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Article

Impact of COVID-19 Vaccination on Healthcare Worker Infection Rate and Outcome during SARS-CoV-2 Omicron Variant Outbreak in Hong Kong

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Abstract: Immune escape is observed with SARS-CoV-2 Omicron (Pango lineage B.1.1.529), the predominant circulating strain worldwide. Booster dose was shown to restore immunity against Omicron infection, however, real world data comparing mRNA (BNT162b2; Comirnaty) and inactivated vaccine (CoronaVac; Sinovac) homologous and heterologous boosting is lacking. A retrospective study was performed to compare the rate and outcome of COVID-19 in healthcare workers (HCWs) with various vaccination regime during a territory-wide Omicron outbreak in Hong Kong. During the study period 1 Feb – 31 Mar 2022, 3167 HCWs were recruited, 871 HCWs reported 746 and 183 episodes of significant household and non-household close contact. 737 HCWs acquired COVID-19 which were all clinically mild. Time dependent Cox regression showed that, comparing with 2-dose vaccination, 3-dose vaccination reduced infection risk by 31.7% and 89.3% in household contact and non-household close contact respectively. Using 2-dose BNT162b2 as reference, 2-dose CoronaVac recipient had significantly higher risk of being infected (HR 1.69 P<0.0001). Three-dose BNT162b2 (HR 0.4778 P< 0.0001) and 2-dose CoronaVac + BNT162b2 booster (HR 0.4862 P=0.0157) were associated with lower risk of infection. Three-dose CoronaVac and 2-dose BNT162b2 + CoronaVac booster were not significantly different from 2-dose BNT162b2. The mean time to achieve negative RT-PCR or E gene cycle threshold 31 or above was not affected by age, number of vaccine dose taken, vaccine type and timing of the last dose. In summary, we have demonstrated lower risk of breakthrough SARS-CoV-2 infection in HCWs given BNT162b2 as booster after 2 doses of BNT162b2 or CoronaVac.

Keywords: SARS-CoV-2; Omicron variant of concern; homologous boosting; heterologous boosting; CoronaVac; BNT162b2; healthcare worker; return-to-work

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1. Introduction

As of the end of Jun 2022, SARS-CoV2 has caused over 500 million cumulative cases of COVID-19 and over 6 million deaths across the globe. [1] Vaccination is considered the most important tool in controlling the pandemic. Omicron (Pango lineage B.1.1.529) variant of concern (VOC) emerged since Nov 2021 in South Africa and soon became the predominant circulating strain worldwide, replacing Alpha, Beta, Gamma and Delta which are now categorized as 'previously circulating VOC'. [1] Waning immunity after vaccination and immune escape from Omicron VOC has rendered various vaccine platforms less effective [2-4], however homologous and heterologous boosting were shown to restore immunity against infection by raising neutralizing activity and T-cell response. [5-8]

Two types of vaccines are available in Hong Kong since early 2021: inactivated COVID-19 Vaccine (CoronaVac; Sinovac), mRNA Vaccine (BNT162b2; Comirnaty). As a result of vaccine hesitancy in the general public, Hong Kong was severely hit by Omicron since late Jan 2022 – "the fifth wave". Daily new cases surged exponentially from few hundred in early Feb to over 70,000 in early March, overwhelming both routine and emergency medical care as well as isolation facilities. [9-11] By the end of Jun 2022, 1.2 million infections were reported in Hong Kong during the fifth wave, resulted in over 9,000 deaths with the majority being elderly with incomplete or no vaccination. [12,13]

HKSH Medical Group, with more than 3100 clinical and non-clinical healthcare workers, provides service to the public via a network of a 600-bed acute hospital (Hong Kong Sanatorium and Hospital), 2 oncology centres and 4 outpatient centres located on different parts of the Hong Kong Island. In responses to the fifth wave, HKSH implemented a series of enhanced measures to prevent nosocomial SARS-CoV-2 transmission through 1/ optimization of staff vaccination rate, 2/ enhancing COVID-19 surveillance (mandatory reverse transcription-polymerase chain reaction [RT-PCR] pre-admission screening for all patients and those who required mask-off procedures; mandatory regular screening for staffs using rapid antigen test [RAT], 3/stringent contact tracing and testing policy. We performed a retrospective study to evaluate the effect of COVID-19 vaccination on staff infection rate, their outcome and time to return-to-work. The study was approved by the Research Ethics Committee of the HKSH Medical Group (REC-2022-05).

2. Materials and Methods

2.1. Recruitment and definitions

All full-time staffs of HKSH with no history of COVID-19 before 1st Feb 2022 were recruited. Their demographics, job category and COVID-19 vaccination history were retrieved from employment record and hospital vaccine record. A case of COVID-19 was defined as RT-PCR or RAT confirmed infection between 1 Feb – 31 Mar 2022.

To evaluate the effect of vaccination on infection rate, the dose of vaccine given within the 14-day period before COVID-19 confirmation was disregarded. Incomplete vaccination was defined as receipt of less than 2 doses; while receipt of 2 or more doses was defined as fully vaccinated. Severe COVID-19 was defined as any case who required oxygen therapy or hospitalization.

For evaluation of time to return-to-work, we only included staffs who were fully vaccinated and diagnosed 26 Feb – 31 Mar 2022. This is because prior to this period, all infected persons in Hong Kong were required to undergo 14-day isolation in community isolation facilities (CIF) or Hospital Authority (HA) hospitals as required by the Department of Health, HKSAR. From 26 Feb 2022 onwards, infected persons may discontinue isolation at their premises after 2 successive negative RAT on day 6 and 7 should they have received at least two doses of COVID-19 vaccines.

2.2. Data collection and follow-up testing for confirmed healthcare worker

COVID-19 confirmed cases were required to provide clinical information including symptoms, onset date, reasons for testing, RAT result (if performed) and exposure history

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via a standard online questionnaire. Upon resolution of fever and improvement of symptoms, fully vaccinated staff underwent RAT on 2 consecutive days, earliest on day 6 and 7 (Day 0 = first specimen with positive RT-PCR). RT-PCR was performed on the 2nd day of negative RAT. For infected staffs with incomplete vaccination, the earliest negative RAT results accepted for RT-PCR testing were day 13 and 14. A negative RT-PCR or a positive RT-PCR with E gene cycle threshold (Ct) value of 31 or above were used as criteria for return-to-work. If the cycle Ct value was less than 31, RT-PCR was repeated daily until it was 31 or above.

2.3. Staff reporting close contact with confirmed COVID-19

Staffs who had exposure to confirmed COVID-19 were requested to inform infection control team (ICT) for risk assessment. Those with significant exposure according to our infection control guideline (annex 1) were offered serial RT-PCR on day 1, 4, 8 (day 1 = exposure day) to rule out infection. Duty could be resumed if day 4 RT-PCR was negative but daily RAT was required till negative RT-PCR on day 8.

2.4. Mandatory RAT COVID-19 screening for staff

RAT screening every 3 days (8 – 15 Feb 2022), everyday (16 – 28 Feb 2022), on alternate days (1 Apr 2022 onward) was mandatory for all clinical and non-clinical staffs before starting their duty. The RAT screening frequency was adjusted according to the intensity of transmission in local community and recommendation from our ICT. Staffs with compatible symptoms but negative RAT were offered RT-PCR to rule out infection.

2.5. Rapid antigen test and reverse transcription-polymerase chain reaction (RT-PCR)

RAT was performed exclusively using nasal swab by INDICAID® COVID-19 Rapid Antigen Test which is an immunochromatographic membrane assay intended for the qualitative detection of SARS-CoV-2 nucleocapsid antigens. The tests were performed according to manufacturer's recommendation and our previous publication. [14]

SARS-CoV-2 RT-PCR was performed using combined nasal and throat swab by detection of virus N gene, E gene, RdRp gene, S gene, M gene or ORF1ab gene using different platforms including Abbott Alinity m, TIB MolBiol/FujiFilm Wako coupled with Roche qPCR platforms, DiaSorin, Cepheid GeneXpert and BioFire FilmArray. All SARS-CoV-2 positive specimen were confirmed by more than one platform and submitted to reference laboratory for final confirmation. The tests were performed according to the manufacturers' recommendation. Specimen from recovering HCWs were tested by Cepheid GeneXpert exclusively for E gene Ct value.

2.6. Statistical analysis

Demographics, history of significant SARS-CoV-2 exposure and rate of COVID-19 were tested using t-test and Fisher's exact test/Chi-squared test. Since vaccination was ongoing during the study period, the study was crossover in nature. To compare the effect of 3-dose, 2-dose group and specific regimes, these variables were treated as a time-varying covariate. Time dependent Cox regression model was used to model dose effect on time to SARS-CoV-2 infection. Time Dependent Cox regression was computed using R software version 4.1.0. [15] The hazard ratio plot was created by R package "survminer". [16]

3. Results

3.1. Demographics and vaccination history

After excluding 8 staffs who had history of COVID-19 before 1 Feb 2022, 3167 staffs (2329, 73.6% female) were included in the analysis of vaccination effectiveness. By 1 Feb 2022, the first day of study period, 2953 (93.2%) were regarded as fully vaccinated (received at least 2 doses). By 31 Mar 2022, the last day of study period, 3103 (98.0%) had received at least 2 doses while booster dose (3rd dose) were given to 1435 (45.3%). One

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hundred and sixty (5.1%) received heterologous boosting while 983 (31.3%) and 291 (9.2%) received homologous boosting with BNT162b2 and CoronaVac respectively. (Table 1)

3.2. Breakthrough COVID-19 and symptoms

During the study period (1 Feb – 31 Mar 2022), 737 staffs acquired COVID-19 which accounted for 23.3% of all full-time employee. The majority were female (80.9%), with a mean age of 37.7 years. COVID-19 was confirmed by RAT alone in 298 (40.4%), RT-PCR alone in 220 (29.9%), both RAT and RT-PCR in 219 (29.7%). New onset of COVID-19 related symptom (53.8%) was the most common reason for testing that led to diagnosis of COVID-19, followed by exposure history to a confirmed/ suspected case (43.3%). At the time of data collection, the majority (n=649, 88.1%) were symptomatic, with sore throat (81.1%) coughing (60.6%) and running nose (46.7%) being the most common symptoms. All of them had mild disease and none required hospitalization. (Table 2)

3.3. Significant SARS-CoV-2 exposure, vaccination regime and risk of COVID-19

A total of 871 staffs (701, 80.48% female) reported 746 and 183 episodes of significant household and non-household close contact. There was no significant nosocomial exposure. Demographics, nature of exposure and rate of COVID-19 stratified by vaccination regime is shown in table 3. Three-dose regimes were associated with lower incidence of COVID-19 than 2-dose regime. Ninety staffs who had incomplete vaccination (0-1 dose) were excluded from further analysis of vaccine effectiveness. Another 5 staffs with uncommon vaccine combination were also excluded. (Footnote of table 3)

Time dependent Cox regression showed that 3-dose vaccination reduced risk of infection by around 50% (hazard ratio 0.5339 P<0.0001) when compared with 2-dose vaccination. Female had significantly higher risk than male (HR 1.43 P=0.0005) while age and job category (clinical vs non-clinical) had no significant effects on infection risk. Household close contact was associated with the highest risk of infection (HR 4.81 P<0.0001) while the risk from non-household close contact is only similar to those with no known close contact. (Table 4 and figure 1) Comparing with 2-dose vaccination, 3-dose vaccination was found to reduce infection risk by 31.7%, 89.3%, 58% in household contact, non-household close contact, and no known contact group respectively. (Table 5)

Further regression analysis (using 2-dose BNT162b2 as reference) showed that 2-dose CoronaVac had significantly higher risk of being infected (HR 1.69 P<0.0001). Three-dose BNT162b2 (HR 0.4778 P< 0.0001) and 2-dose CoronaVac + BNT162b2 booster (HR 0.4862 P=0.0157) were associated with lower risk of infection. Three-dose CoronaVac and 2-dose BNT162b2 + CoronaVac booster were not significantly different from 2-dose BNT162b2. (Table 6, figure 2)

3.4. Time to achieve RAT negative and RT-PCR criteria for return-to-work

During the study period (26 Feb – 31 Mar 2022), 422 recovering staffs, who were previously fully vaccinated, were included in the return-to-work analysis. The mean time taken to achieve 2 consecutive negative RAT was 9.76 days. Upon 2 consecutive negative RAT, only 310 (73 %) fulfilled RT-PCR criteria (negative or E gene Ct value 31 or above) for return-to-work. (Figure 3) The mean time for return-to-work based on RT-PCR criteria was 10.1 days and was not affected by age, number of vaccine doses taken, vaccine type and timing of the last dose. (Table 7).

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Table 1. Vaccination status of 3167 hospital staffs before and at the end of study period.

No. of doses received	Total no. of staff (%) N=3167	No. of staff (%)						
		Non-mixed vaccine platform				Mixed vaccine platform		
		BNT162b2	CoronaVac	mRNA-1273	Sinopharm-CoronaVac	BNT162b2-CoronaVac	BNT162b2-BNT162b2-CoronaVac	CoronaVac-CoronaVac-BNT162b2
Vaccination status as at 1 Feb 2022								
1	126 (3.98%)	83 (2.62%)	43 (1.36%)					
2	2439 (77.01%)	2076 (65.55%)	359 (11.34%)	1 (0.03%)	1 (0.03%)	2 (0.06%)		
3	514 (16.23%)	230 (7.26%)	172 (5.43%)				5 (0.16%)	107 (3.38%)
Vaccination status as at 31 Mar 2022								
1	35 (1.11%)	20 (0.63%)	15 (0.47%)					
2	1669 (52.70%)	1419 (44.81%)	245 (7.74%)	1 (0.03%)	1 (0.03%)	3 (0.09%)		
3	1434 (45.28%)	983 (31.04%)	291 (9.19%)				11 (0.35%)	149 (4.70%)

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Table 2. Demographics and symptoms of staff with COVID-19 during the study period.

			No. of staff (%) N=737
Female			596 (80.9%)
Age (years)	Mean +/- SD	37.7±10.5	
	Median	36	
Staff category	Clinical		576 (78.15%)
		Doctor	6 (0.81%)
		Nurse	270 (36.64%)
		Supporting Staff	250 (33.92%)
		Allied Health	50 (6.78%)
	Non-clinical		161 (21.85%)
		Supporting Staff	87 (11.80%)
		Engineer/Technician	21 (2.85%)
		Food and beverage	53 (7.19%)
Positive RAT at the time of COVID-19 confirmation			517 (70.15%)
Positive RT-PCR at the time of COVID-19 confirmation			439 (59.57%)
Having at least 1 COVID-19 related symptom #			649 (88.06%)
Reason for undergoing the index COVID-19 testing *	New onset of COVID-19 related symptom		349 (53.78%)
	Contact with a confirmed case		215 (33.13%)
	Contact with a person with sign/ symptom of COVID-19		66 (10.17%)
	Government gazettes compulsory testing notice		16 (2.47%)
	Hospital regular rapid antigen test		173(26.66%)
Symptom(s) reported *			
	Sore throat/ throat discomfort		368 (81.06%)
	Cough		275 (60.57%)
	Running nose		212 (46.69%)
	Fatigue		195 (42.95%)
	Headaches		190 (41.85%)
	Fever		188 (41.41%)
	Body aches		158 (34.80%)
	Chills		129 (28.41%)
	Dizziness		57 (12.56%)
	Diarrhea		41 (9.03%)
	Shortness of breath		30 (6.61%)
	Vomiting		18 (3.96%)
	Loss of taste		12 (2.64%)
	Hoarse of voice		6 (1.32%)
	Sputum		5 (1.10%)
	Stuffy nose		5 (1.10%)
	Loss of smell		2 (0.44%)
	Earache		1 (0.22%)

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Bone pain	1 (0.22%)
Nausea	1 (0.22%)

At the time of online questionnaire submission

* More than 1 response was allowed

(Abbreviation: RAT, rapid antigen test; RT-PCT reverse transcription-polymerase chain reaction)

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Table 3. Demographics, history of significant exposure and rate of COVID-19 stratified by vaccination regime.

		Vaccination regime #						p-value ^		
		3-dose regime			2-dose regime					
		BBB	CCC	CCB	BBC	BB	CC	Comparing 3-dose to 2-dose regime as a whole	Comparing within 3-dose regime	Comparing within 2-dose regime
COVID-19 positive rate		4.83%	15.23%	8.70%	12.50%	30.15%	43.01%			
No. of COVID-19/ total vaccinated		37/766	39/256	12/138	1/8	490/1625	120/279	<0.0001	<0.0001	<0.0001
No. of female (%)		514 (67.10%)	159 (62.10%)	91 (65.94%)	5 (62.5%)	1268 (78.03%)	208 (74.55%)	<0.0001	0.5144	0.2141
Mean age (years)		42.35	49.88	50.07	46.38	34.89	44.95	<0.0001	<0.0001	<0.0001
Staff category (%)	**Clinical** (vs non-clinical)	588 (76.76%)	194 (75.78%)	107 (77.54%)	7 (87.5%)	1323 (81.42%)	209 (74.91%)	0.0137	0.9352	0.0141
No. of staff reported significant exposure (%)	Household contact only	91 (11.88%)	44 (17.19%)	24 (17.39%)	0	427 (26.28%)	80 (28.67%)	<0.0001	0.3979	0.3904
	Non-household close contact only	20 (2.61%)	6 (2.34%)	5 (3.62%)	0	81 (4.98%)	9 (3.23%)			
	Both household & non-household close contact	11 (1.44%)	4 (1.56%)	2 (1.44%)	0	34 (2.09%)	3 (1.08%)			

5 cases of BNT162b2-CoronaVac, mRNA-1273, Sinopharm-CoronaVac excluded; 90 cases of incomplete vaccination (0 or 1 dose) excluded

^ Using t-test/Fisher's exact test

(Abbreviation: BBB, BNT162b2-BNT162b2-BNT162b2; CCC, CoronaVac-CoronaVac-CoronaVac; CCB, CoronaVac-CoronaVac-BNT162b; BBC, BNT162b2-BNT162b2-CoronaVac; BB, BNT162b2- BNT162b2; CC, CoronaVac-CoronaVac)

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Table 4. Time Dependent Cox regression analysis on risk of acquiring COVID-19.

	estimate	hazard ratio	p-value	95% CI of hazard ratio
3-dose vaccination (2-dose vaccination as reference)	-0.6276	0.5339	<0.0001	(0.420,0.679)
Non-clinical staff (Clinical staff as reference)	0.1778	1.1945	0.0700	(0.986,1.448)
Female staff (Male staff as reference)	0.3596	1.4328	0.0005	(1.172,1.752)
Age	-0.0019	0.9981	0.6296	(0.991,1.006)
Close contact history (no known close contact as reference)				
- Household close contact only	1.5712	4.8126	<0.0001	(4.121,5.621)
- Non-household close contact only	0.3789	1.4607	0.0656	(0.976,2.186)
- Both household and non-household close contact	0.6426	1.9013	0.0193	(1.110,3.258)

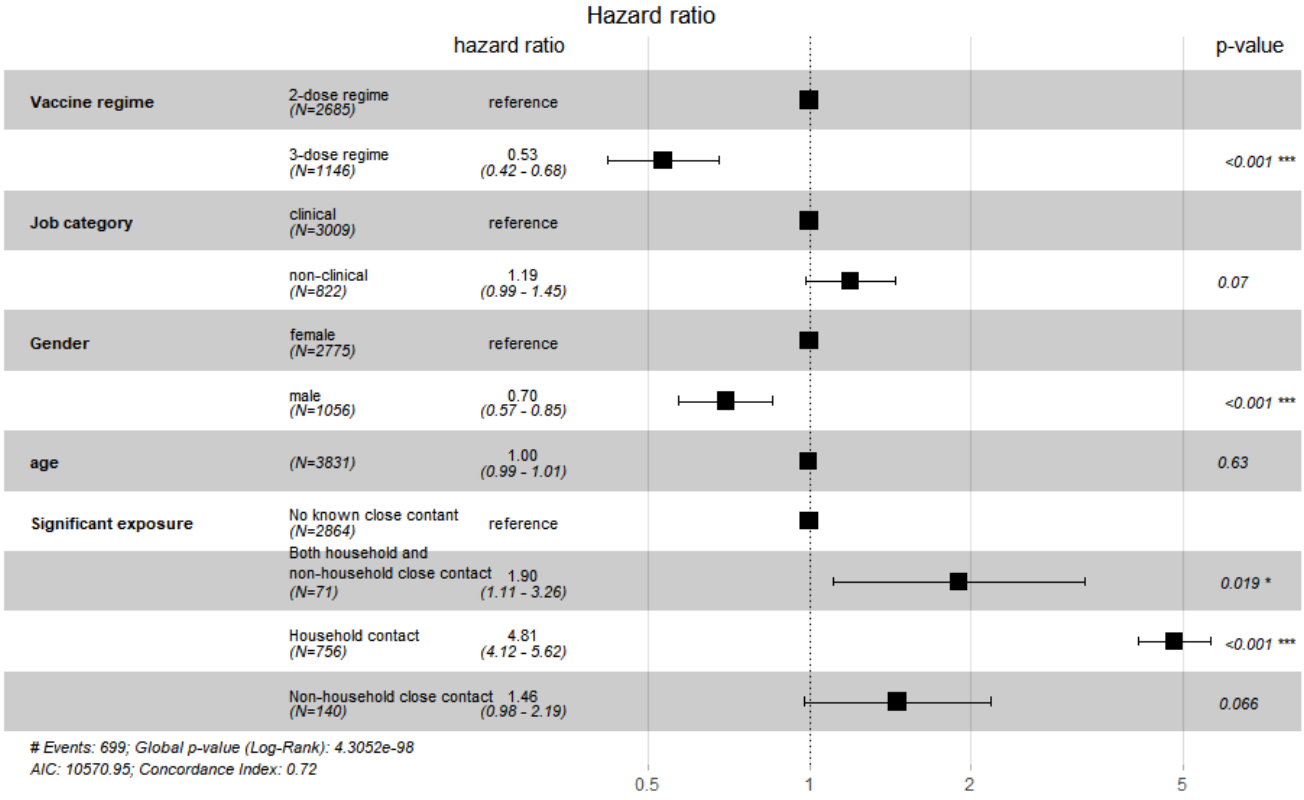

Figure 1. Hazard ratio for COVID-19 and associated 95% confidence interval.

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Table 5. Time Dependent Cox regression analysis on effect of 3-dose vs 2-dose regime on risk of acquiring COVID-19 in household and non-household close contact setting.

	Estimate* (3-dose vs 2-dose)	hazard ratio	p-value	95% CI of hazard ratio
Household contact only	-0.3814	0.6829	0.0248	(0.490,0.953)
Non-household close contact only	-2.2282	0.1077	0.0355	(0.014,0.859)
Both household and non-household close contact**	-0.3925	0.6754	0.652	(0.123,3.717)
No known close contact	-0.8686	0.4196	<0.0001	(0.293,0.601)

*Other variables included job category, gender and age.

**All infected are female.

Table 6. Time Dependent Cox regression analysis on risk of acquiring COVID-19 with different vaccination regime*.

	estimate	hazard ratio	p-value	95% CI of hazard ratio
Vaccination regime (BB as reference)				
- CC	0.5267	1.6933	<0.0001	(1.370,2.093)
- BBB	-0.7385	0.4778	<0.0001	(0.336,0.679)
- BBC	0.2995	1.3491	0.7652	(0.189,9.627)
- CCB	-0.7211	0.4862	0.0157	(0.271,0.873)
- CCC	-0.0760	0.9269	0.6715	(0.653,1.317)

*Other variables included job category, gender, age and exposure history are not shown

(Abbreviation: BBB, BNT162b2-BNT162b2-BNT162b2; CCC, CoronaVac-CoronaVac-CoronaVac; CCB, CoronaVac-CoronaVac-BNT162b; BBC, BNT162b2-BNT162b2-CoronaVac; BB, BNT162b2- BNT162b2; CC, CoronaVac-CoronaVac; B, BNT162b2; C, CoronaVac)

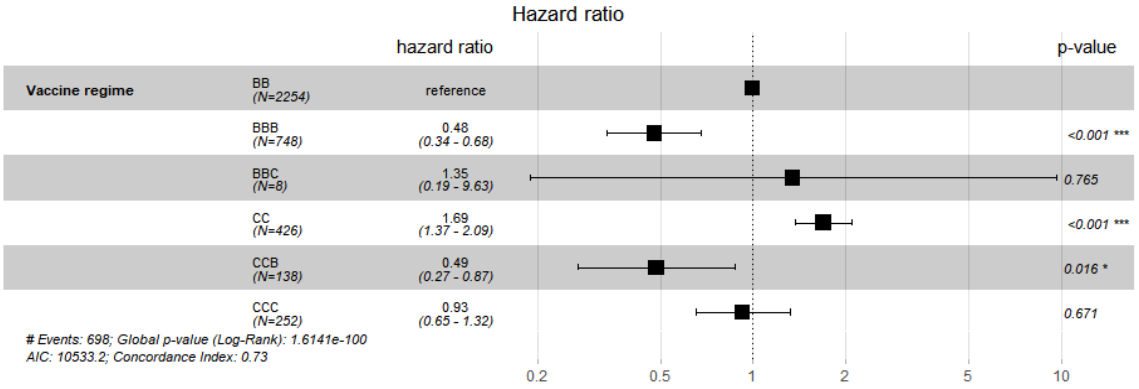

Figure 2. Hazard ratio for COVID-19 and associated 95% confidence interval for different vaccine regime using 2-dose BNT162b2 as reference.

(Abbreviation: BBB, BNT162b2-BNT162b2-BNT162b2; CCC, CoronaVac-CoronaVac-CoronaVac; CCB, CoronaVac-CoronaVac-BNT162b; BBC, BNT162b2-BNT162b2-CoronaVac; BB, BNT162b2-BNT162b2; CC, CoronaVac-CoronaVac; B, BNT162b2; C, CoronaVac).

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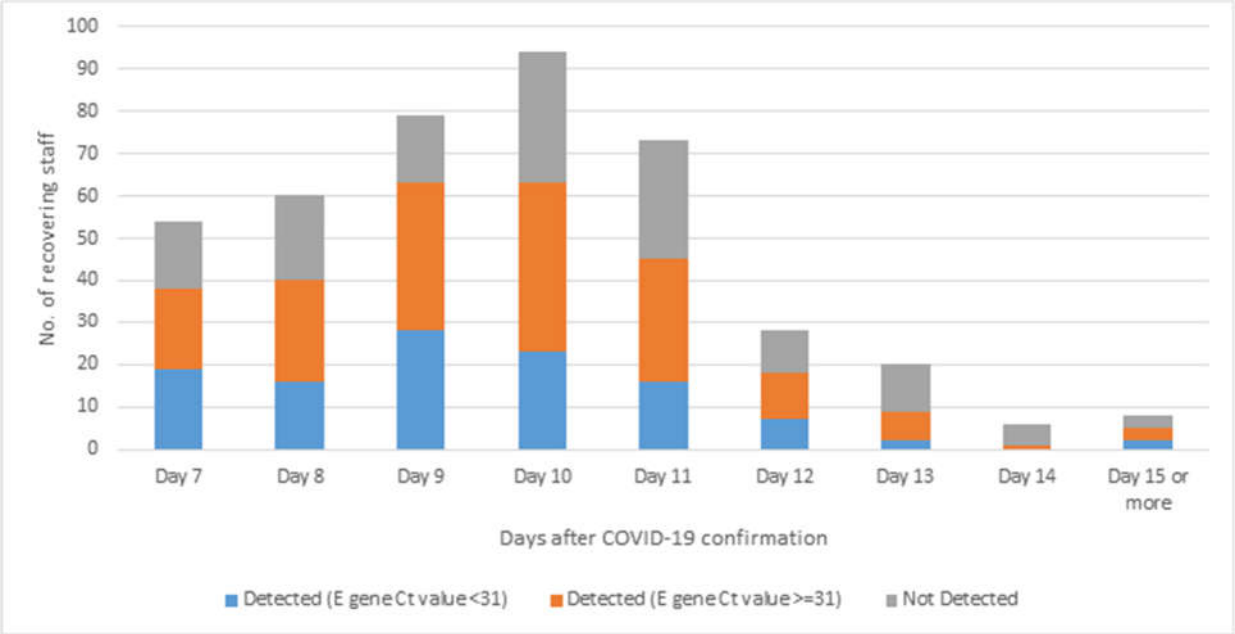

Figure 3. 1st RT-PCR result after 2 consecutive negative rapid antigen test in recovering staffs who were previously fully vaccinated (N= 422).

Table 7. Association between vaccine regime, gender, age and time taken to return-to-work after COVID-19 #.

		N	Mean no. of days taken to fulfil RT-PCR criteria for return-to-work #	P-value *
Vaccine regime	3-dose	423	9.85	0.15
	2-dose		10.20	
	2 or 3 doses BNT162b2	423	10.13	0.8
	2 or 3 doses of CoronaVac		10.08	
	BNT162b2 as 3rd dose	60	9.95	0.865
	CoronaVac as 3rd dose		10.04	
	Last dose within 180 days of COVID-19	423	10.19	0.206
	Last dose > 180 days before COVID-19		9.92	
Gender	Male	423	9.8	0.088
	Female		10.19	
Age	50 years or above	423	10.2	0.676
	Below 50 years		10.1	

* Using t-test

COVID-19 recovered staff with negative RT-PCR or a positive test with E gene Ct value 31 or above can return to work

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4. Discussion

To our knowledge, this is the first study comparing the efficacy of different combination of mRNA and inactivated COVID-19 vaccine in healthcare worker. Our cohort is a relatively young population with high vaccination rate. Since all of our staffs acquired infection from the community, the incidence during the fifth wave mirrored the intensity of SARS-CoV-2 transmission in the general public. By the end of March 2022, the number of confirmed case (by RT-PCR and RAT) in Hong Kong reached 1,164,138 which accounted for 15% of Hong Kong's population. [17] Using mathematical modelling, local epidemiologist estimated 4 million, 60% of the population, had acquired COVID-19 in the same period. With our intense surveillance and testing strategy, we showed that infection rate was 23.3% among our staffs. The lower infection rate was likely due to high vaccination rate and more stringent infection prevention behaviour influenced by their medical background or training. The overrepresentation of female in our cohort and in close contact groups had likely resulted in seemingly increased risk of COVID-19 in female HCWs. The absence of severe case was likely a result of high vaccination coverage and more importantly, relatively young mean age of 37.7 years. The proportion of asymptomatic infection in our cohort was lower than studies described previously from South Africa (23%) and China (46.7%) but was similar to a cohort of healthcare personnel from New York (11%) during Omicron epidemic. [19, 20, 21] The actual proportion of asymptomatic infection in our cohort could be overestimated as the clinical data could have been submitted during pre-symptomatic stage of infection. Although being symptomatic and having exposure history were the most common reasons for undergoing testing, regular mandatory RAT played an important role in promote testing as up to 26.66% of the infected staff were identified as a result of such policy. This could have identified early infection and prevented onward transmission among staffs and patients.

Two types of vaccines are available in Hong Kong since early 2021: inactivated COVID-19 Vaccine (CoronaVac; Sinovac), mRNA Vaccine (BNT162b2; Comirnaty). Although BNT162b2 was found to elicit a more robust humoral response and a higher vaccine effectiveness (VE) against symptomatic infection, both vaccines were shown to be effective in preventing hospitalization and death in the pre-Omicron era [22-24]. As a result of the large number of amino acid substitutions in the receptor-binding domain of spike protein, Omicron VOC is capable of evading immunity from previous vaccination or infection. [25] Reduced VE associated with 2-dose vaccination and immune waning over time were evident. In South African, where Omicron was first identified, VE of 2 doses of BNT162b2 was found to decline from 93% during comparator period to 70% shortly after Omicron had become the dominant strain. [26] Similar decline in VE was observed in different countries when 'previously circulating VOC' were taken over by Omicron. [27, 28] Real world data for CoronaVac's VE against Omicron is scarce. In a study conducted between 6 December 2021 and 26 February 2022 during the Omicron outbreak in Chile, the estimated VE was modest at 38.2% (95% confidence interval [CI], 36.5–39.9) against symptomatic COVID-19 in children 3-5 years of age, although protection against hospitalization and ICU admission remained around 60%. [29] A study from Hong Kong found that 2 doses of BNT162b2 or CoronaVac vaccines provided inadequate 50% plaque reduction neutralization test (PRNT50) antibody immunity against the Omicron variant. Furthermore, only 1 out of the 30 individuals in the COVID-19 convalescent cohort at 4.8–6.5 months post-symptom onset met the protective antibody threshold for the Omicron variant. [30]

To combat the problem of waning immunity and immune escape associated with Omicron variant, booster dose is now widely administered in many countries to restore protection against COVID-19. In Hong Kong, based on the latest available evidence and expert opinion, 3rd dose CoronaVac can be given to 3 years of age or older while 3rd dose BNT162b2 can be given to 5 years of age or older. [32] Additional protection of 3-dose BNT162b2 vaccination is well established with consistent data from multiple large-scale studies. In United Kingdom, vaccine effectiveness against Omicron after two BNT162b2

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doses declined to 8.8% (95% CI, 7.0 to 10.5) at 25 or more weeks and a booster dose increased VE to 67.2% (95% CI, 66.5 to 67.8) at 2 to 4 weeks. [27] In Qatar, BNT162b2 effectiveness was highest at 46.6% (95% CI: 33.4–57.2%) against symptomatic BA.1 and at 51.7% (95% CI: 43.2–58.9%) against symptomatic BA.2 infections in the first three months after the second dose, but declined to ~10% or below thereafter. Effectiveness rebounded to 59.9% (95% CI: 51.2–67.0%) and 43.7% (95% CI: 36.5–50.0%), respectively, in the first month after a booster dose. [26] In our study, the lowest COVID-19 incidence in the 3-dose BNT162b2 group is consistent with these overseas data.

For individuals who completed 2 doses of CoronaVac, using live virus neutralization assay, heterologous boosting with BNT162b2 was found to induce a better neutralizing antibody titre against Wild type, Beta, Delta and Omicron variant than homologous boosting. [30, 33] Using a surrogate neutralizing antibody immunoassay, our group have previously demonstrated in individuals who had negative neutralizing antibody after 2 doses of CoronaVac (primary non-responder or waned antibody), BNT162b2 booster induced a significantly higher percentage of positive neutralizing antibody against Delta and Omicron variant than CoronaVac booster. Using an interferon-gamma release assay, BNT126b2 booster was also found to induce a better T-cell response. [34] Our current study has provided real world data on enhanced protection against Omicron with heterologous boosting after 2 doses of CoronaVac. We showed that 3-dose vaccination significantly reduced the chance of COVID-19 and according to regression analysis, the effect mainly came from BNT162b2 booster. Large scale case control or prospective study is needed to confirm the benefit of mRNA vaccine over inactivated vaccine as booster.

For infected staff to return to work, we took a more stringent approach by using RT-PCR criteria since Ct value strongly correlates with the presence of live virus in individuals with SARS-CoV-2 infection. [35] A study had shown that E gene Ct value of >30 was associated with reduced infectivity and secondary transmission rate. [36] Although negative RATs can be used as a surrogate for reduced infectivity and have been used to end isolation for general public, the performance of our RAT kit (INDICAID COVID-19 Rapid Antigen Test) has not been thoroughly evaluated with respect to such purpose, moreover, RAT sensitivity could be affected by sampling technique. [37] We believe a more stringent approach should be taken for recovering healthcare work to prevent nosocomial transmission. In a viral shedding kinetics study of 45 patients infected with Delta variant, viable virus in cell culture was detected for notably shorter duration in those fully vaccinated. [38] Viral dynamic study from United States and Singapore performed in pre-Omicron era also showed shorter viral clearance time in vaccinated individuals. [39, 40] However, we were not able to demonstrate any difference in the time required to return-to-work with different vaccination regime, nor it was related to age or gender. We postulate this could be due to less effective clearance of Omicron variant by mismatched antibody induced from vaccines using wild type target.

Our study has several limitations: first, our cohort is retrospective in nature with a small sample size and a relatively young age, so the result may not be generalizable to <18 years of age or elderly population. Second, because of the medically trained background, infection prevention practices and risk avoidance behavior may be more meticulous comparing to general public during social activity or within a household especially when there is a confirmed/ suspected case. Third, despite a well-defined definition for significant exposure, we were not able to further quantify the intensity of exposure especially in the context of household contact e.g. continued sharing of toilet in the same apartment was unavoidable for many while some could temporary relocate away from the index case. Fourth, medical history of the participants was not available, although the number of immunocompromised individuals would be extremely small and may not impact the final result. Finally, virus sequencing data was not available and we cannot not rule out the possibility of non-Omicron variant in our cohort. In conclusion, we have demonstrated reduction of breakthrough SARS-CoV-2 infection in healthcare workers with homologous or heterologous BNT162b2 boosting in a territory-wide Omicron outbreak.

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Data Availability Statement: The data used to support the findings of this study are included within the article.

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Annex 1

General guidance on COVID-19 contact tracing for HKSH staff

Contact tracing period: 2 days before symptom onset of the index or 2 days before a positive test (RT-PCR or RAT) if index is asymptomatic until the index is considered no longer infectious according to latest guideline from Centre of Health Protection (CHP) of HKSAR.

1. Definition of significant household contact

- Normally sharing a residence with a person who has tested positive.
- Spending at least one night or day (more than 8 hours) in that residence with the index during contact tracing period

2. Definition of significant non-household close contact in social setting

- Face to face interaction with the index within 6 feet and not wearing surgical mask (any duration).
- Having meal or drink together.
- Cumulative contact time ≥ 15 minutes if only the index not wearing surgical mask during face-to-face interaction.
- When N95 respirator (or equivalent) and eye protection are worn, the contact not considered significant.
- Other factors at the discretion of infection control team e.g. ventilation level, index symptoms and viral load, vaccination history, immunity from natural infection, etc.

3. Definition of significant nosocomial contact

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- Caring for a confirmed COVID-19 case WITHOUT appropriate PPE* for the procedures (any duration).

- Cumulative contact time ⩾ 15 minutes if only index not wearing surgical mask during face-to-face interaction (unless staff wearing N95 respirator and eye protection).

- Cumulative contact time ⩾ 2 hours in the same confined space if both index and staff not wearing surgical mask.

- Other factors at the discretion of infection control team e.g. ventilation level, index symptoms and viral load, vaccination history, immunity from natural infection, etc.

* Appropriate PPE for aerosol generating procedure includes N95 respirator, eye protection, disposable gown and gloves; appropriate PPE in general setting includes surgical mask and eye protection.

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