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Original article

Primary and booster vaccination in reducing severe clinical outcomes associated with Omicron Naïve infection

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ABSTRACT

Background: Little is known about long-term effectiveness of COVID-19 vaccine in reducing severity and deaths associated with Omicron VOC not perturbed by prior infection and independent of oral anti-viral therapy and non-pharmaceutical (NPI).

Methods: A retrospective observational cohort study was applied to Taiwan community during the unprecedented large-scale outbreaks of Omicron BA.2 between April and August, 2022. Primary vaccination since March, 2021 and booster vaccination since January, 2022 were offered on population level. Oral Anti-viral therapy was also offered as of mid-May 2022. The population-based effectiveness of vaccination in reducing the risk of moderate and severe cases of and death from Omicron BA.2 with the consideration of NPI and oral anti-viral therapy were assessed by using Bayesian hierarchical models.

Results: The risks of three clinical outcomes associated with Omicron VOC infection were lowest for booster vaccination, followed by primary vaccination, and highest for incomplete vaccination with the consistent trends of being at increased risk for three outcomes from the young people aged 12 years or below until the elderly people aged 75 years or older with 7 age groups. Before the period using oral anti-viral therapy, complete primary vaccination with the duration more than 9 months before outbreaks conferred the statistically significant 47 % (23–64 %) reduction of death, 48 % (30–61 %) of severe disease, and 46 % (95 % CI: 37–54 %) of moderate disease after adjusting for 10–20 % independent effect of NPI. The benefits of booster vaccination within three months were further enhanced to 76 % (95 % CI: 67–86 %), 74 % (95 % CI: 67–80 %), and 61 % (95 % CI: 56–65 %) for three corresponding outcomes. The additional effectiveness of oral anti-viral therapy in reducing moderate disease was 13 % for the booster group and 5.8 % for primary vaccination.

Conclusions: We corroborated population effectiveness of primary vaccination and its booster vaccination, independent of oral anti-viral therapy and NPI, in reducing severe clinical outcomes associated with Omicron BA.2 naïve infection population.

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Introduction

COVID-19 pandemic has evolved with SARS-CoV-2 variants accompanied with various mitigation strategies adopted by relevant containment measures when health decision-makers are faced with the interplay between the emerging variants and available containment measures mainly including NPI, vaccine, and anti-viral therapy. During the wild type and D614G period, NPIs combined with RT-PCR testing is the only mitigation strategy for containing the
epidemic of COVID-19. When SARS-CoV-2 variants has further evolved into the emerging variant of concern (VOCs) the discovery and the delivery of vaccine has grown pari-ally in chronological order. Health authority would have much cherished full vaccination as the mitigation strategy for lifting NPI in order to return to pre-pandemic life [1]. Unfortunately, as most of vaccines have been developed before the emergence of VOCs the efficacy of mRNA and vector-based RNA vaccines have been challenged by the waning immunity due to the evasiveness of immunity beginning from Delta VOC until the recent Omicron VOC [2–5]. There are several studies that have reported the reduced effectiveness of vaccine in protecting symptomatic infection during the Omicron VOC period [2,3]. Rapid testing, booster vaccination, and personal strategy of NPI such as masking and social distancing are mandatory [1,6]. Evaluation of effectiveness of vaccine in different countries and different periods plays an important role in a better understanding whether and how the effectiveness of vaccine has been attenuated due to the waning immunity of first generation of vaccine. These also include the effectiveness of vaccine in reducing moderate and severe cases and death from COVID-19, which are particularly important for the recent Omicron pandemic [1,7,8]. It should be noted that most countries worldwide have had a series of COVID-19 outbreaks from the wild type or D614G until Delta VOC evaluating the effectiveness of vaccination in reducing the severity and deaths may be affected by the possible T-cell mediated memory immune response rusting from antecedent infections [1,8–10]. The purified effectiveness at population level as a result of full-dose and booster vaccination still remain elusive.

In Taiwan, as there has not been a large-scale community-acquired outbreak before the emergence of Omicron BA.2 [11], the Taiwanese cohort together with naïve Omicron infection provides an opportunity of evaluating pure effectiveness of primary and booster vaccination in reducing the severity of and death from COVID-19 without being largely confounded by prior infection resulting from the antecedent large-scale community-acquired outbreaks.

The aim of this study was to estimate the effectiveness of booster and full-dose vaccination in reducing moderate and severe disease and death from COVID-19 Omicron by using population-based vaccination program in Taiwan where naïve Omicron infection hit the underlying community residents whom had been offered with various kinds of vaccines, albeit dominated by m-RNA types, four-fifths for full-dose and two-thirds for booster vaccination.

Materials and methods

Study design and subjects

On the basis of 23 million residents dwelling in Taiwan, a prospective cohort for assessing vaccine effectiveness was first formed and classified by vaccination status, including incomplete vaccination (the unvaccinated and the vaccinated with one dose), the full primary vaccinated (two-dose), and the booster group before the confirmation as an COVID-19 case between April and August in 2022. This cohort was followed over time to ascertain the following main outcomes including moderate and severe cases, and deaths among confirmed cases during community-acquired outbreak of Omicron VOCs from 20 April up to 13 August, 2022. Fig. 1 shows the framework of study design and study subjects by vaccination status and the frequencies of the main outcomes of each category. The aggregated data used for evaluation were retrieved from the digital COVID-19 surveillance platform reported by Central Epidemic Command Center (CECC), Taiwan and Taiwan Centre for Disease Control daily for the purpose epidemic surveillance. As such an aggregated data was made available to the public, this study thus required no approval from Institutional Review Board.

As we are interested in population-based effectiveness of vaccination but such an evaluation would be also affected by the operation of NPIs on population level, two-stage level confounding would be considered. At first level, we made allowance for age distribution of exposure (vaccination status) and outcomes (moderate and severe COVID-19, and death) because age is representative of the main confounding for population effectiveness affected by transmission and evasive immunity. Age would be adjusted in the following statistical models for removing such confounding effects. The second level influence of population effectiveness of vaccine may be conferred by certain NPIs such as facial masking, social distancing, and personal hygiene which have been still in operation in Taiwan. To make allowance for such an influence from NPIs, age-specific infection rates of confirmed cases are taken into account in the model. The estimates regarding the effect size of population-based effectiveness of vaccination based on the first-level model were compared with those based on the two-stage level model. So doing enables us to estimate the effectiveness of NPIs in preventing the spectrum of COVID-19 disease spectrum.

Collecting the information on COVID-19 disease spectrum

The study period covering April to August, 2022, by when the major community-acquired outbreak took place with the Omicron BA.2 as the dominant strain responsible for more than 96 % of cases in Taiwan [12]. The information on vaccination status (incomplete, full-dose, and booster dose as defined above), age, and disease severity (moderate, severe, and death) were retrieved from the digital COVID-19 surveillance platform maintained and reported on a daily basis by Central Epidemic Command Center (CECC), Taiwan and Taiwan Centre for Disease Control [12]. The disease severity for COVID-19 patients was categorized by using the TCDC clinical guideline.13 Moderate COVID-19 patients were defined for subjects with any of the presentations including SpO2 < 94 % on room air, respiratory rate > 30 breaths/min, PaO2/FiO2 ≤ 300, or lung infiltration > 50 % on plain film and requiring low flow oxygenation supplement. Severe COVID-19 disease was defined for patients with any of the presentations including lung infiltration > 50 %, PaO2/FiO2 ≤ 300 and requiring high flow oxygenation therapy provided by mask or non-invasive positive pressure ventilator or mechanical ventilation or extracorporeal membrane oxygenation (ECMO) as treatment modality. Patients with clinical evidence of organ failure or shock were categorized as having severe COVID-19 disease [13].

Statistical analysis

The outcomes of COVID-19 disease spectrum including moderate and severe disease status and death were treated as ordered categorical data. A Bayesian cumulative logistic regression model was applied to assess the vaccine effectiveness in preventing the spectrum of COVID-19 disease [14]. Fig. 2 (a) shows the Bayesian Directed Acyclic Graph (DAG) model taking into account the characteristics of vaccination status (Vaccine [k, i]) and age group (Age [k, i]) at individual level and the heterogeneity in disease transmission across the periods of outbreak (α[k]) on the risk (r[k, i]) of having multiple outcomes of COVID-19 disease spectrum (Moderate [k, i], Severe [k, i], and Death [k, i]). This can be specified by the random intercept model,

\[
\log(\text{P}(Y[k,i] \leq r) = \alpha[k] + \beta_{\text{vaccine}} \times \text{Vaccine}[k,i] + \beta_{\text{age}} \times \text{Age}[k,i], \alpha[k] \sim \text{Normal}(\alpha_0, \sigma^2_\alpha), r = 1(\text{moderate}), 2(\text{severe}), 3(\text{death}),
\]

where Y[k,i] represents the outcomes of COVID-19 disease spectrum for subject i during period k. The risk for the occurrence of each type of COVID-19 disease (πr) is derived by.
The vaccine effectiveness in averting COVID-19 disease in the form of moderate ($r = 1$), severe ($r = 2$), and death ($r = 3$) are thus captured by regression coefficients $\beta_1$ Vaccine, $\beta_2$ Vaccine, and $\beta_3$ Vaccine, respectively.

The relative risk of being susceptible to moderate and severe COVID-19 and death from COVID-19 adjusting for seven age groups (adjusted relative risk, aRR) can be derived by taking the exponent of the three corresponding estimated regression coefficients, namely $\exp(\beta_1$ Vaccine), $\exp(\beta_2$ Vaccine), and $\exp(\beta_3$ Vaccine), respectively. By further categorizing the vaccination status into primary series and booster vaccination, the corresponding aRRs can be derived for each of clinical outcome in both primary series and booster vaccination without the consideration of NPIs in the Eq. (1) and with the consideration of NPIs captured by the age-specific infection rate in the Eq. (3) in a similar manner. The effectiveness adjusting for seven age groups was derived by $(1-\text{aRR}) \times 100\%$. The third column of Table A.1 in the Supplementary material (random intercept model) shows the estimated regression coefficients derived by using the Bayesian DAG model (Fig. 2 (a)) without considering NPI. Here we show how to derive aRR and effectiveness adjusting for seven age groups. Taking the booster vaccination for example, the estimated results of aRR can be derived by $\exp(\beta_1\text{boost} = -1.78) = 0.17$ for moderate disease, $\exp(\beta_2\text{boost} = -1.84) = 0.16$ for severe disease, and $\exp(\beta_3\text{boost} = -1.85) = 0.16$ for death from Omicron. The corresponding effectiveness $(1-\text{aRR})$ adjusting for seven age groups are thus 84 %, 84 %, and 83 %, respectively.

The regression coefficient $\beta_1$ Vaccine thus represents the effectiveness of vaccination in preventing the rth COVID-19 disease spectrum after separating the effect of NPIs during period $k$ with its effect captured by $\beta_1$ NPI. The effectiveness of NPIs in averting moderate and severe COVID-19 and death can thus be separated from that of vaccination. Note that the final column of Table A.1 in the Supplementary material (random intercept and slope model) shows the estimated regression coefficients derived by using the Bayesian DAG model (Fig. 2 (b)) with considering NPI. By comparing the estimated results on vaccination effectiveness ($\beta_1$ Vaccine) between the model with (the Eq. (3)) and without considering NPI (the Eq. (1)), the proportion of risk reduction attributable to NPI can be derived.

Regarding the univariate analysis derived by using the simplified model containing only vaccination status or seven age groups, the relative risk (RR) of having three COVID-19 outcomes (RR) was

\[
\pi_r = P(Y|k, i| r) = P(Y \leq r) - P(Y \leq r-1).
\] (2)

\[
\text{logit}(P(Y[k, i] \leq r)) = \alpha_r[k] + \beta_1 \text{Vaccine}[k, i] + \alpha_0[k] + \beta_1 \text{NPI}[k] + \alpha_1[k] \times \text{Age-specific infection rate}[k], \alpha_r[k] \sim \text{Normal}(\alpha_0, \sigma_r^2), \beta_1 \text{NPI}[k] \sim \text{Normal}(\beta_0, \sigma_{NPI}^2).
\] (3)
derived from the transformed regression coefficients for both vaccination status and seven age groups and the crude effectiveness of vaccination was derived by \((1-\text{RR}) \times 100\%\) in a manner similar to the aRR.

A Bayesian Markov chain Monte Carlo (MCMC) method was used for estimating the parameters of Bayesian random intercept model and Bayesian random intercept and random slope model mentioned above. Non-informative priors (Normal \((0, 10^2)\)) were used for regression coefficients \((\beta)\) and squared variance parameters \((\sigma^2_\alpha, \sigma^2_\beta)\) with log transformation. The block-wise Metropolis-Hasting sampling algorithm with a burn-in iteration of 50,000 followed by 50,000 iterations with a thinning interval of 10 were applied to derive 5000 posterior samples of parameters [15–17]. The mean and the 95% credible interval (CI) of regression coefficients and the effectiveness of vaccination can be derived on the basis of these 5000 posterior samples on the parameters of interest. The mean value of each regression coefficient was derived by the average of 5000 posterior samples. The corresponding 95% credible interval was obtained from 2.5th and 97.5th of 5000 posterior samples. The transformed regression coefficients to get aRR and the adjusted effectiveness of vaccination and age groups can be also derived [14,18].

## Results

During the study period between April 20 and August 13, 2022, a total of 4787319 COVID-19 cases were reported, including 4756775 (99%) asymptomatic and mild cases and 30544 (0.6%) moderate or severe cases caused by Omicron VOC. Of the 30544 COVID-19 cases, there were 14264 (47%) moderate cases, 7734 (25%) severe cases, and 8546 (28%) deaths. Fig. 3 shows age-specific risks of COVID-19 disease spectrum by vaccination status in Taiwan between 20 April and 13 August, 2022. Regardless of moderate (Fig. 3 (a)), severe (Fig. 3 (b)) and death from COVID-19 (Fig. 3 (c)), the risk was lowest for booster vaccination (green line), followed by primary vaccination (yellowish line), and highest for incomplete vaccination (red line) with the consistent trends that the risks associated with three outcomes increased with advancing age from the young group aged 12 years or below until the old group aged 75 years or older with 7 age groups. The detailed frequencies on the distribution of moderate and severe COVID-19 disease, and death by vaccination status (incomplete vaccination, primary series, and booster vaccination) as a function of seven age groups from the young group aged 12 years or below until the old group aged 75 years or older are listed in the Table A2 in Supplementary material. Following the study design depicted in Fig. 1, the numbers of moderate, severe, and death were 7177, 4093, and 4524 for the incompletely vaccinated group, 1859, 1021, and 1113 for the fully vaccinated group, and 5228, 2620, and 2909 for the booster group, respectively. The risks of three outcomes were similar between the fully vaccinated and the booster group whereas both vaccinated groups were lower than the incompletely vaccinated group (Table A2 in the Supplementary material). The numbers of weekly reported COVID-19 infections by age group through the study period are listed in Table A3 in the Supplementary material, which would be further used as the proxy of NPIs in the two-stage hierarchical model specified above.

Table 1 shows the estimated results on the crude relative risk of being moderate, severe and dead related to COVID-19 disease for full and booster vaccination as opposed to incomplete vaccination adjusting for the reported infections by seven age groups from the young subjects aged 12 years or below until the elderly aged 75 years or older. The effectiveness of booster vaccination (1-RR) conferred the highest reduction of three outcomes, ranging from 84% reduction for being dead (relative risk (RR): 0.156, 95% CI: 0.149–0.164) and severe cases (RR: 0.156, 95% CI: 0.151–0.162), and 84% for moderate cases (RR=0.165, 95% CI: 0.161–0.169). The corresponding estimates for the primary series group were 71% (RR=0.29, 95% CI: 0.27–0.31) for being dead, 71% for severe case (RR=0.29, 95% CI: 0.28–0.30), and 71% for moderate case (RR=0.29, 95% CI: 0.28–0.30), respectively. Regarding children aged 12 years or below who were lacking of the eligible vaccine during the study period, it was expected that the risk of being moderate or severe was higher than the adolescents in the adjacent 12–17 age group. From 18 years of age onwards, the risk of being three outcomes increased with advancing age, particularly in two old age groups, 65–74 and >75 years.

### Overall effectiveness of vaccination in reducing the severity of and death from COVID-19

Table A4 shows the aRR for the effectiveness of vaccination in reducing moderate and severe disease of and death from Omicron VOC. After adjusting for age, booster vaccination conferred the statistically significant reduction in the risk of death from and severe moderate disease of Omicron by 84% (aRR: 0.16, 95% CI: 0.13–0.17), 84% (aRR: 0.159, 95% CI: 0.153–0.164), and 83% (aRR: 0.168, 95% CI: 0.164–0.173), respectively. The corresponding figures for the primary vaccination group were 65% (aRR: 0.35, 95% CI: 0.32–0.37) for being death, 65% (aRR: 0.35, 95% CI: 0.33–0.37) for severe disease, and 65% (aRR: 0.36, 95% CI: 0.34–0.37) for moderate disease, respectively. Consistent with the crude result, the two old age groups (65–74 years and >75 years) were at increased risks for the severity of and death from COVID-19.

### Effectiveness of vaccination in reducing the severity of and death from COVID-19 adjusting for NPIs

Table 2 shows the estimated results on the effectiveness of vaccine with the consideration of NPIs captured by the proxy of age-specific infection rate for each week. Recall that the final column of Table A1 in the Supplementary material shows the estimated results on the parameters derived from the Bayesian random intercept and random slope model sketched by the DAG in Fig. 2 (b).

The estimates were derived by using the data for the entire study period from April to August, 2022 (Table 2 (a)), for the period without oral anti-viral therapy (Table 2 (b)), and that with oral anti-viral therapy (Table 2 (c)). After considering the protection from NPI, the booster vaccination and the primary series were attenuated to slightly lower effectiveness in reducing three sequels of Omicron VOC infection. The booster vaccination conferred 74% (aRR: 0.26, 95% CI: 0.25–0.27), 74% (aRR: 0.26, 95% CI: 0.25–0.27), and 73% (aRR: 0.275, 95% CI: 0.268–0.282) reduction for being death, severe disease, and moderate disease from Omicron infection, respectively (Table 2 (a)). The corresponding figures for the primary series were estimated as 53% (aRR: 0.47, 95% CI: 0.44–0.50) for being death, 52% (aRR: 0.47, 95% CI: 0.46–0.50) for severe disease, and 52% (aRR: 0.48, 95% CI: 0.47–0.50) for moderate disease, respectively (Table 2 (a)). Using the overall protective effect (Table A1 in the Supplementary material) as the comparator, the proportions of the risk reduction in terms of three sequels of COVID-19 attributable to NPI were around 12% (lower panel of Table 2 (a)). Since May 13, 2022, oral anti-viral therapy was available for infected subjects who were eligible to indication [19]. To further purified the effectiveness in preventing moderate and severe disease and death resulting from Omicron infection, we further assess the impact of booster vaccination and primary series by using data collected from the period before (Table 2 (b)) and after (Table 2 (c)) oral anti-viral therapy was available. While the effectiveness in preventing severe disease and death remained close in two periods for booster vaccination, the
administration of oral anti-viral therapies resulted in a protective effect of 74 (aRR: 0.27, 95 % CI: 0.26–0.28, Table 2 (c)), corresponding to a 12 % higher effectiveness compared to the period without oral anti-viral therapy (61 %, aRR: 0.39, 95 % CI: 0.35–0.44, Table 2 (b)).

Regarding the effectiveness of primary series, the effectiveness was increased with the use of oral anti-viral therapies by 6.4 %, 4.7 %, and 5.9 % for death, severe, and moderate COVID-19, respectively.

Table 1

| Vaccination status | Moderate RR | 95 % CI | Severe RR | 95 % CI | Death RR | 95 % CI |
|-------------------|------------|---------|-----------|---------|-----------|---------|
| Booster dose      | 0.165      | (0.161, 0.169) | 0.156     | (0.151, 0.162) | 0.156     | (0.149, 0.164) |
| Primary series    | 0.29       | (0.28, 0.30)   | 0.29      | (0.28, 0.30)   | 0.29      | (0.27, 0.30)   |
| < 12              | 0.009      | (0.008, 0.011) | 0.006     | (0.005, 0.007) | 0.001     | (0.001, 0.003) |
| 12–17             | 0.004      | (0.003, 0.005) | 0.002     | (0.001, 0.003) | 0.001     | (0.000, 0.002) |
| 18–29             | 0.007      | (0.006, 0.008) | 0.005     | (0.004, 0.006) | 0.003     | (0.002, 0.004) |
| 30–49             | 0.019      | (0.018, 0.020) | 0.017     | (0.016, 0.018) | 0.014     | (0.013, 0.016) |
| 50–64             | 0.056      | (0.054, 0.058) | 0.048     | (0.046, 0.051) | 0.043     | (0.041, 0.046) |
| 65–74             | 0.175      | (0.170, 0.180) | 0.16      | (0.15, 0.17)   | 0.15      | (0.14, 0.16)   |
| > =75             | Ref        |         | Ref       |         | Ref       |         |

**Discussion**

Effectiveness of mass vaccination in reducing severe cases and deaths in Omicron Naïve infection

While a body of evidence has shown the effectiveness of reducing in severity and death related to various SARS-CoV-2 variants

![Fig. 3. Age-specific Risk (per 100,000) of COVID-19 disease spectrum by vaccination status in Taiwan between 20 April and 13 August, 2022.](image-url)
including the wild type/D614G [20,21], Alpha VOC (20–22), Beta [22,23], Gamma [24], Delta [25–27], and Omicron [27–30], the recent studies have focused on whether and how prior infections may affect the effectiveness of mass vaccination [7,31–34]. Considering prior infection is particularly important when population-based effectiveness of vaccination against the recent Omicron VOC infection needs to be evaluated as most of countries worldwide have seen incessant large-scale community-acquired outbreaks before Omicron VOC infection [1,7,8]. To tackle this issue, the current study evaluated pure effectiveness of vaccination in reducing severity and death pertaining to Omicron COVID-19 by better utilizing the Omicron naïve infection data derived from Taiwan where there had been modest community-acquired outbreaks before the emerging Omicron VOC. Using such an Omicron BA.2 naïve infection data, we proved substantial starkly effectiveness of mass vaccination in reducing more than 80 % reduction of moderate, severe, and deaths related to Omicron BA.2 naïve infection. Even after making allowance for NPI effectiveness, mass vaccination still led to at least 70 % reduction of three severe outcomes of COVID-19 Omicron BA.2. These findings have significant implications for containing the emerging Omicron VOC infection because of its high transmissibility and easiness to escape immune response but they are very effective in reducing severe cases and deaths from COVID-19 Omicron VOC. Therefore, the main mitigation strategy should target at scaling up vaccination rather than the restricted NPI strategy for precluding the folk people from returning to pre-pandemic life.

In addition to the effectiveness against severe COVID-19 outcomes, adverse effects of vaccination may attenuate the uptake of population-based vaccination program and lead to vaccine hesitancy. Recent cohort studies show that the majority of adverse effects of COVID-19 vaccination were focal reaction such as fatigue, headache and local pain with transient nature [35,36] without involving a significant increase in the risk of adverse events of special interest or mortality among the vaccinated population [37]. This empirical evidence, together with the long-term effectiveness in reducing the risk of severe COVID-19 outcomes as demonstrated in our study, provide reassurance for mass vaccination program against COVID-19. Given the unprecedented nature of COVID-19 vaccines in terms of the novel technology deployed and the time scale of development to global use of these newly manufactured products, a network for post marketing surveillance for vaccine effectiveness and its related adverse effects is warranted.
T-cell mediated immunity induced by COVID-19 vaccine

Taiwan residents were provided with primary series since March, 2021 and booster vaccination since January, 2022 [15]. As the vaccination schedule were completed in four-fifth for primary series by December in 2021 and in two-thirds for booster dose by May, 2022 in Taiwan, our result derived from such an Omicron naïve cohort following up until August 2022 demonstrated the long-term effectiveness of vaccination in averting disease progression. In the early phase of COVID-19 pandemic in 2020, the potential of vaccination in triggering the persistent germinal centre response resulting in memory B cell production associated with permanent immune response and hence protection from being infected by SARS-CoV-2 has been reported [38,39]. However, the waning in the protective effect of vaccination and the emergence of VOCs with the characteristic of immune escape render the booster vaccination required for maintaining the immunity at population level [1–5,40–42]. Recent studies showed that the history of infection and reinfection from VOCs, together with the vaccines received, shape the landscape of immunity and resistance to disease severity and death following infection [10,32], largely due to T cell mediated immune response in modulating the inflammatory response associated with disease progression [8–10,43,44]. While this T cell mediated process led to the benefit of reducing the severity of and death from current Omicron VOCs outbreak, it also hampered the evaluation of protective effectiveness conferred by vaccination [7,8]. Our analysis using Omicron naïve Taiwan population thus provides an unique opportunity to separate pure immunity as a result of mass vaccination from that resulting from prior infection.

The function of T cell immunity in modulating inflammation process also explained why the risk of severe disease and death from COVID-19 increased with advancing age. The reasons may be that the loss regarding the balance between pro-inflammatory and anti-inflammatory pathway mainly associated with helper T cell and type I interferon pathway predisposes the elder population to severe clinical outcomes of COVID-19. This is further aggravated by the compromised physiological conditions including the alternation of ACE2 receptor expression and alveolar macrophages composition, both of which render the elder population vulnerable to the risk of severe disease and highly desirable for booster vaccination [45,46].

Evaluating effectiveness of vaccination, NPI, and oral anti-viral therapy with Bayesian Hierarchical Model

To the best of our knowledge, this is the first time to evaluate the effectiveness of mass vaccination adjusting for NPI and making allowance for oral anti-viral therapy with hierarchical Bayesian multinomial model. The novelty is two-fold. First, the influences of both vaccination and NPI on the reduction of moderate and severe cases, and deaths are operated at different levels. The former is exerted through individual level whereas the latter is operated mainly through policy-making at population level. The hierarchical models as shown in Fig. 2 are tailored for such a purpose. Age-specific infection rate in contrast to vaccination and age that were placed at individual level was incorporated into the second population level in different periods in order to capture the specific effectiveness of NPI. Second, Bayesian hierarchical model with the random intercept as shown in Fig. 2 (a) was first to capture the heterogeneity of the risk of three outcomes beyond the explanation of age and vaccination across three periods, which may include the restrictiveness of NPI and the gradual adaptation of replacing RT-PCR test with the rapid test both of which may affect the reported age-specific infection rates, further leading to age-specific risk of three outcomes. The use of random slope and random intercept model in Fig. 2 (b) further captured the effectiveness of NPI and residual confounding for the risk of three outcomes.

By using the approach of Bayesian Network analysis, Sinclair et al. assessed the balance between the protective effectiveness of one to three doses of BNT162B2 vaccination and the risk of vaccine-associated myocarditis allowing for vaccine coverage, vaccine effectiveness, age groups, and sex during Delta VOC dominant period in Australia [47]. Informed by the inputs derived from the CoRiCal [48], the evidence from Sinclair et al. support the decision on vaccination for all age groups to reduce the COVID-19 mortality. Our results regarding the effectiveness of booster and primary vaccination against the severe clinical outcomes during Omicron outbreak can provide the supplementary and the updated inputs for the Bayesian Network analysis to support an informed decision-making with Bayesian underpinning.

Limitations

Although to Omicron BA.2 naïve infection population data provides an opportunity for assessing the pure population-based effectiveness of vaccination the generalizability of our finding to other SARS-CoV-2 variants is therefore limited. Second, our major goal is to evaluate the effectiveness of vaccination on population level such a finding may not be directly applied to individual level without considering other important personal correlates such as co-morbidity [49]. However, the weakness of lacking of individual trait may still can be strengthened by using Bayesian hierarchical model to capture such an individual heterogeneity. Third, unlike primary vaccination with 9 months of follow-up, the effectiveness of booster vaccination was within three months. Long duration of booster vaccination needs to be verified.

In conclusion, the present study demonstrated population effectiveness of primary vaccination and its booster vaccination, independent of oral anti-viral therapy and NPI, in reducing severe clinical outcomes associated with Omicron BA.2 naïve infection population.

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CRediT authorship contribution statement

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Data Availability

Data and code of analysis are available from the corresponding authors (Professor Chen and Professor Yen) on request.
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