Brief Report

Title:

Vaccine-breakthrough infection by the SARS-CoV-2 Omicron variant elicits broadly cross-reactive immune responses

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42 SUMMARY

43 Highly transmissible SARS-CoV-2 Omicron variant has posted a new crisis for
44 COVID-19 pandemic control. Within a month, Omicron is dominating over Delta
45 variant in several countries probably due to immune evasion. It remains unclear
46 whether vaccine-induced memory responses can be recalled by Omicron infection.
47 Here, we investigated host immune responses in the first vaccine-breakthrough case
48 of Omicron infection in Hong Kong. We found that the breakthrough infection rapidly
49 recruited potent cross-reactive broad neutralizing antibodies (bNAbs) against current
50 VOCs, including Alpha, Beta, Gamma, Delta and Omicron, from unmeasurable IC₅₀
51 values to mean 1:2929 at around 9-12 days, which were higher than the mean peak
52 IC₅₀ values of BioNTech-vaccinees. Cross-reactive spike- and nucleocapsid-specific
53 CD4 and CD8 T cell responses were detected. Similar results were also obtained in
54 the second vaccine-breakthrough case of Omicron infection. Our preliminary findings
55 may have timely implications to booster vaccine optimization and preventive
56 strategies of pandemic control.

57

58 Keywords

59 SARS-CoV-2; VOCs; Omicron; Broad neutralizing antibodies; Breakthrough
60 infection; T cell responses

61

62 Main text

63 Highly transmissible SARS-CoV-2 and its variants have caused more than 279
64 million infections with about 5.4 million deaths globally by December 26, 2021
65 (<https://coronavirus.jhu.edu/map.html>). To fight the ongoing pandemic, 8.9 billion
66 doses of several types of COVID-19 vaccine have already been extensively
67 administered in many countries, which has reduced the rates of hospitalization and
68 death significantly (Baden et al., 2021; Polack et al., 2020; Tanriover et al., 2021;
69 Voysey et al., 2021; Xia et al., 2021). Since these vaccines cannot confer complete

70 prevention of upper airway transmission of SARS-CoV-2, the increasing numbers of
 71 vaccine-breakthrough infections and re-infections have been documented
 72 (Abu-Raddad et al., 2021; Birhane et al., 2021; To et al., 2021). This situation is
 73 becoming worse because of the rapid spread of SARS-CoV-2 variant of concerns
 74 (VOCs) and waning of vaccine-induced immune responses (Peng et al., 2021; Wang
 75 et al., 2021a; Wang et al., 2021b). After World Health Organization (WHO)
 76 designated the Omicron variant of concern (VOC) on the 26th of November 2021, the
 77 extremely rapid spread of this variant has led to another crisis of pandemic control.
 78 Within a month, Omicron is replacing the Delta VOC to become the dominant
 79 SARS-CoV-2 variant in many places in the South Africa, European countries and in
 80 the United States (Shu and McCauley, 2017). Two studies reported that the increased
 81 risk of re-infection was associated with emergence of Omicron in South Africa and
 82 Denmark (Espenhain et al., 2021; Pulliam et al., 2021). Both vaccine-induced
 83 neutralizing antibody (NAb) and current NAb combination therapy for passive
 84 immunization have significantly reduced activities (Lu et al., 2021; Wang et al.,
 85 2021a). Till now, it remains unclear whether vaccine-induced memory responses can
 86 be recalled by the Omicron viral infection. We, therefore, investigated the host
 87 immune responses in two vaccine-breakthrough cases of Omicron infection in Hong
 88 Kong. Our preliminary finding of Omicron-recalled broadly cross-reactive immune
 89 responses in these cases may have timely important implications to booster vaccine
 90 optimization and implementing adequate preventive interventions to control the
 91 pandemic.

92
 93 On mid-November 2021, the first Chinese vaccine-breakthrough case of Omicron
 94 patient (OP1) was diagnosed in a quarantine hotel in Hong Kong (Wong et al., 2021).
 95 OP1 arrived in Hong Kong from Canada and was tested negative by reverse
 96 transcription PCR (RT-PCR) for SARS-CoV-2 within 72 hours before arrival. Seven
 97 days after arrival, OP1 developed mild symptoms and showed a positive result for
 98 SARS-CoV-2 (Ct value 19) on day 8 after arrival and was hospitalized on the same
 99 day. To validate our findings, we subsequently received blood samples from an
 100 imported mild case of Omicron patient 2 (OP2), who was due to a separate
 101 transmission and was diagnosed about 9 days after the OP1. Based on the vaccination
 102 records, OP1 and OP2 were confirmed with Omicron infection at 178 and 53 days
 103 after the second dose of BNT162b2 and mRNA-1273, respectively (**Figure 1A**).
 104 During hospitalization, both cases presented with mild clinical symptoms not
 105 requiring oxygen supplementation or ICU treatment. With patients' informed consent,
 106 we obtained three sequential sera and one peripheral blood mononuclear cells

(PBMCs) samples from each patient to determine whether vaccine-induced memory responses can be recalled by the Omicron viral infection.

We first measured the neutralizing antibody titer (IC_{50}) in their sera samples against the current panel of SARS-CoV-2 VOC pseudoviruses including Alpha (B.1.1.7), Beta (B.1.351), Gamma, Delta (B.1.617.2) and Omicron (B.1.1.529) as compared with D614G (WT). We compared IC_{50} values with 34 local vaccinees, whose blood was collected around mean 30 days after the second BNT162b2-vaccination (Pfizer–BioNTech) (**Figure 1A**) (Peng et al., 2021). Consistent with recent preprint publications by others, we found that the Omicron variant showed the greatest resistance to BNT162b2-vaccine-induced neutralization with an average 5.9-fold deficit relative to D614G (**Figure 1C**). Strikingly, however, the breakthrough infection was able to elicit cross-reactive broad neutralizing antibodies (bNAbs) from the unmeasurable levels ($<1:20$) to mean IC_{50} values of 1:2929 (range 588.5-5508) and from mean IC_{50} 1:24.3 to 1:854.5 at 9 days in OP1 and 12 days in OP2 post symptoms onset (PSO), respectively (**Figure 1D**). Moreover, the amounts of NAb were consistently higher than the mean IC_{50} values of BNT162b2-vaccinees across all VOCs tested. In particular, there were 121.41- and 74.89-fold higher IC_{50} values against Beta and Omicron in OP1 than those in BNT162b2-vaccinees (**Figure 1B**). Besides NAb against the current panel of VOCs, OP1 also displayed enhanced IC_{50} values of NAb against 15/16 SARS-CoV-2 variants with individual mutations or deletions including the E484K mutation, which conferred significant resistance to vaccine-induced NAb (**Figure S1**). These results demonstrated that, although the Omicron VOC evaded BNT162b2-vaccine-induced NAb, the breakthrough infection elicited cross-reactive bNAbs generally against all current VOCs in both OP1 and OP2.

To understand cellular immune responses, we conducted flow cytometry analysis on PBMCs of OP1 and OP2 collected on day 11 and 12 PSO, respectively. Multi-color flow cytometry data showed no sign of severe immune suppression in both OP1 and OP2 who had similar frequencies of T lymphocyte without lymphocytopenia, stable conventional dendritic cell (cDC) : plasmacytoid dendritic cell (pDC) ratio and normal Myeloid-derived suppressor cells (MDSCs) to mild and healthy subjects as we described previously (**Figure S2**) (Zhou et al., 2020). For antigen-specific B cell activation, we measured the frequency of Spike-specific IgG^+ B cells in OP1 and OP2. The levels of 13.2% in OP1 and 2.31% in OP2 were relatively higher than mean 1.12% (range 0.004-7.92%) found among BNT162b2-vaccinees around their peak responses (**Figure 1E**). Unlike naturally infected COVID-19 patients, who display

145 predominantly tissue-like memory (TLM) B cell response (Woodruff et al., 2020),
146 Spike-specific IgG⁺ B cells from OP1 and OP2 exhibited the dominate phenotype of
147 resting memory (RM) (**Figure 1F**), which was also found in our
148 BNT162b2-vaccinees.

149

150 Besides Spike-specific IgG⁺ B cell responses, we measured cross-reactive T cell
151 responses to the Spike and nucleocapsid (NP) peptide pools derived from wildtype
152 SARS-CoV-2 in OP1 and OP2 as compared with BNT162b2-vaccinees by
153 intracellular cytokine staining. The cytomegalovirus (CMV) pp65 peptide pool was
154 used as a positive control. We found that Spike- and NP-specific CD4 IFN- γ
155 responses were 0.61% and 0.12% in OP1 and 0.15% and 0.10% in OP2, respectively
156 (**Figure 1G**). Moreover, Spike- and NP-specific CD8 IFN- γ responses were 0.56%
157 and 0.11% in OP1 and 0.10% and 0.08% in OP2, respectively (**Figure 1G**). These
158 results indicated that cross-reactive CD4 and CD8 T cell responses to wild type
159 SARS-CoV-2 were primarily against the Spike as compared with NP. Moreover, the
160 Spike-specific T cell responses were relatively higher in OP1 or comparable in OP2
161 as compared with mean values in BNT162b2-vaccinees (CD4 T: mean 0.19% and
162 CD8 T: mean 0.10%). Since much weaker or unmeasurable T cell responses were
163 found in severe COVID-19 patients around the same period PSO (Rydzynski
164 Moderbacher et al., 2020; Zhou et al., 2020), T cell responses in OP1 and OP2
165 probably also contributed to disease progression control.

166

167 In this brief report, we provide timely communication on immune responses in two
168 cases of vaccine-breakthrough infections by the SARS-CoV-2 Omicron variant in
169 Hong Kong. Although antibody evasion has been clearly documented against
170 Omicron due to 32 amino acid changes in viral spike protein (Cameroni et al., 2021;
171 Cele et al., 2021; Planas et al., 2021a; Wang et al., 2021a), we report here that
172 Omicron vaccine-breakthrough infections could elicit cross-reactive bNAbs responses
173 against all current SARS-CoV-2 VOCs. Since the amounts of bNAbs responses were
174 higher than the mean IC₅₀ values of in BNT162b2-vaccinees at their peak response
175 period, we believe that the Omicron infection rapidly recruited the vaccine-induced
176 memory immune responses during the acute phase of infection, which probably
177 contributed to protection and was in line with the mild clinical presentation in both
178 patients. Encouragingly, besides rapid bNAbs responses, both spike- and NP-specific
179 CD4 and CD8 T cells cross-reactive to wild type peptide pools were measurable on
180 day 11-12, which probably also contributed to disease progression control (Lipsitch et
181 al., 2020; Zhou et al., 2020).

182

183 Both OP1 and OP2 showed high amounts of bNAbs against the Omicron variant and
 184 other VOCs. According to the GISAID database, during the period from October 4,
 185 2021 to December 26, 2021, the relative variant genome frequency of the current
 186 circulating Delta variant has declined from 89% to 19.6% while the Omicron variant
 187 has increased from 0% to 67.4% in African countries. Besides insufficient vaccination
 188 coverage and preventive masking, high viral infectivity and antibody escape are likely
 189 the key reasons for the rapidity of Omicron spread. Based on *in vitro* experiments, the
 190 Omicron variant showed a 10-fold increase in infectivity than the Beta or Delta
 191 variants (Lu et al., 2021). Consistent with previous findings that the Beta variant
 192 compromised vaccine-induced neutralizing activity (Planas et al., 2021b; Wang et al.,
 193 2021a), similar findings have already been made for the Omicron variant with even
 194 worse antibody evasion (Cameroni et al., 2021; Cele et al., 2021; Planas et al., 2021a;
 195 Wang et al., 2021a). We also made similar findings that a significant drop of
 196 neutralizing activity against Omicron variant was observed among the convalescent
 197 patients and vaccine recipients (Lu et al., 2021; Wang et al., 2022). Since the Omicron
 198 variant caused a higher rate of vaccine-breakthrough infection and reinfection than the
 199 Delta variant (Espenhain et al., 2021), it is worrisome if such infections would lead to
 200 more severe sickness or death due to immune escape. In this study, we demonstrated
 201 that the Omicron breakthrough infection rapidly recruited vaccine-induced memory
 202 bNAbs and T cell immune responses, which very likely contributed to protection to
 203 both OP1 and OP2. Our finding is consistent with and provides a probable immune
 204 mechanism underlying a recent report that most Omicron patients had no signs of
 205 severe COVID-19 as compared with the Delta variant (Espenhain et al., 2021). Future
 206 studies, however, remain necessary to evaluate Omicron-specific T cell immunity for
 207 protection although there were no significant reductions in CD4 and CD8 T cell
 208 responses to the spike peptides-derived from Alpha and Delta spike variants (Jordan
 209 et al., 2021). Our findings, therefore, re-emphasize the importance of complete
 210 vaccination coverage among human populations especially in developing countries.
 211 Since similarly high amounts of bNAbs against both Omicron and other VOCs were
 212 detected in both OP1 and OP2, the rapid development of Omicron-based vaccine is a
 213 reasonable strategy for the booster vaccine optimization.

214

215 The major limitation of this study is the small number of vaccine-breakthrough
 216 infections by the SARS-CoV-2 Omicron variant found in Hong Kong. Some
 217 mutations in Omicron spike are shared with preexisting VOCs, such as D614G in all
 218 VOCs, K417N, E484K and N501Y in Beta variant, and T478K in Delta variant. The

E484K mutation in Beta variant has been reported for evasion of many NABs under clinical development (Wang et al., 2021a). These mutations in combination with additional mutations have led to the striking antibody evasion manifested by the Omicron variant (Wang et al., 2021a). Nevertheless, our preliminary finding, that OP1 and OP2 could generate bNABs against all VOCs after infection, suggested that the Omicron-targeted vaccine might boost a broad protection among existing vaccinees against SARS-CoV-2 VOC infection. Since current vaccines showed weak effect on Omicron, our findings also implicate that the development of Omicron-targeted vaccines is urgent and beneficial to fight all current SARS-CoV-2 VOCs, especially when the increased infectivity of Omicron variant has been preliminarily reported *in vitro* (Lu et al., 2021).

SUPPLEMENTAL INFORMATION

2 supplemental figures.

STAR METHODS

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for resources and reagent should be directed to and will be fulfilled by the Lead Contact, Zhiwei Chen (zchenai@hku.hk).

Materials Availability

This study did not generate new unique reagents.

Data and Code Availability

The study did not generate any unique datasets or codes.

EXPERIMENTAL MODELS AND SUBJECT DETAILS

Human subjects

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref No. UW 21-452). Written informed consent was obtained from all study subjects. Peripheral blood mononuclear cells (PBMCs) from healthy donors and patients were isolated from fresh blood samples using Ficoll-Paque density gradient centrifugation in our BSL-3 laboratory at the same day of blood collection. The majority of purified PBMCs were used for immune cell phenotyping whereas plasma samples were subjected to antibody testing.

256 The rest of the cells were cryopreserved in freezing medium (Synth-a-Freeze
257 Cryopreservation Medium, ThermoFisher Scientific) at 5×10^6 cells/mL at -150°C .

258

259 **Pseudotyped viral neutralization assay**

260 To determine the neutralizing activity of subject' plasma, plasma was inactivated at
261 56°C for 30 min prior to a pseudotyped viral entry assay. In brief, different
262 SARS-CoV-2 pseudotyped viruses were generated through co-transfection of 293T
263 cells with 2 plasmids, pSARS-CoV-2 S and pNL4-3Luc_Env_Vpr, carrying the
264 optimized SARS-CoV-2 S gene and a human immunodeficiency virus type 1
265 backbone, respectively. At 48 h post-transfection, viral supernatant was collected and
266 frozen at -150°C . Serially diluted plasma samples (from 1:20 to 1:14580) were
267 incubated with 200 TCID₅₀ of pseudovirus at 37°C for 1 h. The plasma-virus mixtures
268 were then added into pre-seeded HEK293T-hACE2 cells. After 48 h, infected cells
269 were lysed, and luciferase activity was measured using Luciferase Assay System kits
270 (Promega) in a Victor3-1420 Multilabel Counter (PerkinElmer). The 50% inhibitory
271 concentrations (IC₅₀) of each plasma specimen were calculated to reflect
272 anti-SARS-CoV-2 potency.

273

274 **Flow cytometry analysis**

275 For immune cell profile analysis, PBMCs were incubated for 10 min with Fc Block
276 (BD Biosciences) in staining buffer (PBS containing 2% FBS) followed by staining
277 with the indicated antibodies for 30 min at 4°C . For T cell responses, PBMCs were
278 stimulated with 2 $\mu\text{g/mL}$ COVID-19 Spike or NP peptide pool (15-mer overlapping
279 by 11) or CMV pp65 peptide pool in the presence of 0.5 $\mu\text{g/mL}$ anti-CD28 and
280 anti-CD49d mAbs (BD Bioscience). Cells were incubated at 37°C overnight and BFA
281 was added at 2 h post incubation, as previously described ([Li et al., 2008a](#)). After
282 overnight incubation, cells were washed with staining buffer (PBS containing 2%
283 FBS) and stained with mAbs against surface markers. For intracellular staining, cells
284 were fixed and permeabilized with BD Cytofix/Cytoperm (BD Biosciences) prior to
285 staining with the mAbs against cytokines with Perm/Wash buffer (BD Biosciences).
286 Stained cells were acquired by FACSARIAIII Flow Cytometer (BD Biosciences) inside
287 a BSL-3 laboratory and analyzed with FlowJo software (v10.6) (BD Bioscience).

288

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AUTHOR CONTRIBUTIONS

Z.C. and R.Z. conceived and designed the study. R.Z. and Z.C. designed experiments, analyzed data, and wrote the manuscript. R.Z., H.H., and N.L. performed the flow cytometry analysis. K.K.-W.T., J.M.-C.C., B.H.-S.L., V.W.-M.C. and O.T.-Y.T. collected clinical samples and data. Q.P., D.Y. and K.-K.A. conducted the pseudoviral neutralization assay. J.-P.C. provided technique support. K.-Y.Y. provided critical comments.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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405

406 **Figure legend**

407 **Figure 1. Cross-reactive immune responses elicited by vaccine-breakthrough**
 408 **infection of the SARS-CoV-2 Omicron variant.** (A) Characterization of 2 Omicron
 409 patients and 34 BNT162b2-vaccinees. (B) Neutralizing antibody titers among the
 410 BNT162b2-vaccinees (grey) (n=34) and two Omicron patients (OP1: red and OP2: blue)
 411 at the peak response time. Neutralizing antibody titers represent serum dilution
 412 required to achieve 50% virus neutralization (IC_{50}). The numbers indicate the fold of
 413 enhancement of IC_{50} values relative to mean titer measured among
 414 BNT162b2-vaccinees. (C) Fold-change of mean IC_{50} values relative to the
 415 SARS-CoV-2 D614G strain among the BNT162b2-vaccinees. (D) Longitudinal
 416 neutralizing antibody titers (IC_{50}) of OP1 and OP2 against the full panel of VOCs. Each
 417 symbol with color-coding represents an individual VOC. (E) The gating strategy for
 418 SARS-CoV-2 Spike-specific B cells by flow cytometry. AF488 and AF647 double
 419 positive cells were defined as Spike-specific cells. Representative plots (left) and
 420 quantified results (right) are shown. (F) Phenotypes of Spike-specific B cells were
 421 defined by using CD21 and CD27 markers (left). Pie chart showed the proportion of
 422 activated (AM), tissue-like memory (TLM), intermediate memory (IM) and
 423 resting-memory (RM) B cells. (G) PBMCs were subjected to the ICS assay against
 424 Spike or NP or CMV peptide pools. IFN- γ^+ cells were gated on CD4 and CD8 T cells,
 425 respectively (left). Quantified results (right) depict the percentage of IFN- γ^+ cells.