

1 **Brief Report**

2 **Title:**

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

5

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41

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

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

109

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

133

134 To understand cellular immune responses, we conducted flow cytometry analysis on
135 PBMCs of OP1 and OP2 collected on day 11 and 12 PSO, respectively. Multi-color
136 flow cytometry data showed no sign of severe immune suppression in both OP1 and
137 OP2 who had similar frequencies of T lymphocyte without lymphocytopenia, stable
138 conventional dendritic cell (cDC) : plasmacytoid dendritic cell (pDC) ratio and
139 normal Myeloid-derived suppressor cells (MDSCs) to mild and healthy subjects as we
140 described previously (**Figure S2**) (Zhou et al., 2020). For antigen-specific B cell
141 activation, we measured the frequency of Spike-specific IgG^+ B cells in OP1 and OP2.
142 The levels of 13.2% in OP1 and 2.31% in OP2 were relatively higher than mean 1.12%
143 (range 0.004-7.92%) found among BNT162b2-vaccinees around their peak responses
144 (**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 bNAb responses
173 against all current SARS-CoV-2 VOCs. Since the amounts of bNAb 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 bNAb 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 GASAIID 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

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

230

231 **SUPPLEMENTAL INFORMATION**

232 2 supplemental figures.

233

234 **STAR METHODS**

235 **RESOURCE AVAILABILITY**

236 **Lead Contact**

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

239

240 **Materials Availability**

241 This study did not generate new unique reagents.

242

243 **Data and Code Availability**

244 The study did not generate any unique datasets or codes.

245

246 **EXPERIMENTAL MODELS AND SUBJECT DETAILS**

247

248 **Human subjects**

249 This study was approved by the Institutional Review Board of the University of Hong
250 Kong/Hospital Authority Hong Kong West Cluster (Ref No. UW 21-452). Written
251 informed consent was obtained from all study subjects. Peripheral blood mononuclear
252 cells (PBMCs) from healthy donors and patients were isolated from fresh blood
253 samples using Ficoll-Paque density gradient centrifugation in our BSL-3 laboratory at
254 the same day of blood collection. The majority of purified PBMCs were used for
255 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 Cytotfix/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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301

302 **AUTHOR CONTRIBUTIONS**

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

309

310 **DECLARATION OF INTERESTS**

311 The authors declare no competing interests.

312

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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. $IFN-\gamma^+$ cells were gated on CD4 and CD8 T cells,
425 respectively (left). Quantified results (right) depict the percentage of $IFN-\gamma^+$ cells.

A Subject characterization

	OP1	OP2	Vaccinees (n=34)
Age, median years (IQR)	62	37	30.5 (26.8-35.3)
Gender, male (%)	100%	100%	16 (47.1%)
Vaccination	BNT162b2	mRNA-1273	BNT162b2
The median interval days between the full vaccination and the first blood collection (IQR)	178	53	30 (22-32)
The median intervals days between full vaccination and symptom onset	178	54	Not applied

IQR: interquartile range

