

**Title:** Lack of inflammatory bowel disease flare-up following two-dose BNT162b2 vaccine: a population-based cohort study

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**Patient and public involvement:** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### **Conflict of interest**

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### **Authors Contribution**

*Study concept and design:* X Li, WK Leung, EW Chan

*Funding and data acquisition:* ICK Wong

*Data extractions, cleaning and analysis:* X Tong

*Data validation and cross-check:* K Peng

*Data interpretation:* all authors

*Drafting of the manuscript:* X Li, X Tong

*Critical revision of the manuscript of significant intellectual contribution:* all authors

*Study supervision:* ICK Wong, EW Chan, WK Leung

1 We read with interest the recent paper by Cannatelli *et al*<sup>1</sup> describing the adverse events (AEs)  
2 following COVID-19 vaccination from a large IBD cohort, which showed that patients with IBD  
3 had a similar rate of reported AEs to the general population but with a slightly higher rate of self-  
4 limiting GI symptoms. However, the effects of COVID-19 vaccine on IBD activity, particularly  
5 severe flare resulting in hospitalisation, and the interplay with the use of immunotherapy remain  
6 unknown. To address these questions, we analysed the territory-wide electronic medical records  
7 with vaccination linkage database in Hong Kong<sup>2-7</sup> to examine the association between  
8 BNT162b2 vaccination and IBD flare.

9 From 4,161,762 patient records with affirmed vaccination status between March 6 and  
10 September 30, 2021, we identified 941 IBD patients with two completed doses of BNT162b2,  
11 and 1196 unvaccinated IBD controls (**Supplementary Figure 1**). Vaccinated recipients were  
12 younger and less likely to have pre-existing chronic diseases. Approximately half of these IBD  
13 patients received immunosuppressants and more than 20% were treated with biologics in the  
14 recent year. After inverse propensity treatment weighting, all variables were well balanced  
15 between vaccinated and unvaccinated groups (**Supplementary Table 1**).

16 During a median follow-up of 60 days among two-dose BNT162b2 recipients, six patients (onset  
17 time: 24 to 103 days) had unplanned hospitalisation due to IBD (mean hospitalisation duration:  
18  $5.3 \pm 3.5$  days). The number of unplanned IBD-related admissions in the unvaccinated group was  
19 13 with a median follow-up of 69 days. Two-dose BNT162b2 vaccine was not associated with  
20 unplanned IBD hospitalisation [aIRR: 0.69 (0.35-1.36)], all-cause hospitalisation [aIRR: 0.86  
21 (0.61-1.22)] or 28-day emergency department (ED) attendance [aIRR: 1.00 (0.71-1.41)] (**Table**  
22 **1**). A series of subgroup analyses showed that BNT162b2 was not associated with a higher risk  
23 of IBD flare when compared to those without vaccination (**Table 2**). In the additional analysis  
24 investigating IBD flare within 28 days following the first or second dose, no significant risk was  
25 detected (**Supplementary Table 2**).

26 The current study focused on IBD flare leading to hospitalisation or ED attendance and we found  
27 that the two-dose BNT162b2 vaccine did not increase the risk of severe IBD flare-ups. This  
28 further contributes to understanding the medium-term safety of mRNA COVID-19 vaccine in  
29 immune-mediated inflammatory disease, which was consistently reported in the existing  
30 literature focusing on a broader spectrum of AEs.<sup>1 8</sup> As some treatments for IBD may be

31 associated with an increased risk of severe COVID-19,<sup>9</sup> full vaccination is vital to prevent  
32 adverse COVID-19 outcomes in patients with IBD. In our study cohort, single-dose BNT162b2  
33 recipients were uncommon (n = 4) with no record of subsequent ED attendance and unplanned  
34 hospitalisation - suggestive of a generally well-tolerated first dose and an overall high vaccine  
35 completion rate. Immunosuppressive medications or biologics for IBD patients could attenuate  
36 the anti-SARS-CoV-2 antibody responses following vaccination.<sup>10</sup> However, from a safety  
37 perspective, our analysis among individuals who received immunosuppressants or biologics  
38 suggest no significant association between disease flare-up and two-dose vaccination.

39 This study has limitations. First, outcome assessments are largely dependent on the ICD-9-CM-  
40 based diagnosis and the direct measurement of disease activity and symptoms that did not result  
41 in hospital or emergency admission were not considered. Second, although our study included a  
42 considerable number of patients with IBD, the negative findings could still be driven by  
43 underpowered statistics. This will require future large cohort studies and network analysis to  
44 continue the COVID-19 vaccine safety assessment in patients with immune-mediated diseases.

45 In conclusion, we found no increased risk of severe disease flare-ups following the two-dose  
46 BNT162b2 vaccine in patients with IBD. These observations substantiate the medium-term  
47 safety of BNT162b2 vaccination in patients with IBD.

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**Table 1 Incidence of unplanned IBD-related hospitalisation, all-cause hospitalisation and 28-day emergency department attendance in the main analysis, after IPTW**

	Cases/N	Follow-up time* (person-years)	Crude incidence (per 100 person-years, 95% CI)	Adjusted IRR (95% CI)	P-value
<b>Unplanned IBD-related hospitalisation</b>					
<b>BNT162b2</b>	6/941	181.22	3.31 (1.34, 6.89)	0.69 (0.35, 1.36)	0.288
<b>Unvaccinated</b>	13/1196	253.59	5.13 (2.85, 8.55)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
<b>BNT162b2</b>	21/941	178.89	11.74 (7.48, 17.61)	0.86 (0.61, 1.22)	0.393
<b>Unvaccinated</b>	47/1196	248.21	18.94 (14.08, 24.95)	Ref	-
<b>28-day emergency department attendance</b>					
<b>BNT162b2</b>	25/941	63.93	39.11 (25.87, 56.88)	1.00 (0.71, 1.41)	0.996
<b>Unvaccinated</b>	39/1196	82.12	47.49 (34.24, 64.27)	Ref	-

Abbreviation: CI: confidence interval; IBD: inflammatory bowel disease; IRR: incidence rate ratio; IPTW: inverse probability treatment weighting.

Variables included in the IPTW: age, sex, IBD classification (Ulcerative colitis, Crohn's disease, Indeterminate colitis), medical history of asthma, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure, dementia, diabetes with or without chronic comorbidity conditions, mild liver disease, moderate-severe liver disease, myocardial infarction, peripheral vascular disease, paralysis, stroke or systemic embolism, ulcers; frequency of health service utilisation (emergency admission, hospital admission, specialist out-patient clinic visits, general out-patient clinics visits); medication usage (antibiotics, mesalazine, sulphasalazine, corticosteroids, immunosuppressant, biologics) in the recent year; outcome between two doses.

\* for unplanned IBD and all-cause hospitalisation, follow-up commenced from the second dose vaccination date to hospital admission date or study end date (September 30, 2021), whichever occurred earlier; for emergency department attendance, follow-up commenced from the second dose vaccination date to emergency department attendance date or 28 days since the vaccination, whichever occurred earlier.

**Table 2 Incidence of unplanned IBD-related hospitalisation, all-cause hospitalisation and 28-day emergency department attendance in the subgroup analyses, after IPTW**

	Cases/N	Follow-up time* (person-years)	Crude incidence (per 100 person- years, 95% CI)	Adjusted IRR** (95% CI)	P-value
<b>Ulcerative colitis</b>					
<b>Unplanned IBD-related hospitalisation</b>					
BNT162b2	3/378	64.08	4.68 (1.30, 12.49)	0.78 (0.33, 1.87)	0.583
Unvaccinated	8/560	119.26	6.71 (3.16, 12.66)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
BNT162b2	11/378	63.09	17.44 (9.25, 30.18)	0.98 (0.62, 1.55)	0.936
Unvaccinated	27/560	116.48	23.18 (15.62, 33.22)	Ref	-
<b>28-day emergency department attendance</b>					
BNT162b2	14/378	25.07	55.84 (31.98, 91.19)	1.20 (0.75, 1.94)	0.446
Unvaccinated	20/560	38.57	51.85 (32.67, 78.51)	Ref	-
<b>Crohn's Disease</b>					
<b>Unplanned IBD-related hospitalisation</b>					
BNT162b2	2/553	115.72	1.73 (0.34, 5.54)	0.37 (0.11, 1.18)	0.093
Unvaccinated	5/615	129.65	3.86 (1.46, 8.45)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
BNT162b2	8/553	114.56	6.98 (3.29, 13.18)	0.79 (0.46, 1.35)	0.394
Unvaccinated	20/615	127.04	15.74 (9.92, 23.84)	Ref	-
<b>28-day emergency department attendance</b>					
BNT162b2	10/553	38.31	26.10 (13.40, 46.31)	0.84 (0.51, 1.39)	0.498
Unvaccinated	19/615	42.02	45.22 (28.13, 69.16)	Ref	-
<b>With immunosuppressants</b>					
<b>Unplanned IBD-related hospitalisation</b>					
BNT162b2	5/454	81.63	6.13 (2.32, 13.43)	0.99 (0.46, 2.11)	0.970
Unvaccinated	9/633	137.39	6.55 (3.24, 11.96)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
BNT162b2	15/454	80.29	18.68 (10.91, 30.04)	1.25 (0.82, 1.91)	0.301
Unvaccinated	28/633	134.36	20.84 (14.15, 29.68)	Ref	-
<b>28-day emergency department attendance</b>					

BNT162b2	11/454	30.80	35.71 (18.95, 61.81)	0.97(0.59, 1.57)	0.892
Unvaccinated	21/633	43.22	48.59 (30.98, 72.88)	Ref	-
<b>Without immunosuppressants</b>					
<b>Unplanned IBD-related hospitalisation</b>					
BNT162b2	1/487	99.59	1.00 (0.09, 4.68)	0.35 (0.08, 1.59)	0.175
Unvaccinated	4/563	116.20	3.44 (1.15, 8.18)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
BNT162b2	6/487	98.6	6.09 (2.53, 12.54)	0.62 (0.34, 1.14)	0.125
Unvaccinated	19/563	113.84	16.69 (10.38, 25.53)	Ref	-
<b>28-day emergency department attendance</b>					
BNT162b2	14/487	38.90	35.99 (20.61, 58.77)	1.13(0.70, 1.83)	0.625
Unvaccinated	18/563	33.14	54.32 (33.34, 83.99)	Ref	-
<b>With biologics</b>					
<b>Unplanned IBD-related hospitalisation</b>					
BNT162b2	1/192	32.50	3.08 (0.28, 14.34)	0.47 (0.10, 2.16)	0.334
Unvaccinated	4/287	57.15	7.00 (2.34, 16.64)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
BNT162b2	5/192	31.72	15.76 (5.98, 34.55)	0.92 (0.46, 1.84)	0.812
Unvaccinated	12/287	56.13	21.38 (11.67, 36.21)	Ref	-
<b>28-day emergency department attendance</b>					
BNT162b2	6/192	12.57	47.73 (19,84, 98.39)	1.23 (0.59, 2.55)	0.581
Unvaccinated	9/287	19.91	45.20 (22.33, 82.51)	Ref	-
<b>Without biologics</b>					
<b>Unplanned IBD-related hospitalisation</b>					
BNT162b2	5/749	148.72	3.36 (1.28, 7.37)	0.78 (0.36, 1.66)	0.513
Unvaccinated	9/909	196.44	4.58 (2.26, 8.36)	Ref	-
<b>Unplanned all-cause hospitalisation</b>					
BNT162b2	16/749	147.17	10.87 (6.47, 17.23)	0.88 (0.59, 1.31)	0.519
Unvaccinated	35/909	192.07	18.22 (12.91, 25.04)	Ref	-
<b>28-day emergency department attendance</b>					
BNT162b2	19/749	51.36	36.99 (23.02, 56.58)	0.93 (0.63, 1.38)	0.719
Unvaccinated	30/909	62.21	48.22 (33.19, 67.90)	Ref	-

Abbreviation: CI: confidence interval; IBD: inflammatory bowel disease; IRR: incidence rate ratio; IPTW: inverse probability treatment weighting.

\* for unplanned IBD and all-cause hospitalisation, follow-up commenced from the second dose vaccination date to hospital admission date or study end date (September 30, 2021), whichever occurred earlier; for emergency department attendance, follow-up commenced from the second dose vaccination date to emergency department attendance date or 28 days since the vaccination, whichever occurred earlier.

\*\*some subgroup analyses further adjusted variables with a standard mean difference larger than 0.1 after the IPTW.



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