Comparative effectiveness of 3 or 4 doses of mRNA and inactivated whole-virus vaccines against COVID-19 infection, hospitalization and severe outcomes among elderly in Singapore

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Previous studies have found that two doses of inactivated whole-virus vaccines elicited lower antibody titers and conferred less protection against SARS-CoV-2 infection than two doses of mRNA vaccines.[1,2] To maintain immunity among older persons who are most vulnerable to severe outcomes, a fourth vaccine dose with BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) has been recommended for individuals aged 60 and above in Singapore. CoronaVac (Sinovac) is also offered under the National Vaccination Programme, while BBIBP-CorV (Sinopharm) is available at private healthcare institutions. We aimed to compare the effectiveness of three or four doses of mRNA and inactivated whole-virus vaccines against COVID-19 incidence and severity among elderly aged 60 years and above.

Using administrative data from the Singapore Ministry of Health, we analyzed the incidence of symptomatic SARS-CoV-2 infection, COVID-19-related hospitalization, and severe COVID-19 from 1 February to 14 September 2022 among individuals aged 60 years and older who received three or four vaccine doses. Individuals who had previous documented SARS-CoV-2 infection were excluded. All individuals presenting to a healthcare facility with symptoms of acute respiratory infection were tested for SARS-CoV-2 with a PCR or antigen rapid test. Severe COVID-19 was defined as requiring oxygen supplementation, intensive care unit admission or death.

Individuals were classified as vaccinated with three or four doses 8 days after their last dose to allow for sufficient immune response. Classification was dynamic to account for the time-varying nature of vaccination status, and an individual could contribute person-time to multiple groups. Poisson regression was used to estimate incidence rate ratios (IRR) of infection, hospitalization, and severe disease, adjusting for age, sex, ethnicity, housing type (as a marker of socioeconomic status) and calendar date (to account for varying force of infection across time). Individuals who received three doses of mRNA vaccine served as the reference group for comparisons by number of doses and vaccine type.

The study was conducted under the Infectious Diseases Act, Singapore, for policy decision-making; hence, a separate ethics review by an Institutional Review Board was not required. Data analysis was performed with Stata version 17.0 (StataCorp LLC).

803,911 individuals were included in this study, contributing 128,125,246 and 19,069,740 person-days to the three-dose and four-dose groups respectively. By person-days, 56.5% were aged 60–69 years, 30.5% were aged 70–79 years, and 13.0% were aged 80 years and above, with 54.1% being female. Among the cohort, there were 220,942 symptomatic SARS-CoV-2 infections, 10,860 COVID-19-related hospitalizations, and 1643 cases of severe COVID-19, of whom 213 died.

Compared with three doses of mRNA vaccine, those who received three doses of CoronaVac or BBIBP-CorV were at higher risk of symptomatic SARS-CoV-2 infection (IRR 1.13; 95% CI 1.09–1.16), COVID-19-related hospitalization (IRR 1.52; 95% CI 1.36–1.71) and severe COVID-19 (IRR 1.90; 95% CI 1.45–2.47) (Table 1). Four mRNA vaccine doses provided additional protection against infection (IRR 0.81; 95% CI 0.80–0.83),

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Number of doses and type of vaccine	Person-days at risk	Events			Incidence per million person-days			Adjusted incidence rate ratios (95% CI)[a]		
		Infection	Hospitalization	Severe	Infection	Hospitalization	Severe	Infection	Hospitalization	Severe
3 doses, mRNA[b]	124,822,336	197,657	9453	1439	1584	76	12	1 [Ref]	1 [Ref]	1 [Ref]
3 doses, inactivated whole-virus[c]	2,635,200	4136	291	57	1570	110	22	1.13 (1.09–1.16)	1.52 (1.36–1.71)	1.90 (1.45–2.47)
3 doses, combination[d]	667,710	1250	45	6	1872	67	9	1.31 (1.24–1.38)	1.08 (0.81–1.45)	NA[e]
4 doses, mRNA[b]	18,785,302	17,513	1045	138	932	56	7	0.81 (0.80–0.83)	0.49 (0.46–0.52)	0.39 (0.32–0.47)
4 doses, inactivated whole-virus[c]	115,562	130	10	1	1125	87	9	1.05 (0.88–1.24)	1.02 (0.55–1.90)	NA[e]
4 doses, combination[d]	168,876	256	16	2	1516	95	12	1.24 (1.10–1.41)	1.26 (0.77–2.06)	NA[e]

CI, confidence interval. [a]Adjusted for age, sex, ethnicity, housing type, date of reporting (to control for daily infection rate) and date of last vaccine dose using Poisson regression. [b]BNT-162b2 or mRNA-1273. [c]*CoronaVac or BBIBP-CorV.* [d]Combination of mRNA vaccine and inactivated whole-virus vaccine. [e]Due to the small number of individuals who received a combination of vaccine types or four doses of inactivated whole-virus vaccine, the sample sizes are too small for meaningful analyses.

Table 1: **Incidence and rate ratios of symptomatic SARS CoV-2 infection, COVID-19 related hospitalization and severe COVID-19 by number of doses and type of vaccine.**

hospitalization (IRR 0.49; 95% CI 0.46–0.52) and severe COVID-19 (IRR 0.39; 95% CI 0.32–0.47). However, four doses of inactivated whole-virus vaccine or a combination of both vaccine types did not confer additional risk reduction against infection or hospitalization compared with three mRNA vaccine doses.

Our findings showed vaccination with four doses of mRNA vaccine was associated with lower rates of symptomatic SARS-CoV-2 infection, hospitalization and severe COVID-19 compared with three mRNA vaccine doses and four doses of inactivated whole-virus vaccines or a combination of vaccine types.

Limitations of the study include residual confounding from the shift in circulating Omicron sublineages during the study period, comorbidities and other unobserved factors affecting vaccine choice or disease severity, as well as under-detection of cases with mild or asymptomatic illness who did not seek medical attention. As BNT162b2 and mRNA-1273 were recommended over CoronaVac and BBIBP-CorV in Singapore, numbers of severe disease among individuals who received four doses of inactivated whole-virus vaccines or mixed vaccine type were too small for meaningful analysis.

Our results based on comprehensive national data support the use of four doses of mRNA vaccine over inactivated whole-virus vaccine for greater individual protection against COVID-19 and to reduce burden on the healthcare system.

Contributors

CYT and CJC were involved in the study conception, data interpretation, and writing of the manuscript. VJL was involved in the study conception and provided supervision. BO and DCL were involved in the study conception, critical revision of the manuscript, and provided supervision. KBT was involved in the study conception, data analysis, critical revision of the manuscript, and provided supervision. CYT and KBT accessed and verified the underlying data reported in the manuscript.

Declaration of interests

We declare no competing interests.

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References

1 Mok CKP, Cohen CA, Cheng SMS, et al. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology*. 2022;27(4):301–310. https://doi.org/10.1111/resp.14191.

2 Premikha M, Chiew CJ, Wei WE, et al. Comparative effectiveness of mRNA and inactivated whole virus vaccines against COVID-19 infection and severe disease in Singapore. *Clin Infect Dis*. 2022;75(8):1442–1445. https://doi.org/10.1093/cid/ciac288.