**Title:** Is vaccination against COVID-19 associated with inflammatory bowel disease flare? Self-controlled case series analysis using the UK CPRD.

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**Contributorship Statement**

The study was conceived by Prof Abhishek. All authors were involved in the design of the study. The analysis was carried out by Dr Nakafero. Drs Card and Nakafero jointly wrote the first draft. All authors edited the first and all subsequent drafts and approved the final draft for submission. Prof Abhishek is the guarantor of the article.

### Abstract:

### Objectives: To investigate the association between vaccination against COVID-19 and inflammatory bowel disease (IBD) flare.

### Methods: Patients with IBD vaccinated against COVID-19 who consulted for disease flare between 01/12/2020 and 31/12/2021 were ascertained from the Clinical Practice Research Datalink (CPRD). IBD flares were identified using consultation and corticosteroid prescription records. Vaccinations were identified using product codes and vaccination dates. The study period was partitioned into vaccine-exposed (vaccination date and 21-days immediately after), pre-vaccination (7-days immediately before vaccination), and the remaining vaccine-unexposed periods. Participants contributed data with multiple vaccinations and IBD flares. Season adjusted incidence rate ratios (aIRR) and 95% confidence intervals (CI) were calculated using self-controlled case-series analysis.

### Results: Data for 1911 IBD cases, 52% female, mean age 49 years, and 63% with ulcerative colitis (UC) were included. COVID-19 vaccination was not associated with increased IBD flares in the vaccine-exposed period when all vaccinations were considered (aIRR (95%CI) 0.89 (0.77-1.02), 0.79 (0.66-0.95), and 1.00 (0.79–1.27) in IBD overall, UC, and Crohn’s disease respectively). Analyses stratified to include only first, second or third COVID-19 vaccinations found no significant association between vaccination and IBD flares in the vaccine exposed period (aIRR (95%CI) 0.87 (0.71-1.06), 0.93 (0.75-1.15) and 0.86 (0.63-1.17) respectively). Similarly, stratification by COVID-19 before vaccination, and by vaccination with vectored DNA or mRNA vaccine did not reveal an increased risk of flare in any of these subgroups.

Conclusion: Vaccination against COVID-19 was not associated with IBD flares regardless of prior COVID-19 infection and whether mRNA or DNA vaccines were used.

### Study Highlights

**WHAT IS KNOWN**

* Reports of post vaccination Inflammatory Bowel Disease (IBD) flares may add to vaccine hesitancy in IBD patients.
* There is as yet no definitive study to demonstrate that such flares are not more common post vaccination than would be expected by chance.

**WHAT IS NEW HERE**

* Vaccination against COVID-19 with either vectored DNA or mRNA vaccines was not associated with a short-term increase in IBD flares.
* Prescribing clinicians and vaccine hesitant patients should be reassured that COVID-19 vaccination does not precipitate IBD flares.

**Introduction**

It has been recognized for some years that patients with IBD receiving immunosuppressive medication should be advised to receive vaccination against a number of infections (1,2). These commonly include influenza and pneumococcus, but there are variations around the world (3). Despite this the uptake of vaccination has often been suboptimal (4–7). With rates of vaccination at 60-80% being reported seasonal flu vaccine is relatively well accepted, but one UK hospital reported only 32.5% vaccinated during the H1N1 pandemic of 2009 (4), and less than 50% have been recorded as receiving Hepatitis B or pneumococcal vaccines as recommended (7). A variety of reasons for this have been proposed and have included worries about safety and the risk of IBD flare demonstrated by surveys of patients (8). This has led to interest in the safety of vaccinations in people with IBD, with specific reference to their effect upon disease activity (9).

The recognition that some IBD patients, including those treated with steroids for active flares, are at particular risk from COVID-19, caused inevitable concern (10,11). The rapid development of vaccinations offered the prospect of alleviating this risk. However given the previous experience of vaccination in IBD it is unsurprising that though most patients were willing to accept vaccination it also caused concerns about safety and efficacy among others (12–14). These may have been added to by limited reports of possible exacerbation of IBD post vaccination (15,16).

A small number of subsequent studies have now shown evidence specifically in IBD of immunogenicity (17,18), clinical efficacy and safety(19) of COVID-19 vaccinations. The review by Bhurwal et al did not evaluate the association between vaccination against Coivid-19 and IBD flares(19). These studies have however mainly been case series or surveys from individual or small groups of centres, and/or have related to specific vaccines. The risk of IBD flare with vaccination against COVID-19 originally suggested (15,16) has not to date been conclusively excluded in a large representative population. We have therefore carried out a study in the CPRD population which is representative of the overall UK population to clarify whether COVID vaccination is associated with an increased risk of IBD flare.

**Methods**

Data: Source data were extracted from Clinical Practice Research Datalink (CPRD) Aurum, a longitudinal anonymized electronic database of health records from 19 million patients registered with 738 general practices that dates back to 1995 (20). It includes information on demographic details, lifestyle factors, diagnoses, results of investigations, consultations, primary-care prescription, and vaccinations. Diagnostic and prescription data are recorded using medical codes (a combination of Read 2, SNOMED and local EMIS® codes) and product codes respectively. Data for vaccination against COVID-19, including date of vaccination and vaccine brand are provided by NHS Digital. COVID-19 is defined using primary-care diagnosis, serology, or polymerase chain reaction result.

Approvals: CPRD Research Data Governance (Reference: 21\_000670). This study used anonymized patient health records from the CPRD, and did not require individual participant consent.

Study design: Self-controlled case series analysis. This method quantifies the association between exposure and outcome using data from exposed participants that developed an outcome and is extensively used in vaccine safety studies (21,22). It has the advantage of implicitly controlling for all between-person confounding, by conditioning on the time of events and analyzing when exposures occur in relation to this within each individual.

Population: Adults aged ≥18 years with ≥1 primary-care consultation for IBD; and ≥1 prescription for 5-amino salicylate drugs (mesalazine, balsalazide, olsalazine) or any conventional immunosuppressing drugs i.e. azathioprine, 5-mercaptopurine, methotrexate, mycophenolate mofetil, ciclosporin, tacrolimus, sirolimus prior to 1st December 2020 were eligible to be included in the study, provided they also received ≥1 vaccination against COVID-19 and consulted their primary-care provider for ≥1 IBD flare in the study period. A primary-care diagnosis of IBD recorded in the CPRD has been validated to have a 92% positive predictive value for probable or highly probably diagnosis of IBD(23). Codes are provided in supplemental data, as appendix 1.

Study period: 1st December 2020 to 31st December 2021. Follow-up was censored if death, emigration from participating general practice, or last collection of data from general practice occurred before 31st December 2021.

Exposure: Vaccination against COVID-19 was the exposure of interest and was defined using product codes for vaccines and vaccination dates. Product codes were used to define the vaccine type and brand, specifically vectored DNA (AZD1222) and mRNA (mRNA-1273, BNT1262b2).

Outcome: IBD flare was the outcome of interest. It was defined as primary-care consultation with a diagnostic coding for IBD, diarrhoea, abdominal pain, or rectal-bleeding entered on that date, and accompanied with a corticosteroid prescription on the same or the subsequent date. Date of primary-care consultation for IBD flares was used to define the outcome date and participants could contribute data with multiple flares.

Exposed and unexposed periods: The study period was divided into a pre-vaccination period that immediately preceded vaccination, a vaccine-exposed period that immediately followed vaccination, and the remaining vaccine-unexposed baseline period (Figure 1). The vaccine-exposed period was defined as the date of vaccination and the21-days immediately after the date of vaccination as it takes approximately 2-3 weeks for primary COVID-19 immunization to induce an immunological response(24,25). We hypothesized that this period of immune reconstitution was most likely to be associated with increased disease activity. As patients with disease flare or acute illnesses may delay vaccination, the 7-days immediately preceding vaccination was considered separate from the vaccine-unexposed baseline period to minimize potential confounding. The vaccine-unexposed baseline period comprised of the remaining follow-up time post cohort entry and prior to cohort exit. As illustrated in Figure 1, the vaccine-unexposed baseline period comprised of follow-up time either before or after vaccination against COVID-19.

The study started on the 1st of December 2020, one week before the first COVID-19 vaccine was administered outside of trial setting in the UK to allow each potential vaccinated participant to have 7 days pre-vaccination period.

Statistical analyses: A multinomial Poisson model conditioned on the number of events and adjusted for the four seasons as categories defined in line with the Meteorological Office description(26) was fitted to calculate the adjusted incidence rate ratios (aIRR) and 95% confidence interval (CI) for association between vaccination and IBD flares. The analyses were adjusted for season as vaccination against COVID-19 predominantly occurred in the winter and spring months in the UK and there is a seasonal pattern to UC(27,28) The 7-days before and 21-days after COVID-19 vaccination were the pre-vaccination and vaccine-exposed period respectively. The remaining study period was considered as the vaccine-unexposed baseline period. A sensitivity analysis to account for bias due to late presentation of IBD flares considered 6-week post-vaccination exposed period. Stratified analysis considered 1st, 2nd or 3rd vaccine doses; and IBD type in the entire dataset. Stratified analysis according to vaccine type (AZD1222 vs. BNT1262b2) and prior COVID-19 considered the first vaccination against COVID-19.p<0.05 (two sided) were considered as statistically significant. Data analyses were carried out using Stata v.16.

**Results**

Data for 1911 IBD cases were included (Figure 2). The majority were female (52%) and their mean (standard deviation) age was 49 (17) years. 1209 (63%) had UC, 604 (32%) had Crohn’s disease, 98 (5%) had IBD without any specific coding for subtype. 754 (40%), 1132 (59%), and 23 (1%) participants received BNT162b2, AZD1222 and mRNA-1273 vaccines respectively as their first vaccine dose. 134 (7%) participants had COVID-19 prior to their first vaccine dose. 1005 (53%), 809 (42%), and 97 (5%) participants received three, two, and one vaccination against COVID-19 respectively in the study period. 1754 (91.8%), 137 (7.2%) and 20 (1%) participants had one, two, and more than two IBD flares in the study period. 74 participants (3.9%) did not contribute data for the entire follow-up period due to death (n = 16 (0.8%)) or transfer out of general practice surgery (n = 58 (3%)). 101 of the 108 (93.5%) patients that had an IBD flare in the 3-week vaccine-exposed period immediately after their first vaccination against COVID-19, received another dose of a COVID-19 vaccine. Similarly, 1713 of the 1803 (95%) patients that did not have an IBD flare in the 3-week vaccine exposed period after their first vaccination against COVID-19 received another dose of a COVID-19 vaccine.

Vaccinations against COVID-19 were not associated with IBD flares in the 21-day vaccine-exposed period when all vaccinations were analyzed together in a single dataset or separately (Table 1). The aIRR (95%CI) for flare in the vaccine-exposed period in those with ulcerative colitis (UC) was significantly reduced at 0.79 (0.66-0.95), whereas in Crohn’s disease it was unaltered (aIRR 1.00 (0.79-1.27)) (Table 2). Data for 98 patients that could only be classified as IBD were excluded from this analysis.

On sensitivity analysis that extended the vaccine-exposed period to 6-weeks immediately after vaccination, there was no association between vaccination against COVID-19 and IBD flare, or Crohn’s disease flare with aIRR (95% CI) 0.89 (0.79-1.00) and 1.02 (0.83-1.26) respectively, and a negative association with UC flare with aIRR (95% CI) 0.81(0.69-0.94)).

After the first COVID-19 vaccination, the adjusted rate ratios for IBD flare in the vaccination-exposed periods were comparable in those vaccinated with mRNA-BNT162b2 and vectored DNA vaccines with aIRR (95%CI) 0.81 (0.59-1.10) and 0.83 (0.64-1.08) (Table 2). In patients with previous COVID-19, the first dose of COVID-19 vaccine was associated with a lower risk of IBD flare within 21-days with aIRR (95%CI) 0.58 (0.35-0.95).

Table 1: The association between COVID-19 vaccination and inflammatory bowel disease (IBD) flare

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| COVID-19 vaccination | Risk period | Events(n) | Person-time (days) | Incidence Rate Ratio (95%CI) | Adjusted IRR (95%CI) \* | p-value |
| All 3 doses | Vaccine unexposed baseline | 1701 | 621626 | 1 | 1 | -/- |
| Pre-vaccinations  | 103 | 36183 | 1.04 (0.85-1.26) | 1.00 (0.82-1.23) | 0.978 |
| Vaccine exposed  |  |  |  |  |  |
| 0 - 21 days | 269 | 105221 | 0.93 (0.82-1.06) | 0.89 (0.77-1.02) | 0.09 |
| 0 - 7 days | 105 | 35873 | 1.07 (0.87-1.30) | 1.02 (0.84-1.25) | 0.839 |
| 8 - 14 days  | 77 | 35091 | 0.80 (0.64-1.00) | 0.76 (0.60-0.96) | 0.02 |
| 15 - 21 days | 87 | 34257 | 0.92 (0.74-1.15) | 0.87 (0.70-1.09) | 0.231 |
| 1st dose | Vaccine unexposed baseline | 1701 | 621626 | 1 | 1 | -/- |
| Pre-vaccination  | 41 | 14637 | 1.01 (0.74-1.38) | 0.92 (0.67-1.26) | 0.604 |
| Vaccine exposed  |  |  |  |  |  |
| 0 - 21 days | 114 | 43853 | 0.94 (0.77-1.13) | 0.87 (0.71-1.06) | 0.159 |
| 0 - 7 days | 48 | 14635 | 1.18 (0.89-1.57) | 1.08 (0.81-1.45) | 0.584 |
| 8 - 14 days  | 30 | 14629 | 0.74 (0.51-1.06) | 0.68 (0.47-0.98) | 0.038 |
| 15 - 21 days | 36 | 14589 | 0.89 (0.64-1.24) | 0.83 (0.59-1.15) | 0.264 |
| 2nd dose | Vaccine unexposed baseline | 1701 | 621626 | 1 | 1 | -/- |
| Pre-vaccination  | 42 | 13867 | 1.11(0.81-1.50) | 1.06 (0.77-1.45) | 0.732 |
| Vaccine exposed  |  |  |  |  |  |
| 0 - 21 days | 111 | 41375 | 0.98 (0.81-1.50) | 0.93 (0.75-1.15) | 0.507 |
| 0 - 7 days | 40 | 13840 | 1.06 (0.77-1.44) | 1.00 (0.72-1.38) | 0.999 |
| 8 - 14 days  | 38 | 13796 | 1.01 (0.73-1.39) | 0.94 (0.68-1.31) | 0.726 |
| 15 - 21 days | 33 | 13739 | 0.88 (0.62-1.24) | 0.81 (0.57-1.16) | 0.245 |
| 3rd dose | Vaccine unexposed baseline | 1701 | 621626 | 1 | 1 | -/- |
| Pre-vaccination  | 20 | 7679 | 0.96 (0.61-1.49) | 1.10 (0.63-1.72) | 0.678 |
| Vaccine exposed |  |  |  |  |  |
| 0 - 21 days | 44 | 19993 | 0.81 (0.60-1.09) | 0.86 (0.63-1.17) | 0.335 |
| 0 - 7 days | 17 | 7398 | 0.84 (0.52-1.36) | 0.93 (0.57-1.50) | 0.751 |
| 8 - 14 days  | 9 | 6666 | 0.50 (0.26-0.96) | 0.54 (0.28-1.05) | 0.067 |
| 15 - 21 days | 18 | 5929 | 1.12 (0.70-1.78) | 1.20 (0.72-1.93) | 0.437 |

\*Adjusted for seasons as per the Meteorological Office

Table 2: The association between COVID-19 vaccination and inflammatory bowel disease (IBD) flare: stratified analysis

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Risk period | Events (n) | Person-time (days) | Incidence Rate Ratio (95%CI) | Adj IRR (95%CI)\* | p-value |
|  | **Vaccine type‡** |
| BNT1262b2 | Vaccine unexposed baseline  | 377 | 126741 | 1 | 1 | -/- |
| Pre-vaccination | 19 | 5831 | 1.05 (0.66-1.67) | 0.91 (0.57-1.45) | 0.685 |
| Vaccine exposed |  |  |  |  |  |
| 0 - 21 days | 47 | 17450 | 0.87 (0.64-1.18) | 0.81 (0.59-1.10) | 0.176 |
| 0 – 7 days | 21 | 5829 | 1.16 (0.75-1.81) | 1.04 (0.66-1.62) | 0.870 |
| 8 – 14 days | 11 | 5823 | 0.61 (0.33-1.11) | 0.55 (0.30-1.01) | 0.055 |
| 15 – 21 days | 15 | 5798 | 0.84 (0.50-1.40) | 0.77 (0.46-1.30) | 0.325 |
| Vectored DNA vaccine | Vaccine unexposed baseline  | 545 | 25880 | 1 | 1 | -/- |
| Pre-vaccination | 22 | 8631 | 0.84 (0.54-1.29) | 0.80 (0.52-1.24) | 0.319 |
| Vaccine exposed |  |  |  |  |  |
| 0 - 21 days | 65 | 182595 | 0.83 (0.64-1.07) | 0.83 (0.64-1.08) | 0.16 |
| 0 – 7 days | 26 | 8631 | 1.00 (0.67-1.48) | 0.96 (0.65-1.43) | 0.844 |
| 8 – 14 days | 18 | 8631 | 0.69 (0.43-1.10) | 0.67 (0.42-1.08) | 0.099 |
| 15 – 21 days | 21 | 8618  | 0.81 (0.52-1.25) | 0.80 (0.52-1.25) | 0.329 |
| **Inflammatory bowel disease type ±** |
| Ulcerative colitis  | Vaccine unexposed baseline  | 1088 | 396112 | 1 | 1 | -/- |
| Pre-vaccination | 75 | 23065 | 1.18 (0.93-1.49) | 1.13 (0.89-1.43) | 0.325 |
| Vaccine exposed | 156 | 66959 | 0.84 (0.71-1.00) | 0.79 (0.66-0.95) | 0.011 |
| Crohn’s disease  | Baseline | 534 | 192840 | 1 | 1 | -/- |
| Pre-vaccination | 22 | 11249 | 0.70 (0.46-1.08) | 0.71 (0.46-1.09) | 0.115 |
| Vaccine exposed | 90 | 32826 | 0.99 (0.79-1.23) | 1.00 (0.79-1.27) | 0.992 |
| **COVID-19 infection prior to first vaccination†** |
| No  | Vaccine unexposed baseline  | 1522 | 558607 | 1 | 1 | -/-  |
| Pre-vaccination | 90 | 32389 | 1.02 (0.82-1.26) | 0.98 (0.79-1.22 | 0.872 |
| Vaccine exposed | 250 | 94533 | 0.97 (0.85-1.11) | 0.93 (0.80-1.07) | 0.291 |
| Yes  | Vaccine unexposed baseline  | 179 | 63019 | 1 | 1 | -/- |
|  Pre-vaccination | 13 | 3794 | 1.20 (0.68-2.10) | 1.17 (0.66-2.07) | 0.593 |
| Vaccine exposed | 19 | 10688 | 0.62 (0.36-1.00) | 0.58 (0.35-0.95) | 0.031 |

\*Adjusted for seasons as per the Meteorological Office

**‡** First vaccine dose analysed. People vaccinated with mRNA-1273 vaccine (n=23) were excluded from this analysis.

**±** People with inflammatory bowel disease (IBD) not classified (n=98) were excluded from the IBD type sensitivity analysis

† Primary-care consultation for COVID-19 or complication of COVID-19 or positive test results.

**Discussion**

*Main findings:* Our study has demonstrated in a population representative of IBD patients in the UK, vaccinated with the COVID-19 vaccines commonly in use in the UK that COVID-19 vaccination was not associated with an increase in flares of IBD. This remained true in subgroups of the data defined by the vaccine technology received, the type of IBD (Crohn’s or UC) and the presence or absence of prior COVID-19. It is similarly true no matter which of three doses of the vaccine are studied. In fact, for patients with UC the rate of flare was significantly reduced during the 3 weeks after vaccination.

*Study strengths and limitations:* Strengths of our study are its power, the generalisability of its results and the confidence we are able to have that our results are not influenced by confounding factors which might affect the choice to be vaccinated because we used the SCCS methodology that is widely used in vaccine safety studies(29). The power of the study is derived from the large base population of CPRD from which it is drawn, and its importance in this instance is that it permits our relative risk estimates to be quite precise and so to confidently exclude any large increase in flares post vaccination. To illustrate this overall our adjusted incidence rate ratio for IBD flares was 0.89, and our 95% confidence interval of 0.77-1.02 allows as to state that our data are unlikely to have arisen in a population where there was an excess of flares of over 2% above baseline following vaccination. Our confidence in generalisability of our result to IBD patients in the UK likewise is derived from our data source since CPRD is representative of the over 98% of the UK population registered with a general practitioner(20,30), and we included all adults in this population who received COVID-19 vaccination and experienced a coded IBD flare within the study period.

Finally our use of a self-controlled case series design, ensures that non time dependant between person confounding was excluded since each subject was compared only to themselves at different time points(21). As all subjects who had both received vaccination and experienced an IBD flare were included in our study, there was no selection bias.

As with all studies though, ours has limitations. Firstly, we have been obliged due to a lack of availability of linked inpatient data to adjust our flare definition compared to that which we have previously used in a manner which effectively excludes flares presenting first to hospital for admission. We have done this because previous experience suggests to us that the recording of hospital admission dates in primary-care data may not be adequately precise in this setting and could affect results by causing misclassification bias (31,32). It seems however very unlikely that vaccination would preferentially precipitate this small subset of severe flares without any effect on milder flares and so we do not think this will have biased out results. Similarly, IBD flares that were managed exclusively in hospital out-patient clinics were excluded from this study. However, GPs serve as first point of contact for patients with IBD experiencing a flare, and participate in their initial outpatient management, including with corticosteroid prescription, unless the disease flare is severe enough to warrant hospital admission(33). Any bias from missing data on IBD flares requiring hospitalisation or those that were managed in gastroenterology out-patient clinics is unlikely to affect the validity of our findings as any resulting bias will be non-differential in nature.

Secondly as general practice records do not reliably code for biologics, we are unable to examine whether the subset of patients receiving them have an altered risk of adverse effects from vaccination. We see no reason though to expect more extreme immunologically driven side effects in these groups in whom the vaccine is less immunogenic(17,18). Similarly, we are unable to examine subgroups by the extent or distribution of IBD as this information is not in general coded in primary-care records. Again, we see no reason to believe though that the effect of the vaccine in this regard would be differential between these groups. Another limitation of our method is that since we require steroid prescription to define flare it is possible that there may be an association with more minor flares treated with 5-aminosalicylates alone. Though we cannot exclude this we feel that such minor effects would be unlikely to greatly discourage vaccination uptake and that it is the more significant flares which we have studies which are the primary concern. Patients that experience an IBD flare soon after vaccination against COVID-19 may be discouraged from seeking future vaccinations against COVID-19. This has the potential to bias any association between vaccination and disease flare when data from multiple vaccinations are analyzed together. To minimize such a bias, we presented data on association between vaccination and disease flares according to sequential vaccine doses. Furthermore, our results show that IBD flares temporally associated with first dose of vaccination against COVID-19 did not deter patients from getting further vaccinations against COVID-19. Finally, we can of course study only the vaccinations which have been widely used in the UK NHS as we have no data relevant to other vaccine technologies which may limit the generalisability of our findings in settings where other vaccine technologies are in use.

*Research in context:* Our findings are consistent with those of the recent meta-analysis of studies of the safety of SARS-CoV-2 vaccination in IBD patients(34), showing as they do no increase in flare risk. In contrast to the six small cohorts comprising 4537 patients and 75 flares reported there though, our report represents the experience of 73,626 IBD patients with documented vaccination among whom 1,940 experienced a flare at some time during the study period. In addition rather than reporting the absolute flare incidence post vaccination (flare probability 0.01 (95% CI 0.01-0.03)(34)) we have reported an incidence rate ratio comparing the risk in periods following vaccination to subjects’ experience at other times (IRR 0.89 (95% CI (0.77-1.02)). Of the subjects in the studies included in meta-analysis cited earlier, the majority (n=3316) came from a single study reporting a US cohort study ascertaining data via repeated survey of participants(35). This study, though potentially less representative of typical IBD patients than is ours, was able to report upon biologic and immunomodulator use and therefore to confirm a low absolute risk of disease flare defined using a combination of symptoms and treatment change within 1 month of vaccination against COVID-19 in a population in which the majority were taking biologics or small molecules prior to vaccination. However, it reported a high rate of IBD symptoms e.g. bowel frequency, extra-intestinal manifestations, and abdominal pain in 12%, 12%, and 11% of participants, respectively in this period and did not report comparative estimates leaving the question of association between COVID-19 vaccination and IBD flares unanswered. A further study not within the meta-analysis which is based upon self-reported flares by patients in a questionnaire(36) gives additional assurance that the lack of association does indeed include minor flares since these would be included in the 147 subjective records of flare which they report.

*Clinical implications:* Our study provides population-based evidence that vaccination against COVID-19 in patients with IBD does not increase the risk of flare. Patients expressing concern in this regard should therefore be reassured and encouraged to take up vaccination if they have not already done so.

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2nd dose

1st dose

3rd dose



End

Start

**Figure 1**. Schematic representation of self-controlled case series (SCCS) analysis periods. The vaccine unexposed baseline, pre-vaccination, and vaccine-exposed periods are shaded speckled, solid and lined respectively. Vaccinations against COVID-19 are represented by solid arrows. Unfilled arrows below indicate the start and end of the study period. Not all participants received all three vaccinations. Follow up began on the latest of current registration date in general practice surgery or 1st December 2020 and was censored on the earliest of 31st December 2021, death date, transfer out date, date of last data collection from the general practice surgery.

**Figure 2: Study population selection criteria for self-controlled case-series analysis**

 Inflammatory bowel disease (IBD) cases who received ≥1 SARS-CoV-2 vaccine

n= 73,626

        Excluded n=71,686

71,686: Vaccinated IBD cases without a flare

SARS-CoV-2 vaccinated IBD cases with IBD flare within study period:

n=1,940

        Excluded n=29

28: participants with at least one gap between vaccinations of <4 weeks\*

1: Transfers out of GP surgery before first SARS-CoV-2 vaccine.

Included in the SCCS analysis

n=1,911

\*Rationale for exclusion: Primary vaccination against COVID-19 in the UK were administered ≥4 weeks apart. Thus, vaccination dates <4 week apart may potentially be incorrect entries. Additionally, vaccine exposed period was 3 weeks after vaccination in this study. If the vaccinations are administered less than 4 weeks apart, the pre-vaccination period of the second vaccine truncates the post-vaccine exposed period of the earlier vaccine thus potentially misclassifying outcomes.