COVID-19 mRNA vaccines delay the onset of breakthrough infections with less radiographic abnormalities

Xin Li,[1,2*] Jacky Man-Chun Chan,[3*] Bosco Lam,[4] David Christopher Lung,[5,6] Kwok-Cheung Lung,[7] Christina Kin-Yi Chow,[5] Tracey Tam,[8] Kelvin Hei-Yeung Chiu,[2] Ling-Lung Hung,[2] Ivan Fan-Ngai Hung,[9] Vincent Chi-Chung Cheng,[2] Kelvin Kai-Wang To,[1,2] Kwok-Yung Yuen[1,2#]

[1] State Key Laboratory for Emerging Infection Disease, Carol Yu Centre for Infection, Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, People's Republic of China

[2] Department of Microbiology, Queen Mary Hospital, Hong Kong Special Administrative Region, People's Republic of China

[3] Department of Medicine, Princess Margaret Hospital, Hong Kong Special Administrative Region, People's Republic of China

[4] Department of Microbiology, Princess Margaret Hospital, Hong Kong Special Administrative Region, People's Republic of China

[5] Department of Pathology, Queen Elizabeth Hospital, Hong Kong Special Administrative Region, People's Republic of China

[6] Department of Pathology, Hong Kong Children's Hospital, Hong Kong Special Administrative Region, People's Republic of China

[7] Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong Special Administrative Region, People's Republic of China

[8] Quality & Safety Division, Hospital Authority, Hong Kong Special Administrative Region, People's Republic of China

[9] Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, People's Republic of China

* These authors contributed equally.

 # Correspondence:

Kwok-Yung Yuen

Email: kyyuen@hku.hk

State Key Laboratory of Emerging Infectious Diseases, Carol Yu Centre for Infection, Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, People's Republic of China

Abstract

This retrospective study of incoming travelers with COVID-19 showed that individuals immunized by mRNA vaccines had significantly longer post-vaccination interval (median: 30.5 days) to breakthrough infection, lower WBC and LDH on admission, and less radiographic abnormalities than those immunized by inactivated virus vaccine who paradoxically had lower respiratory viral load.

Keywords: COVID-19, vaccine breakthrough infection, mRNA vaccine, inactivated whole-virus vaccine

Background

Breakthrough coronavirus disease 2019(COVID-19) in vaccinated individuals were increasingly reported. However, the characteristics of breakthrough infections after vaccination with different types of COVID-19 vaccines are uncertain. In this study, we analyzed the differences in breakthrough infections in individuals fully vaccinated with either inactivated or mRNA vaccines which are used in our locality. The findings may impact on our requirement and choice of the third vaccine dose to consolidate the population immunity to combat the severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) variants of concern(VOCs).

Methods

This is a retrospective study on cases of breakthrough COVID-19 infections in Hong Kong SAR. All in-bound travelers arriving from overseas were requested to undergo compulsory quarantine and regular testing after arrival, and all laboratory confirmed COVID-19 cases were admitted to hospitals under the Hospital Authority(HA). Data on the demographics, travel history, vaccination history, viral strain, clinical details, radiographic findings, and laboratory tests were retrieved from the electronic records of HA and daily press release by Centre for Health Protection. The abnormal chest X-rays(CXR) were scored by two clinicians independently using the Brixia scoring system [1], and the mean scores were used for analysis. Statistical analysis was performed using Prism 9.1.2(GraphPad Software, San Diego, CA). Numerical variables were compared using Mann-Whiney test. Categorical variables were compared using Chi-square or Fisher's exact tests. Hazard ratios were calculated using logrank test. The study was approved by the Institutional Review Board of HA (CIRB-2021-013-4).

Results

From 16 May to 4 November 2021, 336 cases of vaccine breakthrough infections were recorded in Hong Kong SAR, including 333 imported cases, 1 locally-acquired case, and 2 cases with epidemiologic linkage to imported cases. Amongst them, 166 individuals received the

BNT162b2(Pfizer, Inc., and BioNTech) or the mRNA-1273(ModernaTX, Inc.) mRNA vaccines, and 87 individuals received the CoronaVac whole-virion inactivated vaccine (Sinovac Life Sciences), including 154 and 85 individuals who have completed two doses of vaccination at least 14 days before the onset of breakthrough in each category. Only fully vaccinated cases were included in the subsequent analysis.

There was no statistically significant difference in the age, presence of underlying illness, and percentage with clinical symptoms between the two groups(Figure 1A). Females and Asians were overrepresented in CoronaVac vaccine group, likely because the CoronaVac vaccine was distributed in several countries in the Western Pacific Region, from where most female domestic helpers coming into Hong Kong originated. Whole genome sequencing was performed on the SARS-CoV-2 isolates from 39 individuals, and the Delta variant comprised the majority. More than 97% of individuals in both groups had positive antibody against the receptor-binding domain(RBD) on admission with no statistically significant difference in the antibody levels. The median days to onset of breakthrough infection after second dose vaccination were 111.5 days and 81 days, respectively, in those who received the mRNA vaccines and inactivated vaccine(p<0.0001). The hazard ratio of breakthrough infection between the mRNA vaccine group and the inactivated vaccine group was 0.58(95% confidence interval 0.43-0.78)(Figure 1B).

Notably, individuals who developed breakthrough infections after the inactivated vaccine had significantly lower SARS-CoV-2 load(higher Ct values) in combined nasopharyngeal and throat swab(NPS+TS) or deep throat saliva(DTS), but more of them had abnormal radiological findings through the course of infection(33.8% vs. 18.7%, p=0.015) and had higher Brixia scores(Supplementary Figure 1), indicating more severe pulmonary disease. The effect of vaccine type on the days to breakthrough infection, SARS-CoV-2 viral load, and radiographic abnormalities was not affected by gender(Supplementary File). Individuals who received the inactivated vaccine also had significantly higher admission white cell count(WCC) and lactate dehydrogenase(LDH) level. Only eight individuals received medications for COVID-19 treatment, including six individuals who were given dexamethasone, amongst whom three received mRNA vaccines, and three received

inactivated vaccine. None required intubation or intensive care unit admission in this cohort, with no mortality reported at the time of writing.

Discussion

In this study, majority of the individuals with breakthrough COVID-19 infections in either group of vaccines had asymptomatic infection with no mortality. This is consistent with most studies showing their good effectiveness in preventing severely symptomatic infection and mortality. But these vaccines do not offer complete protection against infection by SARS-CoV-2, especially at the upper airway. Vaccine breakthrough infections can affect individuals with normal immune responses, but with lower viral loads in recently fully vaccinated individuals [2]. However, no previous studies have compared the characteristics of breakthrough infections after completion of mRNA or inactivated virus vaccination. We showed that mRNA vaccine can delay the onset and reduce the radiographic changes of COVID-19 despite a higher viral load in their upper respiratory tract specimens.

Although neutralizing antibody (Nab) titer has been widely recognized as a potential surrogate marker of immune correlate for COVID-19 vaccine protection, and Bergwerk *et al*. demonstrated that the risk of breakthrough infection correlated with Nab titers during the peri-infection period [3], no significant difference in the anti-RBD antibody titers was observed at the time of presentation between our two groups. One inherent problem of immune correlate is the lack of a standalone marker that can recapitulate the complex immune response to natural infection or vaccination. In non-human primate studies, vaccine-elicited ELISpot responses, and CD4+ and CD8+ intracellular cytokine staining responses, did not correlate with protection [4]. However, evidence from both human and animal studies suggested that recovery from COVID-19 requires a robust cell-mediated response, including both cytotoxic CD8+ and Th1 CD4+ T cell response, probably more so than high titers of Nab [5]. T-cell immunity as measured by interferon-γ ELISpot was found comparable between convalescent COVID-19 patients with undetectable SARS-CoV-2 IgG and those with strong antibody response, suggesting that immunity may be mediated through T cells [6].

Moreover, the protective role of antibody-dependent cellular cytotoxicity (ADCC) against spike or internal proteins of SARS-CoV-2 are still uncertain, though ADCC mediated by diverse epitope specificities may contribute [7].

Despite a higher viral load in the upper respiratory tract specimen which could be related to higher virus exposure or less mucosal immunity in the mRNA vaccine group with more non-Asians, we postulated that the mRNA vaccine likely induces a more solid protection by rapid recruitment of T-cell responses and protects the patient from lung damage. Inactivated whole virion vaccines with alum adjuvant generate poor cytotoxic T- or cell-mediated immunity. These vaccine recipients generally had lower T-cell response as measured by the ELISpot method [8]. Here, though both vaccine groups had comparable antibody titer, the extent of protection differs as evident by the significantly higher percentage of radiological abnormalities and higher peripheral blood WBC and LDH in those who received the inactivated vaccine. Without adequate T-cell response, the time taken to recruit cytotoxic T cells to clear the SARS-CoV-2 breakthrough infection may be longer in those whose immune system was primed by the inactivated vaccine, thus more radiological changes of inflammation which signifies the clearance of viral infected cells at the time of presentation. Our recent study showed that the BNT162b2 mRNA vaccine induced higher Nab response and spike-specific CD4+ T cell response than the inactivated vaccine against the original SARS-CoV-2 and VOCs [9]. Studies in non-human primates also showed that the mRNA-1273 vaccine induced high levels of Th1 response with low-to undetectable Th2 response, providing high-level protection with minimal risk of vaccine-associated enhanced respiratory disease [10]. Although another study suggested that inactivated vaccine induced stronger T-cell response measured *in vitro* [11], the clinical correlation is uncertain, as indiscriminatory T-cell reactivity may paradoxically induce more inflammatory damage if a longer time is needed for immune recruitment and allows more virus replication before immune control starts.

Our study suggested that mRNA vaccines offered longer protection against breakthrough infection than inactivated vaccines, as evidenced by the longer time to breakthrough after the completion of 2 doses. Besides a more robust T-cell response, the BNT162b2 mRNA vaccine was

known to elicit strong spike-specific memory B cells that lasted at least 6 months [12]. Though the protective efficacy wanes with time, viral load control by BNT162b2 in breakthrough infection was restored after a booster dose [2].

There are limitations of this study. First, more Asians and females were in the inactivated vaccine group with more severe pulmonary radiographic disease despite a lower viral load in upper respiratory tract secretions. However, Asian females may be more compliant with masking and therefore had lower dose of viral exposure. Moreover, COVID-19 severity should be lower in females due to innate immune and endocrine differences with males. Second, few whole genome sequencing was performed as viral loads were sometimes too low for genome analysis for viral variant. However, epidemiological evidence that the variants are associated with difference in disease severity were largely context dependent. Third, incomplete reporting of the underlying illness was possible in retrospective study. More studies on the protective efficacy of a third dose of mRNA or inactivated vaccine in individuals previously vaccinated by 2 doses of inactivated vaccine with alum adjuvant are warranted. In conclusion, although vaccine protection wanes with time, the mRNA COVID-19 vaccines appeared to provide more prolonged and solid protection against lung involvement in breakthrough infections than the inactivated vaccine.

Funding source

This study was partly supported the Consultancy Service for Enhancing Laboratory Surveillance of Emerging Infectious Diseases and Research Capability on Antimicrobial Resistance for Department of Health of the HKSAR; and donations of Richard Yu and Carol Yu, Shaw Foundation Hong Kong, Michael Seak-Kan Tong, May Tam Mak Mei Yin, Lee Wan Keung Charity Foundation Limited, the Providence Foundation Limited (in memory of the late Lui Hac Mih), Hong Kong Sanatorium & Hospital, Respiratory Viral Research Foundation Limited, Hui Ming, Hui Hoy and Chow Sin Lan Charity Fund Limited, Chan Yin Chuen Memorial Charitable Foundation, Marina Man-Wai Lee, the Hong Kong Hainan Commercial Association South China Microbiology Research Fund, the Jessie & George Ho Charitable Foundation, Kai Chong Tong, Tse Kam Ming Laurence, Foo Oi Foundation Limited, Betty Hing-Chu Lee, and Ping Cham So. The funding sources had no role in the study design, data collection, analysis, interpretation, or writing of the report.

Conflict of interest

KYY and KKWT report collaboration with Sinovac and Sinopharm. Other authors declare no conflict of interest.

References

1. Borghesi, A. and R. Maroldi, *COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression.* La Radiologia medica, 2020. **125**(5): p. 509-513.
2. Levine-Tiefenbrun, M., I. Yelin, H. Alapi, et al., *Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2.* Nature Medicine, 2021.
3. Bergwerk, M., T. Gonen, Y. Lustig, et al., *Covid-19 Breakthrough Infections in Vaccinated Health Care Workers.* New England Journal of Medicine, 2021. **385**(16): p. 1474-1484.
4. Mercado, N.B., R. Zahn, F. Wegmann, et al., *Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques.* Nature, 2020. **586**(7830): p. 583-588.
5. Sadarangani, M., A. Marchant, and T.R. Kollmann, *Immunological mechanisms of vaccine-induced protection against COVID-19 in humans.* Nature Reviews Immunology, 2021. **21**(8): p. 475-484.
6. Schwarzkopf, S., A. Krawczyk, D. Knop, et al., *Cellular Immunity in COVID-19 Convalescents with PCR-Confirmed Infection but with Undetectable SARS-CoV-2-Specific IgG.* Emerg Infect Dis, 2021. **27**(1).
7. Yu, Y., M. Wang, X. Zhang, et al., *Antibody-dependent cellular cytotoxicity response to SARS-CoV-2 in COVID-19 patients.* Signal Transduction and Targeted Therapy, 2021. **6**(1): p. 346.
8. Zhang, Y., G. Zeng, H. Pan, et al., *Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial.* The Lancet Infectious Diseases, 2021. **21**(2): p. 181-192.

9. Peng, Q., R. Zhou, Y. Wang, et al., *Waning immune responses against SARS-CoV-2 among vaccinees in Hong Kong.* bioRxiv, 2021: p. 2021.12.22.473934.

10. Corbett, K.S., B. Flynn, K.E. Foulds, et al., *Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates.* New England Journal of Medicine, 2020. **383**(16): p. 1544-1555.

11. Mok, C.K.P., C.A. Cohen, S.M.S. Cheng, et al., *Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong.* Respirology, 2021.

12. Ciabattini, A., G. Pastore, F. Fiorino, et al., *Evidence of SARS-CoV-2-Specific Memory B Cells Six Months After Vaccination With the BNT162b2 mRNA Vaccine.* Frontiers in Immunology, 2021. **12**: p. 3751.

Figure legend

Figure 1A. Demographics and clinical details of the two vaccine groups. CXR – chest X-ray; RBD – receptor-binding domain of spike protein; CRP – C-reactive protein; WCC – white cell count; LDH – lactate dehydrogenase; NPS + TS – combined nasopharyngeal and throat swab; DTS – deep throat saliva. **Figure 1B.** Kaplan Meier plot showing days to breakthrough infection after second dose vaccination in each vaccine group.

Figure 1

	mRNA vaccines	Inactivated vaccine	*p* value
Total No. of breakthrough cases	166	87	
No. of breakthrough cases that have completed 2 doses vaccination ≥14 days	154	85	
Age – median (range)	38 (13-79)	38 (21-69)	0.891
Gender – male%	57.8% (89/154)	35.3% (30/85)	0.001*
Presence of underlying illness	40.2% (39/97)	40.4% (23/57)	>0.9999
Hypertension	12.4% (12/97)	14.0% (8/57)	
Diabetes mellitus	4.1% (4/97)	10.5% (6/57)	
Hyperlipidemia	9.3% (9/97)	8.8% (5/57)	
Cardiovascular disease	2.1% (2/97)	1.8% (1/57)	
Malignancy	2.1% (2/97)	0 (0/57)	
Obesity	12.4% (12/97)	17.5% (10/57)	
Imported case	99.4% (153/154)	98.8% (84/85)	>0.9999
WHO region of origin:			<0.0001*
African Region	2.0% (3/153)	6.0% (5/84)	
Region of the Americas	22.2% (34/153)	3.6% (3/84)	
South-East Asian Region	2.6% (4/153)	19.0% (16/84)	
European Region	36.6% (56/153)	10.7% (9/84)	
Eastern Mediterranean Region	15.7% (24/153)	16.7% (14/84)	
Western Pacific Region	20.9% (32/153)	44.0% (37/84)	
Ethnicity:			<0.0001*
Asian	62.9% (78/124)	91.1% (72/79)	
White	37.1% (46/124)	7.6% (6/79)	
Black or African Americans		1.3% (1/79)	
Lineage available:	21.4% (33/154)	7.1% (6/85)	0.143
Alpha	6.1% (2/33)	16.7% (1/6)	
Delta	87.9% (29/33)	66.7% (4/6)	
Mu	3.0% (1/33)		
Delta plus	3.0% (1/33)		
Eta		16.7% (1/6)	
Symptomatic case	42.2% (65/154)	30.6% (26/85)	0.095
Chest X-ray abnormality	18.7% (28/150)	33.8% (27/80)	0.015*
Brixia score of abnormal CXRs – median	2.0	3.5	0.024*
Positive anti-RBD Ab (AU/mL) on admission	98.7% (152/154)	97.6% (83/85)	0.617
Anti-RBD Ab titer - median (interquartile range)	4416 (1718-17719)	6127 (568.6-32407)	0.757
First CRP (mg/L) – median (interquartile range)	2.2 (0-7.1)	1.6 (0-8.1)	0.800
First WCC (x 10^9/L) – median (interquartile range)	6.9 (5.8-8.1)	8.1 (5.9-9.6)	0.004*
First lymphocyte (x 10^9/L) – median (interquartile range)	1.6 (1.2-2.1)	1.7 (1.4-2.4)	0.206
First LDH (U/L) – median (interquartile range)	155.5 (140.0-184.3)	164.0 (150.0-189.0)	0.044*
Ct value in NPS + TS – median (interquartile range)	22.55 (16.68-33.58)	33.45 (22.13-41.03)	<0.0001*
Ct value in DTS -median	25.77	31.30	0.021*

Figure 1A.

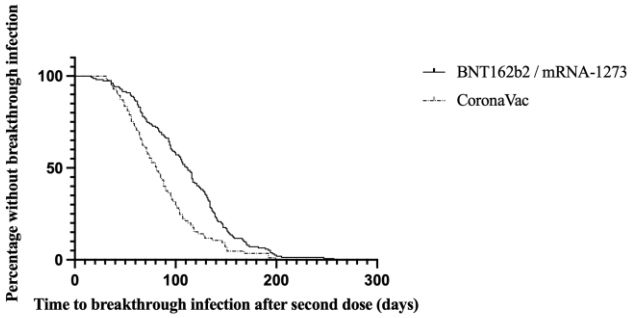

Figure 1B.