

1 **Rosenbaum JE, Ochoa KC, Hasan F, Goldfarb A, Tang V, Tomer G, Wallach, TE.**
2 **Epidemiologic Assessment of Pediatric Inflammatory Bowel Disease Presentation in**
3 **NYC During COVID-19. Journal of Pediatric Gastroenterology, and Nutrition.**
4 **Contributors' Statement Page**

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6 Dr. Wallach conceptualized the study and organized the consortium of institutions. Dr.
7 Rosenbaum and Dr. Wallach designed the study, data collection instrument, and analytical
8 framework. Drs Castro Ochoa, Tang, Tomer, Hasan, and Goldfarb collected data,
9 organized local IRB approval at their respective institutions, and edited the manuscript. Dr.
10 Rosenbaum harmonized, cleaned, and analyzed the data. Dr. Castro Ochoa, Dr.
11 Rosenbaum, and Dr. Wallach wrote the manuscript. All authors reviewed, revised, and
12 approved the final manuscript as submitted and agree to be accountable for all aspects of
13 the work.
14

15
16 **Abstract:**

17 Inflammatory Bowel Disease (IBD) pathogenesis is thought to be induced by a mix of
18 genetic susceptibility, microbial populations, and immune triggers such as infections.
19 SARS-nCoV2 may have increased capacity to generate autoimmune disease as evidenced
20 by known spikes in diseases such as Type 1 Diabetes Mellitus. Public health interventions
21 like masking and closures additionally created remarkable drops in typical viral infections,
22 with remarkable shifts in ILI reporting in 2020. This study aims to evaluate the impact of
23 SARS-nCoV2 and associated interventions on pediatric IBD presentation in NYC using
24 records of new diagnoses at a consortium of four institutions between 2016 and June 2022.
25 We fit time series model (ARIMA) to monthly and quarterly number of cases of each
26 disease for January 2016-March 2020 and forecast the period between April 2020 and June
27 2022. We note no decrease in Ulcerative Colitis or Crohn's Disease in the aftermath of
28 historic low levels of overall viral illness, and statistically significant increases in Crohn's
29 Disease diagnoses and elevation in UC diagnoses creating a trend suggesting overall
30 increase in IBD diagnoses exceeding the baseline rate of increase. These data suggest a
31 possible linkage between SARS-nCoV2 infection rates and subsequent pediatric IBD
32 presentation.

33 **What is Known**

- 34 • Infections may precipitate IBD pathogenesis
35 • SARS-nCoV2-related mitigation interventions substantially decreased viral infections
36 in NYC
37 • SARS-nCoV2 has been associated with increases in some autoimmune diseases

38 **What is New**

- 39 • IBD rates did not decrease despite overall drop in viral illness
40 • Crohn's Disease Rates increased 4-6 months after initial SARS-nCoV2 spike in NYC
41 • Rates of IBD diagnoses appear higher than expected

42 **Introduction**

43 The SARS-nCoV2 pandemic has created multiple profound secondary effects in
44 healthcare, but perhaps one of the most concerning is a possible capacity to generate
45 increased rates of autoimmune disorders. Both pediatric and adult studies have
46 demonstrated an increase in Type 1 diabetes diagnoses, and case reports and series suggest
47 possible impacts in other autoimmune disorders¹⁻⁵. Inflammatory Bowel Disease (IBD) is
48 one of our greatest autoimmune disease concerns in the framework of pediatric
49 gastroenterology. As currently understood, IBD pathogenesis appears to be a mix of
50 genetic susceptibility, microbial interaction, and immune triggers such as infections.
51 SARS-nCoV2 has a known predilection for intestinal tissue: gastrointestinal illness and
52 protracted viral activity and shedding in stool accompany infection⁶⁻⁹. With interventions
53 such as face masks and social distancing adopted at the onset of the SARS-nCoV2
54 pandemic, influenza-like-illness and other infectious disease incidence plummeted in the
55 United States^{10,11}. Based on our theoretical understanding of IBD pathogenesis, reduced
56 infectious disease during the pandemic would be expected to decrease IBD presentation
57 rates, but decreased IBD incidence has not been observed clinically. As the location of
58 many cases early in the SARS-nCoV2 pandemic, New York City (NYC) represents a
59 valuable source of data to examine for any possible linkage with infections and IBD
60 presentations, either positive or negative. Our study evaluated the association between the
61 pandemic and new IBD diagnoses in NYC using data from a consortium of four NYC
62 institutions: SUNY Downstate (Brooklyn), Maimonides Medical Center (Brooklyn), NYU
63 Hassenfeld Children’s Hospital (Manhattan), and the Children’s Hospital at Montefiore
64 (Bronx). We compared IBD rates after the SARS-nCoV2 pandemic with rates from the
65 five years prior.

66

67 **Methods**

68 **Data**

69 We extracted data for IBD patients presenting in pediatric GI clinic at 4 institutions
70 between January 2016 to June 2022 (n=587) from electronic health records (EHRs) after
71 institutional review board approval of respective institutions.

72 **Measures**

73 Date of diagnosis was coded as year and month of diagnosis with the day removed
74 for identifiability reasons. We measured the following demographic variables: age in years
75 at diagnosis, EHR-recorded sex, race, and ethnicity. Age was categorized by FDA SARS-

76 nCoV2 vaccination approval age groups: 0-4, 5-11, 12-15, and 16-21. Race and ethnicity
77 were measured by a free-entry field in the medical record, and more than one race and
78 ethnicity were possible; however, race was often not reported for Hispanic/Latino-
79 identified participants.

80 Individual-level association between SARS-nCoV2 infection and subsequent IBD
81 would give stronger inference than temporal changes in IBD infection. For that aim, we
82 gathered data about past SARS-nCoV2 infection before diagnosis.

83 **Analysis**

84 Due to potentially different seasonal variation and time to presentation, we
85 analyzed CD and UC separately and excluded 29 cases of indeterminate IBD. Using April
86 2020 as the first month of the SARS-nCoV2 pandemic, we compared pre-pandemic versus
87 pandemic periods with the Pearson chi-square test. For each disease, we also fit simple
88 Poisson regression models for quarterly counts of CD and UC with an indicator for the
89 pandemic that accounted for overdispersion, greater variance than expected in a Poisson
90 distribution.

91 The quarterly counts of CD and UC appeared to be normal using both visual
92 inspection of a quantile-quantile plot and the Shapiro-Wilk test: CD ($p=0.06$) and UC
93 ($p=0.6$). We therefore fit an autoregressive integrated moving average model (ARIMA) to
94 the quarterly number of cases of each disease for January 2016-March 2020 and forecast
95 the subsequent 9 quarters (April 2020-June 2022) with 80% and 95% prediction intervals
96 using the forecast library.⁵ We repeated the ARIMA analysis with monthly data by fitting
97 a model to pre-pandemic data and forecasting the subsequent 27 months (April 2020-June
98 2022).

99 **Results**

100 Of patients reviewed in this study, 43.1% were female. Median age at diagnosis
101 was 14.0 years (range 2-21 years): 4.3% were ages 0-4 years, 25.6% were ages 5-11,
102 35.9% were ages 12-15, and 36.3% were 16-21. Race and ethnicity were provided as free-
103 entry fields: 47.4% were White, 9.5% Black, 5.3% Asian, and 8.7% not reported; 22.5%
104 were Hispanic, and 11.8% had Hispanic ethnicity status not reported. Patients diagnosed
105 with IBD during the pandemic were less likely to be White and more likely to be
106 Hispanic; patients did not differ in diagnosis, gender, age, Black or Asian identity, or
107 county of residence from patients diagnosed before the pandemic [**Table 1**]. The
108 distribution of quarterly counts of CD and UC before and during the pandemic did not
109 differ according to a Wilcoxon test (Table 1) or Poisson regression with overdispersion

110 (CD incidence rate ratio (IRR) 1.26 (0.94, 1.68) with dispersion factor of 2.0; UC IRR
111 1.18 (0.78, 1.76) with dispersion factor of 1.6).

112 The quarterly pre-pandemic model for ulcerative colitis was ARIMA(0,0,0) (white
113 noise) with a mean of 5.76 cases per quarter (se=0.79), residual standard deviation of 11.3;
114 during the pandemic period, the forecast was an average of 5.76 cases per quarter with
115 80% prediction interval (1.45, 10.1) and 95% prediction interval (-0.83, 12.4). **[Figure 1]**

116 The monthly pre-pandemic model for ulcerative colitis was ARIMA(1,0,0) with a
117 mean of 1.91 cases per month (se=0.28), lag-1 autocorrelation (AR1) of 0.30 (se=0.13),
118 residual standard deviation of 2.00. The forecast varied only slightly across the interval.
119 For ulcerative colitis, beginning in August 2020 an average of 1.90 cases were forecast
120 with 80% prediction interval (0.00, 3.80) and 95% prediction interval (-1.00, 4.81). We
121 noted more UC cases than forecast in May 2021 (5 cases), October 2021 (5 cases), and
122 May 2022 (6 cases), compared with upper limit of 95% prediction interval of 4.81 cases
123 **[Figure 2]**.

124 Overall, and trend for increased UC diagnoses was noted in the post-SARS-nCoV2
125 period, exceeding expected increases from the pre-pandemic trend. The pre-pandemic
126 model for ulcerative colitis was ARIMA(1,0,0) with a mean of 1.91 cases per month
127 (se=0.28) and lag-1 autocorrelation (AR1) of 0.30 (se=0.13). The residual standard
128 deviation is 2.00.

129 The quarterly pre-pandemic model for Crohn's disease was ARIMA(0,0,0) (white
130 noise) with a mean of 14.0 cases per quarter (se=1.09), residual standard deviation of 21.4;
131 during the pandemic period, the forecast was an average of 14.0 cases per quarter with
132 80% prediction interval (8.07, 19.93) and 95% prediction interval (4.94, 23.06). We noted
133 more CD cases than forecast in the third quarter of 2020 and first quarter of 2022, which
134 had respectively 26 cases and 31 cases compared with upper limit of 95% prediction
135 interval of 23.0 **[Figure 1]**.

136 The monthly pre-pandemic model for Crohn's disease was ARIMA(0,0,0) (white
137 noise) with mean of 4.67 cases per month (se = 0.37), and residual standard deviation of
138 6.99. The forecast was uniform across the interval because the number of Crohn's disease
139 cases per month were white noise. For Crohn's disease, an average of 4.67 cases was
140 forecast with 80% prediction interval (1.28, 8.05) and 95% prediction interval (-0.51,
141 9.85). We noted more CD cases than forecast in July 2020 (12 cases), September 2020 (10
142 cases), February 2022 (11 cases), and March 2022 (13 cases), compared with upper limit
143 of 95% prediction interval of 9.85 cases **[Figure 2]**.

144 One patient had a positive antibody test before diagnosis and 7 patients had positive
145 PCRs test before diagnosis. No records indicated negative tests.

147 **Discussion**

148 We observe two key findings: first, a tremendous decrease in overall rates of viral
149 infection did not decrease CD and UC presentation rates, suggesting either diminished
150 importance of viral infection as a pathogenic trigger of IBD or a strong capacity for
151 SARS-nCoV2 to drive IBD pathogenesis. Second, we observe a significant increase in
152 CD diagnoses with a possible temporal linkage of 4-6 months after pre-omicron peak
153 SARS-nCoV2 infection in NYC in March/April 2020, as well as peaks in diagnoses at
154 approximately the same timing occurring in the aftermath of the Omicron wave starting
155 November 2021. The demographic shifts in IBD diagnosis corresponds with SARS-
156 nCoV2 infection demographics: more common in Hispanic populations and less likely in
157 White populations¹². Our finding of a decreased proportion of Caucasian patients and
158 increased proportions of Hispanic patients aligns well with documented SARS-nCoV2
159 prevalence in the time frame of our study, suggesting a possible linkage. These temporal
160 and demographic associations suggest an effect, but they do not demonstrate a linkage of
161 CD with SARS-nCoV2 due to lack of testing data in the EHRs and multiple confounding
162 effects which could generate an elevation in IBD: delays in care during lockdowns
163 initially, recurrence of other viral infections, and overall delays in presentation for CD
164 diagnosis.

165 Our study also shows the importance of incorporating SARS-nCoV2 test
166 data and vaccination data into EHRs. We anticipate that SARS-nCoV2 infections were
167 underestimated because children were under-tested during the early pandemic,¹³ and
168 because children may have been tested through programs that did not submit to the EHR,
169 such as the NYC school-based surveillance testing program, NYC's testing program run by
170 the public hospital system (NYC Health and Hospital Corporation), urgent care clinics,
171 other health systems, or by home rapid tests. The results of school testing programs are
172 reported to public health authorities, but these results do not come to the EHR except
173 through ad hoc self-report. These problems will be compounded by at-home rapid tests that
174 are not even reported to public health authorities.

175 Our study provides unique data from a city that experienced a substantial SARS-
176 nCoV2 burden at the start of the pandemic from a population of patients attending
177 pediatric gastroenterology clinics, as well as some of the most profound non-

178 pharmaceutical interventions and decreases in viral illness in the United States. However,
179 our study shows temporal and demographic associations with the pandemic but not
180 individual associations due to lack of testing data in the EHRs. The 4-6 month lag between
181 the city's peak infection rate and CD could be consistent with a SARS-nCoV2 infection
182 pathogenesis or with delayed presentation from cases during the lockdown period,
183 although later trends suggesting elevation in CD diagnoses at other periods suggest a need
184 for more detailed evaluation at a larger scale. IBD does not present with consistent
185 patterns, resulting in wide variability in data. We also do not have documentation of the
186 timing of SARS-nCoV2 infections, but specific variant lineage may drive different levels
187 of autoimmunity; MISC incidence was lower when Omicron was the dominant variant
188 compared with earlier variants of concern.

189 Our data does not include all pediatric gastroenterology groups in NYC, which
190 may be impacted by variations in choice of institution for gastroenterology care. Vaccines
191 were available for over a year for two-thirds of the patients in the cohort with new
192 diagnoses since April 2020, and vaccines were widely available to NYC children and
193 adolescents through mass vaccination sites and widespread vaccine bus visits including to
194 all public schools. However, our study is not able to assess the impact of vaccinations due
195 to significant heterogeneity in vaccine documentation. It is challenging to assess the
196 potential impact on data beyond 2020 due to a partial recurrence of viral infections,
197 however data derived from the New York State Department of Health Influenza-Like-
198 Illness tracker demonstrates a substantial drop over regional baseline which continued
199 through the '21-22 season¹⁴.

200 **Conclusions**

201 Our study suggests two possible interpretations with substantial potential impact
202 on IBD. First, our data may reflect that the underlying known increase in pediatric IBD
203 has continued, which would strongly suggest that viral infection is not substantially related
204 to IBD pathogenesis. Alternatively, our findings suggest that SARS-nCoV2 may have
205 substantial capacity to generate autoimmunity. Large increases of SARS-nCoV2 infection
206 in pediatric patients may have driven increases in IBD diagnoses, particularly Crohn's
207 disease. Data infrastructure must be improved to incorporate SARS-nCoV2 test results and
208 vaccine records to enable monitoring of ongoing changes in IBD incidence as new viral
209 lineages emerge and during future pandemics.

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Table 1: Demographics of participants (2016- June 2022)

	All participants	Jan. 2016 – Mar. 2020	April 2020 – Jun. 2022	P-value
N	587	351	236	
Diagnosis				0.6
Crohn's Disease (CD)	399 (68.0%)	238 (67.8%)	161 (68.2%)	
Ulcerative Colitis (UC)	159 (27.1%)	98 (27.9%)	61 (25.8%)	
Undetermined	29 (4.9%)	15 (4.3%)	14 (5.9%)	
Quarterly CD cases	Mean 15.3 (Variance 34.3) Median 14.5, IQR (11, 17)	Mean 14.0 (Variance 21.4) Median 13, IQR (11, 16)	Mean 17.7 (Variance 54.5) Median 16, IQR (14, 21)	0.2
Quarterly UC cases	Mean 6.1 (Variance 9.5) Median 6, IQR (4, 8)	Mean 5.8 (Variance 11.3) Median 4, IQR (4, 8)	Mean 6.8 (Variance 6.2) Median 7, IQR (6, 8)	0.3
Documented SARS-nCoV2 infection	8 (1.4%)	0	8 (3.4%)	n.a.
Gender				0.7
Male	333 (56.7%)	197 (56.1%)	136 (57.9%)	
Female	253 (43.1%)	154 (43.9%)	99 (41.9%)	
Missing	1 (0.2%)	0	1 (0.4%)	
Age at diagnosis				0.8
0-4	15 (4.3%)	9 (2.6%)	4 (1.7%)	
5-11	150 (25.6%)	92 (26.2%)	58 (25.6%)	
12-15	211 (35.9%)	121 (34.5%)	90 (38.1%)	
16-21	213 (36.3%)	129 (36.8%)	84 (35.6%)	
Institution				0.01
Downstate	36 (6.1%)	15 (4.3%)	21 (8.9%)	
Maimonides	91 (15.5%)	63 (17.9%)	28 (11.9%)	
Montefiore	274 (46.7%)	155 (44.2%)	119 (50.4%)	
NYU	186 (31.7%)	118 (33.6%)	68 (28.8%)	
Race and ethnicity				
White	278 (47.4%)	183 (52.1%)	95 (40.3%)	0.03
Black	56 (9.5%)	30 (8.5%)	26 (11.0%)	0.2
Asian	31 (5.3%)	14 (4.0%)	17 (7.2%)	0.06
Hispanic	132 (22.5%)	70 (19.9%)	62 (26.3%)	0.02
Race missing	51 (8.7%)	22 (6.3%)	29 (12.3%)	
Ethnicity missing	69 (11.8%)	31 (8.8%)	38 (16.1%)	
Year of diagnosis				n.a.
2016	67 (11.4%)	67 (19.1%)	0 (0%)	
2017	85 (14.5%)	85 (24.2%)	0 (0%)	
2018	80 (13.6%)	80 (22.8%)	0 (0%)	
2019	90 (15.3%)	90 (25.6%)	0 (0%)	
2020	97 (16.5%)	29 (8.3%)	68 (28.8%)	
2021	102 (17.4%)	0 (0%)	102 (43.2%)	
2022	66 (11.2%)	0 (0%)	66 (11.2%)	
Location				0.3
Manhattan	35 (6.0%)	20 (5.7%)	15 (6.4%)	
Brooklyn	230 (39.2%)	150 (42.7%)	80 (33.9%)	
Queens	21 (3.6%)	12 (3.4%)	9 (3.8%)	
Bronx	172 (29.3%)	100 (28.5%)	72 (30.5%)	
Staten Island	12 (2.0%)	6 (1.7%)	6 (2.5%)	
Westchester	54 (9.2%)	28 (8.0%)	26 (11.0%)	
Rockland	36 (6.1%)	18 (5.1%)	18 (7.6%)	
Long Island	12 (2.0%)	10 (2.8%)	2 (0.8%)	
Other NY or PA or CT or NJ	5 (0.9%)	2 (0.6%)	3 (1.3%)	
Not reported	10 (1.7%)	5 (1.4%)	5 (2.1%)	

All percentages are column percentages. Race and ethnicity were reported in a free-entry field; they do not add to 100% because patients could be identified with multiple racial and ethnic categories. P-value from chi-square test of association between time period (pre-pandemic versus pandemic) and each variable. The distribution of quarterly counts were compared with a Wilcoxon test; we present the means and variances for reference, but the Wilcoxon test does not compare these.

Figure 1. Time series (ARIMA) of UC and CD. A) ARIMA time series analysis of UC presentation by 3-month period from 2016- June 2022 with 80% and 95% prediction intervals. B) ARIMA time series analysis of CD presentation by 3-month period from 2016- June 2022 with 80% and 95% prediction intervals.

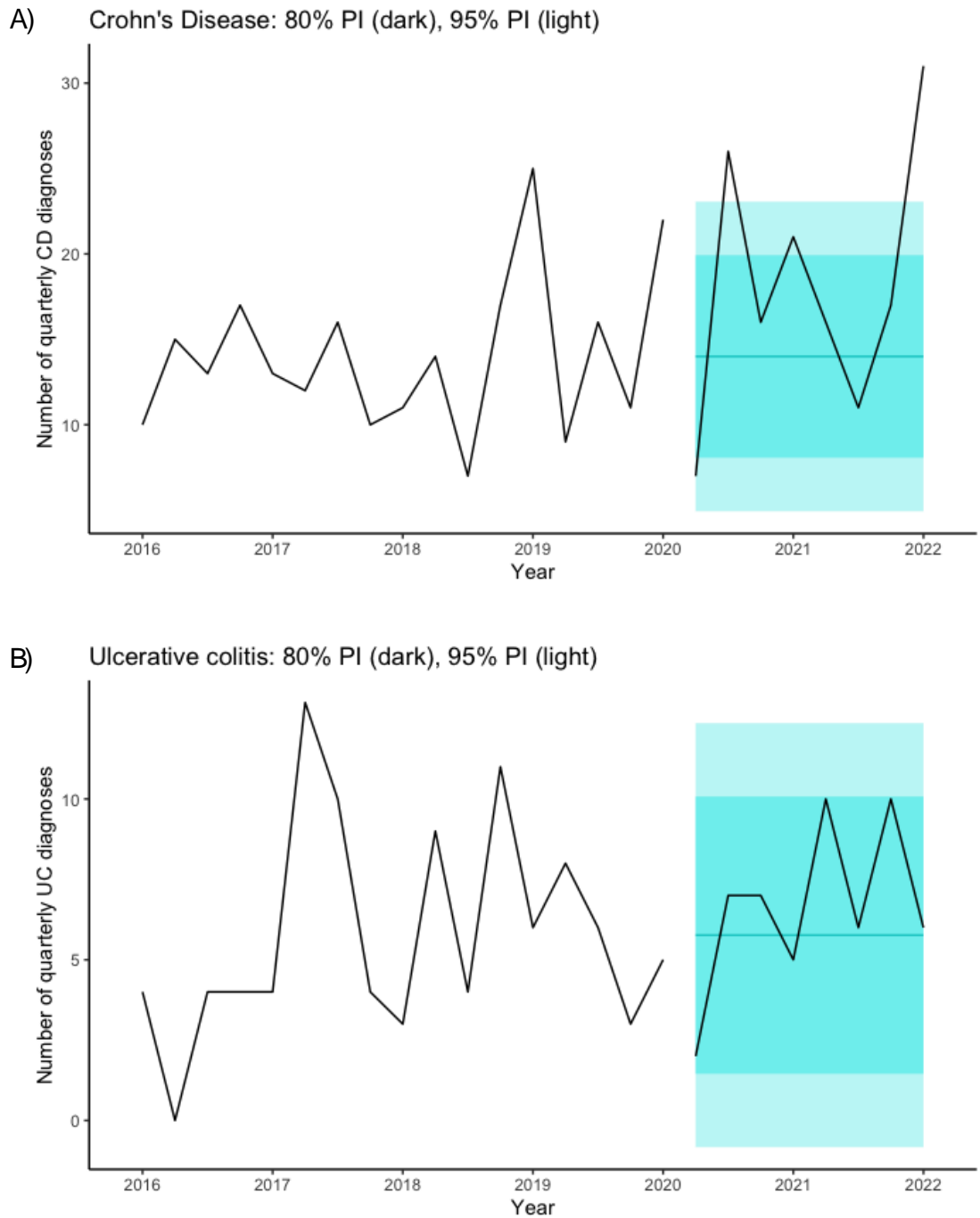
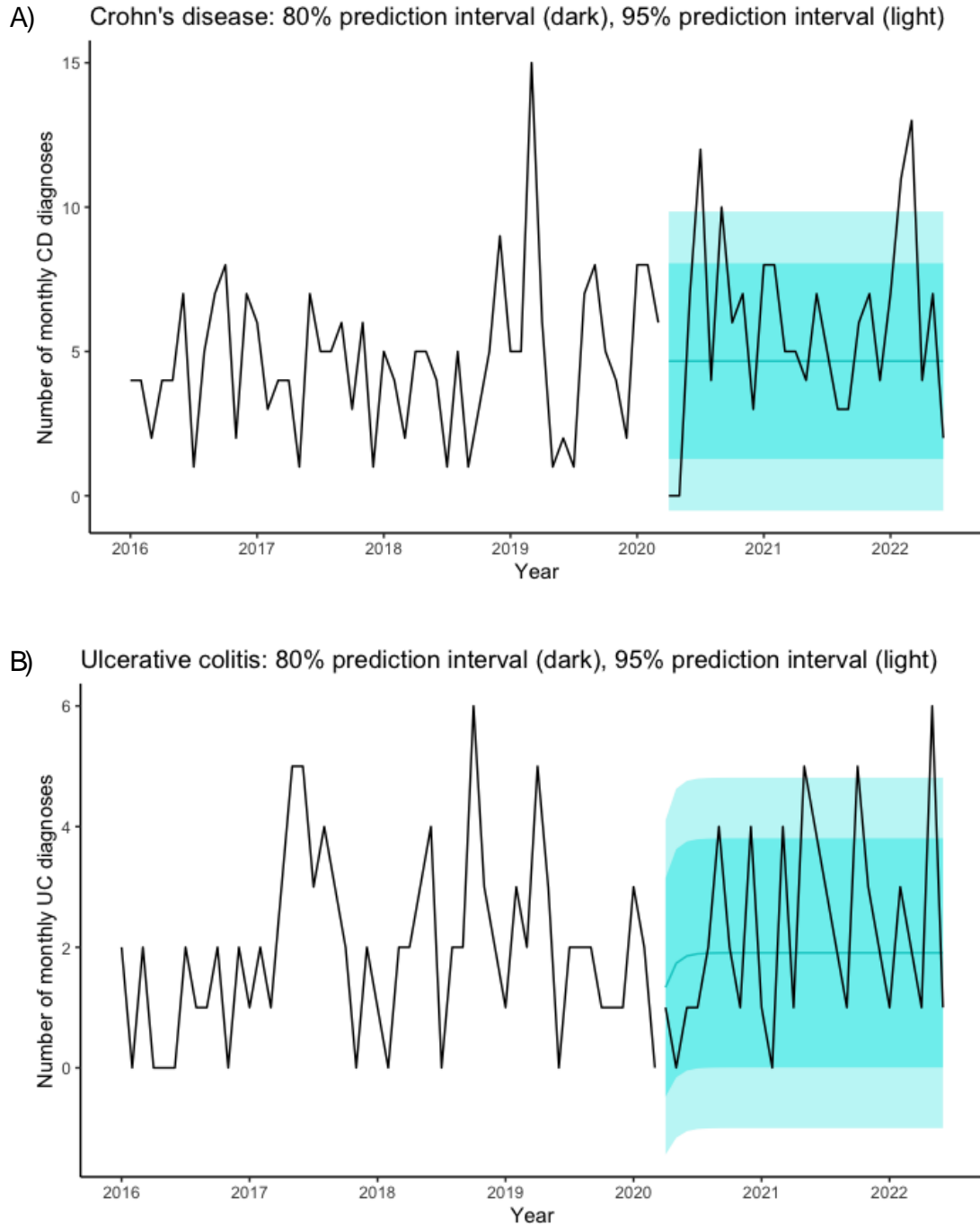


Figure 2. Time series (ARIMA) of UC and CD. A) ARIMA time series analysis of UC presentation by month from 2016- June 2022 with 80% and 95% prediction intervals. B) ARIMA time series analysis of CD presentation by month period from 2016- June 2022 with 80% and 95% prediction intervals.



Supplemental Table 1: Estimated and actual quarterly and monthly rates of UC and CD. Estimates are according to the ARIMA models; these data are displayed in Figures 1 and 2.

		UC cases		UC estimate, 95% CI	
		Quarterly	Monthly	Quarterly	Monthly
2020 Q2	April 2020	2	1	5.76 (-0.83, 12.36)	1.33 (-1.44, 4.10)
	May 2020		0		1.73 (-1.16, 4.63)
	June 2020		1		1.85 (-1.05, 4.76)
2020 Q3	July 2020	7	1	5.76 (-0.83, 12.36)	1.89 (-1.01, 4.80)
	August 2020		2		1.90 (-1.00, 4.81)
	September 2020		4		1.90 (-1.00, 4.81)
2020 Q4	October 2020	7	2	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)
	November 2020		1		1.91 (-1.00, 4.81)
	December 2020		4		1.91 (-1.00, 4.81)
2021 Q1	January 2021	5	1	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)
	February 2021		0		1.91 (-1.00, 4.81)
	March 2021		4		1.91 (-1.00, 4.81)
2021 Q2	April 2021	10	1	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)
	May 2021		5		1.91 (-1.00, 4.81)
	June 2021		4		1.91 (-1.00, 4.81)
2021 Q3	July 2021	6	3	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)
	August 2021		2		1.91 (-1.00, 4.81)
	September 2021		1		1.91 (-1.00, 4.81)
2021 Q4	October 2021	10	5	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)

	November 2021		3		1.91 (-1.00, 4.81)
	December 2021		2		1.91 (-1.00, 4.81)
2022 Q1	January 2022	6	1	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)
	February 2022		3		1.91 (-1.00, 4.81)
	March 2022		2		1.91 (-1.00, 4.81)
2022 Q2	April 2022	8	1	5.76 (-0.83, 12.36)	1.91 (-1.00, 4.81)
	May 2022		6		1.91 (-1.00, 4.81)
	June 2022		1		1.91 (-1.00, 4.81)

		CD cases		CD estimate, 95% CI	
		quarterly	monthly	quarterly	monthly
2020 Q2	April 2020	7	0	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	May 2020		0		4.67 (-0.51, 9.85)
	June 2020		7		4.67 (-0.51, 9.85)
2020 Q3	July 2020	26	12	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	August 2020		4		4.67 (-0.51, 9.85)
	September 2020		10		4.67 (-0.51, 9.85)
2020 Q4	October 2020	16	6	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	November 2020		7		4.67 (-0.51, 9.85)
	December 2020		3		4.67 (-0.51, 9.85)
2021 Q1	January 2021	21	8	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	February 2021		8		4.67 (-0.51, 9.85)
	March 2021		5		4.67 (-0.51, 9.85)
2021 Q2	April 2021	16	5	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	May 2021		4		4.67 (-0.51, 9.85)
	June 2021		7		4.67 (-0.51, 9.85)
2021 Q3	July 2021	11	5	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	August 2021		3		4.67 (-0.51, 9.85)
	September 2021		3		4.67 (-0.51, 9.85)
2021 Q4	October 2021	17	6	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	November 2021		7		4.67 (-0.51, 9.85)

	December 2021		4		4.67 (-0.51, 9.85)
2022 Q1	January 2022	31	7	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	February 2022		11		4.67 (-0.51, 9.85)
	March 2022		13		4.67 (-0.51, 9.85)
2022 Q2	April 2022	14	5	14 (4.94, 23.06)	4.67 (-0.51, 9.85)
	May 2022		7		4.67 (-0.51, 9.85)
	June 2022		2		4.67 (-0.51, 9.85)