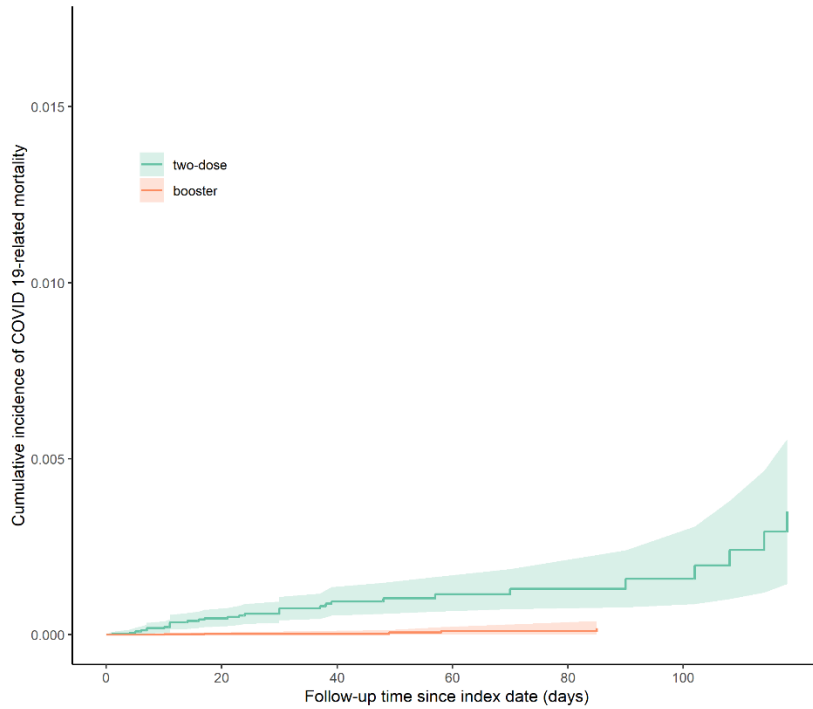


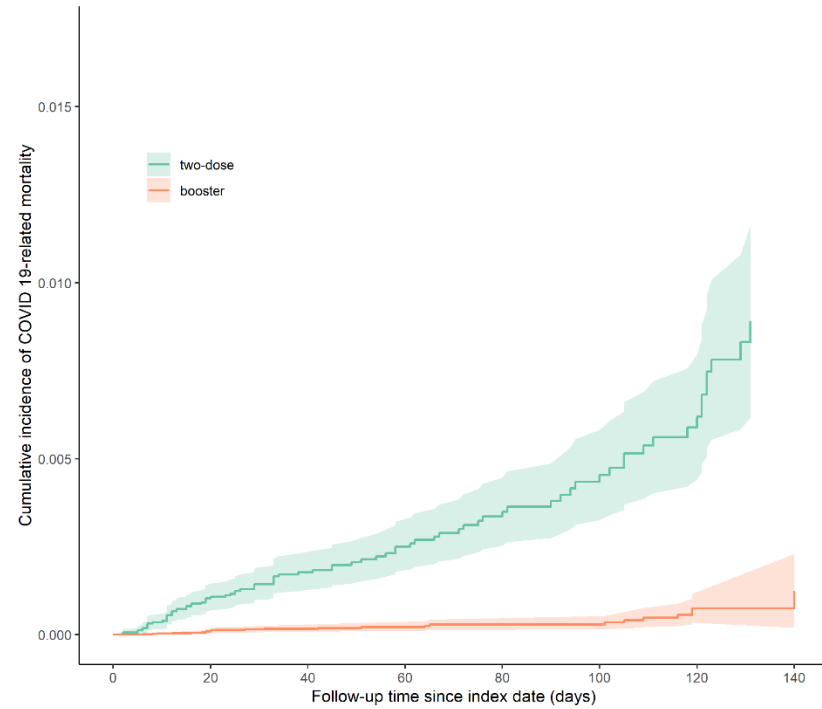
Supplementary Figure 1. Weighted and unweighted distribution of time from second dose vaccination for the two vaccine groups, with and without booster vaccination respectively

BNT162b2 cumulative incidence plot, unweighted



two-dose	33435	25229	14176	8533	4970	2680
booster	87289	66322	37104	22840	13728	7745
	Numbers at risk					

CoronaVac cumulative incidence plot, unweighted



two-dose	32341	25422	15696	10787	7415	5099	3287	610
booster	94977	75007	45789	32080	22658	16032	10493	2022
	Numbers at risk							

Supplementary Figure 2. Unweighted cumulative incidence of COVID-19-related mortality with 95% confidence interval represented by shaded area. The index date is operationalized as the date of booster vaccination or the matched pseudo index date for the two-dose vaccinated.

Supplementary Table 1. Diagnostic codes used to operationalize chronic conditions and multimorbidity

Chronic conditions	International Classification of Diseases, Ninth Revision	International Classification of Primary Care
Alcohol misuse	265.2, 291.1–291.3, 291.5–291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0–571.3, 980, V11.3	P15
Asthma	493	R96
Atrial fibrillation	427.3	K78
Cancer, lymphoma	200–202, 203.0, 238.6	B72
Cancer, metastatic	196–199	B74, D74, D76, D77, L71, N74, S77, T71, U75, U76, U77, W72, X77, Y78
Cancer, non-metastatic (breast, cervical, colorectal, lung, prostate)	153-154, 162-163, 174, 180, 185, 230.3-230.6, 231.2, 233.0-233.1, 233.4	D75, R84, X75, X76, Y77
Chronic heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428	K77
Chronic kidney disease	583, 584, 585, 586, 592, 593.9	U14
Chronic pain	307.80, 307.89, 338.0, 338.2, 338.4, 719.41, 719.45 - 719.47, 719.49, 720.0, 720.2, 720.9, 721.0 - 721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3 - 723.9, 724.0 - 724.6, 724.70, 724.79, 724.8, 724.9, 729.0 - 729.2, 729.4, 729.5	A01
Chronic pulmonary disease	416.8, 416.9, 490–492, 494-505, 506.4, 508.1, 508.8	R95
Chronic viral hepatitis B	70.2-70.3	D72
Cirrhosis	571.2, 571.5, 571.6, 456.0, 456.1, 456.20, 456.21, 567.0, 567.2, 567.21, 567.29, 567.8, 567.9, 572.2, 572.4, 789.5 (Exclude 567.81, 567.82, 789.51)	-
Dementia	290, 294.1, 331.2	P70
Depression	296.2, 296.3, 296.5, 300.4, 309, 311	P76
Diabetes	250	T89-T90
Epilepsy	345	N88
Hypertension	401-405	K86-K87
Hypothyroidism	240.9, 243, 244, 246.1, 246.8	T86
Inflammatory bowel disease	555, 556	-
Irritable bowel syndrome	564.1 (Exclude 153-154, 157, 183.0, 197.5, 198.6, 235.2, 239.0, 555-556, 571.2, 571.5, 577.1, 579)	D93

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Multiple sclerosis	323, 340, 341.0, 341.9, 377.3	N86
Myocardial infarction	410	K75
Parkinson’s disease	332	N87
Peptic ulcer disease	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9	D86
Peripheral vascular disease	440.2	K92
Psoriasis	696.1	S91
Rheumatoid arthritis	446.5, 710.0–710.4, 714.0–714.2, 714.8, 725	L88
Schizophrenia	295	P72
Severe constipation	560.1, 560.30, 560.39, 560.9, 564.0, 569.83, 569.89 (Exclude 152-154, 158, 179-189, 197.5-197.6, 235.2, 239.0, 555-556, 568.0, 614.6, (560.9 if 789.01, 789.02, 789.06))	D12
Stroke or transient ischemic attack	362.3, 430, 431, 433.x1, 434.x1, 435, 436	K90

Supplementary Table 2. British National Formulary codes for the operationalization of medication use

Medications	British National Formulary code
Renin-angiotensin-system agents	2.5.5
Beta blockers	2.4
Calcium channel blockers	2.6.2
Diuretics	2.2
Nitrates	2.6.1
Lipid lowering agents	2.12
Insulins	6.1.1
Antidiabetic drugs	6.1.2
Antiarrhythmic drugs	2.3.2
Oral anticoagulants	2.8.2
Antiplatelets	2.9
Steroid	6.3.2
Antidepressants	4.3
Antiviral drugs	5.3
Antibacterial drugs	5.1
Immunosuppressants	8.2

0

Supplementary Table 3. Incidence rate ratio of COVID-19-related mortality between the booster-vaccinated and the two-dose vaccinated by vaccine type (BNT162b2 versus CoronaVac) among those aged 60 years or older

Vaccination	No.	No. of COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a,b}
BNT162b2					
Two-dose	19950	32/895134	35.7	1	1
Booster	62233	5/2799540	1.8	0.05 (0.02-0.12)	0.06 (0.02-0.16)
CoronaVac					
Two-dose	22750	84/1186805	70.8	1	1
Booster	76216	24/3997630	6.0	0.09 (0.05-0.13)	0.07 (0.04-0.11)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 4. Incidence rate ratio (95% CI) of COVID-19-related mortality associated with booster vaccination, age, and other covariates estimated from multivariable Poisson regression ^a

	BNT162b2		CoronaVac	
	Without age modification ^b	With age modification ^b	Without age modification ^b	With age modification ^b
Booster vaccination	0.051 (0.019-0.133)	0.029 (0-19.422)	0.102 (0.063-0.164)	0.203 (0.006-7.109)
Age	1.049 (1.016-1.083)	1.048 (1.014-1.083)	1.102 (1.079-1.125)	1.104 (1.079-1.129)
Booster vaccination X Age		1.008 (0.924-1.099)		0.991 (0.947-1.037)
Men (women as referent)	0.98 (0.477-2.013)	0.98 (0.477-2.012)	2.106 (1.35-3.286)	2.102 (1.347-3.28)
Time since second dose	1.003 (0.998-1.009)	1.003 (0.998-1.009)	1.004 (1.001-1.007)	1.004 (1.001-1.007)
Chronic conditions				
Alcohol misuse	1.691 (0.197-14.515)	1.691 (0.197-14.526)	2.296 (0.66-7.99)	2.316 (0.665-8.066)
Asthma	0 (0-Inf)	0 (0-Inf)	0.235 (0.032-1.716)	0.234 (0.032-1.713)
Cancer, lymphoma	1.26 (0.135-11.784)	1.244 (0.132-11.697)	3.809 (1.046-13.862)	3.856 (1.058-14.053)
Cancer, metastatic	5.586 (1.702-18.331)	5.574 (1.697-18.316)	2.844 (1.345-6.011)	2.851 (1.349-6.026)
Cancer, non-metastatic	2.368 (0.779-7.201)	2.356 (0.773-7.183)	1.997 (1.032-3.864)	2.006 (1.037-3.882)
Chronic pain	1.689 (0.679-4.2)	1.69 (0.68-4.201)	1.061 (0.605-1.862)	1.063 (0.606-1.867)
Chronic pulmonary disease	2.395 (0.788-7.28)	2.392 (0.787-7.268)	1.238 (0.664-2.305)	1.243 (0.667-2.316)
Chronic viral hepatitis B	1.284 (0.165-9.995)	1.286 (0.165-10.004)	0.33 (0.045-2.419)	0.329 (0.045-2.416)
Cirrhosis	1.228 (0.151-9.981)	1.222 (0.15-9.941)	3.155 (1.145-8.695)	3.162 (1.147-8.716)
Dementia	2.234 (0.269-18.549)	2.247 (0.271-18.66)	3.896 (1.99-7.627)	3.884 (1.982-7.61)
Depression	0.269 (0.031-2.299)	0.271 (0.032-2.314)	0.364 (0.083-1.594)	0.363 (0.083-1.591)
Diabetes	0.85 (0.311-2.324)	0.85 (0.311-2.324)	1.091 (0.623-1.913)	1.092 (0.623-1.916)
Hypertension	1.361 (0.581-3.184)	1.358 (0.58-3.179)	0.515 (0.317-0.838)	0.513 (0.315-0.835)
Hypothyroidism	0.739 (0.097-5.603)	0.737 (0.097-5.593)	0.933 (0.291-2.991)	0.939 (0.293-3.01)
Inflammatory bowel disease	0 (0-Inf)	0 (0-Inf)	0 (0-Inf)	0 (0-Inf)
Irritable bowel syndrome	0 (0-Inf)	0 (0-Inf)	0 (0-Inf)	0 (0-Inf)
Parkinson's disease	4.877 (0.981-24.246)	4.896 (0.985-24.322)	2.317 (0.706-7.602)	2.32 (0.707-7.613)
Peptic ulcer disease	0.935 (0.12-7.287)	0.936 (0.12-7.291)	1.213 (0.507-2.902)	1.204 (0.503-2.886)
Peripheral vascular disease	0 (0-Inf)	0 (0-Inf)	2.275 (0.309-16.733)	2.29 (0.311-16.85)
Psoriasis	4.926 (0.631-38.451)	4.92 (0.63-38.408)	0 (0-Inf)	0 (0-Inf)
Rheumatoid arthritis	0 (0-Inf)	0 (0-Inf)	3.939 (1.458-10.642)	3.931 (1.454-10.626)
Schizophrenia	0 (0-Inf)	0 (0-Inf)	3.056 (0.73-12.796)	3.075 (0.734-12.876)
Severe constipation	0.95 (0.397-2.276)	0.952 (0.397-2.28)	0.947 (0.58-1.544)	0.944 (0.579-1.541)
Atrial fibrillation	2.199 (0.703-6.878)	2.2 (0.704-6.872)	2.205 (1.178-4.126)	2.21 (1.181-4.135)
Congestive heart failure	1.072 (0.369-3.112)	1.068 (0.368-3.102)	1.221 (0.642-2.324)	1.219 (0.64-2.319)
Chronic kidney disease	4.444 (2.101-9.402)	4.432 (2.094-9.382)	1.843 (1.161-2.926)	1.843 (1.16-2.927)
Epilepsy	0 (0-Inf)	0 (0-Inf)	1.175 (0.161-8.595)	1.179 (0.161-8.627)
Multiple sclerosis	0 (0-Inf)	0 (0-Inf)	0 (0-Inf)	0 (0-Inf)
Myocardial infarction	0 (0-Inf)	0 (0-Inf)	2.86 (1.224-6.68)	2.852 (1.221-6.663)

Stroke or TIA	1.277 (0.401-4.063)	1.273 (0.4-4.052)	1.85 (1.014-3.374)	1.856 (1.017-3.387)
Medication use in the past year				
Renin-angiotensin-system agents	0.561 (0.269-1.174)	0.562 (0.269-1.176)	0.705 (0.455-1.092)	0.705 (0.455-1.092)
Beta blockers	0.796 (0.372-1.702)	0.796 (0.372-1.701)	0.922 (0.587-1.448)	0.924 (0.588-1.452)
Calcium channel blockers	0.548 (0.262-1.146)	0.549 (0.263-1.148)	1.301 (0.826-2.048)	1.302 (0.827-2.05)
Diuretics	6.441 (2.964-13.999)	6.434 (2.961-13.984)	2.148 (1.363-3.384)	2.146 (1.362-3.382)
Nitrates	0.954 (0.321-2.835)	0.954 (0.321-2.833)	0.977 (0.522-1.826)	0.981 (0.525-1.834)
Lipid lowering agents	1.094 (0.502-2.384)	1.094 (0.502-2.384)	0.904 (0.575-1.419)	0.906 (0.576-1.423)
Insulins	1.844 (0.739-4.597)	1.849 (0.742-4.609)	2.368 (1.331-4.213)	2.37 (1.331-4.218)
Antidiabetic drugs	1.325 (0.467-3.757)	1.322 (0.466-3.748)	0.886 (0.501-1.569)	0.887 (0.501-1.571)
Antiarrhythmic drugs	1.178 (0.287-4.827)	1.172 (0.286-4.808)	1.793 (0.789-4.077)	1.791 (0.788-4.075)
Oral anticoagulants	1.951 (0.631-6.034)	1.95 (0.631-6.025)	0.519 (0.232-1.163)	0.52 (0.232-1.165)
Antiplatelets	1.46 (0.656-3.252)	1.461 (0.656-3.254)	0.919 (0.567-1.491)	0.918 (0.566-1.488)
Steroids	2.163 (0.925-5.059)	2.168 (0.926-5.073)	2.161 (1.239-3.771)	2.167 (1.241-3.781)
Antidepressants	3.178 (1.159-8.715)	3.162 (1.152-8.681)	1.333 (0.7-2.54)	1.329 (0.698-2.533)
Antiviral drugs	1.936 (0.687-5.459)	1.94 (0.688-5.469)	1.422 (0.689-2.934)	1.422 (0.689-2.934)
Antibacterial drugs	2.888 (1.298-6.427)	2.884 (1.296-6.42)	2.294 (1.478-3.561)	2.289 (1.474-3.555)
Immunosuppressants	0.706 (0.073-6.868)	0.707 (0.073-6.857)	0.683 (0.139-3.344)	0.678 (0.139-3.323)

^a IRR = incidence rate ratio; CI = confidence interval

^b Age modification of booster vaccination's association with COVID-19-related mortality

Supplementary Table 5. Incidence rate ratio of COVID-19-related mortality between all four included vaccine groups

Vaccination	No.	No. of COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a b}
CoronaVac					
Two-dose	32341	88/1657144	53.1	1	1
Booster	94977	26/4931857	5.3	0.02 (0.01-0.05)	0.03 (0.01-0.08)
BNT162b2					
Two-dose	33435	34/1454857	23.4	0.44 (0.29-0.65)	0.49 (0.31-0.78)
Booster	87289	5/3860900	1.3	0.01 (0.06-0.15)	0.07 (0.04-0.11)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 6. Incidence rate ratio of COVID-19-related mortality between heterologous booster-vaccinated and two-dose vaccinated

Vaccination	No.	No. of COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a b}
CoronaVac					
Two-dose	32299	100/1857170	53.8	1	1
Booster with BNT162b2	27678	2/1649254	1.2	0.02 (0.00-0.07)	0.02 (0.00-0.06)
BNT162b2					
Two-dose	32561	30/1179736	25.4	1	1
Booster with CoronaVac	943	0/33836	0	-	-

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 7. Incidence rate ratio of SARS-CoV-2 infection between the booster-vaccinated and the two-dose vaccinated by vaccine type (BNT162b2 versus CoronaVac)

Vaccination	No.	No. of COVID-19 infections /No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a b}
BNT162b2					
Two-dose	33435	1792/1409050	1271.8	1	1
Booster	87289	1517/3825119	396.6	0.31 (0.29-0.33)	0.32 (0.30-0.34)
CoronaVac					
Two-dose	32341	2422/1595428	1518.1	1	1
Booster	94977	2344/4875440	480.1	0.32 (0.30-0.34)	0.31 (0.29-0.33)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 8. Sensitivity analysis with main analysis repeated with each of the multimorbidity component chronic conditions removed (BNT162b2 cohort)

Condition removed from analysis	No. events (booster/two-dose)	n (booster/two-dose)	No. person-days (booster/two-dose)	Incidence rate (booster/two-dose)	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a,b}
Alcohol misuse	5/34	86714/33108	3835886/1440569	0.1/2.4	0.055 (0.019-0.129)	0.053 (0.018-0.157)
Asthma	5/34	84979/32424	3754700/1413860	0.1/2.4	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Cancer, lymphoma	5/34	87128/33382	3853695/1452811	0.1/2.3	0.055 (0.019-0.129)	0.052 (0.018-0.156)
Cancer, metastatic	5/33	86676/33174	3831949/1444970	0.1/2.3	0.057 (0.020-0.134)	0.054 (0.018-0.162)
Cancer, non-metastatic	5/33	85529/32747	3784102/1427242	0.1/2.3	0.057 (0.020-0.134)	0.053 (0.018-0.156)
Chronic pain	4/33	82848/31397	3664110/1368462	0.1/2.4	0.045 (0.013-0.114)	0.047 (0.014-0.158)
Chronic pulmonary disease	5/33	86391/33087	3821506/1439467	0.1/2.3	0.057 (0.020-0.134)	0.054 (0.018-0.161)
Chronic viral hepatitis B	5/34	84117/32214	3719193/1401721	0.1/2.4	0.055 (0.019-0.129)	0.053 (0.018-0.160)
Cirrhosis	5/34	87017/33333	3849475/1450089	0.1/2.3	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Dementia	5/33	87156/33389	3854167/1452471	0.1/2.3	0.057 (0.020-0.134)	0.053 (0.018-0.160)
Depression	4/34	83777/31648	3706196/1383785	0.1/2.5	0.044 (0.013-0.110)	0.046 (0.014-0.157)
Diabetes	5/30	47302/18218	2094424/782715	0.2/3.8	0.062 (0.021-0.147)	0.062 (0.021-0.183)
Hypertension	5/29	32948/13138	1446981/558660	0.3/5.2	0.067 (0.023-0.158)	0.059 (0.021-0.165)
Hypothyroidism	5/34	83850/31999	3709567/1396534	0.1/2.4	0.055 (0.019-0.129)	0.053 (0.018-0.157)
Inflammatory bowel disease	5/34	87112/33354	3852845/1451503	0.1/2.3	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Irritable bowel syndrome	5/34	87026/33302	3848559/1449948	0.1/2.3	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Parkinson's disease	5/32	87094/33377	3852526/1451980	0.1/2.2	0.059 (0.020-0.138)	0.056 (0.018-0.168)
Peptic ulcer disease	5/34	86563/33151	3827340/1442138	0.1/2.4	0.055 (0.019-0.129)	0.053 (0.018-0.159)
Peripheral vascular disease	5/34	87157/33393	3854333/1453141	0.1/2.3	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Psoriasis	5/34	86977/33286	3847182/1448468	0.1/2.3	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Rheumatoid arthritis	5/34	86637/33169	3833735/1444573	0.1/2.4	0.055 (0.019-0.129)	0.052 (0.017-0.157)
Schizophrenia	5/34	86821/33177	3839574/1444933	0.1/2.4	0.055 (0.019-0.129)	0.052 (0.018-0.157)
Severe constipation	5/33	81180/31292	3572990/1360978	0.1/2.4	0.058 (0.020-0.135)	0.056 (0.018-0.173)
Atrial fibrillation	4/33	86020/32994	3805102/1436321	0.1/2.3	0.046 (0.014-0.115)	0.048 (0.014-0.163)
Congestive heart failure	4/34	86774/33229	3841367/1446737	0.1/2.4	0.044 (0.013-0.111)	0.045 (0.013-0.151)
Chronic kidney disease	5/33	84005/32104	3712744/1397690	0.1/2.4	0.057 (0.020-0.133)	0.057 (0.018-0.175)
Epilepsy	5/34	87018/33284	3849893/1447965	0.1/2.3	0.055 (0.019-0.129)	0.052 (0.018-0.157)
Multiple sclerosis	5/34	87227/33399	3858436/1453185	0.1/2.3	0.055 (0.019-0.129)	0.052 (0.017-0.156)
Myocardial infarction	5/34	86850/33223	3843918/1445792	0.1/2.4	0.055 (0.019-0.129)	0.053 (0.018-0.158)
Stroke or transient ischemic attack	5/33	85169/32524	3770267/1414478	0.1/2.3	0.057 (0.019-0.133)	0.050 (0.017-0.142)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 9. Sensitivity analysis with main analysis repeated with each of the multimorbidity component chronic conditions removed (CoronaVac cohort)

Condition removed from analysis	No. events (booster/two-dose)	n (booster/two-dose)	No. person-days (booster/two-dose)	Incidence rate (booster/two-dose)	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a,b}
Alcohol misuse	26/86	94479/32109	4905985/1644784	0.5/5.2	0.101 (0.064-0.155)	0.080 (0.050-0.127)
Asthma	26/88	93284/31739	4838003/1626073	0.5/5.4	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Cancer, lymphoma	26/87	94865/32301	4925955/1654835	0.5/5.3	0.100 (0.064-0.153)	0.078 (0.049-0.124)
Cancer, metastatic	26/83	94565/32076	4911690/1643761	0.5/5.0	0.105 (0.066-0.160)	0.081 (0.050-0.129)
Cancer, non-metastatic	25/83	93481/31726	4856577/1627344	0.5/5.1	0.101 (0.063-0.155)	0.076 (0.047-0.122)
Chronic pain	26/84	90631/30745	4700488/1579422	0.6/5.3	0.104 (0.066-0.159)	0.081 (0.051-0.129)
Chronic pulmonary disease	24/83	93738/31919	4865897/1634525	0.5/5.1	0.097 (0.060-0.150)	0.077 (0.048-0.125)
Chronic viral hepatitis B	26/88	91800/31182	4755655/1598177	0.5/5.5	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Cirrhosis	24/86	94744/32243	4919687/1652441	0.5/5.2	0.094 (0.058-0.145)	0.074 (0.046-0.119)
Dementia	26/83	94789/32220	4924092/1651349	0.5/5.0	0.105 (0.066-0.161)	0.078 (0.049-0.125)
Depression	26/88	92165/31253	4782829/1604950	0.5/5.5	0.099 (0.063-0.151)	0.078 (0.049-0.123)
Diabetes	19/80	50434/17461	2594842/881557	0.7/9.1	0.081 (0.048-0.130)	0.066 (0.039-0.112)
Hypertension	18/74	34690/12533	1757183/633636	1.0/11.7	0.088 (0.051-0.143)	0.074 (0.043-0.126)
Hypothyroidism	26/87	91946/31227	4774374/1603283	0.5/5.4	0.100 (0.064-0.153)	0.079 (0.050-0.126)
Inflammatory bowel disease	26/88	94885/32309	4926333/1655254	0.5/5.3	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Irritable bowel syndrome	26/88	94791/32278	4923227/1653444	0.5/5.3	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Parkinson's disease	26/86	94786/32272	4923270/1653272	0.5/5.2	0.102 (0.064-0.155)	0.079 (0.049-0.125)
Peptic ulcer disease	25/87	94137/32059	4886309/1641915	0.5/5.3	0.097 (0.061-0.148)	0.075 (0.047-0.120)
Peripheral vascular disease	26/88	94812/32300	4922944/1655343	0.5/5.3	0.099 (0.063-0.152)	0.078 (0.049-0.124)
Psoriasis	26/88	94757/32265	4920033/1653284	0.5/5.3	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Rheumatoid arthritis	26/88	94520/32174	4908466/1649107	0.5/5.3	0.099 (0.063-0.151)	0.079 (0.049-0.125)
Schizophrenia	25/88	94536/32061	4911784/1642679	0.5/5.4	0.095 (0.060-0.146)	0.073 (0.046-0.116)
Severe constipation	24/82	89011/30559	4597038/1566071	0.5/5.2	0.100 (0.062-0.155)	0.079 (0.049-0.128)
Atrial fibrillation	24/87	93327/31845	4847615/1631784	0.5/5.3	0.093 (0.058-0.143)	0.074 (0.046-0.119)
Congestive heart failure	24/86	94417/32118	4905112/1645117	0.5/5.2	0.094 (0.058-0.145)	0.072 (0.044-0.115)
Chronic kidney disease	23/87	91594/31254	4750699/1600553	0.5/5.4	0.089 (0.055-0.138)	0.069 (0.043-0.112)
Epilepsy	26/88	94807/32227	4924668/1651391	0.5/5.3	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Multiple sclerosis	26/88	94951/32334	4930326/1656887	0.5/5.3	0.099 (0.063-0.151)	0.078 (0.049-0.124)
Myocardial infarction	26/87	94531/32129	4911021/1646115	0.5/5.3	0.100 (0.063-0.153)	0.078 (0.049-0.124)
Stroke or transient ischemic attack	25/86	92265/31294	4792902/1603501	0.5/5.4	0.097 (0.061-0.149)	0.076 (0.048-0.122)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 10. Incidence rate ratio of COVID-19-related mortality (COVID-19 positive within 7 or 14 days before death) between the booster-vaccinated and the two-dose vaccinated by vaccine type (BNT162b2 versus CoronaVac)

Vaccination	No.	No. of COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a,b}
COVID-19 within 7 days before mortality					
BNT162b2					
Two-dose	33435	22/1454857	15.1	1	1
Booster	87289	5/3860900	1.3	0.09 (0.03-0.21)	0.09 (0.03-0.30)
CoronaVac					
Two-dose	32341	69/1657144	41.6	1	1
Booster	94977	22/4931857	4.5	0.11 (0.07-0.17)	0.09 (0.05-0.14)
COVID-19 within 14 days before mortality					
BNT162b2					
Two-dose	33435	31/1454857	21.3	1	1
Booster	87289	5/3860900	1.3	0.06 (0.02-0.14)	0.06 (0.02-0.18)
CoronaVac					
Two-dose	32341	83/1657144	50.1	1	1
Booster	94977	24/4931857	4.9	0.10 (0.06-0.15)	0.08 (0.05-0.13)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 11. Incidence rate ratio of COVID-19-related mortality between the booster-vaccinated and the two-dose vaccinated by vaccine type (BNT162b2 versus CoronaVac) with index date set 14 days after booster vaccination

Vaccination	No.	No. of COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a, b}
BNT162b2					
Two-dose	27057	21/1022032	20.5	1	1
Booster	71181	4/2728630	1.5	0.07 (0.02-0.19)	0.10 (0.03-0.39)
CoronaVac					
Two-dose	27236	63/1232739	51.1	1	1
Booster	80293	22/3683044	6.0	0.12 (0.07-0.19)	0.08 (0.05-0.14)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 12. Adjusted hazard ratio of COVID-19-related mortality between the booster vaccinated and two-dose vaccinated considering the competing risk from non-COVID-19-related mortality (Fine-Gray model)

Vaccination	No.	No. of COVID-19-related deaths/ No. of non-COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unadjusted HR (95% CI) ^a	Adjusted HR (95% CI) ^{a b}
CoronaVac					
Two-dose	33435	34/100/1454857	23.4	1	1
Booster	87289	5/34/3860900	1.3	0.10 (0.06-0.15)	0.10 (0.06-0.16)
BNT162b2					
Two-dose	32341	88/153/1657144	53.1	1	1
Booster	94977	26/54/4931857	5.3	0.06 (0.02-0.14)	0.05 (0.02-0.14)

^a HR = hazard ratio; CI = confidence interval

^b Multivariable adjustment was used in the Fine-Gray regression model to adjust for potential confounding from covariates including age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Supplementary Table 13. Incidence rate ratio of COVID-19-related mortality between the booster-vaccinated and the two-dose vaccinated by vaccine type (BNT162b2 versus CoronaVac) with those with a COVID-19 history before the second dose excluded

Vaccination	No.	No. of COVID-19-related deaths/No. person-days	No. of events per one-million-person-days	Unweighted IRR (95% CI) ^a	Weighted IRR (95% CI) ^{a b}
BNT162b2					
Two-dose	33418	34/1454003	23.4	1	1
Booster	87284	5/3860656	1.3	0.06 (0.02-0.13)	0.05 (0.02-0.16)
CoronaVac					
Two-dose	32315	88/1655230	53.2	1	1
Booster	94971	26/4931538	5.3	0.10 (0.06-0.15)	0.08 (0.05-0.12)

^a IRR = incidence rate ratio; CI = confidence interval

^b Propensity score-based inverse probability of treatment weighting was used to weight the sample according to age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date

Appendix I – Data sources

Routine healthcare records provided by the Hospital Authority of Hong Kong were linked with population-based vaccination records at the Department of Health to identify COVID-19 vaccine recipients with multimorbidity. Matching between electronic health records and vaccination records was based on the anonymized Hong Kong Identity Number or other personal identification document numbers, such as foreign passports numbers, conducted by the Hospital Authority and the Department of Health.

The Hospital Authority serves as the sole provider of public inpatient services and a major provider of outpatient services in Hong Kong, with a comprehensive electronic health record system for facilitation of clinical management. Each resident has a unique Identity Number which allowed the Hospital Authority to create a unique anonymized reference key for each patient to link attendances to all public healthcare facilities. The electronic health records include demographics, diagnoses, medication dispensing records, outpatient and primary care clinics, emergency room attendances, laboratory tests and hospitalization details. The data from Hospital Authority has frequently been used for high-quality pharmacovigilance studies to evaluate the safety of medicines and vaccines at population level.¹⁻⁸ Previous research showed high coding accuracy for various health outcomes in the electronic health record of the Hospital Authority based on the International Classification of Diseases, Ninth Revision.⁹⁻¹¹ Our database was updated to 31 March 2022.

Appendix II - Analysis

1. Main analysis

Stratified by vaccine type (BNT162b2 versus CoronaVac), propensity score-based inverse-probability-of-treatment weighted Poisson regression was used to estimate the weighted incidence rate ratio (IRR) of mortality related to COVID-19 between those who received the booster dose and those who received only two doses.

Covariates for the weighting included age, sex, time from second dose to index (or pseudo index) date (days), each of the 30 conditions used to define multimorbidity, as well as a range of chronic medications within one year prior to the index (or pseudo index) date, namely, renin-angiotensin-system agents, beta blockers, calcium channel blockers, diuretics, nitrates, lipid lowering agents, insulins, antidiabetic drugs, antiarrhythmic drugs, oral anticoagulants, antiplatelets, steroids, antidepressants, antiviral drugs, antibacterial drugs, and immunosuppressants.

2. Subgroup and extended analyses

In a subgroup analysis, we only included those aged 60 years^{12, 13} or older to assess potential differences between the older and middle-aged or younger adults. The potential interaction between booster vaccination and age (as a continuous variable) was tested in a multivariable Poisson regression including participants of all age ranges. To enable a cross-platform comparison, we used propensity score-based (multinomial logistic regression) inverse probability of treatment weighting for multiple treatments to generate IRRs for each group using the two-dose CoronaVac group as the referent (IRR = 1). In addition, we repeated the main analysis on those receiving heterologous booster vaccination, i.e., BNT162-BNT162b2-CoronaVac and CoronaVac-CoronaVac-BNT162b2 compared with the two-dose vaccinated. As an extended analysis, we further investigated the outcome of SARS-CoV-2 infection indicated by a positive polymerase chain reaction test result in a public healthcare facility, with the same methods in the main analysis.

3. Sensitivity analyses

As a sensitivity analysis, the main analyses were repeated using a leave-one-out approach, i.e., 30 times with each component disease removed from the list used to define multimorbidity to observe any changes in the incidence rate ratios. Another set of analyses with COVID-19-related mortality indicated by positive polymerase chain reaction test result within seven and 14 days before death rather than 28 days was conducted to test for robustness with the variation in the outcome definition. In addition, repeated analysis was conducted with index (and pseudo index) date being set 14 days following the booster vaccination date or the original pseudo index date for the comparison cohort as vaccination typically takes a couple of weeks to take effect.¹⁴ Considering the potential impact of non-COVID-19-related mortality, we further conducted a Fine-Gray model to estimate adjusted hazard ratios between the booster vaccinated and two-dose vaccinated. Lastly, we repeated the analysis excluding those with a history of COVID-19 indicated by a positive polymerase chain reaction test result before the second dose.

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