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Yishiow (Christina) Kuo — Date

Estimation of COVID-19 Vaccine Effectiveness against Mortality During April to December 2022 of COVID Infections in Taiwan

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Abstract

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By Yishiow (Christina) Kuo

Taiwan's response to the COVID-19 pandemic underwent a significant shift in strategy, transitioning from stringent non-pharmaceutical interventions (NPIs) established in January 2020 to prioritizing mass vaccination as the Omicron variant emerged in April 2022. This thesis presents findings from an observational study conducted in Taiwan from April to December 2022, aimed at evaluating the effectiveness of the mass vaccination campaign against the Omicron BA.2 variant. The study employed Poisson regression models to estimate vaccine effectiveness against COVID-19 mortality in the population. Vaccine effectiveness was assessed across two distinct time periods: April 19th, 2022, to August 19th, 2022, designated as Wave 1, and August 20th, 2022, to December 4th, 2022, designated as Wave 2, corresponding to peaks in infections and deaths, comparing vaccinated individuals with unvaccinated counterparts and varying numbers of vaccine doses received. The analysis revealed a substantial reduction in COVID-19 mortality post-vaccination, with an overall vaccine effectiveness of 91.0% (95% confidence interval 90.7%-91.3%) estimated for the study period. Notably, vaccine effectiveness for individuals receiving two doses of the vaccine exhibited higher efficacy compared to those receiving a single dose, with vaccine effectiveness for Wave 2 surpassing that of Wave 1 across all comparison groups. Comparisons with similar studies conducted in Israel and Hong Kong highlighted Taiwan's vaccine effectiveness alignment with Hong Kong's findings. Discrepancies in vaccine effectiveness outcomes were attributed to variations in vaccine compositions and dominant virus strains. This research contributes valuable insights into the effectiveness of Taiwan's mass vaccination campaign amidst evolving pandemic dynamics, informing future public health interventions and policy decisions.

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Chapter 1 Introduction

As of March 17, 2024, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to 774 million infections and 7.04 million deaths worldwide (*WHO COVID-19 Dashboard*, 2024). The Taiwan Center for Disease Control (CDC) has ceased requesting general population to report mild COVID-19 infections, and discontinued public release of COVID-19 related infections and deaths in March 2023, but by that time, had already reported 10.2 million COVID-19 infections and 18,993 COVID-19 related deaths in Taiwan (Ministry of Health and Welfare, 2023; *Area, Age, and Gender Statistical table_19CoV (Daily)- By Date of Confirmation*, 2022; *Statistics table of area, age, sex of death cases - COVID-19 (by date of death)*, 2022). Throughout 2020 and 2021, Taiwan succeeded in containing COVID-19 using non-pharmaceutical interventions (NPIs) including border control, case-based interventions, and population-based interventions without a lockdown. Shortly after the introduction of Omicron BA.1 and BA.2 into Taiwan in January 2022, daily cases surged to a peak of 89,000 in May 2022. Finding itself in a difficult situation after lifting travel restrictions, Taiwan counted on mass vaccination as its main tool to reduce the burden of COVID-19. It is of great interest to quantify the effectiveness of the COVID-19 mass vaccination campaign in Taiwan in preventing fatalities during the Omicron wave.

The first case of COVID-19 in Taiwan was recorded on January 21, 2020, in a woman who had traveled to Taiwan from Wuhan, China. The first locally transmitted COVID-19 case, her husband, followed one week later (Y.-C. Liu et al., 2020). Despite Taiwan's perceived elevated risk due to close geographic and economic relations to China, Taiwan kept COVID-19 cases and deaths relatively low throughout 2020 and 2021. Up to the first Omicron peak in April 2022,

Taiwan had only experienced 23 thousand cumulative cases and 853 cumulative deaths due to COVID-19 by limiting community outbreaks to lows unobserved in other countries (*Area, Age, and Gender Statistical table_19CoV (Daily)- By Date of Confirmation*, 2022).

Evidence suggests the combination of non-pharmaceutical interventions (NPIs) incorporating border control, case-based interventions, and population-based interventions were responsible for Taiwan's early success in containing COVID-19 transmission (Ng et al., 2021). Based on its experience in 2003 with the Severe Acute Respiratory Syndrome (SARS) outbreak, the Taiwan CDC recognized early on the importance of acting quickly and decisively to combat the pandemic's spread. The Taiwan CDC activated the Central Epidemic Command Center (CECC) on January 20, 2020, and in February banned travel from key epidemic centers in China. Shortly after on March 19, 2020, due to continuous importation of COVID-19 cases, a travel ban for foreign nationals was enforced. While Taiwanese citizens were allowed to enter the country, 14-day quarantine was required for all incoming travelers as well as mandatory case-based interventions, such as contact tracing and quarantine for close contacts of confirmed cases. Use of face masks, personal hygiene, and social distancing were also highly encouraged and adhered to. Effective application of NPIs, traditionally dependent on manpower, relied heavily on Taiwan's linkage of national health and immigration databases, organized by the National Health Insurance Administration (NHIA). These technologies were instrumental in adopting an electronic contact tracing system to monitor adherence to quarantine, and equitable distribution of face masks to the public (Y.-H. Chen & Fang, 2024; H.-Y. Cheng, 2024).

After a year of no community outbreaks, a community outbreak occurred in April 2021 when a Taiwanese airline crew from China Airlines was mistakenly quarantined in a hotel housing non-quarantine customer, a violation of Taiwan's pandemic prevention policy. Confirmed cases in

Taiwan exceeded a hundred within one week, but in three months, the Taiwanese public health response mitigated the spread using the same NPIs which served them well up to that point.

While the outbreak in 2021 was unprecedented and raised the alarm for many in Taiwan, it would not compare to the scale of the outbreak in 2022, which progressed in three waves. The timing of the first wave aligned with Taiwan's drastic shift in COVID-19 policy. On April 8, 2022, Taiwan announced it would no longer maintain its previous border control policy and instead relax measures in a return to normalcy (*Taiwan Launches New Pandemic Response Strategy*, 2022). The rollback of pandemic prevention was based on newfound evidence the new Omicron variant was much less lethal than previous Delta and Alpha strains. Omicron BA.1 and BA.2 entered Taiwan in January 2022, and has been confirmed to have made up most of new COVID-19 infections in 2022 (Y.-H. Chen et al., 2023). Taiwan quickly found itself in a new situation, as its easing of contact tracing and border control coincided with a rapid increase in COVID-19 infections. By choosing to forgo previous NPIs, Taiwan did not have a choice but to rely on widespread vaccine uptake to control the pandemic from spreading uncontrollably. A variety of vaccines were available in Taiwan at that point, including vaccines manufactured by Pfizer (BNT162B2), Moderna (mRNA-1273), Novavax (NVX-CoV2373), and AstraZeneca (ChAxOx1-S), as well as the domestic vaccine produced by Medigen (MVC-COV1901). In addition, heterologous vaccine schedules were common, with many receiving ChAxOx1-S for the first two doses, and mRNA-1273 or BNT162b2 for the booster. Heterologous vaccine schedules were shown to have higher immunity compared to homologous schedules (Sheng et al., 2023). The infection and vaccination situation in Taiwan was quite unique relative to the rest of the world, and it remains unknown how effective such a mass vaccination strategy worked in preventing COVID-19 death in Taiwan.

Chapter 2 Literature Review

2.1 Vaccine efficacy

While there has been much discussion on the complications of interpreting vaccine clinical trial results, the benefit of a vaccine has traditionally been measured by vaccine efficacy, defined as one minus the relative risk of the outcome, comparing vaccinated to unvaccinated individuals (Olliaro et al., 2021). Traditionally, vaccine efficacy is estimated under conditions controlled by the investigator in experimental designs known as randomized controlled trials (RCTs). The vaccine efficacy is the ratio between the risk of COVID-19 among the vaccinated to that of the unvaccinated. In other words, it measures how many more times likely a vaccinated person is to survive from COVID-19 compared to someone unvaccinated. The main criticism of vaccine efficacy is its independence of the background risk of the population – a vaccine efficacy of 95% could refer to a 0.05% to 1% vaccinated to unvaccinated ratio, or a 0.5% to 10% ratio. An alternative to the vaccine efficacy is the absolute risk reduced (ARR), or difference between the risk of COVID-19 among the vaccinated and that of the unvaccinated. ARR for the hypothetical populations above would be 0.95% and 9.5%, a noticeable difference. In this study, we focus on the vaccine effectiveness due to its ubiquity in the vaccine literature and ease of comparison to other studies.

2.2 Vaccine effectiveness

Much of the early evidence on COVID-19 vaccine efficacy relied on RCTs conducted as part of phase 3 clinical trials led by the world's largest private pharmaceutical companies including Pfizer (Polack et al., 2020), Moderna (Baden et al., 2021), AstraZeneca (Voysey et al., 2021), Novavax (Heath et al., 2021), and Janssen (Sadoff et al., 2021). While RCTs are traditionally regarded as the gold standard for evaluating vaccine efficacy, issues with external validity can

make clinical trial results difficult to generalize to the mass vaccination campaigns conducted in different countries. RCTs are designed to eliminate concerns with confounding, but do not always consider cultural, social, and pandemic policy differences. Observational studies provide the best opportunity to understand the true benefit of the COVID-19 vaccine in combating the spread of COVID-19 on a case-by-case basis.

The analogue to vaccine efficacy in RCTs for observational studies is called *vaccine effectiveness*. The difficulty with estimating vaccine effectiveness (VE) instead of vaccine efficacy is that one must be able to compute the relative risk of COVID-19 death between the vaccinated and unvaccinated in the presence of confounding. Estimating vaccine effectiveness for mass vaccination on the population scale requires a 2 × 2 table for the entire Taiwanese population with dimensions of vaccination status and death by COVID-19. The cells in this table are computable using death registry, vaccine coverage, and census data. In addition to the necessary data, a valid estimate of vaccine effectiveness in observational studies is dependent on the inclusion of the proper confounding variables. All variables which are related to both vaccination status and COVID-19 death should be included in the analysis. Because vaccination was not mandatory and administered to the entire Taiwanese population, the vaccinated and unvaccinated populations could differ in more ways than just their vaccination status. A crude unadjusted vaccine effectiveness runs the risk of biasing the true effect. Without properly accounting for differences between the vaccinated and unvaccinated populations (which we are not able to measure and adjust for outside of an RCT) we may mistakenly attribute a decrease in COVID-19 mortality to the vaccine, when in fact it may just be a sign healthy people get vaccinated at higher rates.

There has been much research on vaccine effectiveness of the main COVID-19 vaccines (C.-J. Cheng et al., 2021; Higdon et al., 2022). However, few studies have evaluated real-world effectiveness of the vaccines to the Omicron BA.2 subvariant, measured the vaccine effectiveness of boosters (more than two doses) compared to no boosters (two or one dose), and been conducted in Taiwan. Higdon et al. (2022) analyzed 107 observational studies estimating vaccine effectiveness for eight different COVID-19 vaccines. However, most of them were conducted early in the pandemic, and did not estimate vaccine effectiveness for the BA.2 subvariant, which happened to be the dominant strain during Taiwan's peak epidemic starting April 2022.

Later studies began measuring the vaccines' effectiveness against death from the Omicron variant in countries with detailed records of mortality and vaccine coverage data. Using nationwide registry data, Haas et al. (2021) used a negative binomial model to estimate vaccine effectiveness adjusting for age group, sex, and calendar week for BNT162b2 in Israel when Omicron variant B.1.1.7 was the dominant strain. McMenamin et al. (2022) used the same study design, statistical model, and covariates to estimate vaccine effectiveness for BNT162b2 and CoronaVac in Hong Kong, when the Omicron BA.2 subvariant was dominant, and extended the analysis to three, two, and one dose of vaccine. They demonstrated the positive dose-response relationship of BNT162b2 for preventing death.

Kirsebom et al. (2022) and Kirsebom, Andrews, Sachdeva, et al. (2022) estimated vaccine effectiveness for BA.2 in England, but only for symptomatic infection and hospitalization instead of death. Tsang et al. (2023) conducted a rare prospective cohort study to estimate vaccine effectiveness against infection using Cox proportional hazards models adjusting for age, sex, coexisting illnesses, and various sociodemographic factors which may confound test positivity.

Lau et al. (2023) estimated vaccine effectiveness for three and four doses of BNT162b2 against Omicron BA.2 infection in the beginning of the Omicron surge in January to July 2022 in Hong Kong. They decided not to estimate vaccine effectiveness against COVID-19 related death because data on oral antiviral use like Nirmatrelvir/Ritonavir (Paxlovid produced by Pfizer) was inaccessible. Teasing apart the protective effect of both the vaccine and the oral antivirals was not feasible without the proper data. A separate study circumvented this issue and estimated vaccine effectiveness of BNT162b2 by dose against death in Hong Kong by conducting a case-control study of adults infected with COVID-19 Omicron who died during the BA.2 surge, where oral antiviral use was available from hospital data (Wei et al., 2023). In Taiwan, the use of oral antiviral drugs (Paxlovid and Molnupiravir) began on May 1st, 2022. According to the Central Epidemic Command Center (CECC) in Taiwan, 1,077,922 treatments of Paxlovid and 235,522 treatments of Molnupiravir were distributed as of April 23, 2023; 790,193 treatments of Paxlovid and 167,216 treatments of Molnupiravir were prescribed during the analytic period of this research. Unfortunately, due to unavailability of individual level oral antiviral use data, we are not able to fully incorporate this data into our analysis and assume it is negligible with regards to COVID-19 mortality.

Vaccine effectiveness has also been evaluated extensively in the United States by the Center for Disease Control (CDC) through their Mortality and Morbidity Weekly Reports (MMWR). While all vaccines approved for use in the US were shown to be highly effective in reducing the risk of several COVID-19 outcomes, VE was shown to decrease over time most likely due to waning effectiveness against the quickly evolving COVID-19 variants emerging throughout the pandemic. In the year 2021 when Delta dominated beginning in June and Omicron dominated in December, a study conducted in 25 U.S. jurisdictions reported crude VE for COVID-19 related

death between fully vaccinated individuals vs. unvaccinated at 95% during April to May, 94% in June, and 94% from July to December (Johnson, 2022). Another study from March 2021 to January 2022 found fully vaccinated individuals with two or three doses of an mRNA COVID-19 vaccine had a risk reduction of 90% for COVID-19 related invasive mechanical ventilation or death (Tenforde, 2022). Besides COVID-19 related death, the CDC also looked at other COVID-19 outcomes including COVID-19 infection and hospitalization. VE against COVID-19 infection was estimated to be 93% in April-May, 89% in June, 80% from July to November, and 68% in December (Johnson, 2022). A study conducted from March to August 2021 compared the effectiveness between the Pfizer, Moderna, and Janssen vaccines for preventing COVID-19 hospitalization, and found VE for Moderna (93%) and Pfizer (88%) were higher than for Janssen (71%). The data from the United States shows while vaccine effectiveness against COVID-19 infection and hospitalization suffered with the rise of Delta and then Omicron variants, the vaccines remained highly effective against COVID-19 related death.

To our knowledge, there has yet to be a peer-reviewed study estimating vaccine effectiveness by dose of the mass vaccination campaign against the Omicron BA.2 variant in the Taiwanese population. Studies include the original phase 2 trial results from Medigen (Hsieh et al., 2021), and a study estimating the vaccine effectiveness of COVID-19 boosters in a vulnerable population of hemodialysis (HD) patients on oral antiviral agents (P.-C. Chen et al., 2023). This is likely due to the low incidence and local transmission of COVID-19 in Taiwan through the first two years of the pandemic, like the evidence base available in Hong Kong (McMenamin et al., 2022). Much of the COVID-19 literature regarding Taiwan has focused on the epidemiological nature of the Taiwanese pandemic (L.-T. Liu et al., 2023; Y.-C. Liu et al., 2020; Shao et al., 2023)or lessons to be learned from NPIs implemented in the early stages (H.-Y.

Cheng, 2024; Ng et al., 2021; Wang et al., 2020). Nevertheless, estimating vaccine effectiveness in Taiwan is possible due to the detailed COVID-19 recordkeeping maintained by the Taiwan CDC and other government institutions at the time.

Chapter 3 Manuscript

3.1 Introduction

Following the relaxation of NPI's such as border control and contact tracing in April 2022, Taiwan experienced two large waves in both COVID-19 infections and deaths due to the Omicron BA.2 subvariant, at a scale completely unprecedented in Taiwan since the pandemic began in December 2019. With no NPIs to rely on, vaccines became the main tool for prevention and spread of COVID-19. While studies of real-world vaccine effectiveness of the COVID-19 vaccines have been published, contributing valuable evidence of the benefit of vaccines in reducing disease burden and strain on healthcare systems, none yet have been conducted in Taiwan. Taiwan offers a unique case study for evaluating vaccine effectiveness due to high prevalence of heterologous vaccine schedules, and a massively successful containment strategy resulting in near zero community outbreaks from the beginning of the pandemic to April 2022. This thesis addresses the gap in the literature by analyzing publicly available mortality and vaccination data released by the Taiwanese government to estimate real-world vaccine effectiveness of the Taiwanese mass vaccination campaign in preventing COVID-19 related death, from April to December 2022. The findings in this thesis will contribute to the evidence base of real-world effectiveness of COVID-19 vaccinations and help guide future Taiwanese pandemic preparedness policies.

3.2 Methods

In this thesis, we estimate the vaccine effectiveness for the entire population at-risk of more than two, two and one dose of Taiwan's mass vaccination program in preventing COVID-19 related deaths during the rise of the Omicron BA.2 subvariant in two distinct time periods: Wave 1 which denotes April 19, 2022, to August 19, 2022, Wave 2 which denotes August 20, 2022, to

December 4th, 2022, and the overall period beginning in Wave 1 and ending in Wave 2. We use death registry data on all COVID-19 related deaths, where each death reports the number of doses of vaccine prior to their death, as well as vaccine coverage and census data. We compare the RCT-reported vaccine efficacy for each approved vaccine in Taiwan to our estimated real-world vaccine effectiveness of mass vaccination in Taiwan. We also compare vaccine effectiveness in Taiwan to countries where strong healthcare system record keeping have allowed for similar mass vaccination analyses: including Israel, England, and Hong Kong.

3.2.1 Study design and population

We conducted an observational study to estimate overall vaccine effectiveness (VE) of the Taiwanese mass vaccination campaign against COVID-19, particularly against the Omicron BA.2 subvariant. The study population was Taiwanese citizens of all ages from April 19th, 2022, to December 4th, 2022. The unvaccinated and vaccinated population at one, two and greater than two doses was determined by combining vaccination rate data from the Taiwan Centers for Disease Control (Taiwan CDC) (*COVID-19 疫苗統計資料 [COVID-19 Vaccine Statistics Data]*, 2024) and census data from the Taiwan Department of Household Registration, Ministry of Interior (Taiwan) (M.O.I.) which is published monthly (中華民國內政部戶政司 [Taiwan Ministry of Interior], 2022). The individual level data on all COVID-19 deaths was also provided by the Taiwan CDC and contained information on vaccine dosage, age, and date of reported death for all COVID-19 related deaths (Statistics table of area, age, sex of death cases - COVID-19 (by date of death), 2022; 衛生福利部 [Ministry of Health and Welfare], 2023). While not stated explicitly, we assumed all deaths listed under COVID-19 that were reported by the Taiwan CDC were any death occurring simultaneously with COVID-19 infection. According to the Taiwan Ministry of Health and Welfare, a COVID-19 infection was defined differently before

and after June 2022 (Ministry of Health and Welfare, 2020). The case definition for COVID-19 infection prior to June 2022 was any positive RT-PCR test. After June 2022, the case definition was expanded to any rapid antigen test administered by a healthcare professional, or at-home COVID-19 antigen or nucleic acid test approved by the Taiwan Food and Drug Administration and confirmed by a physician. It is unclear how comorbidities were handled in the dataset; therefore, we assume any death with a positive COVID-19 infection was a result of COVID-19 related death.

3.2.2 Statistical Analysis

We estimated the relative risk (RR) of COVID-19 related death by vaccine dosage over three different time periods (Study period: April 19th, 2022 to December 4th, 2022, Wave 1: April 19th, 2022 to August 19th, 2022, Wave 2: August 20th, 2022 to December 4th, 2022). RR refers to the ratio of risk of COVID-19 related death among the vaccinated to the risk of that among the unvaccinated. Vaccine effectiveness (VE), the target parameter, was then computed as $(1-RR) \times 100\%$. For each of the three time periods, VE's were estimated for four different comparison groups: vaccinated vs. unvaccinated (C1), only one dose vs. unvaccinated (C2), only two doses vs. unvaccinated (C3), and greater than two doses vs. unvaccinated (C4). We calculated 95% confidence intervals for each of the estimated VE's.

RRs for each time period-comparison combination were estimated using Poisson regression models, computed with SAS Version 9.4, with offsets inversely proportional to the population in the given vaccination group at the beginning of the time period. For example, an unvaccinated individual in Wave 1 would receive a weight we stratified the data by each of the twelve unique time period-comparison groups and fit a separate Poisson regression for each. For clarity, the regression model fit was.

$$\log Y_i = \log N_i + \beta X_i$$

Where i ranges from 1 to n and indicates the individual, Y_i is a binary indicator where a one means individual i died from COVID-19, N_i is a weight inversely proportional to the population at the beginning of the time period, X_i is a binary indicator for vaccination status of individual i (0 is the unexposed/reference group, 1 is the treatment group), and β is the RR of the treatment relative to the unexposed group in X_i, to be estimated by the regression model. All analysis was done in SAS Version 9.4 and proc genmod.

3.3 Results

At the beginning of the study period on April 19th, 2022, the population of Taiwan was 23.4 million, across all ages and sexes. Figure 1 details the complete timeline of COVID-19 infections, deaths, and vaccinations from January 2020 to June 2023. From April 19th, 2022 to December 4th, 2022, approximately 13,628 COVID-19 related deaths were recorded with 8,712 (63.9% of all deaths in the study period) occurring in Wave 1 and 4,916 (36.1%) occurring in Wave 2. Males and the elderly were the highest risk demographic groups for fatal COVID-19 outcomes, with male deaths accounting for 57.5% and 57.0% of COVID-19 related deaths in Waves 1 and 2, respectively, and age over 60 deaths accounting for 90.3% of deaths in Wave 1 and 91.1% of deaths in Wave 2. At the beginning of the study period, 19.6 million (84.0% of the total population) had received at least one dose of the COVID-19 vaccine, irrespective of vaccine producer. At the end of Wave 1, that number had increased to 21.4 million (92.0%) and at the end of Wave 2 reached 21.8 million (94.2%). Coverage with at least two doses of vaccine, at the same time points, were 18.5 million (79.1%), 20.0 million (86.3%), and 20.6 million (89.6%). Table 1 details the descriptive characteristics of COVID-19 deaths, including demographic breakdown and vaccination status.

Figure 1. Timeline of COVID-19 confirmed cases, death cases, and vaccine administrations in Taiwan.

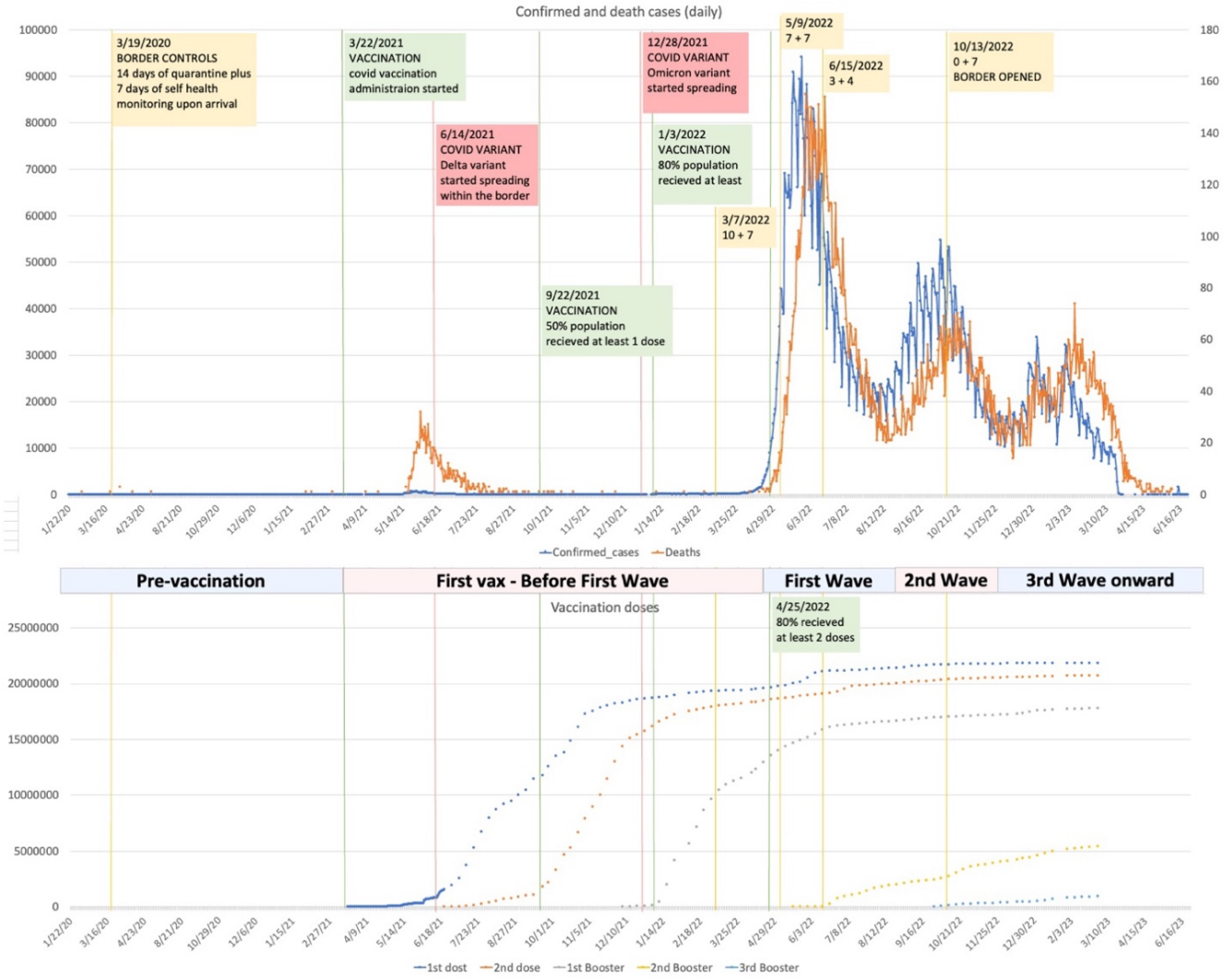

Table 1. Descriptive characteristics of COVID-19 death cases in Taiwan between April 19th to December 4th, 2022

	Overall		First wave (04/19/2022 - 08/19/2022)		Second wave (08/20/2022 - 12/04/2022)	
	n	Median % (95% CI)	n	Median % (95% CI)	n	Median % (95% CI)
TOTAL DEATH	13628	100.0	8712	63.9 (63.1, 64.7)	4916	36.07 (35.3, 36.9)
Gender						
Male	7731	57.3 (56.5, 58.2)	4930	57.5 (56.5, 58.6)	2801	57.0 (55.6, 58.4)
Female	5753	42.7 (41.8, 43.5)	3638	42.5 (41.4, 43.5)	2115	43.0 (41.6, 44.4)
Age						
< 20	52	0.4 (0.3, 0.5)	38	0.4 (0.3, 0.6)	14	0.3 (0.1, 0.4)
20-59	1236	9.1 (8.6, 9.6)	811	9.3 (8.7, 9.9)	425	8.7 (7.9, 9.4)
> 60	12340	90.6 (90.0, 91.0)	7863	90.3 (89.6, 90.9)	4477	91.1 (90.3, 91.9)
VACCINATION STATUS AMONG COVID-19 DECEDENTS						
Vaccinated (any)	7388	54.6 (53.7, 55.4)	4837	56.1 (55.0, 57.1)	2551	51.9 (50.5, 53.3)
1 dose only	1228	16.6 (15.8, 17.5)	832	18.0 (16.9, 19.1)	396	14.3 (13.0, 15.7)
At least 2 doses	6247	83.6 (82.7, 84.4)	4092	83.1 (82.1, 84.2)	2155	84.5 (83.1, 85.9)
2 doses only	1646	22.0 (21.1, 23.0)	1121	22.8 (21.6, 23.9)	525	20.6 (19.0, 22.2)
3+ doses	4601	61.6 (60.5, 62.7)	2971	60.3 (59.0, 61.7)	1630	63.9 (62.0, 65.8)
Not vaccinated	6153	45.4 (44.6, 46.3)	3788	43.9 (42.9, 45.0)	2365	48.1 (46.7, 49.5)

- Gender and vaccination status were missing on June 22nd, 2022, with 144 missing in Gender variable and 87 missing in Vaccine status variable.

Table 2 reports estimated VE by wave and vaccination status. The estimated VE between vaccinated and unvaccinated of Taiwan's mass vaccination campaign was 91.0% (90.7-91.3) for the study period, 89.2% (88.7-89.6) for Wave 1, and 93.0% (92.6-93.4) for Wave 2. For a single dose vs. unvaccinated, the estimated VE was lower at 74.6% (73.0-76.1) for the study period, 71.4% (69.2-73.5) for Wave 1, and 79.2% (76.9-81.3) for Wave 2. Exactly two doses had significantly higher protection where VE was estimated at 86.3% (85.5-87.0) for the study period, 84.0% (82.9-85.1) for Wave 1, and 89.3% (88.3-90.3) for Wave 2. When comparing

vaccinated individuals with greater than two doses vs. those with zero dose, the estimated VE was 93.0% (92.7-93.3) for the study period, 91.5% (91.0-91.9) for Wave 1, and 94.5% (94.2-94.9) for Wave 2. For all comparison groups, estimated VE for Wave 2 was higher than that of Wave 1.

Table 2. Vaccine effectiveness (relative risk reduction) estimated by the twelve models within the two waves, including risk ratio.

	Overall	**First wave (04/19/2022 - 08/19/2022)**	**Second wave (08/20/2022 - 12/04/2022)**
Any vaccination vs None			
Risk ratio	9.0 (8.7, 9.3)	10.8 (10.4, 11.3)	7.0 (6.6, 7.4)
Relative Risk Reduction (VE)	91.0 (90.7, 91.3)	89.2 (88.7, 89.6)	93.0 (92.6, 93.4)
Only 1 dose vs None			
Risk ratio	25.4 (23.9, 27.0)	28.6 (26.5, 30.8)	20.8 (18.7, 23.1)
Relative Risk Reduction (VE)	74.6 (73.0, 76.1)	71.4 (69.2, 73.5)	79.2 (76.9, 81.3)
2 dose or more vs None			
Only 2 dose vs none			
Risk ratio	13.7 (13.0, 14.5)	16.0 (14.9, 17.1)	10.7 (9.7, 11.7)
Relative Risk Reduction (VE)	86.3 (85.5, 87.0)	84.0 (82.9, 85.1)	89.3 (88.3, 90.3)
3+ doses vs None			
Risk ratio	7.0 (6.7, 7.3)	8.5 (8.1, 9.0)	5.5 (5.1, 5.8)
Relative Risk Reduction (VE)	93.0 (92.7, 93.3)	91.5 (91.0, 91.9)	94.5 (94.2, 94.9)

3.4 Discussion

In this study, we estimated VE against COVID-19 mortality in Taiwan during the period following emergence of the Omicron BA.2 subvariant. Like other previously published data, we found very high protection against COVID-19 related mortality, with an overall VE of 91.0% (95% CI: 90.7%-91.3%). We compared the estimated VE's for Taiwan in our study to studies in other locations conducted during similar analytic time periods and COVID-19 variants. Haas et al. (2021) estimated VE of BNT162b2 against COVID-19 infection, symptomatic infection,

asymptotic infection, hospitalization, severe or critical COVID-19 related hospitalization, and COVID-19 related death in Israel for the first four months of their mass vaccination campaign from January 24 to April 3, 2021. The estimated adjusted VE against COVID-19 related death was 96.7% (96.0-97.3) for exactly two doses compared to unvaccinated individuals, where two doses was defined as seven days after administration of the second dose. For 14 days after administration, the VE was estimated to be 98.1% (97.6-98.5). Adjustment variables included age, sex, and calendar week, but there was little difference between estimated all-ages VE with and without adjustment. A similar study in Hong Kong (McMenamin et al., 2022) estimated VE of two separate vaccines: BNT162B2 and CoronaVac over the time period of December 31, 2020 to March 16, 2022. They did not estimate VE for all ages, but the estimated VE for COVID-19 related death for one dose of BNT162b2 vs. unvaccinated was 95.4% (90.7-98.1) for ages 20-59, 70.0% (51.8-82.0) for ages 60-69, 72.2% (56.7-82.6) for ages 70-79, and 75.0% (61.1-84.2) for ages 80 and up. For two doses, the estimated VE's were 96.3% (94.9-97.3) for ages 20-59, 91.1% (86.9-94.0) for ages 60-69, 89.8% (85.1-93.1) for ages 70-79, and 86.9% (80.5-91.3) for ages 80 and up. Their models also adjusted for age group, sex, and calendar day with again little difference in VE's with and without adjustment. While VE's estimated in the Israel study were considerably higher than those we estimated for Taiwan, our estimated VE's are comparable to those in the Hong Kong study for older age groups (60 and above).

One possible explanation for the observed differences in vaccine effectiveness between Taiwan and Israel could be the vaccine composition in each population. Many Taiwanese received a heterologous vaccine schedule and were given the AstraZeneca vaccine for their first two doses before receiving boosters from Pfizer and Moderna, whereas the Israel study measured the VE of the Pfizer vaccine for the first two doses only. In addition, the dominant strain in Israel at the

time was the Alpha variant, which the vaccines were universally shown to be very effective against death relative to later variants like Omicron (DeCuir, 2023). The Omicron BA.2 subvariant was much more dominant in the study periods analyzed in our study and McMenamin et al. (2022) which can explain the shared lower magnitude of estimated VE. Despite the different types of vaccines implemented in the first two doses, the similarity between our two studies could signify the dominant COVID-19 strain in the population was a much larger determining factor in VE compared to the type of vaccine manufacturer. We found our estimate of vaccine effectiveness in Taiwan agreed nicely with that published in Hong Kong under a similar pandemic variant and vaccination campaign.

Our analysis has several strengths. First, this study is the first we know of which tackles the challenge of estimating vaccine effectiveness of the COVID-19 mass vaccination campaign in Taiwan. Most literature on the pandemic in Taiwan study the ways in which Taiwan avoided community outbreaks in the first year of the pandemic from 2020-2021, and the NPIs which got them to that point. While NPIs were critical to Taiwan's containment success, they were unsustainable in the long run without sacrificing the Taiwanese economy and citizens' state of well-being and the government ultimately had to rely on vaccines to return to normal. Our work is important to understand the vaccine's ability to mitigate the spread of the virus. Second, our analysis takes advantage of individual level data to model vaccine effectiveness, with detailed data on vaccine status, age, and sex of COVID-19 related deaths. Unfortunately, age and sex were not usable due to other data limitations, but we believe there is strong potential in Taiwan's data for further detailed analyses.

Our study also has important limitations. First, while we were able to access individual-level data on all COVID-19 related deaths in Taiwan by age, sex, and vaccine dosage, we were not able to

estimate VE by these important demographics due to limited age-sex data on the entire vaccinated and unvaccinated populations. Estimates of VE require demographic data not just among COVID-19 deaths but also among survivors. In addition, because our study was retroactive and not designed to track individuals throughout the pandemic, we could not measure follow-up time for everyone to calculate mortality rates instead of just estimates of risk.

Other limitations relate to the inability of our study to account for other sources of variation among the population, besides age and sex. No publicly available data source had information on the proportion of the population which received which vaccine at which dosages. Therefore, our study measures the vaccine effectiveness of the entire mass vaccination campaign rollout, rather than the effectiveness of a particular vaccine or set of vaccines. In McMenamin et al. (2022), the authors note age was an important variable to adjust because younger people had a strong preference for BNT162b2, while older people preferred the Chinese manufactured CoronaVac. While CoronaVac was not one of the five COVID-19 vaccines approved for use in Taiwan, similar vaccine manufacturer preferences by age group are likely to have existed within the Taiwanese population and could be important effect modifiers. Heterologous vaccine schedules were particularly prevalent in Taiwan, with ChAdOx-1-S being the dominant vaccine of choice at the beginning of the pandemic, before Medigen, BNT162b2 and mRNA-1273 received approval later with the rise of Omicron.

The timeframe of our study period (April 19th, 2022, to December 4th, 2022) also coincided with the introduction of the Pfizer-manufactured oral anti-viral agent Paxlovid into the country in April 2022. As noted in Lau et al. (2023), estimated vaccine effectiveness could be influenced by Paxlovid use in the population. For example, if Paxlovid was in higher use among the unvaccinated population, VE could be underestimated due to unaccounted for lower risk of

COVID-19 related death in the unexposed group. We assumed the effect of these agents was either negligible or balanced between the vaccinated and unvaccinated groups.

Chapter 4 Conclusion

In this study, we estimated the vaccine effectiveness of the COVID-19 mass vaccination campaign from April to December 2022 in Taiwan based on real-world publicly available data released by the Taiwan CDC and MOI. Our findings indicate a high level of protection against COVID-19 related mortality provided by the vaccines, with an overall effectiveness rate of 86.3% for individuals receiving exactly two doses and 93.0% for fully vaccinated individuals. These results are encouraging and are evidence of the benefit of widespread vaccination efforts in controlling the pandemic. Increased vaccination coverage in the population directly correlates with reductions in COVID-19 related deaths. However, continued research for vaccine effectiveness against other COVID-19 related outcomes, differing vaccine effectiveness by vaccine manufacturer and heterologous vaccine schedule, and effect modification by age and other demographic characteristics are essential to assess the long-term effectiveness and impact of the COVID-19 vaccines. Overall, our study supports the global vaccination campaign and underscores the critical role of vaccines in mitigating the impact of COVID-19 on public health and society.

Chapter 5 Implications

The public health implications of our study are vast. Most importantly – the mass COVID-19 vaccination campaign in Taiwan was immensely successful in preventing COVID-19 related death during the Omicron BA.2 subvariant waves in 2022. Lower deaths in the general population lead to several beneficial downstream effects including reduced strain on the healthcare system, lower hospitalizations, and decreased emotional burden on families from losing friends and loved ones. The country also benefits economically from not losing its citizens to the disease and reduces the cost of resources spent on addressing COVID-19. Internationally, any reduction of COVID-19 related death in one country is beneficial for all other countries due to the large extent of globalization in the world today. International travel contributed to several key transmission events, and a vaccination success story like Taiwan encourages other countries to conduct or continue their own mass vaccination campaigns, while being more willing to open their borders to a country with a COVID-19 pandemic under control.

While our study pooled all ages together due to data limitations, it is likely that the mass vaccination campaign in Taiwan was highly effective in protecting vulnerable populations, particularly the elderly. It is well known that global COVID-19 mortality was most concentrated in the elderly unvaccinated population (*Rates of COVID-19 Cases or Deaths by Age Group and Vaccination Status*, 2023). In our study, we found that the mortality rate among the unvaccinated population was approximately 10 times greater than that among the vaccinated resulting in a vaccine effectiveness of about 91%. Much of this benefit has been shown to be achieved primarily by reducing mortality among the elderly, as the younger unvaccinated population is already at low risk of COVID-19 related death relative to older. COVID-19 mortality rates in general were much lower for the Omicron BA.2 subvariant compared to the earlier Alpha and

Delta variants. The problem with the Omicron variant was how quickly it was able to spread, evidenced by its high reproduction number R0, with some studies citing it to be nearly 4 times as transmissible as the Delta variant (Y. Liu & Rocklöv, 2022).

The high transmissibility of Omicron ties directly to one of the key questions of not just the effectiveness of the vaccination campaign – but also its timing relative to Taiwan's decision to open its borders and relax several key NPIs such as contact tracing and quarantine that had been in place since the beginning of the pandemic in 2020. The Omicron subvariant lead to an astronomical increase in COVID-19 infections, and subsequently deaths, immediately following the lifting of restrictions. It is of interest to isolate the protective effect of Taiwan's NPI's (border control, quarantine, contact tracing, etc.) and the mass vaccination campaign in preventing COVID-19 related death. The timing of Taiwan's open border policy was an opportunity to conduct a natural experiment to answer that exact question. Prior to the open border policy, vaccinations were slower on the uptake especially for the booster shots. After the launch of the open border policy in April 2022, vaccinations also began to increase. Unfortunately, we again did not have the necessary data to answer this key question, but the high vaccine effectiveness of the mass vaccination campaign and near zero community outbreaks prior to the open border policy suggest both the vaccine and NPI's were essential in reducing COVID-19 related death.

One of the key advantages of measuring vaccine effectiveness is how it isolates the effect of the vaccine relative to a time-series or cross-sectional study. By directly comparing mortality rates between the vaccinated and unvaccinated groups, we get a much more accurate picture of the effect of the vaccine compared to just looking at how vaccination rates change along with COVID-19 infection and mortality rates. A standard argument against vaccine use (besides the prevalence of harmful side effects) during the COVID-19 pandemic was that vaccine use

increased with COVID-19 infection and mortality rates at around the same time (Lee et al., 2022). While correlation does not imply causation, the correlation between vaccine use and COVID-19 burden put some people off from the vaccine, or induced apathy as some believed the vaccine had no benefit. However, our vaccine effectiveness estimates in Taiwan show this is not the case. The vaccines worked incredibly well during the two waves of the Omicron BA.2 subvariant in preventing COVID-19 death. The surge in absolute number of deaths during this period was primarily due to a large increase in infections rather than an increase in the COVID-19 mortality rate. If the population had not been vaccinated, the COVID-19 deaths could potentially have been much higher. Wider education on public health association measures like vaccine effectiveness and relative risk can reduce the amount of misinformation on vaccination use and encourage earlier increased uptake of vaccines in the general populations for future pandemics. While Taiwan for the most part had very high vaccination rates, other countries like the United States lagged far behind and better understanding of vaccine effectiveness and vaccine efficacy could be helpful for overcoming anti-vaccination sentiments in the population and achieving herd immunity quicker.

Our analysis demonstrates that the mass vaccination campaign against COVID-19 in Taiwan was highly effective in preventing COVID-19 related death, contributing further evidence of the success of COVID-19 vaccines around the world. High vaccine effectiveness directly translates to significant reductions in mortality, hospitalizations, strain on healthcare systems and emotional burden for families. Taiwan was only able to open its borders to the world after a long period of quarantine in the middle of the Omicron pandemic because vaccines prevented death effectively. While COVID-19 related deaths did peak in 2022 in two significant waves, the vaccines allowed Taiwan to operate at a normal level. Taiwan’s entire pandemic preparedness

response, from NPIs to vaccination has been a success, and will be an important case study to learn from for all nations preparing against future pandemics.

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