

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 Covid-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 the 21-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
1 st 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
2 nd 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
3 rd 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 us 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 studied 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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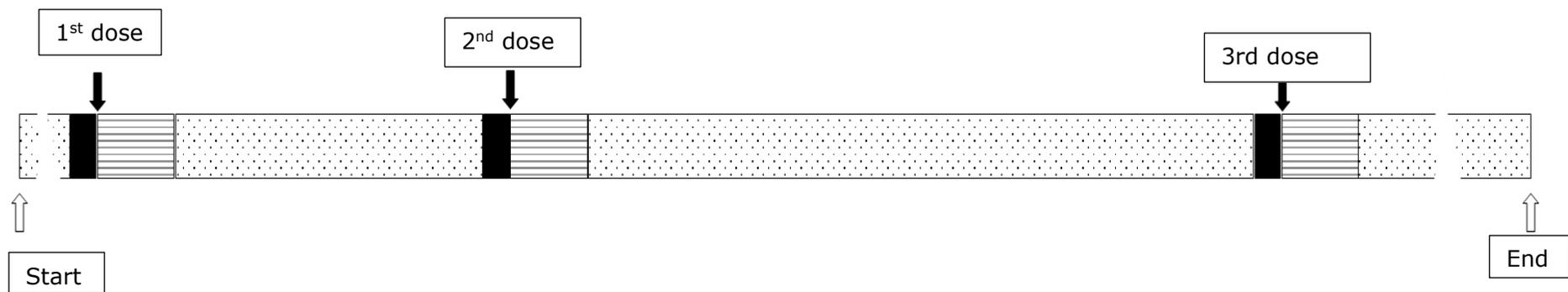
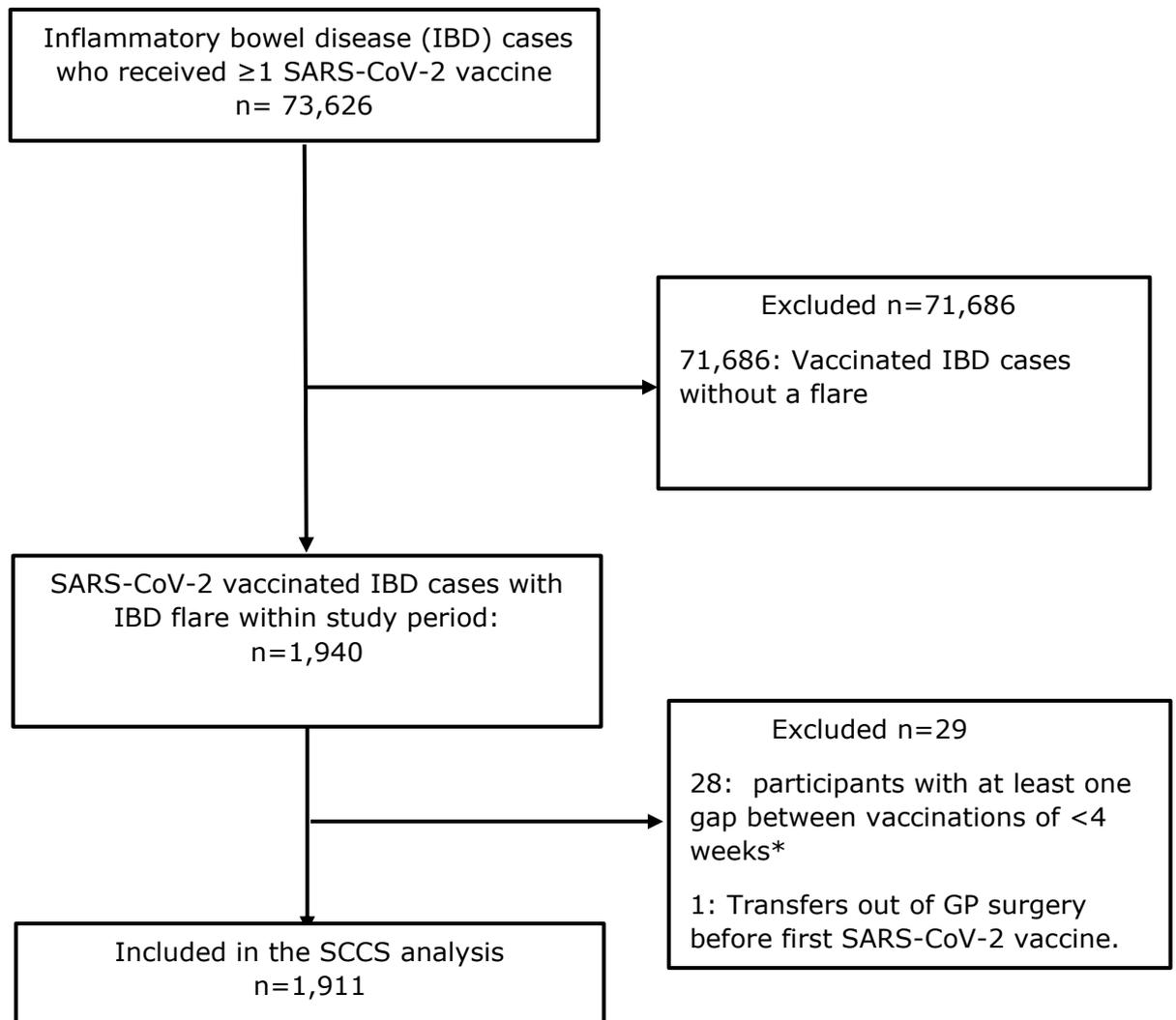


Figure 1. Schematic representation of self-controlled case series (SCCS) analysis periods. The vaccine unexposed baseline, pre-vaccination, and vaccine-exposed periods are shaded speckled, solid and lined respectively. Vaccinations against COVID-19 are represented by solid arrows. Unfilled arrows below 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



*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.

Appendix 1

Codes used to define cases exposures and outcomes.

Table of codes used to identify IBD

term	medcodeid	originalreadcode
Adverse reaction to Modulen IBD	1026501000006110	ALLERGY1227NEMIS
Ulcerative colitis	107644019	J4101
Crohn's disease NOS	1222351011	J40z-1
Regional enteritis - Crohn's disease	179501000006113	J40
Management of inflammatory bowel disease	2269891000000116	8Cc5
Management of IBD (inflammatory bowel disease)	2269901000000115	8Cc5-1
Management of IBD (inflammatory bowel disease)	2269901000000115	8Cc5-1
Dietary education for inflammatory bowel disease	2338581000000110	8CA4W
Exacerbation of Crohn's disease of large intestine	2532950019	J4012
Exacerbation of ulcerative colitis	2532953017	J4104
Exacerbation of Crohn's disease of small intestine	2532958014	J4005
Crohn's disease of rectum	2559781000006115	^ESCTCR255978
Crohn's proctitis	2559801000006116	^ESCTCR255980
Crohn disease of rectum	2559821000006114	^ESCTCR255982
Idiopathic proctocolitis	2579429013	J41
Crohn disease of large bowel	2621151000006116	^ESCTCR262115
Crohns disease, large intestine	2621161000006119	^ESCTCR262116
Ulcerative pancolitis	2872721013	J413
IBD - Inflammatory bowel disease	2891431000006118	^ESCTIB289143
IBD - Inflammatory bowel disease	2891431000006118	^ESCTIB289143
Orofacial Crohn's disease	302322010	J08z9
Crohn's disease of the ileum unspecified	302939018	J4003
Crohn's disease of the ileum NOS	302940016	J4004
Crohn's disease of the small bowel NOS	302941017	J400z
Regional ileocolitis	302946010	J402
Ulcerative ileocolitis	302953018	J4100
Ulcerative proctocolitis NOS	302956014	J410z
Other idiopathic proctocolitis	302959019	J41y
Other idiopathic proctocolitis NOS	302961011	J41yz
Idiopathic proctocolitis NOS	302962016	J41z
[X]Other Crohn's disease	303761010	Jyu40
[X]Other ulcerative colitis	303762015	Jyu41
CD - Crohn's disease	3047391000006119	^ESCTCD304739
Crohn disease	3047411000006119	^ESCTCR304741
Crohns disease	3047421000006110	^ESCTCR304742
Arthropathy in ulcerative colitis	309743013	N0310
Arthropathy in Crohn's disease	309744019	N0311
Juvenile arthritis in Crohn's disease	309833017	N0453

Juvenile arthritis in ulcerative colitis	309836013	N0454
Crohn's ileitis	3113541000006111	^ESCTCR311354
Crohn disease of ileum	3113551000006113	^ESCTCR311355
Crohn's disease of colon	3316751000006117	^ESCTCR331675
Crohn disease of colon	3316801000006112	^ESCTCR331680
Crohns disease, colon	3316811000006110	^ESCTCR331681
Chronic ulcerative proctitis	3346671000006113	^ESCTCH334667
UC - Ulcerative colitis confined to rectum	3346681000006111	^ESCTUC334668
Ulcerative colitis confined to rectum	3346691000006114	^ESCTUL334669
Chronic ulcerative rectosigmoiditis	3351311000006117	^ESCTCH335131
Chronic ulcerative proctosigmoiditis	3351321000006113	^ESCTCH335132
Ulcerative colitis confined to rectum and sigmoid colon	3351341000006118	^ESCTUL335134
Ulcerative proctosigmoiditis	3351351000006116	^ESCTUL335135
Crohn's disease of duodenum	3414681000006119	^ESCTCR341468
Crohn's duodenitis	3414701000006116	^ESCTCR341470
Crohn disease of duodenum	3414711000006118	^ESCTCR341471
Crohn disease of small intestine	3420881000006117	^ESCTCR342088
Crohns disease, small intestine	3420891000006119	^ESCTCR342089
UC - Ulcerative colitis	3553391000006113	^ESCTUC355339
Crohn's disease of the large bowel NOS	396357012	J401z
Inflammatory bowel disease	41137017	J4-2
Ulcerative proctocolitis	435370011	J410
Crohn's disease of oral soft tissues	4784091000006115	^ESCTCR478409
Oral Crohn's disease	4784111000006112	^ESCTOR478411
Crohn disease of terminal ileum	4785581000006112	^ESCTCR478558
Arthropathy in Crohn disease	4808981000006112	^ESCTAR480898
Juvenile arthritis in Crohn disease	4809351000006111	^ESCTJU480935
Ulcerative proctitis	496249010	J4103
Ulcerative rectosigmoiditis	496332018	J4102
Crohn's disease	56765016	J40-1
Crohn's colitis	601031000006119	J401z-1
Crohn's disease of the terminal ileum	601091000006115	J4002
Modulen IBD	655231000033115	DRGA1227NEMIS
Exacerbation of Crohn disease of large intestine	6853111000006114	^ESCTEX685311
Exacerbation of Crohn disease of small intestine	6853131000006115	^ESCTEX685313
Ulcerative (chronic) enterocolitis	85891000006115	J411
Ulcerative (chronic) ileocolitis	85901000006116	J412
Ulcerative colitis and/or proctitis	85931000006112	J41-2
Regional enteritis - Crohn	886291000006112	J40-99
[RFC] Crohns disease	906051000006118	HNG0087
[RFC] Ulcerative colitis	906191000006113	HNG0081

Table of codes used to identify COVID-19 vaccination

prodcode	Term
13739541000033100	Comirnaty COVID-19 mRNA Vaccine 30micrograms/0.3ml dose concentrate for dispersion for injection multidose vials (Pfizer Ltd)
13739441000033100	COVID-19 Vaccine AstraZeneca (ChAdOx1 S [recombinant]) 5x10,000,000,000 viral particles/0.5ml dose suspension for injection multidose vials (AstraZeneca UK Ltd)
13764941000033100	Spikevax COVID-19 mRNA (nucleoside modified) Vaccine 0.1mg/0.5ml dose dispersion for injection multidose vials (Moderna, Inc)

Table of codes used to identify symptoms of possible flare of IBD

term	medcodeid	originalreadcode
Diarrhoea	103578017	19F2
General abdominal pain-symptom	1218836019	197A-1
Fecal occult blood positive	12190101000006119	^ESCT1219010
Colicky abdominal pain	1236016018	1962
Epigastric pain	132601013	1972
Upper abdominal pain	137890011	197B
Bloody diarrhoea	1566381000006119	EMISNQBL1
Referral to rectal bleeding clinic	1779671000006113	EMISNQRE289
Loose stools	1786047017	19F-2
[D]Functional abdominal pain syndrome	1786591000006112	R090P
O/E - PR - blood	1805301000006115	EMISNQOE16
Abdominal pain score	1858471000006119	JHCAB1
Manchester triage - Abdominal pain in adult	1983911000006113	EMISNQMA113
Manchester triage - Abdominal pain in child	1983921000006117	EMISNQMA114
Manchester triage - Diarrhoea and vomiting	1984091000006117	EMISNQMA131
Rectal bleeding	20792019	J5730-1
Referral to rectal bleeding clinic	2111911000000119	8HTE0
Noninfective diarrhoea	221051000000112	J4-3
Altered blood in stools	221161000000111	J681-2
Blood in stools altered	221171000000116	J681-3
Generalised abdominal pain	252305018	197A
No abdominal pain	252570014	1961
Non-colicky abdominal pain	252571013	1963
Central abdominal pain	252584016	1971
Left flank pain	252587011	1975
Right flank pain	252588018	1976
Painful rectal bleeding	2534219010	196B
Painless rectal bleeding	2534250012	196C
O/E - umbilical pain on palp.	254357017	25C-4
Melena	2545151000006112	^ESCTME254515
Altered blood passed per rectum	2545171000006119	^ESCTAL254517

Acute abdominal pain syndrome	2646781000006115	^ESCTAC264678
Intestinal colic	2659101000006115	^ESCTIN265910
Spasmodic abdominal pain	2659121000006113	^ESCTSP265912
Colicky abdominal pain	2659131000006111	^ESCTCO265913
PR - Bleeding per rectum	2692001000006117	^ESCTPR269200
Blood per rectum	2692011000006119	^ESCTBL269201
PR - Blood per rectum	2692021000006110	^ESCTPR269202
RB - Rectal bleeding	2692031000006113	^ESCTRB269203
Rectal hemorrhage	2692051000006118	^ESCTRE269205
AP - Abdominal pain	2842251000006112	^ESCTAP284225
Appendicular colic	302696014	J23z0
Irritable bowel syndrome with diarrhoea	303172010	J5210
Haemorrhage of rectum and anus NOS	303317017	J573z
[D]Upper abdominal pain	303651000006110	R090H
[D]Abdominal pain	317562013	R090
[D]Abdominal colic	317564014	R0901
[D]Colic NOS	317565010	R0902
[D]Epigastric pain	317568012	R0905
[D]Umbilical pain	317569016	R0906
[D]Recurrent acute abdominal pain	317577017	R090E
[D]Other specified abdominal pain	317586010	R090y
[D]Abdominal pain NOS	317587018	R090z
[X]Other and unspecified abdominal pain	318003010	Ryu11
Diarrhea of presumed infectious origin	3196731000006117	^ESCTDI319673
Occult blood in stools	3468331000006119	^ESCTOC346833
Occult blood in stool	3468351000006114	^ESCTOC346835
Diarrhea	3512721000006112	^ESCTDI351272
D - Diarrhoea	3512731000006110	^ESCTDD351273
D - Diarrhea	3512741000006117	^ESCTDD351274
Observation of diarrhoea	3512751000006115	^ESCTOB351275
Observation of diarrhea	3512761000006118	^ESCTOB351276
Chronic diarrhoea	353856013	J43z-1
Abdominal pain	36112013	1969
Non-infective diarrhea	3637781000006111	^ESCTNO363778
Left colic flexure	3680511000006116	^ESCTLE368051
Site of abdominal pain	369361010	197-3
Flank pain	369363013	197-1
Abdominal pain type	369368016	196-1
Diarrhoea and vomiting	372283012	19G
Lower GI hemorrhage	3926391000006110	^ESCTLO392639
Lower GI bleeding	3926401000006112	^ESCTLO392640
Lower GI haemorrhage	3926411000006110	^ESCTLO392641
Lower GIT - gastrointestinal haemorrhage	3926421000006119	^ESCTLO392642
Lower GIT - gastrointestinal hemorrhage	3926431000006116	^ESCTLO392643

Haemorrhage of rectum and anus	396382012	J573
Diarrhoea symptoms	397927015	19F
Diarrhoea symptom NOS	397928013	19FZ
Faeces: fresh blood present	404540010	4762
Haemorrhagic diarrhoea	4058311000006112	^ESCTHA405831
Hemorrhagic diarrhea	4058321000006116	^ESCTHE405832
Bloody diarrhea	4058331000006118	^ESCTBL405833
Generalized abdominal pain	4077761000006110	^ESCTGE407776
[D]Nonspecific abdominal pain	455443010	R090N
On examination - abdominal pain - right hypochondrium	4559791000006113	^ESCTON455979
On examination - abdominal pain - epigastrium	4559811000006112	^ESCTON455981
On examination - abdominal pain - left hypochondrium	4559831000006118	^ESCTON455983
On examination - abdominal pain - right lumbar	4559851000006113	^ESCTON455985
On examination - abdominal pain - umbilical	4559871000006115	^ESCTON455987
On examination - abdominal pain - left lumbar	4559901000006115	^ESCTON455990
On examination - abdominal pain - right iliac	4559921000006113	^ESCTON455992
On examination - abdominal pain - hypogastrium	4559941000006118	^ESCTON455994
On examination - abdominal pain - left iliac	4559961000006119	^ESCTON455996
PRB - Rectal bleeding	464499018	J5730-2
Rectal haemorrhage	464500010	J5730
Irritable bowel syndrome with diarrhea	4786241000006112	^ESCTIR478624
Chronic diarrhea	5089171000006111	^ESCTCH508917
Blood in stool	517981000006116	J681-1
Type of abdominal pain	5243121000006113	^ESCTTY524312
Diarrhea and vomiting	5272811000006119	^ESCTDI527281
D+V - Diarrhoea and vomiting	5272821000006110	^ESCTDV527282
D&V - Diarrhoea and vomiting	5272831000006113	^ESCTDV527283
Hemorrhage of rectum and anus	5493021000006119	^ESCTHE549302
Diarrhea symptom	5498121000006114	^ESCTDI549812
Feces: fresh blood present	5514661000006113	^ESCTFE551466
C/O - melena	5533081000006117	^ESCTCO553308
Complaining of melena	5533091000006119	^ESCTCO553309
Diarrhea and vomiting, symptom	5571851000006116	^ESCTDI557185
Melena - O/E of feces	5576641000006110	^ESCTME557664
Melena on examination of feces	5576651000006112	^ESCTME557665
Diarrhoea	619741000006114	19F-1
Diarrhoea & vomiting -? infect	619761000006113	A083-1
Diarrhoea & vomiting, symptom	619771000006118	19FZ-1
Diarrhoea - presumed non-infectious	619781000006115	J4zz-1
LS - Loose stools	6596461000006117	^ESCTLS659646
Loose motion	6596471000006112	^ESCTLO659647
Bright red blood in stool	6717721000006115	^ESCTBR671772

Bright red blood per rectum	6717731000006117	^ESCTBR671773
BRBPR - Bright red blood per rectum	6717751000006112	^ESCTBR671775
Feces: blood	6717761000006114	^ESCTFE671776
Faeces: blood	6717781000006116	^ESCTFA671778
Diarrhoea of presumed infectious origin	72144015	A083
Diarrhoea & vomiting	854661000006115	EGTON6
Anal/rectal haemorrhage	886471000006110	J573-99
Lower abdominal pain	90723010	197C
[RFC] Loose stools	909311000006110	HNGZ003
Colicky abdominal pain control	958281000006114	EMISNQCO8
Colicky abdominal pain present	958291000006112	EMISNQCO9
Colicky abdominal pain absent	958301000006113	EMISNQCO10
Blood in stools	961941000006111	EMISCBL2
Diarrhoea/loose stools	982731000006112	EMISCDI58

List of codes used to identify corticosteroid prescriptions to define IBD flare.

prodcodeid	termfromemis
10212141000033111	Prednisolone 10mg tablets
10212341000033114	Prednisolone 20mg tablets
10212441000033115	Pevanti 2.5mg tablets (Advanz Pharma)
10212541000033119	Pevanti 5mg tablets (Advanz Pharma)
10212641000033118	Pevanti 10mg tablets (Advanz Pharma)
10212741000033110	Pevanti 20mg tablets (Advanz Pharma)
10212941000033113	Pevanti 25mg tablets (Advanz Pharma)
10266841000033117	Prednisolone 5mg/5ml oral solution unit dose
10494341000033117	Prednisolone 10mg/ml oral solution sugar free
10988941000033111	Prednisolone Dompe Oral solution 5 mg/5 ml unit dose
1114241000033116	Prednisolone 2.5mg gastro-resistant tablets
1114341000033114	Prednisolone 5mg gastro-resistant tablets
1115641000033119	Predfoam 20mg/application enema (Chemidex Pharma Ltd)
1115641000033119	Predfoam 20mg/application enema (Chemidex Pharma Ltd)
1115741000033111	Prednisolone 20mg/application foam enema
1119141000033110	Prednisolone Injection 16 mg/ml
1119241000033115	Prednisolone 25mg/1ml suspension for injection ampoules
1119341000033113	Prednisolone Sodium Phosphate Injection 16 mg/1 ml
1126741000033110	Prednisolone 20mg/100ml rectal solution
1126841000033117	Predsol 20mg/100ml retention enema (RPH Pharmaceuticals AB)
1126941000033113	Predenema 20mg/100ml long tube (Forest Laboratories UK Ltd)
1127041000033114	Prednisolone 20mg/100ml enema long tube
1127141000033113	Predenema 20mg/100ml standard tube (Forest Laboratories UK Ltd)
1127341000033111	Prednisolone 5mg soluble tablets
1128341000033110	Prednisolone Suppositories 5 mg
1129341000033115	Predsol 5mg suppositories (Focus Pharmaceuticals Ltd)

1130741000033110	Prednisolone 25mg tablets
1130841000033117	Prednisolone Steaglate Tablets 6.65 mg
1131741000033117	Prednisolone 1mg tablets
1131841000033110	Prednisolone 2.5mg tablets
1131941000033119	Prednisolone 5mg tablets
1132041000033113	Prednisone Tablets 1 mg
1132141000033112	Prednisone Tablets 5 mg
1137341000033113	Prednesol Soluble tablets 5 mg
11507841000033115	Prednisolone 1mg gastro-resistant tablets
11664841000033116	Prednisolone 30mg tablets
1266341000033117	Scheriproct ointment (LEO Pharma)
1266941000033118	Scheriproct suppositories (LEO Pharma)
1357541000033112	Solu-Medrone 40mg powder and solvent for solution for injection vials (Pfizer Ltd)
1361441000033110	Solu-Medrone 1g powder and solvent for solution for injection vials (Pfizer Ltd)
1361541000033111	Solu-Medrone 125mg powder and solvent for solution for injection vials (Pfizer Ltd)
1361641000033112	Solu-Medrone 2g powder and solvent for solution for injection vials (Pfizer Ltd)
1361741000033115	Solu-Medrone 500mg powder and solvent for solution for injection vials (Pfizer Ltd)
2509341000033118	*Prednisolone Tablets
2509441000033112	*Prednisolone Granules
2509541000033113	*Prednisolone Liquid
2509641000033114	*Prednisolone Powder
2509741000033117	*Prednisolone Pills (Sucrose)
3229241000033116	Methylprednisolone 40mg/1ml / Lidocaine 10mg/1ml (1%) suspension for injection vials
3229341000033114	Methylprednisolone 80mg/2ml / Lidocaine 20mg/2ml (1%) suspension for injection vials
3269741000033119	Cinchocaine 0.5% / Prednisolone 0.19% ointment
3280241000033117	Cinchocaine 1mg / Prednisolone hexanoate 1.3mg suppositories
420641000033117	Depo-Medrone 120mg/3ml suspension for injection vials (Pfizer Ltd)
420741000033114	Depo-Medrone 80mg/2ml suspension for injection vials (Pfizer Ltd)
421341000033117	Depo-Medrone with Lidocaine suspension for injection 2ml vials (Pfizer Ltd)

422841000033117	Deltastab 25mg/1ml suspension for injection ampoules (Advanz Pharma)
423141000033116	Depo-Medrone 40mg/1ml suspension for injection vials (Pfizer Ltd)
423641000033114	Depo-Medrone with Lidocaine suspension for injection 1ml vials (Pfizer Ltd)
431541000033114	Deltacortril 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
431641000033110	Deltacortril 5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
5990141000033115	Prednisone 1mg modified-release tablets
5990241000033110	Prednisone 2mg modified-release tablets
5990341000033117	Prednisone 5mg modified-release tablets
5990641000033113	Lodotra 1mg modified-release tablets (Napp Pharmaceuticals Ltd)
5990741000033116	Lodotra 2mg modified-release tablets (Napp Pharmaceuticals Ltd)
5990841000033114	Lodotra 5mg modified-release tablets (Napp Pharmaceuticals Ltd)
8046741000033113	Prednisolone sodium phosphate 5mg suppositories
8494441000033110	Dilacort 2.5mg gastro-resistant tablets (Crescent Pharma Ltd)
8494541000033111	Dilacort 5mg gastro-resistant tablets (Crescent Pharma Ltd)
878641000033113	Methylprednisolone acetate 40mg/1ml suspension for injection vials
879841000033115	Methylprednisolone Sodium Succinate Injection 1 gram/vial
879941000033111	Methylprednisolone Sodium Succinate Injection 125 mg/vial
880041000033110	Methylprednisolone Sodium Succinate Injection 500 mg/vial
880141000033114	Methylprednisolone acetate 120mg/3ml suspension for injection vials
880241000033119	Methylprednisolone acetate 80mg/2ml suspension for injection vials
886141000033111	Methylprednisolone Acetate Injection 10 mg/1 ml
887041000033114	Methylprednisolone Sodium Succinate Injection 40 mg/vial
889441000033114	Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials
889541000033110	Methylprednisolone sodium succinate 125mg powder and solvent for solution for injection vials
889641000033111	Methylprednisolone sodium succinate 2g powder and solvent for solution for injection vials
889741000033119	Methylprednisolone sodium succinate 40mg powder and solvent for solution for injection vials

889841000033112	Methylprednisolone sodium succinate 500mg powder and solvent for solution for injection vials
898441000033115	Medrone 100mg tablets (Pfizer Ltd)
898541000033119	Methylprednisolone 100mg tablets
899641000033110	Medrone 16mg tablets (Pfizer Ltd)
899741000033118	Medrone 2mg tablets (Pfizer Ltd)
899841000033111	Medrone 4mg tablets (Pfizer Ltd)
903141000033113	Methylprednisolone 16mg tablets
904141000033111	Methylprednisolone 2mg tablets
904241000033116	Methylprednisolone 4mg tablets
9119141000033118	Prednisolone 15mg/5ml oral solution
914641000033116	Min-I-Mix Methylprednisolone Injection 1 g/vial
915541000033118	Min-I-Mix Methylprednisolone Injection 0.5 g/vial
744541000033116	Hydrocortisone 10mg tablets
744641000033115	Hydrocortone 10mg tablets (Auden McKenzie (Pharma Division) Ltd)
13010241000033114	Hydventia 10mg tablets (OcXia)
744741000033112	Hydrocortone 20mg tablets (Auden McKenzie (Pharma Division) Ltd)
742241000033110	Hydrocortisone 20mg tablets
13010341000033116	Hydventia 20mg tablets (OcXia)
740241000033111	Hydrocortisone 10mg/5ml oral suspension
2149441000033113	Hydrocortisone 25mg/5ml oral suspension
1830141000033115	Hydrocortisone 5mg/5ml oral suspension
2623741000033116	Hydrocortisone 5mg/5ml oral suspension sugar free
8142041000033116	Hydrocortisone 20mg modified-release tablets
8142241000033112	Plenadren 20mg modified-release tablets (Shire Pharmaceuticals Ltd)
8142141000033117	Plenadren 5mg modified-release tablets (Shire Pharmaceuticals Ltd)
8141941000033110	Hydrocortisone 5mg modified-release tablets
12633741000033117	Alkindi 1mg granules in capsules for opening (Diurnal Ltd)
12633341000033118	Hydrocortisone 1mg granules in capsules for opening

12633441000033112	Hydrocortisone 2mg granules in capsules for opening
12633841000033110	Alkindi 2mg granules in capsules for opening (Diurnal Ltd)
12633641000033114	Alkindi 0.5mg granules in capsules for opening (Diurnal Ltd)
12633241000033111	Hydrocortisone 500microgram granules in capsules for opening
12633541000033113	Hydrocortisone 5mg granules in capsules for opening
12633941000033119	Alkindi 5mg granules in capsules for opening (Diurnal Ltd)
12890041000033114	Hydrocortisone 10mg soluble tablets sugar free
3160541000033119	Hydrocortisone 1% / Pramocaine 1% foam enema
741241000033116	Hydrocortisone 25mg suppositories
733541000033119	Hydrocortisone 10% foam aerosol enema
327541000033113	Colifoam 10% aerosol (Mylan)
1489941000033111	Uniroid HC suppositories (Chemidex Pharma Ltd)
3269441000033114	Cinchocaine 5mg / Hydrocortisone 5mg suppositories
1128841000033118	Proctosedyl suppositories (Sanofi)
68541000033118	Anugesic-HC suppositories (Pfizer Ltd)
68141000033110	Anusol HC suppositories (Church & Dwight UK Ltd)
2131641000033110	Anusol Plus HC suppositories (Church & Dwight UK Ltd)
4518241000033113	Hydrocortisone 100mg suppositories
13604641000033111	Hydrocortisone 50mg suppositories
1115541000033115	Proctofoam HC foam enema (Meda Pharmaceuticals Ltd)
742341000033117	Hydrocortistab Tablets 20 mg