Research

Booster vaccination with inactivated whole-virus or mRNA vaccines and COVID-19–related deaths among people with multimorbidity: a cohort study

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Abstract

Background: Multimorbidity is a prevalent risk factor for COVID-19–related complications and death. We sought to evaluate the association of homologous booster vaccination using BNT162b2 (Pfizer-BioNTech) or CoronaVac (Sinovac) with COVID-19–related deaths among people with multimorbidity during the initial Omicron wave of the COVID-19 pandemic.

Methods: Using routine clinical records from public health care facilities in Hong Kong, we conducted a territory-wide retrospective cohort study comparing people aged 18 years or older with 2 or more chronic conditions who received a homologous booster (third) dose with those who received only 2 doses, between Nov. 11, 2021, and Mar. 31, 2022. The primary outcome was death related to COVID-19.

Results: We included 120 724 BNT162b2 recipients (including 87 289 who received a booster), followed for a median of 34 (interquartile range [IQR] 20–63) days and 127 318 CoronaVac recipients (including 94 977 who received a booster), followed for a median of 38 (IQR 22–77) days. Among BNT162b2 recipients, booster-vaccinated people had fewer COVID-19–related deaths than those who received 2 doses (5 v. 34, incidence rate 1.3 v. 23.4 per million person-days, weighted incidence rate ratio [IRR] 0.05, 95% confidence interval [CI] 0.02–0.16). We observed similar results among recipients of CoronaVac booster vaccination compared with those who received only 2 doses (26 v. 88, incidence rate 5.3 v. 53.1 per million person-days, weighted IRR 0.08, 95% CI 0.05–0.12).

Interpretation: Among people with multimorbidity, booster vaccination with BNT162b2 or CoronaVac was associated with reductions of more than 90% in COVID-19–related mortality rates compared with only 2 doses. These results highlight the crucial role of booster vaccination for protecting vulnerable populations as the COVID-19 pandemic continues to evolve.

Compared with the general population, people living with multimorbidity are disproportionately burdened by the ongoing COVID-19 pandemic.[1] Research shows a higher risk of SARS-CoV-2 infection[2] and death related to COVID-19 among those with multimorbidity.[3,4] The global roll-out of SARS-CoV-2 vaccines, therefore, has rightfully prioritized people with underlying chronic conditions and multimorbidity.[5] By late 2021, most eligible people had received at least 2 doses of the vaccines in many jurisdictions.[6] Amid the emergence of new SARS-CoV-2 variants, however, people with multimorbidity may further benefit from booster vaccination, given an established tolerable safety profile of the vaccines in this particular population.[7,8] Some studies have shown the effectiveness of certain vaccines against infection with new variants in the general population, such as the mRNA vaccines.[9,10] However, the effectiveness of SARS-CoV-2 booster vaccination has not been well explored in people living with multimorbidity.

Despite an absence of evident local transmission of SARS-CoV-2 in Hong Kong from mid to late 2021,[11] the city reported the world's highest COVID-19–related mortality rate in proportion to population size amid the Omicron (BA.2) variant epidemic, which started in late December 2021.[12] As of April 2022, more than 9000 deaths in Hong Kong were related to COVID-19, of a population of 7.5 million.[11] Booster vaccination with 2 of the most widely used vaccines worldwide, namely the BNT162b2 mRNA

vaccine (Fosun-BioNTech, equivalent to Pfizer-BioNTech outside China) and the CoronaVac inactivated whole-virus vaccine (Sinovac), has been available to eligible Hong Kong residents since Nov. 11, 2021. Older people, health care professionals and other priority groups were allowed to receive the booster vaccination first, before it was extended to all other adults on Jan. 1, 2022. More than 3 million people received the booster vaccination within the first 4 months of 2022.[13]

We sought to evaluate the effectiveness of a homologous booster dose of these vaccines in lowering the risk of COVID-19–related death among people with multimorbidity using a territory-wide electronic health record database in Hong Kong amid the Omicron wave of the pandemic.

Methods

Data sources

We identified SARS-CoV-2 vaccine recipients with multimorbidity from routine health care records provided by the Hospital Authority of Hong Kong, linked with population-based vaccination records at the Department of Health. The Hospital Authority serves as the sole provider of public inpatient services and is a major provider of outpatient services in Hong Kong, with a comprehensive electronic health record system for facilitation of clinical management. Further details are available in Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.221068/tab-related-content.

Study design

We used a retrospective cohort study design to compare the risk of COVID-19–related deaths among adults with multimorbidity who had received a homologous booster dose against those who had received only 2 doses. We identified adults aged 18 years or older with diagnoses of 2 or more chronic conditions (of a widely adopted list of 30 conditions; Appendix 1, Supplementary Table 1) who had received a booster dose between Nov. 11, 2021 (the date of the official roll-out of booster vaccination), and Mar. 31, 2022, of the same SARS-CoV-2 vaccine they had received for the first 2 doses (BNT162b2 or CoronaVac).[14,15] Both vaccines were made freely available to all residents of Hong Kong during the study period. Dozens of community vaccination centres that provided either vaccine were set up in geographically convenient public facilities for a wider reach to the community. Given its easier storage, the CoronaVac vaccine was made available in private clinics as well. The supply of both vaccines has been more than adequate since their roll-out in early 2021 (Feb. 23 for CoronaVac and Mar. 6 for BNT162b2). In general, Hong Kong residents were encouraged to receive the booster vaccine at least 180 days after their second dose. However, they were allowed to receive the booster vaccine from 90 days after the second dose for reasons such as having an underlying, immunocompromising condition. Residents could receive a booster dose less than 90 days after their second dose only with medical advice to do so, or in other exceptional cases.

We considered adults with multimorbidity (deceased or alive by the end of data availability) who had received their second vaccine dose at least 180 days before Mar. 31, 2022, but had not received the booster dose as the comparison cohort (i.e., the 2-dose group). We conducted random matching by age and sex so that a randomly chosen, booster-vaccinated individual was mapped to each 2-dose individual of the same age and sex; the date of booster vaccination served as the pseudo-index date for the 2-dose group. We adopted the 180-day interval as a criterion to ensure each age- and sex-matched 2-dose individual was assigned a pseudo-index date well after the date of their second dose. We built such a comparison cohort for each of the 2 vaccine types. We excluded people who had received heterologous vaccines and those who had received a second booster (fourth) dose from the main analysis. Hence, we included 2 study cohorts in the main analysis, namely the BNT162b2 cohort and the CoronaVac cohort.

We followed individuals from the index date (booster vaccination) or pseudo-index date until the outcome of interest, death related to COVID-19; we censored individuals upon death unrelated to COVID-19 or at the end of data availability (Mar. 31, 2022), whichever came first. We defined a death related to COVID-19 as one that was unrelated to injury or poisoning (*International Classification of Diseases, 10th Revision* code S00-T88), with a positive test result from a polymerase chain reaction test for SARS-CoV-2 within 28 days before death.[16] We excluded people who received 2 doses but died before the pseudo-index date and people (2 doses or 3 doses) who developed multimorbidity only after the index (or pseudo-index) date.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist to guide transparent reporting of this study.[17]

Statistical analysis

We used propensity score–based, inverse probability of treatment, weighted Poisson regression, stratified by vaccine type (BNT162b2 v. CoronaVac) to estimate the weighted incidence rate ratio (IRR) of death related to COVID-19, comparing those who received the booster dose and those who received only 2 doses. Covariates for weighting included age, sex, time from second dose to index or pseudo-index date (d), presence of each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within 1 year before the index or pseudo-index date (see Appendix 1, Supplementary Table 2). Details regarding subgroup, secondary and sensitivity analyses are provided in the Appendix 1.

All statistical tests were 2-sided, and we considered p values less than 0.05 to be statistically significant. We conducted statistical analysis using R version 4.0.3 (www.R-project.org). We used the svyjskm package to generate a weighted Kaplan–Meier cumulative incidence plot. Two investigators (V.K.C.Y. and X.Y.) conducted the statistical analyses independently for quality assurance.

Ethics approval

As only anonymized secondary data analyses were involved, no informed consent was required. This research is approved by the Hospital Authority Central Institutional Review Board (CIRB-2021–005–4) and the Department of Health Ethics Committee (LM171/2021).

Results

We identified 3 290 178 people aged 18 years or older who had received at least 2 doses of SARS-CoV-2 vaccines as of Mar. 31, 2022, in the database, of which 519 191 had 2 or more of the 30 chronic conditions. After further removing ineligible participants by our exclusion criteria, we included 120 724 BNT162b2 recipients (including 87 289 who received a booster) and 127 318 CoronaVac recipients (including 94 977 who received a booster) in the analyses (Figure 1). The median follow-up time was 34 (interquartile range [IQR] 20–63) days for BNT162b2 recipients and 38 (IQR 22–77) days for CoronaVac recipients.

Cohort characteristics

Table 1 and Table 2 show the BNT162b2 and CoronaVac cohort characteristics, respectively, before and after applying inverse probability of treatment weighting. People who received the booster dose were slightly older than those who received only 2 doses (64.9 v. 61.2 yr among BNT162b2 recipients; 67.9 v. 65.0 yr among CoronaVac recipients); the CoronaVac recipients were slightly older than the BNT162b2 recipients. The ratio of males to females was similar between groups, with slightly more males included. As of the index or pseudo-index date, about 20–30 more days had passed since the second dose vaccination among those who had received the booster than among those who received only 2 doses (Appendix 1, Supplementary Figure 1). For all 4 groups, the most prevalent chronic condition was hypertension (> 80%) followed by diabetes (> 60%), severe constipation (> 10%), chronic kidney disease (about 10%) and chronic pain (about 10%). More than 60% of participants had used calcium-channel blockers and about 60% had used lipid-lowering agents in the past year, followed by renin–angiotensin-system agents (about 50%) and antidiabetic medications (> 40%). After weighting, all characteristics had a standardized mean difference lower than 0.1, indicating a good balance between the booster and 2-dose groups for both vaccine cohorts.

COVID-19–related deaths

The weighted cumulative incidence of COVID-19–related deaths across the follow-up period was higher among people who were vaccinated with 2 doses than among those who received a booster (Figure 2). CoronaVac recipients had a higher rate of

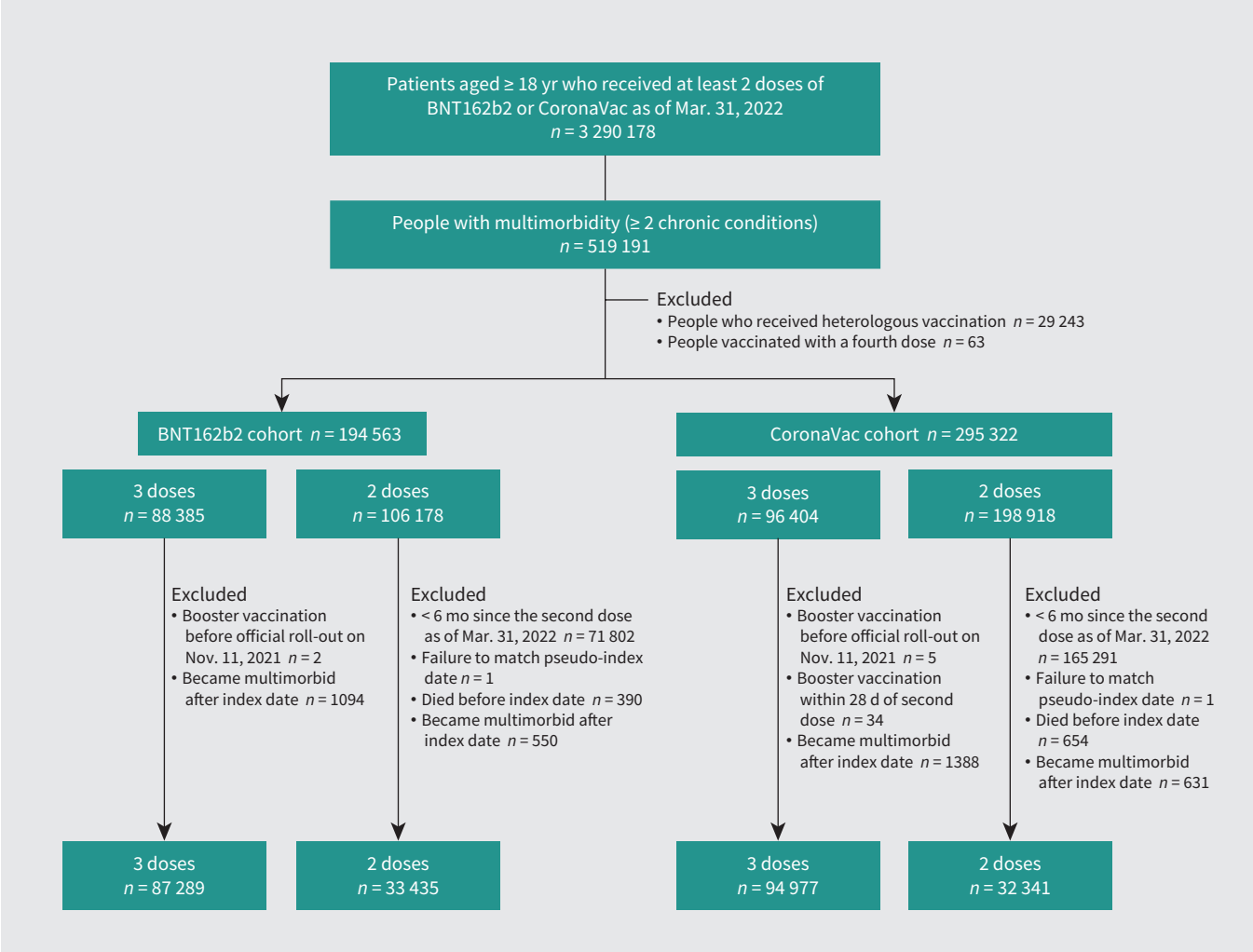

Figure 1: Flow chart showing cohort selection.

Table 1 (part 1 of 2): Cohort characteristics before and after inverse probability of treatment weighting for recipients of BNT162b2 vaccine (booster v. 2 doses)

Characteristic	Unweighted no. (%) of patients*			Weighted no. (%) of patients*†		
	2 doses *n* = 33 435	Booster *n* = 87 289	SMD	2 doses *n* = 118 632	Booster *n* = 119 679	SMD
Age, yr, mean ± SD	61.19 ± 12.44	64.85 ± 11.15	0.311	63.74 ± 11.97	63.93 ± 11.59	0.016
Sex, male	16 945 (50.7)	48 187 (55.2)	0.090	63 163 (53.2)	64 516 (53.9)	0.013
Time since second dose, mean ± SD, d	183.92 ± 52.58	207.07 ± 40.79	0.504	205.06 ± 55.52	201.97 ± 42.09	0.063
Chronic conditions						
Alcohol misuse	552 (1.7)	1111 (1.3)	0.031	1714 (1.4)	1656 (1.4)	0.005
Asthma	1642 (4.9)	4097 (4.7)	0.009	5588 (4.7)	5686 (4.8)	0.002
Cancer, lymphoma	106 (0.3)	305 (0.3)	0.005	470 (0.4)	434 (0.4)	0.005
Cancer, metastatic	503 (1.5)	1196 (1.4)	0.011	2022 (1.7)	1808 (1.5)	0.015
Cancer, nonmetastatic	1235 (3.7)	3353 (3.8)	0.008	4895 (4.1)	4704 (3.9)	0.010
Chronic pain	3484 (10.4)	8254 (9.5)	0.031	11 649 (9.8)	11 639 (9.7)	0.003
Chronic pulmonary disease	729 (2.2)	1953 (2.2)	0.005	2761 (2.3)	2684 (2.2)	0.006
Chronic viral hepatitis B	2039 (6.1)	5439 (6.2)	0.006	7094 (6.0)	7350 (6.1)	0.007
Cirrhosis	224 (0.7)	589 (0.7)	< 0.001	877 (0.7)	833 (0.7)	0.005
Dementia	126 (0.4)	329 (0.4)	< 0.001	548 (0.5)	468 (0.4)	0.011
Depression	2684 (8.0)	6001 (6.9)	0.043	8608 (7.3)	8604 (7.2)	0.003
Diabetes	20 655 (61.8)	55 099 (63.1)	0.032	73 712 (62.1)	74 888 (62.6)	0.009
Hypertension	26 991 (80.7)	73 013 (83.6)	0.079	97 491 (82.2)	98 975 (82.7)	0.014
Hypothyroidism	2247 (6.7)	5512 (6.3)	0.015	7772 (6.6)	7676 (6.4)	0.006
Inflammatory bowel disease	102 (0.3)	244 (0.3)	0.005	337 (0.3)	342 (0.3)	< 0.001
Irritable bowel syndrome	194 (0.6)	470 (0.5)	0.005	646 (0.5)	659 (0.6)	0.001
Parkinson disease	134 (0.4)	376 (0.4)	0.004	536 (0.5)	515 (0.4)	0.003
Peptic ulcer disease	595 (1.8)	1584 (1.8)	0.003	2180 (1.8)	2180 (1.8)	0.001
Peripheral vascular disease	96 (0.3)	297 (0.3)	0.010	365 (0.3)	392.8 (0.3)	0.004
Psoriasis	250 (0.7)	554 (0.6)	0.013	780 (0.7)	794 (0.7)	0.001
Rheumatoid arthritis	406 (1.2)	1036 (1.2)	0.002	1514 (1.3)	1467 (1.2)	0.005
Schizophrenia	421 (1.3)	835 (1.0)	0.029	1333 (1.1)	1264 (1.1)	0.006
Severe constipation	3913 (11.7)	11 811 (13.5)	0.056	15 274 (12.9)	15 643 (13.1)	0.006
Atrial fibrillation	1044 (3.1)	2989 (3.4)	0.018	4118 (3.5)	4062 (3.4)	0.004
Congestive heart failure	586 (1.8)	1416 (1.6)	0.009	2195 (1.9)	2052 (1.7)	0.010
Chronic kidney disease	2864 (8.6)	7476 (8.6)	0.001	10 661 (9.0)	10 498 (8.8)	0.008
Epilepsy	246 (0.7)	480 (0.5)	0.022	730 (0.6)	724 (0.6)	0.001
Multiple sclerosis	57 (0.2)	102 (0.1)	0.014	166 (0.1)	155 (0.1)	0.003
Myocardial infarction	459 (1.4)	897 (1.0)	0.031	1539 (1.3)	1394 (1.2)	0.012
Stroke or TIA	1902 (5.7)	4530 (5.2)	0.022	6713 (5.7)	6463 (5.4)	0.011

mortality related to COVID-19 than BNT162b2 recipients. Appendix 1, Supplementary Figure 2 shows the unweighted cumulative incidence plots.

In total, 39 BNT162b2 recipients (including 5 who received a booster) and 114 CoronaVac recipients (including 26 who received a booster) died in relation to COVID-19, constituting an incidence rate of 0.7 per 100 000 person-days for BNT162b2 and and 1.7 per 100 000 person-days for CoronaVac. Weighted analysis estimated that a booster dose was associated with a reduced risk of COVID-19–related death among both BNT162b2 recipients (IRR 0.05, 95% confidence interval [CI] 0.02–0.16) and CoronaVac recipients (IRR 0.08, 95% CI 0.05–0.12) (Table 3).

Results were similar in a weighted subgroup analysis including only those aged 60 years or older (BNT162b2: IRR 0.06, 95% CI 0.02–0.16; CoronaVac: IRR 0.07, 95% CI 0.04–0.11) (Appendix 1, Supplementary Table 3). Interaction between booster vaccination

Table 1 (part 2 of 2): Cohort characteristics before and after inverse probability of treatment weighting for recipients of BNT162b2 vaccine (booster v. 2 doses)

Characteristic	Unweighted no. (%) of patients*			Weighted no. (%) of patients*†		
	2 doses *n* = 33 435	Booster *n* = 87 289	SMD	2 doses *n* = 118 632	Booster *n* = 119 679	SMD
Medication use in the previous year						
Renin-angiotensin system agents	16 021 (47.9)	42 901 (49.1)	0.027	57 966 (48.9)	58 484 (48.9)	< 0.001
β-blockers	8042 (24.1)	21 432 (24.6)	0.012	29 149 (24.6)	29 393 (24.6)	< 0.001
Calcium-channel blockers	20 750 (62.1)	55 890 (64.0)	0.043	75 033 (63.2)	76 006 (63.5)	0.005
Diuretics	2926 (8.8)	7260 (8.3)	0.015	10 690 (9.0)	10 318 (8.6)	0.014
Nitrates	1482 (4.4)	4396 (5.0)	0.028	5976 (5.0)	5920 (4.9)	0.004
Lipid-lowering agents	19 258 (57.6)	54 932 (62.9)	0.112	72 246 (60.9)	73 635 (61.5)	0.013
Insulins	1859 (5.6)	4444 (5.1)	0.020	6643 (5.6)	6400 (5.3)	0.011
Antidiabetic drugs	15 132 (45.3)	40 069 (45.9)	0.016	53 918 (45.4)	54 644 (45.7)	0.004
Antiarrthymic drugs	209 (0.6)	375 (0.4)	0.027	692 (0.6)	613 (0.5)	0.010
Oral anticoagulants	578 (1.7)	1769 (2.0)	0.022	2478 (2.1)	2378 (2.0)	0.007
Antiplatelets	5154 (15.4)	15 100 (17.3)	0.052	20 261 (17.1)	20 314 (17.0)	0.003
Steroids	1284 (3.8)	2793 (3.2)	0.035	4633 (3.9)	4262 (3.6)	0.018
Antidepressants	3212 (9.6)	8254 (9.5)	0.004	11 369 (9.6)	11 434 (9.6)	0.001
Antiviral drugs	1055 (3.2)	2720 (3.1)	0.002	3918 (3.3)	3815 (3.2)	0.006
Antibacterial drugs	5777 (17.3)	14 028 (16.1)	0.034	20 773 (17.5)	20 044 (16.7)	0.020
Immunosuppressants	281 (0.8)	809 (0.9)	0.009	1212 (1.0)	1154 (1.0)	0.006

Note: SD = standard deviation, SMD = standardized mean difference (raw difference for proportions), TIA = transient ischemic attack.
*Unless indicated otherwise.
†Group totals were calculated from the sum of weights. The effective sample sizes for the 2-dose and booster groups were 26 631 and 83 826 patients, respectively."

and age was not significant for either vaccine in the multivariable Poisson regression analysis (BNT162b2: p = 0.9; CoronaVac: p = 0.7) (Appendix 1, Supplementary Table 4).

In an analysis combining the vaccine cohorts, 2 doses of BNT162b2 (IRR 0.49, 95% CI 0.31–0.78), booster vaccination with CoronaVac (IRR 0.03, 95% CI 0.01–0.08) and booster vaccination with BNT162b2 (IRR 0.07, 95% CI 0.04–0.11) were all associated with a lower risk of COVID-19–related death, compared with 2 doses of CoronaVac (Appendix 1, Supplementary Table 5). In an analysis of people who received a heterologous booster vaccine, no COVID-19–related deaths were recorded for those vaccinated with a BNT162b2-BNT162b2-CoronaVac series, and a reduced incidence of COVID-19–related deaths (IRR 0.02, 95% CI 0.00–0.06) was observed for those vaccinated with a CoronaVac-CoronaVac-BNT162b2 series, compared with 2 doses of CoronaVac (Appendix 1, Supplementary Table 6). In a weighted analysis similar to the primary analysis , the incidence of SARS-CoV-2 infection was also reduced with booster vaccination compared with 2-dose vaccination for both BNT162b2 (IRR 0.32, 95% CI 0.30–0.34) and CoronaVac (IRR 0.31, 95% CI 0.29–0.33) (Appendix 1, Supplementary Table 7).

Sensitivity analyses (including one in which each comorbidity was removed from the analysis; others in which the definition of COVID-19–related mortality required a positive polymerase chain reaction test for SARS-CoV-2 within 7, 14 or 28 days before death; one in which the index date was set 14 days after booster vaccination, with adjustment for potential competing risks from non-COVID-19–related deaths; and one with exclusion of people who developed COVID-19 before receiving their second vaccine dose showed consistent results with the main analysis (Appendix 1, Supplementary Tables 8–13).

Interpretation

We found a substantially reduced risk of COVID-19–related death in adults with multimorbidity who received a homologous booster dose of BNT162b2, an mRNA vaccine, or CoronaVac, an inactivated whole-virus vaccine. These results support the effectiveness of booster doses of vaccines of 2 different technological platforms in lowering mortality among those with multimorbidity amid the Omicron epidemic. Subgroup and sensitivity analyses showed similar results, supporting the robustness of our results. As the data on SARS-CoV-2 vaccination records used for this study was provided by the sole operator of vaccine roll-out in Hong Kong, with a unified recording system, and with linked clinical records provided by a territory-wide public health care provider, our data should be highly reliable and representative. Numerous previous high-impact pharmacovigilance studies have been generated from this database.[8,18–25]

Table 2 (part 1 of 2): Cohort characteristics before and after inverse probability of treatment weighting for recipients of CoronaVac vaccine (booster v. 2 doses)

Characteristic	Unweighted no. (%) of patients*			Weighted no. (%) of patients*†		
	2 doses *n* = 32 341	Booster *n* = 94 977	SMD	2 doses *n* = 120 552	Booster *n* = 125 921	SMD
Age, yr, mean ± SD	65.02 ± 10.99	67.88 ± 10.33	0.268	67.07 ± 10.99	67.27 ± 10.61	0.018
Sex, male	15 855 (49.0)	49 893 (52.5)	0.070	60 978 (50.6)	64 844 (51.5)	0.018
Time since second dose, mean ± SD, d	170.12 ± 55.85	200.99 ± 40.87	0.631	196.05 ± 58.07	194.73 ± 43.04	0.026
Chronic conditions						
Alcohol misuse	433 (1.3)	1040 (1.1)	0.022	1457 (1.2)	1445 (1.1)	0.006
Asthma	1104 (3.4)	3364 (3.5)	0.007	4186 (3.5)	44 22 (3.5)	0.002
Cancer, lymphoma	87 (0.3)	220 (0.2)	0.007	3689 (0.3)	319 (0.3)	0.010
Cancer, metastatic	554 (1.7)	896 (0.9)	0.067	1815 (1.5)	1587 (1.3)	0.021
Cancer, nonmetastatic	1236 (3.8)	3084 (3.2)	0.031	4622 (3.8)	4478 (3.6)	0.015
Chronic pain	3175 (9.8)	8602 (9.1)	0.026	11 575 (9.6)	11 707 (9.3)	0.010
Chronic pulmonary disease	925 (2.9)	2723 (2.9)	< 0.001	3494 (2.9)	3651 (2.9)	< 0.001
Chronic viral hepatitis B	2051 (6.3)	5732 (6.0)	0.013	7185 (6.0)	7616 (6.0)	0.004
Cirrhosis	230 (0.7)	517 (0.5)	0.021	836 (0.7)	772 (0.6)	0.010
Dementia	357 (1.1)	562 (0.6)	0.056	1086 (0.9)	988 (0.8)	0.013
Depression	1866 (5.8)	5106 (5.4)	0.017	6780 (5.6)	6921 (5.5)	0.006
Diabetes	20 820 (64.4)	62 303 (65.6)	0.026	77 551 (64.3)	81 852 (65.0)	0.014
Hypertension	27 228 (84.2)	82 409 (86.8)	0.073	102 778 (85.3)	108 183 (85.9)	0.019
Hypothyroidism	1890 (5.8)	5315 (5.6)	0.011	6806 (5.6)	7084 (5.6)	0.001
Inflammatory bowel disease	51 (0.2)	132 (0.1)	0.005	172 (0.1)	184 (0.1)	0.001
Irritable bowel syndrome	120 (0.4)	332 (0.3)	0.004	423 (0.4)	449 (0.4)	0.001
Parkinson disease	171 (0.5)	415 (0.4)	0.013	636 (0.5)	616 (0.5)	0.005
Peptic ulcer disease	633 (2.0)	1914 (2.0)	0.004	2432 (2.0)	2527 (2.0)	0.001
Peripheral vascular disease	115 (0.4)	369 (0.4)	0.005	483 (0.4)	486 (0.4)	0.002
Psoriasis	158 (0.5)	477 (0.5)	0.002	589 (0.5)	629 (0.5)	0.002
Rheumatoid arthritis	256 (0.8)	789 (0.8)	0.004	1094 (0.9)	1082 (0.9)	0.005
Schizophrenia	473 (1.5)	818 (0.9)	0.056	1361 (1.1)	1282 (1.0)	0.011
Severe constipation	3648 (11.3)	12 067 (12.7)	0.044	14 867 (12.3)	15 680 (12.5)	0.004
Atrial fibrillation	1272 (3.9)	3931 (4.1)	0.010	5215 (4.3)	5235 (4.2)	0.008
Congestive heart failure	770 (2.4)	1820 (1.9)	0.032	2865 (2.4)	2652 (2.1)	0.018
Chronic kidney disease	2890 (8.9)	8505 (9.0)	0.001	11 364 (9.4)	11 539 (9.2)	0.009
Epilepsy	212 (0.7)	353 (0.4)	0.040	631 (0.5)	584 (0.5)	0.009
Multiple sclerosis	21 (0.1)	55 (0.1)	0.003	89 (0.1)	80 (0.1)	0.004
Myocardial infarction	463 (1.4)	1015 (1.1)	0.033	1701 (1.4)	1510 (1.2)	0.019
Stroke or TIA	2230 (6.9)	5966 (6.3)	0.025	8378 (6.9)	8231 (6.5)	0.016

Since the roll-out of the BNT162b2 vaccine, observational studies worldwide have consistently shown its effectiveness against infection, severe disease and death.[9,10,26–29] More recent research on the booster dose has suggested substantial extra protection, in addition to that conferred by the first and second doses.[27,28,30,31] An Israeli cohort study of people aged 50 years or older reported a 90% reduced hazard of COVID-19–related death associated with the booster dose of BNT162b2 compared with only 2 doses.[28] In another cohort study of people aged 12 years or older, the reduced risk of COVID-19–related death was estimated at 81%.[32] Our estimates of 95% reduced risk among those with BNT162b2 booster vaccination are possibly the highest risk reductions reported to date, plausibly because of the selection of a high-risk population with multimorbidity, although the adopted age was as low as 18 years. Another potential explanation for the high effectiveness observed in our cohort may be the

Table 2 (part 2 of 2): Cohort characteristics before and after inverse probability of treatment weighting for recipients of CoronaVac vaccine (booster v. 2 doses)

Characteristic	Unweighted no. (%) of patients*			Weighted no. (%) of patients*†		
	2 doses *n* = 32 341	Booster *n* = 94 977	SMD	2 doses *n* = 120 552	Booster *n* = 125 921	SMD
Medication use in the previous year						
Renin-angiotensin system agents	16 082 (49.7)	47 891 (50.4)	0.014	60 484 (50.2)	63 262 (50.2)	0.001
β-blockers	8409 (26.0)	23 761 (25.0)	0.023	31 264 (25.9)	31 989 (25.4)	0.012
Calcium-channel blockers	21 490 (66.4)	64 322 (67.7)	0.027	80 807 (67.0)	84 771 (67.3)	0.006
Diuretics	3206 (9.9)	8365 (8.8)	0.038	11 771 (9.8)	11 685 (9.3)	0.017
Nitrates	1715 (5.3)	5170 (5.4)	0.006	7052 (5.9)	6932 (5.5)	0.015
Lipid-lowering agents	19 799 (61.2)	61 924 (65.2)	0.083	76 578 (63.5)	80 832 (64.2)	0.014
Insulins	1892 (5.9)	4658 (4.9)	0.042	6779 (5.6)	6618 (5.3)	0.016
Antidiabetic drugs	15 398 (47.6)	45 363 (47.8)	0.003	56 921 (47.2)	59 850 (47.5)	0.006
Antiarrthymic drugs	203 (0.6)	401 (0.4)	0.028	694 (0.6)	644 (0.5)	0.009
Oral anticoagulants	760 (2.3)	2169 (2.3)	0.004	3009 (2.5)	2970 (2.4)	0.009
Antiplatelets	6028 (18.6)	18 012 (19.0)	0.008	23 847 (19.8)	24 080 (19.1)	0.017
Steroids	1170 (3.6)	2346 (2.5)	0.067	4107 (3.4)	3735 (3.0)	0.025
Antidepressants	2700 (8.3)	7476 (7.9)	0.017	9969 (8.3)	10 140 (8.1)	0.008
Antiviral drugs	1076 (3.3)	2669 (2.8)	0.030	3799 (3.2)	3768 (3.0)	0.009
Antibacterial drugs	5980 (18.5)	14 337 (15.1)	0.091	21 129 (17.5)	20 465 (16.3)	0.034
Immunosuppressants	174 (0.5)	453 (0.5)	0.009	738 (0.6)	699 (0.6)	0.008

Note: SD = standard deviation, SMD = standardized mean difference (raw difference for proportions), TIA = transient ischemic attack.
*Unless indicated otherwise.
†Group totals were calculated from the sum of weights. The effective sample sizes for the 2-dose and booster groups were 24 667 and 89 823 patients, respectively.

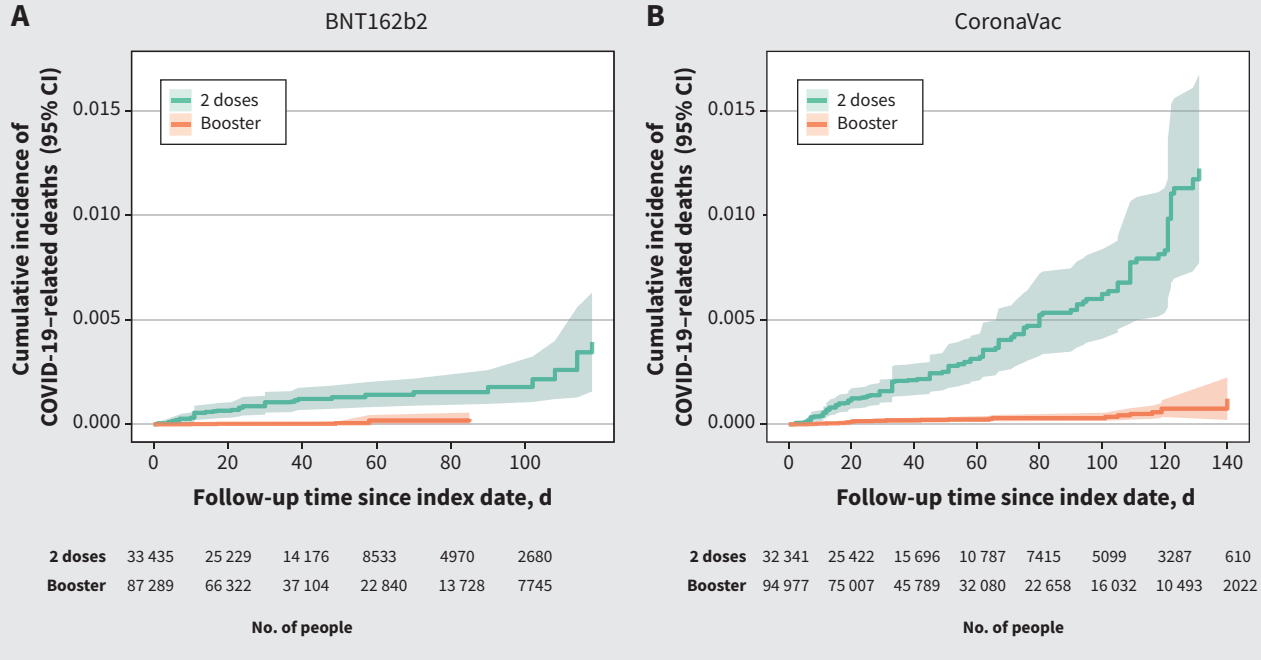

Figure 2: Weighted cumulative incidence of COVID-19–related deaths after (A) BNT162b2 or (B) CoronaVac 2-dose or booster vaccination, with 95% confidence intervals (CIs) represented by the shaded area. The index date is operationalized as the date of booster vaccination or the matched pseudo-index date for those who received 2 doses of vaccine.

Table 3: COVID-19–related deaths among people who received either 2 doses or booster vaccination, by vaccine type (BNT162b2 or CoronaVac)

Vaccination	No. of people	No. of COVID-19–related deaths	No. of person-days	No. of events per 1 million person-days	Unweighted IRR (95% CI)*	Weighted IRR (95% CI)*
BNT162b2						
2 doses	33 435	34	1 454 857	23.4	1.00	1.00
Booster	87 289	5	3 860 900	1.3	0.06 (0.02–0.13)	0.05 (0.02–0.16)
CoronaVac						
2 doses	32 341	88	1 657 144	53.1	1.00	1.00
Booster	94 977	26	4 931 857	5.3	0.10 (0.06–0.15)	0.08 (0.05–0.12)

Note: CI = confidence interval, IRR = incidence rate ratio.
*Propensity score–based, inverse probability of treatment weighting was used to weight the sample according to age, sex, days from second dose to index or pseudo-index date, presence of each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within 1 year before the index or pseudo-index date.

waning of protection conferred by the first and second doses, given that the average number of days since the second dose well exceeded 180 days in both the weighted and unweighted cohorts; this extended period may have incurred a reduction of effectiveness by more than 20–30 percentage points, compared with 14 days after vaccination, according to a systematic review.[33,34] Certain underlying conditions and old age in this population may also accelerate this waning protection.[35]

Given its much wider use in developing countries than in developed countries, CoronaVac's effectiveness has not been investigated as extensively as BNT162b2 beyond clinical trials, wherein vaccination (including booster vaccination) generally showed good efficacy against infection, severe disease and death.[29,36–39] In the cross-platform comparison, we showed that 2 doses of CoronaVac confer lower protection than 2 doses of BNT162b2, which agrees with the existing efficacy data, but 3 doses of either CoronaVac or BNT162b2 offered similar protection. Our large postmarketing cohort study thereby supports the effectiveness of a booster dose of CoronaVac against death related to COVID-19. Our findings should inform public health policies in countries that are considering the roll-out of booster doses of CoronaVac, especially for the aging population and in populations with a high prevalence of multimorbidity.

Limitations

Similar to other pharmacoepidemiologic studies, residual confounding may be present as randomization was not possible. Specifically, people with multimorbidity who chose to receive a booster dose earlier than others may be better educated, more health aware and more proactive in health-seeking behaviours. These people may therefore be better at self-care to minimize the risk of SARS-CoV-2 infection and, thus, the analysis may overestimate the effectiveness of the booster dose. Nevertheless, people in the comparison cohort had already received 2 doses (rather than including a mix of vaccinated and unvaccinated people), and such an overestimation, if any, should be minimal and may not affect the results substantially. The outcome of this study was operationalized as death with COVID-19 rather than death from COVID-19 because the adoption of the latter requires a thorough causality assessment for each outcome event, and it was not feasible, given the limited information in the database of electronic health records for such an assessment and the large number of events. The list of conditions for multimorbidity was far from exhaustive and may not be perfectly applicable to Hong Kong, but research has suggested that prevalence tends to converge at the inclusion of 12 or more prevalent conditions.[40] Moreover, the sensitivity analysis showed no substantial effects of the change of multimorbidity components on the findings. Further research should investigate the impact of an increased burden of multimorbidity on vaccine effectiveness. Although we adjusted for the presence of chronic conditions, we did not determine or adjust for their severity. We did not have a sufficient sample size to evaluate the effectiveness of heterologous booster doses across platforms, which future research with adequate data should investigate.[41] People who received 2 doses and who were discouraged from receiving a booster dose owing to a recent SARS-CoV-2 infection may have had increased immunity during the follow-up period. Nevertheless, this should bias the result only toward the null hypothesis and not affect our conclusion. The 2-dose vaccinated cohort may have been infected with SARS-CoV-2 and acquired a certain degree of immunity. We did not adjust for this possibility as we took an intention-to-treat perspective. We did not have data on the exact variant type for each individual in the database. Nevertheless, the observation period coincides with the Omicron BA.2 outbreak, which has been widely reported.[12] We can reasonably generalize the findings and conclusions to Omicron BA.2. The population in Hong Kong is predominantly ethnic Chinese.[42] Replication of the analysis should be conducted to test for generalizability to other populations.

Conclusion

The mass roll-out of the booster dose of SARS-CoV-2 vaccines in Hong Kong in November 2021 coincided with the arrival of the Omicron variant in late 2021. Our findings suggest that this timely, massive public health measure has plausibly played a pivotal role in lowering the mortality rate amid the epidemic, especially among people living with multimorbidity. They also

highlight the potential benefit from booster vaccination, specifically in vulnerable populations living with multimorbidity, and support the recent focus on older people and those with chronic conditions for future booster doses of SARS-CoV-2 vaccines beyond the first booster.[43]

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