

1 Comparative Effectiveness of mRNA and Inactivated Whole Virus Vaccines against COVID-19
2 Infection and Severe Disease in Singapore

3
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18 **Running Title:** Effectiveness of COVID-19 Vaccines

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1 **ABSTRACT**

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

6 **Keywords:** COVID-19; SARS-CoV-2; vaccines; mRNA vaccine; inactivated vaccine

7

ACCEPTED MANUSCRIPT

1 **INTRODUCTION**

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

11 COVID-19 cases in Singapore increased in September 2021, driven by the more
12 transmissible Delta variant first detected locally in May 2021 to a peak of over 5,000 cases a
13 day. While the majority of cases (~99%) were mild, the number of severe cases and deaths
14 increased, disproportionately driven by unvaccinated individuals¹.

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

1 **MATERIALS & METHODS**

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

12 Using a Poisson regression model, we estimated the incidence rate ratio (IRR) of
13 confirmed COVID-19 infection and severe disease, controlling for age group, gender, ethnicity,
14 residency status and housing type (as a marker of socioeconomic status) as covariates. In
15 addition, we controlled for the time since second dose and varying force of infection (exposure
16 risk) across time by including months from second dose and daily dummy variables into the
17 model. The IRRs were obtained by comparing persons vaccinated with Moderna, Sinovac-
18 CoronaVac and Sinopharm against Pfizer-BioNTech/Comirnaty as reference, as that is the most
19 commonly used vaccine in Singapore. Vaccine effectiveness against severe disease for these
20 three vaccines were estimated by assuming the vaccine effectiveness of Pfizer-
21 BioNTech/Comirnaty to be 90%,^{5,6} and then applying their respective IRRs and confidence

1 intervals for relative effectiveness observed in our study. Data was collected from official
2 databases maintained by the Ministry of Health, Singapore and analysis was performed using
3 Stata Statistical Software Release 17 (StataCorp LP, College Station, TX, USA).

4 **RESULTS**

5 2,709,899 individuals within the 14 to 120-day period after being vaccinated with two
6 doses were included in the study cohort, of whom 2,001,181 (74%) received Pfizer-
7 BioNTech/Comirnaty, 628,012 (23%) received Moderna, 60,407 (2%) received Sinovac-
8 CoronaVac and 20,299 (1%) received Sinopharm. 107,220 individuals were confirmed by PCR to
9 be infected with COVID-19 over the study period, and 644 developed severe disease.

10 After adjusting for age, gender, ethnicity, residency status, socioeconomic status, time
11 since second dose and daily infection rate, individuals vaccinated with Sinovac-CoronaVac were
12 more likely to be infected (adjusted IRR 2.37; 95% CI 2.29 – 2.46), and more likely to develop
13 severe disease (adjusted IRR 4.59; 95% CI 3.25 – 6.48); individuals vaccinated with Sinopharm
14 were also at higher risk of infection (adjusted IRR 1.62; 95% CI 1.43 – 1.85), while individuals
15 vaccinated with Moderna were at lower risk of severe disease (adjusted IRR 0.42; 95% CI 0.25 –
16 0.70), compared with those who received Pfizer-BioNTech/Comirnaty (Table 1).

17 As migrant workers on work permits mostly received Moderna and were predominantly
18 male, the analysis was re-run on a subset of the study cohort excluding work permit holders,
19 and similar IRR estimates were observed (Supplementary Materials Table S1).

20

1 **DISCUSSION**

2 We observed a lower relative effectiveness of two inactivated whole virus vaccines
3 (Sinovac-CoronaVac and Sinopharm) against COVID-19 infection compared with two mRNA
4 vaccines (Pfizer-BioNTech/Comirnaty and Moderna). Assuming the vaccine effectiveness
5 against severe disease for Pfizer-BioNTech/Comirnaty of 90% as suggested by systematic
6 reviews,^{5,6} applying the IRRs obtained in our study would estimate vaccine effectiveness against
7 severe disease for Moderna, Sinovac-CoronaVac and Sinopharm to be 96% (93% – 98%), 54%
8 (35% – 68%) and 84% (60% – 94%) respectively.

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

19 Sinopharm demonstrated a higher relative effectiveness against COVID-19 infection
20 than Sinovac-CoronaVac in our study, although lower than the mRNA vaccines. To date, there
21 has not been any study directly comparing these two inactivated virus vaccines. A study of 57

1 healthy adult volunteers showed that individuals vaccinated with Sinopharm had lower levels of
2 specific IgG antibodies and T-cell response as compared to those vaccinated with Pfizer-
3 BioNTech/Comirnaty.¹² Another prospective cohort study of 288 Jordanian adults also
4 corroborated that fully vaccinated recipients of Pfizer-BioNTech/Comirnaty had higher IgG
5 titres as compared to Sinopharm recipients.¹³

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

16 Our findings suggest that the Moderna vaccine is more effective than Pfizer-
17 BioNTech/Comirnaty against severe disease, which is supported by other studies. In a report by
18 the US Centers for Disease Control and Prevention, vaccine effectiveness against COVID-19
19 hospitalisation was slightly higher after 2 doses of Moderna than Pfizer-BioNTech, likely
20 attributed to higher mRNA content in the Moderna vaccine and longer time interval between

1 doses.³ A higher incidence rate of breakthrough infections was also seen in persons vaccinated
2 with Pfizer-BioNTech compared with Moderna in another study.¹⁵

3 Our study is based on comprehensive national data on COVID-19 vaccination, PCR-
4 confirmed infections and disease severity. However, there are several limitations. First, we rely
5 on the assumption that all four vaccines did not experience differential waning of immunity.
6 Restriction to individuals who completed their second dose within 120 days was done to
7 mitigate any potential impact. Second, there might be residual confounding from comorbidities
8 as well as unknown factors that influence an individual's choice of vaccine, risk of exposure or
9 healthcare-seeking behaviour. Third, there is under-detection of asymptomatic cases who did
10 not present to the healthcare system. Finally, as 96% of the eligible population had been fully
11 vaccinated, comparison to unvaccinated individuals was not feasible and only relative
12 effectiveness was determined.

13 **CONCLUSION**

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

22 **NOTES**

23 **Funding:** This study was not funded.

24 **Details of Ethics Approval:** This study was conducted as part of national COVID-19 public health
25 response under the Infectious Diseases Act (IDA), Ministry of Health, Singapore to support
26 policy decision-making and evaluation, hence no IRB review was required.

27 **Disclosure of Interests:** The authors declare that they have no conflict of interest.

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1 **TABLES & FIGURES**

2 **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 (%) | 1,117,310 (56%) | 254,196 (40%) | 29,708 (49%) | 10,976 (54%) |
| Age group (%) | | | | |
| 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 (%) | | | | |
| 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 (%) | | | | |
| 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 | 1334 | 613 |
| Adjusted IRR* (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* (95% CI) | 1.00 (Ref) | 0.42 (0.25 – 0.70) | 4.59 (3.25 – 6.48) | 1.58 (0.63 – 3.97) |

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

5