative case-control study has been utilized extensively for the evaluation of VE for infectious diseases such as influenza and COVID-19, as this design is efficient and can somewhat control for healthcare-seeking behavior. In essence, individuals tested for SARS-CoV-2 with negative results serve as controls, while individuals tested for SARS-CoV-2 with positive results serve as cases. We then look at the distribution (odds) of vaccinees and non-vaccinees to compare these to calculate the odds ratio. The odds ratio can be further used to estimate vaccine effectiveness in percentage. A schematic of a test-negative case-control study (study to measure VE against severe COVID-19 as an example) is illustrated below.



Covariates to Consider for Multivariable Analyses

When estimating VE, investigators assume a causal relationship between vaccination and infection/disease and it is necessary to rely on observational studies as trials are not ethically possible. Therefore, investigators need to carefully consider and incorporate potential confounders/biases into the design/analysis. These are included in the sample lists of information to be collected in the appendices.

Minimum

VE against symptomatic infection

- Age or age group
- Sex
- Specimen collection timing or disease onset (e.g., epidemiologic week of testing)
- Place of testing (e.g., testing/healthcare facility that the participant visited)
- Prior SARS-CoV-2 infection (desirably by variant type)
- Priority groups for vaccination (e.g., healthcare workers, older adults, individuals with comorbidities)
- Comorbidity (presence or absence)

VE against severe disease

- Age or age group
- Sex
- Specimen collection timing, disease onset, or hospitalization timing (e.g., epidemiologic week of testing)
- Admitted healthcare facilities
- Prior SARS-CoV-2 infection
- Priority groups for vaccination (e.g., healthcare workers, older adults, individuals with comorbidities)
- Comorbidity (Immunocompromised status can be included as a separate covariate; 0, 1, 2, 3+)
- Immunocompromised status
- Smoking status
- Pregnancy status

Desired

VE against symptomatic infection

- Sociodemographic group (e.g., race and ethnicity)

- Proxy for socioeconomic status (e.g., education, monthly income)
- Test-seeking (e.g., SARS-CoV-2 diagnostic test in the past month)
- Influenza test results and/or influenza vaccination status
- Pneumococcal disease test results and/or pneumococcal vaccination status
- History of close contact
- Additional information regarding behaviors, public health and social measures (non-pharmaceutical interventions) that are considered to be risk/preventive factors for SARS-CoV-2 infection in the local context (especially the ones that may be different between vaccinees and non-vaccinees) (e.g., mask wearing, social gathering)
- Other factors that may be confounders in the target population (e.g., occupation)

VE against severe disease

- Sociodemographic group (e.g., race and ethnicity)
- Proxy for socioeconomic status (e.g., education, monthly income)
- Healthcare-seeking (e.g., history of hospital admission in the past year)
- Influenza test results and/or influenza vaccination status
- Pneumococcal disease test results and/or pneumococcal vaccination status
- Other factors that may be confounders in the target population

Eligibility Criteria

VE against Symptomatic Infection

Inclusion criteria:

All symptomatic individuals tested at each study site are included. It is important to prespecify a list of symptoms or use ILI or acute respiratory infection (ARI) definitions.

Exclusion criteria:

- Individuals who did or could not consent to participate in the study (if the study is prospective and requires informed consent)
- Individuals who have already been enrolled within the same variant period
- Individuals who are tested two weeks after symptom onset or unknown onset date (this can be applied at the analysis stage as long as onset date is collected)

VE against Severe COVID-19

Inclusion criteria:

Individuals admitted to each study site since the vaccination rollout started in the target population. It is important to prespecify a list of symptoms or use SARI definition. It is also important to collect information such as oxygen use or intubation as it is possible to restrict the analysis to individuals receiving such care.

Exclusion criteria:

- Individuals who have already been enrolled within the same variant period
- Individuals who are tested two weeks after symptom onset or unknown onset date (this can be applied at the analysis stage as long as onset date is collected)
- Individuals who are hospitalized 2 weeks after symptom onset or unknown onset date (this can be applied at the analysis stage as long as onset date is collected)

Alternative definitions

- It might be challenging to set criteria base on syndromic definition, especially for retrospective studies. If this is the case, it is possible to use ICD-10 codes, discharge diagnoses, or claim data to define eligibility criteria. It is critical to manually review the medical charts at least part of these patients to ensure that ICD-10 codes, discharge diagnosis, or claim data accurately represent accurate diagnosis.

Definition of COVID-19 Disease Severity and Vaccination Status

Definition of COVID-19 Disease Severity

WHO definitions of disease severity for COVID-19 will be used to classify with slight modifications to fit the local context and research design.

- Hospitalized COVID-19: any individuals hospitalized with COVID-19
- Severe COVID-19: individuals who have oxygen saturation < 90% on room air/individuals who are requiring oxygen therapy
- Critical COVID-19: individuals with COVID-19 who require the provision of life-sustaining treatments such as mechanical ventilation and/or ICU admission

Definition of COVID-19 Vaccination Status

- Unvaccinated: Individuals who have not received COVID-19 vaccines
- Partially vaccinated: Individuals who completed at least one dose of COVID-19 vaccines 14 days before but are not considered fully vaccinated based on the below definition.
- Fully vaccinated: Individuals who completed the primary series of COVID-19 vaccination (one or two doses depending on the vaccine type) 14 days before.
- Vaccinated with a booster dose(s): Individuals who completed booster dose(s) of COVID-19 vaccination (one or two doses depending on the vaccine type) 14 days before.
- To evaluate waning effectiveness, we will also classify the vaccinees by time since vaccination (month, two months, or three months, depending on sample size).

Initiation of the Study, Pilot Description of Data, and Interim Analyses

Initiation of the Study

- At the initial implementation stage, it is important for central investigators to visit each site to make sure that data collection is done properly.

Pilot Description of Data

- Descriptive statistics should be utilized after 1-2 months of data collection to understand the study population to ensure that the participants are what the investigators expect.

Interim Analyses

- Logistic regression is used to estimate the odds of being vaccinated among cases relative to controls.
- Example covariates to be included for multivariable analysis are: age group, sex, presence of any comorbidity, occupation (healthcare/long-term care worker or not), SARS-CoV-2 diagnostic test in the past month, self-reported past SARS-CoV-2 infection (categorized by the period of infection), history of close contact, healthcare facility that the participant visited, calendar week, mask wearing, high-risk behavior (dining at a restaurant/bar at night with alcohol consumption in a group as a proxy), and influenza vaccination status for the 2022–2023 season.
- Finally, VE is estimated using the following equation: VE = (1 - adjusted odds ratio [aOR]) × 100%.
- In the setting where booster doses are rolled out, in addition to absolute VE (aVE; VE comparing the vaccinated and unvaccinated), it is possible to calculate relative VE (rVE; VE comparing individuals who have received a booster dose versus individuals who only received primary series) to evaluate the added effect of the booster.

Variant-specific VE

- It would be ideal to be able to sequence viral genomes or use variant-specific PCR for cases. However, this may not always be possible. If so, it is possible to divide the study period by dominant variant (e.g., the investigators may search for national or regional data, or if unavailable, GISAID on variant proportion by week. If a particular variant is responsible for at least 75-80% of the circulating viruses, it may be considered a dominant variant as per previous reports). If one is replaced by another, it may be necessary to have a replacement (or washout) period in between periods where each of the two variants is dominant.

Considerations of Biases and Confounders with Choice of Covariate

Vaccine effectiveness studies are important to assess the capacity of COVID-19 vaccines in the context/setting of (1) emergence of variants, (2) waning immunity, and (3) vaccine types/boosters when randomized control trials are no longer ethical, but due to its observational nature, careful consideration is necessary to reduce bias. The Below table list potential biases and how the investigators may approach each.

Bias	**Problem**	**Approach to reduce bias**
Care seeking behaviour/access to care	Those more likely to get vaccine seek care more, thus more likely to be cases	Test-negative design can partially address this.
Care seeking based on vaccine status	Vaccinated persons less likely to seek care/testing due to COVID-19-like illness due to perception of protection	(Breakthrough infection common enough that individuals are expected to get tested even after vaccination)
Collider bias	Health seeking and SARS-CoV-2 infection both lead to testing	Adjust for health seeking behaviors
Confounding factors	Potential confounding factors include age, sex, race/ethnicity, socioeconomic status, occupation, chronic medical conditions, close contact history, date of onset/specimen collection, priority groups for vaccination	Including these factors in the questionnaire and adjust as appropriate
Diagnostic bias	Health workers more likely to test unvaccinated persons for COVID-19	Health workers asked to not decide who to test based on vaccination status
Misclassification of the outcome	False positives and false negatives	Use PCR that has high sensitivity and specificity; sensitivity analysis on symptomatic individuals

		with onset within two weeks
Misclassification of the exposure	Measurement error/vaccine effect may start before/after specified cut-off for considering individual vaccinated	Ascertain vaccination history with vaccine certificate (Japan) and administrative records (Philippines)
Non-specific vaccine effect	Vaccine prevents diseases for which controls seek care	Not possible to control for but the magnitude is expected to be small due to antigenic specificity
Prior infection	If known prior SARS-CoV-2 infection, less likely to get vaccinated	Adjust for prior infection; sensitivity analysis excluding those with prior SARS- CoV-2 infection by history or lab
Spurious waning	Unvaccinated individuals become immune through natural infection faster than vaccinated	Conduct study soon after vaccine introduction
Other respiratory infectious diseases	Bias can arise if vaccination intention is correlated between COVID-19 vaccine and other vaccines (e.g., flu vaccine)	Exclude individuals with influenza or adjust for influenza vaccination status

Reference: Evaluation of COVID-19 vaccine effectiveness Interim guidance [1]

Acknowledgment

This guidance was developed by Takeshi Arashiro (National Institute of Infectious Diseases (NIID), Japan; World Health Organization (WHO); London School of Hygiene and Tropical Medicine (LSHTM); Nagasaki University, Japan) with technical input from:

Appendices

Appendix 1: sample information to be collected for VE against symptomatic SARS-CoV-2 infection
Appendix 2: sample information to be collected for VE against severe COVID-19

There are several options for delivering the questionnaires to fit the local context (healthcare facility situation, literacy rate, etc.)

- Paper-based self-written questionnaire
- Web-based self-report questionnaire
- Interview by a trained staff such as a research nurse (using RedCap would facilitate swift analysis)

If some data are already collected in the existing ILI/SARI surveillance system, information that is not collected can be additionally collected.

If the investigators plan to link the test results and other information collected, identifiers such as name, date of birth, and/or some sort of ID number to link the two are needed.

Appendix 1: sample information to be collected for VE against symptomatic SARS-CoV-2 infection

Healthcare facility name or code: ( )

SARS-CoV-2 test results (circle one): positive negative undetermined

(If available) SARS-CoV-2 variant-specific PCR or sequencing results: ( )

(If available) Influenza test results (circle one): positive negative undetermined

1. Subject ID (for this study)	( )
2. SARS-CoV-2 test date	year 202 (_____) /month (_____) /date (_____)
3. Age	(_____) years
4. Sex	□1. Male □2. Female
5. Prioritization group for COVID-19 vaccination*	□0. No □1. Health worker □2. Longterm care worker
6. Date of symptom onset	year 202 (_____) /month (_____) /date (_____)
7. During this episode, have you had any of the following symptoms? (check all that apply)	□1. Fever above 37.5°C □2. Malaise □3. Chills □4. Joint pain □5. Headache □6. Runny nose □7. Cough □8. Sore throat □9. Shortness of breath □10. Vomiting, diarrhea, stomach ache □11. Loss of taste/smell
8. Comorbidities/risk factors for severe COVID-19 (check all that apply) check "none" if no comorbidities	□1. Hypertension (high blood pressure) □2. Heart disease (heart failure, coronary heart disease/heart attack) □3. Diabetes mellitus □4. Kidney disease □5. Liver disease □6. Asthma □7. Chronic obstructive pulmonary disease □8. Cancer □9. Dementia □10. Depression/schizophrenia □11. Stroke (bleeding and infarct) □12. Down syndrome □13. Obesity (BMI:_____)

	□14. Immunodeficiency □15. HIV □16. TB □17. Immunosuppressant use □18. Other medical history that may be pertinent: (_____) □19. Admission in the past 1 year (this hospital) □20. Admission in the past 1 year (other hospitals) □21. Pregnancy □**22. None**
9. Have you been identified as a close contact of a case with SARS-CoV-2?	□1. Yes □2. No
10. Past SARS-CoV-2 infection	□1. No □2. Unknown □3. Yes: Diagnosed in Year ( ) Month ( ) (Provide all dates if infected more than once)
11. Vaccination data source	□1. From interview (according to participant's recall) □2. From vaccination card
12. COVID-19 vaccination history	□1. Vaccinated once □2. Vaccinated twice □3. Vaccinated three times □4. Vaccinated four times □5. Vaccinated five times □**0. Unvaccinated**
13. Vaccination type	□1. Pfizer BioNTech □2. Oxford AstraZeneca □3. Sinovac (CoronaVac) □4. Gameleya Sputnik V □5. Janssen/Johnson and Johnson □6. Bharat BioTech □7. Moderna □8. Sinopharm □9. Unknown □10. Other (_____) □11. Received two or more types (if so, please specify which vaccines: First dose: (_____) Second dose: (_____) Third dose: (_____) Fourth dose: (_____) Fifth dose: (_____)

14. Date of first vaccination	year 202 (_____) /month (_____) /date (_____)
15. Date of second vaccination	year 202 (_____) /month (_____) /date (_____)
16. Date of third vaccination	year 202 (_____) /month (_____) /date (_____)
17. Date of fourth vaccination	year 202 (_____) /month (_____) /date (_____)
18. Date of fifth vaccination	year 202 (_____) /month (_____) /date (_____)
19. How long has it been since your last COVID-19 vaccine?	□1. Less than a week (day of vaccination to day 6 post-vaccination†) □2. A week or longer to less than two weeks (7-13 days post-vaccination†) □3. 2 weeks or longer (14 days or longer post-vaccination†)
20. Number of SARS-CoV-2 PCR tests in the past month	(_____) (Exclude today's test; If none, write "0".)
21. Under what circumstances did you typically wear a mask? (check all that apply)	□1. When at home □2. When going out (outdoors) □3. When going out (indoors in public) □4. When talking with others □5. When at work (exclude option 6) □6. As protection against specific occupational hazard (e.g. as healthcare worker, chemical plant, etc.): specify job type: (_____) □7. Almost never
22. (Example‡) How many times did you go out to eat or go to a bar/restaurant with others where you and/or others consumed alcohol in the evening within the past two weeks	( )
23. Did you receive influenza vaccine this season?	□1. Yes: year 202 (_____) /month (_____) /date (_____) □2. No
24. Reason for testing (check all that apply)	□1. Have COVID-19-like symptoms (any of the above) □2. Close contact with COVID-19 cases □3. Worried about getting infected (without symptom or history of close contact) □4. Screening (specific: job, medical procedure ( ) □5. Other: ( )

*If there is any other priority group, list these as well

†vaccination date = day 0

‡Additional questions regarding behaviors, public health and social measures (non-pharmaceutical interventions) that are considered to be risk/preventive factors for SARS-CoV-2 infection in the local context (especially the ones that may be different between vaccinees and non-vaccinees)

Appendix 2: sample information to be collected for VE against severe COVID-19

Information to be collected at admission

1.	Healthcare facility name	( )
2.	Name of the person recording	( )
3.	Subject ID (for this study)	( )
4.	Medical chart ID	( )
5.	Age **when admitted**	(_____) years
6.	Sex	□1. Male □2. Female
7.	Prioritization group for COVID-19 vaccination*	□0. No □1. Health worker □2. Longterm care worker
8.	SARS-CoV-2 test results	□1. Test **positive** (case) □2. Test **negative** (control)
9.	SARS-CoV-2 test type	□1. PCR □2. Rapid antigen kit □3. Quantitative antigent test □4. Other (_____) □5. Unknown
10.	SARS-CoV-2 test date	year 202 (_____) /month (_____) /date (_____)
11.	Date of onset	year 202 (_____) /month (_____) /date (_____)
12.	Date of admission	year 202 (_____) /month (_____) /date (_____)
13.	Date of oxygen use	year 202 (_____) /month (_____) /date (_____)
14.	Date of intubation (if intubated)	year 202 (_____) /month (_____) /date (_____)
15.	**Case only**: Oxygen requirement thought to be mainly due to COVID-19	□1. Yes □2. No (reason: _____) □3. Indeterminate (reason: _____)
16.	**Case only (if intubated)**: Intubation thought to be mainly due to COVID-19	□1. Yes □2. No (reason: _____) □3. Indeterminate (reason: _____)
17.	**Case only**: specific treatment before oxygen use (check all that apply)	□0. None □1. Casirivimab/imdevimab (Ronapreve) □2. Sotrovimab (Xevudy) □3. Tixagevimab/cilgavimab (Evusheld) □4. Remdesivir (Veklury) □5. Molnupiravir (Lagevrio) □6. Nirmatrelvir/ritonavir (Paxlovid) □7. Other (_____)
18.	**Case only (if intubated)**:	□0. None □1. Casirivimab/imdevimab (Ronapreve)

specific treatment before intubation (check all that apply; including before oxygen use)	□2. Sotrovimab (Xevudy) □3. Tixagevimab/cilgavimab (Evusheld) □4. Remdesivir (Veklury) □5. Molnupiravir (Lagevrio) □6. Nirmatrelvir/ritonavir (Paxlovid) □7. Corticosteroid (Dexamethasone) □8. Baricitinib (Olumiant) □9. Tocilizumab (Actemra) □10. Heparin (treatment) □11. Heparin (prevention) □12. Proning □13. Other（_____）
19. **Control only**: diagnosis/reason for oxygen requirement (check all that apply)	□1. Bacterial pneumonia (*Streptococcus pneumoniae*) □2. Bacterial pneumonia (others) □3. Lung cancer □4. COPD exacerbation □5. Interstitial pneumonia □6. Heart failure □7. Influenza (tested positive since onset) □8. Other（_____）
20. Comorbidities/risk factors for severe COVID-19 (check all that apply) check "none" if no comorbidities	□1. Hypertension (high blood pressure) □2. Heart disease (heart failure, coronary heart disease/heart attack) □3. Diabetes mellitus □4. Dyslipidemia □5. Chronic kidney disease □6. Chronic liver disease □7. Asthma □8. Chronic obstructive pulmonary disease □9. Cancer □10. Dementia □11. Depression/schizophrenia □12. Stroke (bleeding and infarct) □13. Down syndrome □14. TB □15. Obesity (BMI:_____) □16. Immunodeficiency □17. Immunosuppressant use □18. HIV

	□19. Other medical history that may be pertinent: (_____) □20. Admission in the past 1 year (this hospital) □21. Admission in the past 1 year (other hospitals) □22. Pregnancy □**23. None**
21. History of smoking	☐1. Never ☐2. Used to smoke ☐3. Currently smoke
22. Past SARS-CoV-2 infection	☐0. No □1. Yes: diagnosed on year 202 (____) /month (_____)
23. Vaccination data source	□1. From interview (according to participant's recall) □2. From vaccination card
24. COVID-19 vaccination history	□1. Vaccinated once □2. Vaccinated twice □3. Vaccinated three times □4. Vaccinated four times □5. Vaccinated five times □**0. Unvaccinated**
25. Vaccination type	□1. Pfizer BioNTech □2. Oxford AstraZeneca □3. Sinovac (CoronaVac) □4. Gameleya Sputnik V □5. Janssen/Johnson and Johnson □6. Bharat BioTech □7. Moderna □8. Sinopharm □9. Unknown □10. Other (_____) □11. Received two or more types (if so, please specify which vaccines: First dose: (_____) Second dose: (_____) Third dose: (_____) Fourth dose: (_____) Fifth dose: (_____)
26. Date of first vaccination	year 202 (_____) /month (_____) /date (_____)
27. Date of second vaccination	year 202 (_____) /month (_____) /date (_____)
28. Date of third vaccination	year 202 (_____) /month (_____) /date (_____)
29. Date of fourth vaccination	year 202 (_____) /month (_____) /date (_____)
30. Date of fifth vaccination	year 202 (_____) /month (_____) /date (_____)
31. How long has it been since your last COVID-19 vaccine?	□1. Less than a week (day of vaccination to day 6 post-vaccination†) □2. A week or longer to less than two weeks (7-13 days post-vaccination†)

	□3. 2 weeks or longer (14 days or longer post-vaccination†)
32. Note	

*If there is any other priority group, list these as well

†vaccination date = day 0

Information to be collected at <u>discharge (for COVID-19 case only)</u>

1. Healthcare facility name	
2. Name of the person recording	
3. Medical chart ID	
4. Outcome	□1. Improved and discharged □2. Improved and transferred □3. Did not improve or worsened and transferred □4. Worsened and transferred (need invasive ventilation) □5. Worsened and transferred (need ECMO) □6. Worsened and transferred (others) □7. Died
5. Date of extubation (if intubated)	year 202（_____）/month（_____）/date（_____）
6. Date of outcome occurrence	year 202（_____）/month（_____）/date（_____）
7. Code at discharge	□1. Full □2. DNR only □3. DNI only □4. DNRI □5. Unknown □6. Other（_____）
8. Maximum oxygen therapy	□1. Nasal cannula □2. Mask □3. High flow nasal cannula □4. CPAP/NPPV □5. Invasive ventilation □6. ECMO
9. Death thought to be mainly due to COVID-19	□1. Yes □2. No （reason: _____） □3. Indeterminate（reason: _____）
10. Proning after intubation	□1. Did not perform □2. Performed
11. **Case only**: specific treatment after oxygen use (check all that apply)	□0. None □1. Remdesivir (Veklury) □2. Corticosteroid (Dexamethasone) □3. Baricitinib (Olumiant) □4. Tocilizumab (Actemra) □5. Heparin (treatment) □6. Heparin (prevention) □7. Oral anticoagulant □8. Other（_____）

Main References

1. World Health Organization (WHO). Evaluation of COVID-19 vaccine effectiveness: interim guidance. 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1
2. World Health Organization (WHO). Guidance on conducting vaccine effectiveness evaluations in the setting of new SARS-CoV-2 variants: Interim guidance, 22 July 2021. Addendum to Evaluation of COVID-19 vaccine effectiveness: interim guidance. 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-variants-2021.1
3. World Health Organization (WHO). Evaluation of COVID-19 vaccine effectiveness in a changing landscape of COVID-19 epidemiology and vaccination: interim guidance, 1 October 2022: second addendum to Evaluation of COVID-19 vaccine effectiveness: interim guidance. 2022. Available from: https://apps.who.int/iris/handle/10665/363344