Comparison of bivalent and monovalent mRNA vaccine boosters

Running title: Bivalent vs monovalent COVID-19 vaccine

Authors: Carlos K.H. WONG [1,2,3,4 *#] PhD, Kristy T.K. LAU [1#] MSc, Ivan C.H. AU [1#] BSc, Eric H.Y. LAU [2,5] PhD, Benjamin J. COWLING [2,5] PhD

[*]corresponding author; [#]co-first authors

Affiliations:

[1] Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[2] Laboratory of Data Discovery for Health ($D^2$4H), Hong Kong SAR, China

[3] Department of Family Medicine and Primary Care, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[4] Vaccine Confidence Project, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

[5] WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Corresponding author:

Dr Carlos King Ho Wong, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. 26 Sassoon Road, Pokfulam, Hong Kong SAR, China. Phone: (+852) 2831-5055 Fax: (+852) 2814-7475 Email: carlosho@hku.hk

Abstract

In this cohort study conducted in Hong Kong where both bivalent and monovalent formulations of BNT162b2 were available, there was no significant differences in the mortality or hospitalization between those who received bivalent and monovalent mRNA as second boosters. Bivalent and monovalent mRNA boosters appear equally protective against clinical outcomes.

Keywords: COVID-19; vaccine; BNT162b2; bivalent; monovalent

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Introduction

Bivalent mRNA vaccines that encode the spike proteins of both ancestral strain and Omicron BA.4/5 sublineages have been developed,[1, 2] with higher neutralizing antibody titers against BA.4/5 and other Omicron sublineages than the original monovalent vaccine.[3-5] During the predominance of Omicron BA.2 and BA.5 (including BQ and XBB) sublineages, administration of the updated bivalent mRNA booster has been associated with higher protection against symptomatic infection, hospitalization and death compared to previous vaccination with 2-4 monovalent doses.[6-8] Therefore, this observational study aims to perform head-to-head comparison of bivalent and monovalent BNT162b2 vaccines given as a second booster (fourth dose) against severe Omicron infection.

Methods

Data sources, study design and population

This observational study assessed the effectiveness of bivalent versus monovalent mRNA vaccine boosters from 1st December 2022 to 12th February 2023 in Hong Kong. During the study period, Hong Kong residents could choose to be immunized with the following COVID-19 vaccines: BioNTech BA.4/5-adapted bivalent mRNA vaccine (BioNTech/Fosun Pharma), BNT162b2 monovalent mRNA vaccine (BioNTech/Fosun Pharma), or inactivated vaccine CoronaVac (Sinovac). Unlike most other locations that withdrew the monovalent formulation of BNT162b2 for booster doses after the bivalent formulation with BA.4/BA.5 became available, Hong Kong has allowed individuals to continue to choose either formulation.

From the population-based records on SARS-CoV-2 infection and COVID-19 vaccination status of the Centre for Health Protection, Department of Health, we included patients who had confirmed SARS-CoV-2 infection diagnosis via either a positive reverse transcription polymerase chain reaction or rapid antigen test from 1st December 2022 to 5th February 2023, who had received the two-dose primary series and first booster of monovalent BNT162b2 vaccine, and a bivalent or monovalent mRNA vaccine second booster (i.e. fourth dose) at least 7 days prior to the infection. Electronic medical records and clinical outcomes of COVID-19 patients managed under the public healthcare system were extracted from the Hospital Authority database. Two linked databases have previously evaluated the effectiveness of COVID-19 vaccination and drug treatment in Hong Kong.[9-12] Those with vaccination records of bivalent mRNA vaccines before 31st August 2022 (date of which the Emergency Use Authorization for Omicron BA.4/5-adapted bivalent mRNA vaccines were granted)[13] were excluded for data validity purposes. Those who were under 18 years old, with missing age or sex, had SARS-CoV-2 infection diagnosis or symptom onset date on or after that of hospitalization (hospital-acquired infection or community-acquired infection without known infection date but testing positive during the admission) or registered death, or had received Moderna COVID-19 (monovalent mRNA-1273; bivalent mRNA-1273.214 or mRNA-1273.222) vaccines (not locally available in Hong Kong) were also excluded from the current analysis.

Index date of each eligible patient was set at the date of first SARS-CoV-2 infection diagnosis or symptom onset, whichever occurred earlier. Patients were followed up from the index date until death, outcome event occurrence, 28 days after the index date, or the end of the observational period (12th February 2023), whichever came first.

Exposure

Bivalent group included COVID-19 patients who had received three doses of BNT162b2 monovalent mRNA vaccine and BioNTech BA.4/5-adapted bivalent mRNA vaccine as the fourth dose (i.e. second booster). Patients who had received four doses of BNT162b2 monovalent mRNA vaccine were allocated to the monovalent group for comparison.

Study outcomes

Primary outcome was a composite outcome of all-cause mortality or hospitalization. Secondary outcomes included (i) all-cause mortality; (ii) all-cause hospitalization; and (iii) respiratory-related hospitalization, i.e. hospitalizations associated with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 460-519.

Statistical analyses

Baseline covariates of patients included age, sex, Charlson Comorbidity index, secular time of SARS-CoV-2 infection (1st December 2022 to 8th January 2023 predominated by Omicron BA.4/5 sublineages; and 9th January to 5th February 2023 predominated by descendant lineages of BA.2), and time since last COVID-19 vaccine dose to index date. We used propensity-score models conditional on the above baseline covariates in a logistic regression model, and 1:1 propensity-score matching without replacement using a caliper width of 0·05. Balance of baseline covariates between bivalent and monovalent groups was indicated by standardized mean differences (SMD) ≤0·1.[14] Cox regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for each study outcome between the two groups.

Sensitivity analysis of all-cause mortality was also performed analysis by including 144 (Bivalent: 72; Monovalent: 72) patients with SARS-CoV-2 infection diagnosis or symptom onset date on or after that of hospitalization.

Results

After matching, 1,622 patients who had received the bivalent mRNA vaccine and 1,622 patients who had received monovalent BNT162b2 vaccine as their fourth dose were included (Supplementary Figure 1). Timing of fourth dose administration is illustrated in Supplementary Figure 2. Baseline characteristics of patients in the two groups before and after matching are presented in Supplementary Tables 1 and 2, respectively. Cumulative incidences of mortality and hospitalizations were fairly low (≤1%) in this boosted patient cohort (Table). No significant differences in the study outcomes were identified between the recipients of bivalent and monovalent vaccines as a second booster. Results from sensitivity analysis were broadly consistent with main results (Supplementary Table 3).

Our post-hoc power analysis would detect significance difference in primary outcome between the two groups under two circumstances: 1) cumulative incidence among monovalent recipients was increased from 0.80% to 2.31%, or at least 1.51% greater in difference (i.e. from -0.25% to 1.26%; and 2) cumulative incidence among monovalent recipients was decreased from 0.80% to 0.26%, or at least 0.54% greater in difference (i.e. from -0.25% to -0.79%). Therefore, the upper bound on difference of 1.51% was estimated for reaching statistical significance.

Discussions

This is one of the first real-world studies to assess the effectiveness of bivalent and monovalent mRNA vaccine boosters against mortality and hospitalization. Amid the Omicron wave when both bivalent and monovalent mRNA vaccines were available as a second booster, their effectiveness against severe COVID-19 outcomes are comparable. Our non-significant findings are similar to that observed in nationwide cohort analyses of four Nordic countries comparing bivalent to monovalent mRNA vaccines as the fourth dose against hospitalization[15], which may be explained by immunogenicity of bivalent and monovalent boosters. Two recent studies indicated neutralizing antibody responses against Omicron and ancestral strains of SARS-CoV-2 after bivalent boosters were not superior than those after monovalent boosters.[16, 17] In the changing landscape of circulating SARS-CoV-2 variants (when XBB became dominant), further boosting with the first generation (monovalent) vaccines may not be the optimal strategy to sustain the population immunity against infection.

Notably, such observations may not correspond to earlier evidence demonstrating higher effectiveness of the bivalent than monovalent mRNA vaccine as an additional booster (versus no additional booster) against severe COVID-19.[18] Vaccine effectiveness is also higher comparing the bivalent to monovalent vaccine as a booster dose,[18, 19] and regardless of the number of monovalent vaccine doses previously administered.[18, 20] Noticeably, the bivalent booster offers better protection with increasing time since the last monovalent dose, presumably restoring the vaccine-induced immunity that has waned relative to the most recent immunization.[8, 20, 21] Further studies with longer follow-up are needed to determine the duration and any waning of protection induced by bivalent boosters.

Current study had limitation on the likely underestimated prior infection status. Assessment of vaccine effectiveness can be complicated by the interaction between immune escape variants, effects of waning immunity, host immune responses, and any prior infections.[22] Secondly, despite adapting propensity-score matching to balance the characteristics of patients who received the bivalent or monovalent mRNA vaccines as second boosters, retrospective cohort design may be limited by unmeasured residual confounding, selection and misclassification, missing clinical outcomes and information when patients attended the private healthcare system. Finally, considering ≤1% of cumulative incidence and small sample size in both groups, lack of statistical power cannot be ruled out to explain the non-significant findings.

In conclusion, there was no significant differences in the mortality or hospitalization between those who received bivalent and monovalent mRNA as second boosters. Both bivalent and monovalent mRNA boosters appear equally protective against clinical outcomes. Even in places with limited supply of or accessibility to bivalent mRNA boosters, monovalent mRNA boosters can still be administered for protection against clinical outcomes.

Ethics approval: This study was approved by the institutional review board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference no. UW 20-341). Individual patient-informed consent was not required for this retrospective cohort study using anonymized data.

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Authors' contributions: C.K.H.W. designed the study, contributed to the interpretation of the analysis, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. C.K.H.W. and K.T.K.L. reviewed the literature and wrote the

manuscript. I.C.H.A. conducted analysis and revised the manuscript. I.C.H.A., E.H.Y.L. and C.K.H.W. accessed and verified the underlying data. E.H.Y.L. and B.J.C. reviewed and revised the manuscript. C.K.H.W., K.T.K.L. and I.C.H.A. contributed equally to the current study.

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Table. Outcomes of all-cause mortality, all-cause hospitalization, and respiratory-related hospitalization among second booster recipients of the bivalent versus monovalent mRNA vaccines

Outcomes	Bivalent 4th dose (N=1,622)					Monovalent 4th dose (N=1,622)					Bivalent vs Monovalent		
	Cumulative incidence		Crude incidence rate (Events / 100,000 person-days)			Cumulative incidence		Crude incidence rate (Events / 100,000 person-days)			HR	95% CI	P-value
	New events	Rate	Estimate	95% CI	Person-days	New events	Rate	Estimate	95% CI	Person-days			
All-cause mortality or hospitalization	17	1.0%	38.8	(22.6, 62.1)	43,818	13	0.8%	29.7	(15.8, 50.7)	43,829	1.309	(0.634, 2.705)	0.467
All-cause mortality	0	0.0%	0.0	NA	44,103	3	0.2%	6.8	(1.4, 19.9)	44,003	NA	NA	NA
All-cause hospitalization	17	1.0%	38.8	(22.6, 62.1)	43,818	12	0.7%	27.4	(14.1, 47.8)	43,829	1.418	(0.675, 2.980)	0.356
Respiratory-related hospitalization	9	0.6%	20.5	(9.4, 38.9)	43,935	3	0.2%	6.8	(1.4, 19.9)	43,949	3.005	(0.811, 11.128)	0.100

Notes: CI=confidence interval; HR=hazard ratio

Bivalent group includes patients who had received three doses of BNT162b2 monovalent mRNA vaccine and BioNTech BA.4/5-adapted bivalent mRNA vaccine as the fourth dose; Monovalent group includes those who had received four doses of BNT162b2 monovalent mRNA vaccine.