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BRIEF REPORT

Comparative Effectiveness of mRNA and Inactivated Whole-Virus Vaccines Against Coronavirus Disease 2019 Infection and Severe Disease in Singapore

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Compared with individuals vaccinated with Pfizer-BioNTech/Comirnaty, recipients of Sinovac-CoronaVac and Sinopharm were 2.37 (95% CI, 2.29–2.46) and 1.62 (95% CI, 1.43–1.85) times more likely to be infected with coronavirus disease 19, respectively, while individuals vaccinated with Moderna were 0.42 (95% CI, 0.25–0.70) times less likely to develop severe disease.

Keywords. COVID-19; SARS-CoV-2; vaccines; mRNA vaccine; inactivated vaccine.

Vaccination is a key strategy to reduce the spread and severity of coronavirus disease 2019 (COVID-19). Singapore launched its National Vaccination Program (NVP) for COVID-19 on 30 December 2020 with the Pfizer-BioNTech/Comirnaty vaccine (BNT162b2). The Moderna (mRNA-1273) and Sinovac-CoronaVac vaccines were subsequently approved for use under the NVP on 3 February 2021 and 23 October 2021, respectively. From 30 August 2021, the Sinopharm vaccine (BBIBP-CorV) was also available at private healthcare institutions via a special access route and not under the NVP. As of 12 December 2021, 96% of the eligible population in Singapore (excluding children <12 years old) have received at least 2 doses of the Pfizer-BioNTech/Comirnaty, Moderna, Sinovac-CoronaVac, or Sinopharm vaccines.

COVID-19 cases in Singapore increased in September 2021, driven by the more transmissible Delta variant first detected locally in May 2021 to a peak of over 5,000 cases a day. While the majority of cases (~99%) were mild, the number of severe cases and deaths increased, disproportionately driven by unvaccinated individuals [1].

As several studies have suggested that mRNA vaccines have higher vaccine efficacy than non-mRNA vaccines [2, 3], this study aims to compare the relative effectiveness of the 4 available vaccines in Singapore in preventing COVID-19 infection and severe disease. While a few studies have compared the efficacies of various COVID-19 vaccines [4–6], we aimed to compare the mRNA and inactivated whole-virus vaccines in the same population as the findings will be useful for guiding policy recommendations to prevent infection and reduce strain on the healthcare system.

METHODS

We examined the incidence of COVID-19 infection and severe disease during the study period from 1 October to 21 November 2021 among individuals aged 20 years and above who had received 2 doses under the NVP in Singapore. The age cutoff was selected in view of the minimum age (18 years) required to receive Moderna and Sinovac-CoronaVac under the NVP. Individuals who were partially vaccinated or boosted with a third dose or had a previous history of COVID-19 infection were excluded. We restricted the cohort to those 2 weeks after completion of 2 doses of vaccine to allow for sufficient immune response and who had received their second vaccine dose within 120 days of our analysis to control for immunity waning. Severe disease was defined as ever requiring oxygen supplementation in hospital, admission to an intensive care unit (ICU), or death.

Using a Poisson regression model, we estimated the incidence rate ratio (IRR) of confirmed COVID-19 infection and severe disease, controlling for age group, gender, ethnicity, residency status, and housing type (as a marker of socioeconomic status) as covariates. In addition, we controlled for the time since second dose and varying force of infection (exposure risk) across time by including months from the second dose and daily dummy variables into the model. The IRRs were obtained by comparing persons vaccinated with Moderna, Sinovac-CoronaVac, and Sinopharm against Pfizer-BioNTech/Comirnaty as the reference, as that is the most commonly used vaccine in Singapore. Vaccine effectiveness against severe disease for these 3 vaccines was estimated by assuming the vaccine effectiveness of Pfizer-BioNTech/Comirnaty to be 90% [5, 6], and then applying their respective IRRs and confidence intervals (CIs) for relative effectiveness observed in our study. Data were collected from official databases maintained by the Ministry of Health, Singapore, and

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analysis was performed using Stata Statistical Software release 17 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 2,709,899 individuals within the 14- to 120-day period after being vaccinated with 2 doses were included in the study cohort, of whom 2,001,181 (74%) received Pfizer-BioNTech/Comirnaty, 628,012 (23%) received Moderna, 60,407 (2%) received Sinovac-CoronaVac, and 20,299 (1%) received Sinopharm. A total of 107,220 individuals were confirmed by polymerase chain reaction (PCR) to be infected with COVID-19 over the study period, and 644 developed severe disease.

After adjusting for age, gender, ethnicity, residency status, socioeconomic status, time since second dose, and daily infection rate, individuals vaccinated with Sinovac-CoronaVac were more likely to be infected (adjusted IRR, 2.37; 95% CI, 2.29–2.46), and more likely to develop severe disease (adjusted IRR, 4.59; 95% CI, 3.25–6.48); individuals vaccinated with Sinopharm were also at higher risk of infection (adjusted IRR, 1.62; 95% CI, 1.43–1.85), while individuals vaccinated with Moderna were at lower risk of severe disease (adjusted IRR, 0.42; 95% CI, 0.25–0.70), compared with those who received Pfizer-BioNTech/Comirnaty (Table 1).

As migrant workers on work permits mostly received Moderna and were predominantly male, the analysis was rerun on a subset of the study cohort excluding work permit holders, and similar IRR estimates were observed (Supplementary Table 1).

DISCUSSION

We observed a lower relative effectiveness of 2 inactivated whole-virus vaccines (Sinovac-CoronaVac and Sinopharm) against COVID-19 infection compared with 2 mRNA vaccines (Pfizer-BioNTech/Comirnaty and Moderna). Assuming a vaccine effectiveness against severe disease for Pfizer-BioNTech/Comirnaty of 90% as suggested by systematic reviews [5, 6], applying the IRRs obtained in our study would estimate vaccine effectiveness against severe disease for Moderna, Sinovac-CoronaVac, and Sinopharm to be 96% (93%–98%), 54% (35%–68%), and 84% (60%–94%), respectively.

In its phase III clinical trial in Brazil, 2 doses of Sinovac-CoronaVac demonstrated a vaccine efficacy of 50.7% against symptomatic infection by earlier COVID-19 strains prior to the Delta variant [7], lower than Pfizer-BioNTech/Comirnaty and Moderna, which achieved vaccine efficacies of more than 90% [8, 9]. A Hong Kong study showed that those who received 2 doses of BNT162b2 vaccine had a more than 10 times higher level of neutralizing antibody titers compared with 2 doses of Sinovac-CoronaVac [10]. In Chile, 2 doses of Sinovac-CoronaVac demonstrated a vaccine effectiveness of 87.5% for the prevention of hospitalization [11]. The higher vaccine effectiveness observed there could be due to different circulating variants (predominantly Alpha and Gamma variants in the Chilean study vs Delta variant in our study, which is more infectious and virulent).

Sinopharm demonstrated a higher relative effectiveness against COVID-19 infection than Sinovac-CoronaVac in our study, although lower than the mRNA vaccines. To date, there has not been any study directly comparing these 2 inactivated virus vaccines. A study of 57 healthy adult volunteers showed that individuals vaccinated with Sinopharm had lower levels of specific immunoglobulin G (IgG) antibodies and T-cell response as compared with those vaccinated with Pfizer-BioNTech/Comirnaty [12]. Another prospective cohort study of 288 Jordanian adults also corroborated that fully vaccinated recipients of Pfizer-BioNTech/Comirnaty had higher IgG titers as compared with Sinopharm recipients [13].

In view of the lower efficacy of Sinovac-CoronaVac and lack of data on its efficacy against the Delta and Omicron variants, Singapore recommended that only persons unable to complete the full 2-dose regime of an mRNA vaccine due to medical reasons should receive the Sinovac-CoronaVac vaccine, and to be considered fully vaccinated, 3 doses of Sinovac-CoronaVac is required for the primary vaccination series (the second dose given 28 days after the first, and the third 90 days after the second). This policy is aligned with the World Health Organization's Strategic Advisory Group of Experts (SAGE) recommendation of a third dose for individuals aged 60 and above who received inactivated vaccines [14]. Similarly, individuals vaccinated with 2 doses of Sinopharm vaccine are recommended to receive a third dose 90 days later to be considered fully vaccinated in Singapore.

Our findings suggest that the Moderna vaccine is more effective than Pfizer-BioNTech/Comirnaty against severe disease, which is supported by other studies. In a report by the US Centers for Disease Control and Prevention, vaccine effectiveness against COVID-19 hospitalization was slightly higher after 2 doses of Moderna than Pfizer-BioNTech, likely attributed to higher mRNA content in the Moderna vaccine and longer time interval between doses [3]. A higher incidence rate of breakthrough infections was also seen in persons vaccinated with Pfizer-BioNTech compared with Moderna in another study [15].

Our study is based on comprehensive national data on COVID-19 vaccination, PCR-confirmed infections, and disease severity. However, there are several limitations. First, we rely on the assumption that all 4 vaccines did not experience differential waning of immunity. Restriction to individuals who completed their second dose within 120 days was done to mitigate any potential impact. Second, there might be residual confounding from comorbidities as well as unknown factors that influence an individual's choice of vaccine, risk of exposure, or healthcare-seeking behavior. Third, there is underdetection of asymptomatic cases who did not present to the healthcare

Table 1. Relative Vaccine Effectiveness Against COVID-19 Infection and Severe Disease

	Pfizer-BioNTech/Comirnaty	Moderna	Sinovac-CoronaVac	Sinopharm
No. of individuals in cohort (%)	2,001,181 (74%)	628,012 (23%)	60,407 (2%)	20,299 (1%)
Person-days at risk	95,856,682	30,271,743	2,714,464	488,039
Female, n (%)	1,117,310 (56%)	254,196 (40%)	29,708 (49%)	10,976 (54%)
Age group, n (%)				
20–29 years	494,163 (25%)	161,281 (26%)	10,795 (18%)	2,625 (13%)
30–39 years	625,136 (31%)	181,047 (29%)	21,294 (35%)	4,518 (22%)
40–49 years	409,601 (20%)	168,854 (27%)	12.079 (20%)	4,452 (22%)
50–59 years	246,334 (12%)	83,617 (13%)	7,233 (12%)	3,520 (17%)
60–69 years	116,886 (6%)	19,704 (3%)	4,855 (8%)	2,784 (14%)
70–79 years	64,504 (3%)	8,604 (1%)	3,080 (5%)	1,562 (8%)
≥80 years	44,557 (2%)	4,905 (1%)	1,071 (2%)	838 (4%)
Ethnicity, n (%)				
Chinese	1,240,960 (62%)	333,433 (53%)	57,871 (96%)	18,474 (91%)
Malay	255,909 (13%)	90,238 (14%)	807 (1%)	536 (3%)
Indian	253,696 (13%)	124,372 (20%)	507 (1%)	567 (3%)
Others	250,616 (13%)	79,969 (13%)	1,222 (2%)	722 (4%)
Housing type, n (%)				
1–2-room public housing	63,925 (3%)	23,417 (4%)	931 (2%)	400 (2%)
3-room public housing	291,896 (15%)	87,047 (14%)	9,388 (16%)	2,483 (12%)
4-room public housing	560,545 (28%)	152,249 (24%)	15,014 (25%)	5,138 (25%)
5-room public housing	421,293 (21%)	116,080 (18%)	11,033 (18%)	4,249 (21%)
Private housing	393,091 (20%)	106,975 (17%)	18,600 (31%)	6,616 (33%)
Others	270,431 (14%)	142,244 (23%)	5,441 (9%)	1,413 (7%)
Confirmed COVID-19 infection				
No. of cases	77,039	26,260	3,622	299
Incidence per million person-days	804	867	1,334	613
Adjusted IRR[a] (95% CI)	1.00 (Ref)	0.84 (0.82–0.86)	2.37 (2.29–2.46)	1.62 (1.43–1.85)
Severe COVID-19 disease				
No. of cases	558	34	47	5
Incidence per million person-days	6	1	17	10
Adjusted IRR[a] (95% CI)	1.00 (Ref)	0.42 (0.25–0.70)	4.59 (3.25–6.48)	1.58 (0.63–3.97)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; IRR, incidence rate ratio.

[a]Adjusted for age group, gender, ethnicity, residency status, housing type, time from second vaccination dose (in months), and date of notification using Poisson regression.

system. Finally, as 96% of the eligible population had been fully vaccinated, comparison to unvaccinated individuals was not feasible and only relative effectiveness was determined.

In conclusion, individuals vaccinated with 2 doses of inactivated whole-virus vaccines were observed to have lower protection against COVID-19 infection compared with those vaccinated with mRNA vaccines. Nevertheless, both mRNA vaccines and inactivated whole-virus vaccines provide sufficient protection against COVID-19 severe disease and vaccination remains a key strategy against the pandemic. Studies such as UK COV-BOOST have suggested that a third dose provides additional protection against COVID-19, and future studies should continue to monitor the effectiveness of these vaccines and evaluate how they are enhanced by further booster doses.

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

Ethics approval. This study was conducted as part of national COVID-19 public health response under the Infectious Diseases Act (IDA), Ministry of Health, Singapore, to support policy decision making and evaluation; hence, no Institutional Review Board (IRB) review was required.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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