

# COPD Exacerbations Before and During COVID-19 in France, Germany, Italy, the UK and the US

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**Background:** Exacerbations of chronic obstructive pulmonary disease (COPD) were reported less frequently during the COVID-19 pandemic. We report real-world data on COPD exacerbation rates before and during this pandemic.

**Methods:** Exacerbation patterns were analysed using electronic medical records or claims data of patients with COPD before (2017–2019) and during the COVID-19 pandemic (2020 through early 2022) in France, Germany, Italy, the United Kingdom and the United States. Data from each country were analysed separately. The proportions of patients with COPD receiving maintenance treatment were also estimated.

**Results:** The proportion of patients with exacerbations fell 45–78% across five countries in 2020 versus 2019. Exacerbation rates in most countries were reduced by >50% in 2020 compared with 2019. The proportions of patients with an exacerbation increased in most countries in 2021. Across each country, seasonal exacerbation increases seen during autumn and winter in pre-pandemic years were absent during the first year of the pandemic. The percentage of patients filling COPD prescriptions across each country increased by 4.53–22.13% in 2019 to 9.94–34.17% in 2021.

**Conclusion:** Early, steep declines in exacerbation rates occurred in 2020 versus 2019 across all five countries and were accompanied by a loss of the seasonal pattern of exacerbation.

**Keywords:** COPD exacerbation, chronic obstructive pulmonary disease, COVID-19, electronic health records, real-world study

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable chronic respiratory condition.<sup>1</sup> According to the estimated global burden of disease, there were 212.3 million prevalent cases of COPD and 3.3 million deaths due to COPD globally in 2019.<sup>2</sup> The natural history of COPD is punctuated by acute worsening episodes (known as exacerbations) that require treatments based on their characteristics and severity and are associated with increased morbidity and mortality.<sup>1,3</sup> The exacerbation rate varies between patients, and the future risk of exacerbations is best predicted by the individual's prior history of such events.<sup>4,5</sup>

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, was declared a global pandemic in March 2020 by the World Health Organization.<sup>6,7</sup> To curtail the surge in COVID-19 cases, many countries announced nationwide lockdowns and implemented social-distancing policies that considerably restricted movement and social contact. Mask-wearing and social distancing contributed to the reductions in acute exacerbations of COPD during the COVID-19 pandemic observed in 2020.<sup>8–10</sup> In addition, other changes associated with lockdowns—including a decline in other viral respiratory tract infections and improvements in air quality and in self-management—may have led to a reduction in the rate of COPD exacerbation during the pandemic.<sup>11,12</sup> Several studies conducted across various geographical

regions of the world found reductions in the rate of COPD exacerbations.<sup>13–16</sup> However, questions remained regarding the exacerbation rates and the possible seasonality of these rates in multiple nations, especially those of Western Europe and the US.

We conducted a real-world data analysis to evaluate the impact of the COVID-19 pandemic on the occurrence of exacerbations and their seasonal patterns in patients who have COPD and experienced at least one exacerbation before (2017–2019) or during the COVID-19 pandemic (2020, 2021 and early 2022) in four European countries (France, Germany, Italy and the United Kingdom [UK]) and the United States (US); the analytical approach was the same for all five countries.

## Methods

### Study Design

This was a retrospective study using de-identified electronic medical records from France (LPD France), Germany (Disease Analyzer Germany), Italy (LPD Italy), the UK (IQVIA Medical Research Data incorporating THIN, a Cegedim database), and a claims database from the US (PharMetrics® Plus). [Supplementary Table 1](#) provides characteristics of these databases. The data were extracted using the IQVIA E360® platform (IQVIA Inc., Durham, North Carolina, US).<sup>17</sup>

Data from these databases were de-identified in compliance with the regulations set forth in the applicable data protection laws; hence, further ethics approval was not required.

### Study Population and Time Frame

Inclusion criteria were age  $\geq 40$  years, a COPD diagnosis, and continuous availability for follow-up in the database for at least 6 months before (look-back period, starting no earlier than 1 July 2016) and 15 days after (follow-up period) the first COPD diagnosis. Patients were excluded if they had a documented diagnosis of asthma, pneumonia, lung cancer, heart failure or pulmonary hypertension within the 6-month look-back period. The analytic period was from 1 January 2017 to 15 April 2022 for France, Italy and the UK; 1 January 2017 to 31 March 2022 for Germany; and 1 January 2017 to 31 December 2021 for the US. The window before the pandemic was from 1 January 2017 to 31 December 2019, and during the pandemic from 1 January 2020 to the end of the analytic period.

### Identification of Exacerbation

An exacerbation was indicated by any of the following:<sup>18</sup> a COPD exacerbation diagnostic code, prescriptions for a COPD-specific antibiotic and oral corticosteroid (OCS) within 7 days of each other, at least two diagnoses of respiratory symptoms of exacerbation (eg, cough, sputum, breathlessness) within 7 days of each other and a prescription for an antibiotic or OCS within the next 7 days. A list of antibiotics and oral corticosteroids is included in the [Supplementary Methods](#). Exacerbations that occurred within 30 days of each other were considered the same exacerbation.<sup>18</sup>

### Study Analysis Cohorts

One main cohort and two sub-analysis cohorts were analysed in this study. The main cohort consisted of patients fulfilling all the above-mentioned inclusion criteria. The two additional sub-cohorts were the exacerbation cohort and the continuous follow-up cohort. The exacerbation cohort consisted of patients in the main cohort with at least one exacerbation during the analytic period. The continuous follow-up cohort consisted of patients with a diagnosis of COPD in 2016 and were active and continuously available for follow-up in the database between 2017 and 2021.

### Outcomes

The primary outcome of the study was exacerbation rate, defined as the number of unique exacerbations divided by the number of person-years contributed by all patients within the analysis cohort. Other outcomes of interest included exacerbation frequency, proportion of patients with exacerbation, and seasonal trends of exacerbations before and during the COVID-19 pandemic for the main and exacerbation cohorts.

An analysis of exacerbation frequency from 2017 through 2021 was performed for the continuous follow-up cohort. The number and percentage of distinct patients with zero, one or two or more exacerbations during the year were calculated. Patients were categorised according to their exacerbation frequencies before and during the pandemic, and the categories were no exacerbation, infrequent exacerbation, recurrent exacerbations and frequent exacerbations (Table 1). To depict and understand the transitions of patients among categories before and during the pandemic, a high-level view of changes in the frequency of exacerbations before and during the pandemic was generated by cross-tabulating the pre-pandemic and pandemic exacerbation categories. Moreover, we estimated the proportion of patients in each pre-pandemic and pandemic category who filled a prescription for their last COPD maintenance treatment.

## Statistical Analyses

All outcomes were assessed separately for each country during the individual years from 2017 to 2021. Descriptive statistics were used to analyse the demographic and clinical characteristics of patients. Categorical data were presented as frequencies and percentages, and continuous data were presented as mean values  $\pm$  standard deviations, and/or median values and interquartile ranges.

To minimize bias, all analyses were restricted to patients who met all inclusion criteria. Given the descriptive nature of the study, no missing values were imputed. Data were analysed using the IQVIA E360<sup>®</sup> platform and Python 3.9.12 (Python Software Foundation, Wilmington, DE, US).

## Results

### Patient Characteristics

The majority of patients with COPD were >60 years old (Table 2). The sex distribution was skewed toward males in France and Italy, whereas it was mostly balanced in Germany, the UK and the US.

### Main Cohort

When the 2020 main cohorts were compared with those from 2019, a reduction in the proportion of patients with exacerbation was found in all countries, ranging from 46.3% reduction in the US main cohort to 78.3% reduction in the UK main cohort (Supplementary Table 2). In 2021, the proportion of patients with exacerbation rebounded or began to rebound to pre-pandemic levels in most countries; for example, the proportions rose from 4.1% in 2020 to 7.6% in 2021 in the UK and from 8.8% in 2020 to 14.4% in 2021 in the US. The exacerbation rates for the main cohorts in four countries were approximately 50% less in 2020 than in 2019; however, the exacerbation rates from 2020 to 2021 increased (Supplementary Table 2).

**Table 1** Definitions of Exacerbation Categories

Category	Pre-Pandemic Definition	Pandemic Definition
No exacerbation	<ul style="list-style-type: none"> <li>No exacerbation recorded in any of the three pre-pandemic years (2017, 2018, 2019)</li> </ul>	<ul style="list-style-type: none"> <li>No exacerbation recorded in either of the two years during the pandemic (2020, 2021)</li> </ul>
Infrequent exacerbations	<ul style="list-style-type: none"> <li>At least one exacerbation recorded during a pre-pandemic year (2017, 2018 or 2019), but not in consecutive years</li> </ul>	<ul style="list-style-type: none"> <li>At least one exacerbation recorded in one but not two years of the pandemic (2020, 2021)</li> </ul>
Recurrent exacerbations	<ul style="list-style-type: none"> <li>At least one exacerbation in two consecutive pre-pandemic years (2017, 2018 or 2019), but excluding those who had recorded “two or more exacerbations” in at least two consecutive pre-pandemic years (2017, 2018 or 2019)</li> </ul>	<ul style="list-style-type: none"> <li>At least one exacerbation in both years of the pandemic, but excluding those who had recorded “two or more exacerbations” in both years of the pandemic (2020, 2021)</li> </ul>
Frequent exacerbations	<ul style="list-style-type: none"> <li>A record of “two or more exacerbations” in at least two consecutive pre-pandemic years (2017, 2018 or 2019)</li> </ul>	<ul style="list-style-type: none"> <li>A record of “two or more exacerbations” in both years of the pandemic (2020, 2021)</li> </ul>

**Table 2** Characteristics of the Total COPD Population

Characteristic	France	Germany	Italy	UK	US
Age category, n (%)					
40–50 years	2379 (5.2)	16,279 (7.7)	1651 (3.7)	1543 (3.2)	59,665 (5.9)
51–60 years	7596 (16.6)	40,504 (19.3)	4666 (10.6)	7118 (14.6)	242,059 (24.1)
61–70 years	12,896 (28.2)	57,717 (27.4)	9278 (21.0)	13,074 (26.9)	455,569 (45.3)
71–80 years	12,819 (28.1)	47,906 (22.8)	13,133 (29.8)	16,194 (33.3)	148,443 (14.8)
81+ years	9960 (21.8)	47,395 (22.5)	15,371 (34.8)	10,734 (22.1)	100,389 (10.0)
Sex, n (%)					
Male	26,364 (57.8)	105,146 (50.0)	24,825 (56.3)	24,546 (50.4)	490,721 (48.8)
Female	19,287 (42.2)	104,989 (49.9)	19,285 (43.7)	24,117 (49.6)	515,404 (51.2)

**Notes:** Age category was missing for some patients in France, Germany and Italy; therefore, the total number of patients categorised according to age may not be similar to the total number categorised according to sex.

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

## Exacerbation Cohort

Reductions in the proportion of patients with exacerbation were between 44.5% (US) and 77.9% (UK) in the exacerbation cohort in 2020 compared with 2019 (Table 3). The percentage of patients with at least one exacerbation declined in 2020 (Table 4) but approached or reached pre-pandemic levels in four of the five countries in 2021 (35.0% in France, 24.9% in Germany, 24.1% in the UK, and 42.5% in the US).

The exacerbation rates in 2020 were lower than those in 2019, and the exacerbation rates rebounded to levels seen before the pandemic in all five countries in 2021 (Figure 1a).

**Table 3** Exacerbations and Patients in the Exacerbation Cohort and Continuous Follow-Up Cohort from 2017 to 2021

Country	Patients and Exacerbations	2017	2018	2019	2020	2021
<b>Exacerbation cohort<sup>a</sup></b>						
	<b>France</b>					
	N	7463	7635	7364	6449	5460
	Number of patients with exacerbation <sup>b</sup>	2388	3018	3177	1421	1911
	Proportion of patients with exacerbation <sup>c</sup>	32.0	39.5	43.1	22.0	35.0
	% annual change in proportion of patients with exacerbation <sup>d</sup>		23.5	9.1	−48.9	58.8
<b>Germany</b>	Number of exacerbations	3236	4271	4399	1987	2721
	N	18,299	18,564	18,442	17,362	15,907
	Number of patients with exacerbation <sup>b</sup>	4549	6533	7808	3397	3958
	Proportion of patients with exacerbation <sup>c</sup>	24.9	35.2	42.3	19.6	24.9
	% annual change in proportion of patients with exacerbation <sup>d</sup>		41.6	20.3	−53.8	27.2
<b>Italy</b>	Number of exacerbations	6187	9159	10,771	4729	5941
	N	6815	6887	6618	5961	4853
	Number of patients with exacerbation <sup>b</sup>	3011	3207	3222	1452	1332
	Proportion of patients with exacerbation <sup>c</sup>	44.2	46.6	48.7	24.4	27.4
	% annual change in proportion of patients with exacerbation <sup>d</sup>		5.4	4.6	−50.0	12.7
<b>UK</b>	Number of exacerbations	4236	4529	4613	2020	1879
	N	15,811	15,552	14,854	12,717	10,573
	Number of patients with exacerbation <sup>b</sup>	3428	6514	8629	1635	2543
	Proportion of patients with exacerbation <sup>c</sup>	21.7	41.9	58.1	12.9	24.1
	% annual change in proportion of patients with exacerbation <sup>d</sup>		93.2	38.7	−77.9	87.1
	Number of exacerbations	5183	10,895	14,426	2681	4320

(Continued)

Table 3 (Continued).

Country	Patients and Exacerbations	2017	2018	2019	2020	2021
<b>US</b>	N	262,988	262,857	255,505	229,893	194,406
	Number of patients with exacerbation <sup>b</sup>	87,405	107,399	122,528	61,215	87,405
	Proportion of patients with exacerbation <sup>c</sup>	33.2	40.9	48.0	26.6	45.0
	% annual change in proportion of patients with exacerbation <sup>d</sup>		22.9	17.4	-44.5	68.8
	Number of exacerbations	122,952	159,978	183,391	88,760	122,415
<b>Continuous follow-up cohort<sup>e</sup></b>						
<b>France</b>	N	4911				
	Number of patients with exacerbation <sup>b</sup>	735	675	661	439	472
	Proportion of patients with exacerbation <sup>c</sup>	15.0	13.7	13.5	8.9	9.6
	% annual change in proportion of patients with exacerbation <sup>d</sup>		-8.7	-1.5	-34.1	7.9
	Number of exacerbations	1054	992	966	654	735
<b>Germany</b>	N	16,577				
	Number of patients with exacerbation <sup>b</sup>	1427	1441	1453	1098	947
	Proportion of patients with exacerbation <sup>c</sup>	8.6	8.7	8.8	6.6	5.7
	% annual change in proportion of patients with exacerbation		1.2	1.1	-25.0	-13.6
	Number of exacerbations	2296	2330	2357	1893	1711
<b>Italy</b>	N	1214				
	Number of patients with exacerbation <sup>b</sup>	168	203	175	128	108
	Proportion of patients with exacerbation <sup>c</sup>	13.8	16.7	14.4	10.5	8.9
	% annual change in proportion of patients with exacerbation <sup>d</sup>		21.0	-13.8	-27.1	-15.2
	Number of exacerbations	248	300	246	167	144
<b>UK</b>	N	1447				
	Number of patients with exacerbation <sup>b</sup>	351	406	399	339	371
	Proportion of patients with exacerbation <sup>c</sup>	24.3	28.1	27.6	23.4	25.6
	% annual change in proportion of patients with exacerbation <sup>d</sup>		15.6	-1.8	-15.2	9.4
	Number of exacerbations	603	718	729	617	651
<b>US</b>	N	58,799				
	Number of patients with exacerbation <sup>b</sup>	14,924	14,714	15,267	12,219	13,205
	Proportion of patients with exacerbation <sup>c</sup>	25.4	25.0	26.0	20.8	22.5
	% annual change in proportion of patients with exacerbation <sup>d</sup>		-1.6	4.0	-20.0	8.2
	Number of exacerbations	23,604	23,203	24,868	19,967	21,482

**Notes:** <sup>a</sup>The exacerbation cohort consisted of patients with at least one exacerbation during the observed time. <sup>b</sup>An exacerbation was indicated by any of the following: a COPD exacerbation diagnostic code; prescriptions for a COPD-specific antibiotic and an oral corticosteroid (OCS) within 7 days; or two or more respiratory symptoms of exacerbation (eg cough, sputum production, breathlessness) with COPD-specific antibiotics or OCS within the next 7 days. <sup>c</sup>Proportion of patients with exacerbation was calculated by multiplying the exacerbation ratio by 100. <sup>d</sup>The % annual change in proportion of patients with exacerbation was calculated on the basis of the previous year as reference. <sup>e</sup>The continuous follow-up cohort consisted of patients who had a diagnosis of COPD between 1 January 2016 and 31 December 2016 and had complete information available for 2019, 2020 and 2021.

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

**Table 4** Frequency of Exacerbation<sup>a</sup> for Patients in the Exacerbation Cohort

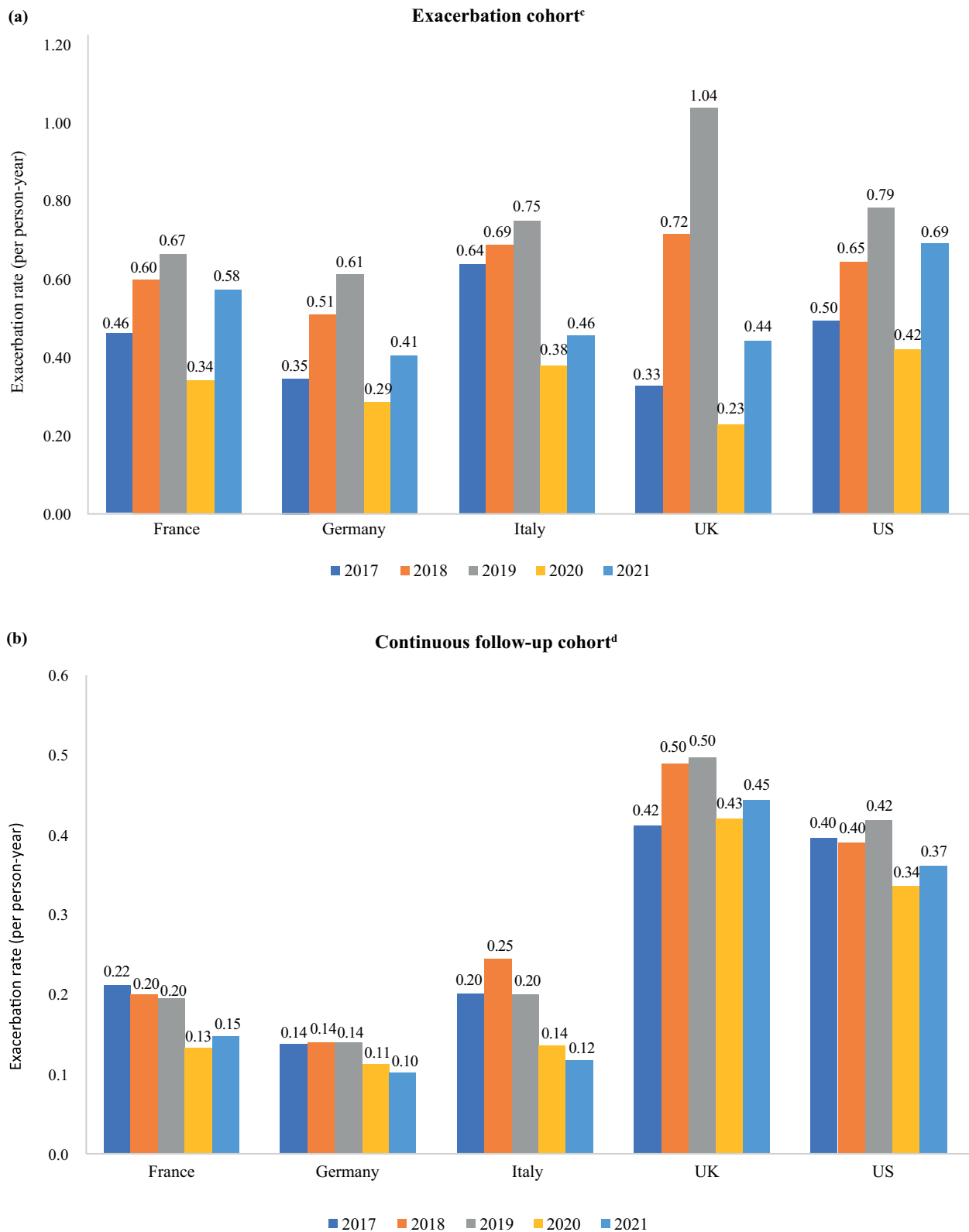
Number of Exacerbations	Patients with Exacerbations, n (%)				
	2017	2018	2019	2020	2021
<b>France</b>					
0	5075 (68.0)	4617 (60.5)	4187 (56.9)	5028 (78.0)	3549 (65.0)
≥1	2388 (32.0)	3018 (39.5)	3177 (43.1)	1421 (22.0)	1911 (35.0)
1	1798 (24.1)	2230 (29.2)	2397 (32.6)	1072 (16.6)	1435 (26.3)
≥2	590 (7.9)	788 (10.3)	780 (10.6)	349 (5.4)	476 (8.7)
<b>Germany</b>					
0	13,750 (75.1)	12,031 (64.8)	10,634 (57.7)	13,965 (80.4)	11,949 (75.1)
≥1	4549 (24.9)	6533 (35.2)	7808 (42.3)	3397 (19.6)	3958 (24.9)
1	3567 (19.5)	5008 (27.0)	6104 (33.1)	2647 (15.3)	2924 (18.4)
≥2	982 (5.4)	1525 (8.2)	1704 (9.2)	750 (4.3)	1034 (6.5)
<b>Italy</b>					
0	3804 (55.8)	3680 (53.4)	3396 (51.3)	4509 (75.6)	3521 (72.6)
≥1	3011 (44.2)	3207 (46.6)	3222 (48.7)	1452 (24.4)	1332 (27.4)
1	2048 (30.1)	2160 (31.4)	2136 (32.3)	984 (16.5)	895 (18.4)
≥2	963 (14.1)	1047 (15.2)	1086 (16.4)	468 (7.9)	437 (9.0)
<b>UK</b>					
0	12,383 (78.3)	9038 (58.1)	6225 (41.9)	11,082 (87.1)	8030 (76.0)
≥1	3428 (21.7)	6514 (41.9)	8629 (58.1)	1635 (12.9)	2543 (24.1)
1	2307 (14.6)	3953 (25.4)	5308 (35.7)	1024 (8.1)	1559 (14.8)
≥2	1121 (7.1)	2561 (16.5)	3321 (22.4)	611 (4.8)	984 (9.3)
<b>US</b>					
0	175,583 (66.8)	155,458 (59.1)	132,977 (52.0)	168,678 (73.4)	111,872 (57.5)
≥1	87,405 (33.2)	107,399 (40.9)	122,528 (48.0)	61,215 (26.6)	82,534 (42.5)
1	63,954 (24.3)	74,831 (28.5)	84,918 (33.2)	44,140 (19.2)	58,234 (30.0)
≥2	23,451 (8.9)	32,568 (12.4)	37,610 (14.7)	17,075 (7.4)	24,300 (12.5)

**Notes:** <sup>a</sup>An “exacerbation” refers to an acute exacerbation of chronic obstructive pulmonary disease (COPD). An exacerbation was indicated by any of the following: a COPD exacerbation diagnostic code; prescriptions for a COPD-specific antibiotic and an oral corticosteroid (OCS) within 7 days; or two or more respiratory symptoms of exacerbation (eg cough, sputum production, breathlessness) with COPD-specific antibiotics or OCS within the next 7 days.

## Continuous Follow-Up Cohort

Similar to the results of the other two cohorts, the number and proportion of patients with exacerbations decreased during 2020 when compared with 2019 across all countries in the continuous follow-up cohort. The reductions ranged from 34.1% (France) to 27.1% (Italy) (Table 3). The proportion of patients experiencing exacerbation began to rebound to pre-pandemic levels in three of the five countries (France, the UK and the US) in 2021 (Table 3). The exacerbation rates of the continuous follow-up cohort across the five countries were relatively stable before the pandemic but declined during the pandemic (Figure 1b).

Analysis of the cross-tabulated patient exacerbation categories before and during the pandemic further showed that patients had exacerbations less frequently during the pandemic. Of the patients who had recurrent exacerbations before the pandemic, 85% (France), 83% (Germany), 88% (Italy), 67% (UK) and 76% (US) experienced either infrequent or no exacerbations during the pandemic (Table 5 and Supplementary Figures 1–5). Among the patients who had infrequent exacerbations before the pandemic, 74.3% (France), 75.3% (Germany), 74.7% (Italy), 60.3% (UK) and 59.1% (US) experienced no exacerbations during the pandemic (Table 5). Much smaller proportions of patients with no exacerbation before the pandemic developed recurrent or infrequent exacerbations during the pandemic (8% in France, 5% Germany, 9% in Italy, and 16% each in the UK and US). However, the proportions of patients who had frequent exacerbations were relatively consistent over time: 24.8% (France), 40.1% (Germany), 15.6% (Italy), 37.8% (UK), and 26.1% (US) of all patients with frequent exacerbations before the pandemic continued to experience them during the pandemic.



**Figure 1** Annual exacerbation<sup>a</sup> rates<sup>b</sup> for the exacerbation cohort (a) and the continuous follow-up cohort (b) in France, Germany, Italy, the UK and the US. <sup>a</sup>An exacerbation was indicated by any of the following: a COPD exacerbation diagnostic code; prescriptions for a COPD-specific antibiotic and an oral corticosteroid (OCS) within 7 days; or two or more respiratory symptoms of exacerbation (eg cough, sputum production, breathlessness) with COPD-specific antibiotics or OCS within the next 7 days. <sup>b</sup>The exacerbation rate was the number of exacerbations per attributable person-time for the period of interest. <sup>c</sup>The exacerbation cohort consisted of patients with at least one exacerbation during the observed time. <sup>d</sup>The continuous follow-up cohort consisted of patients with a diagnosis of COPD in 2016 and who were continuously enrolled in the database from 2017 to 2021. **Abbreviation:** COPD, chronic obstructive pulmonary disease.

**Table 5** Cross-Tabulated Transition View of COPD Exacerbation Frequency for Each Country Before and During the COVID-19 Pandemic<sup>a</sup>

Country	Exacerbation Category	During the Pandemic n (% of row total)				
	Before the Pandemic	No Exacerbation	Infrequent Exacerbations	Recurrent Exacerbations	Frequent Exacerbations	Total (% of Row; % of Column)
France	No exacerbations	3254 (92.4)	248 (7.0)	14 (0.4)	7 (0.2)	3523 (100; 71.7)
	Infrequent exacerbations	723 (74.3)	195 (20.0)	46 (4.7)	9 (0.9)	973 (100; 19.8)
	Recurrent exacerbations	169 (55.2)	91 (29.7)	35 (11.4)	11 (3.6)	306 (100; 6.2)
	Frequent exacerbations	23 (21.1)	39 (35.8)	20 (18.4)	27 (24.8)	109 (100; 2.2)
Germany	No exacerbations	13,033 (95.4)	557 (4.1)	55 (0.4)	13 (0.1)	13,658 (100; 82.4)
	Infrequent exacerbations	1552 (75.3)	394 (19.1)	80 (3.9)	34 (1.7)	2060 (100; 12.4)
	Recurrent exacerbations	306 (54.0)	164 (28.9)	62 (10.9)	35 (6.2)	567 (100; 3.4)
	Frequent exacerbations	73 (25.0)	66 (22.6)	36 (12.3)	117 (40.1)	292 (100; 1.8)
Italy	No exacerbations	768 (90.7)	68 (8.0)	10 (1.2)	<5	847 (100; 69.8)
	Infrequent exacerbations	189 (74.7)	57 (22.5)	<5	<5	253 (100; 20.8)
	Recurrent exacerbations	47 (57.3)	25 (30.5)	8 (9.8)	<5	82 (100; 6.8)
	Frequent exacerbations	9 (28.1)	16 (50.0)	<5	5 (15.6)	32 (100; 2.6)
USA	No exacerbations	26,098 (82.8)	4647 (14.7)	651 (2.1)	123 (0.4)	31,519 (100; 53.6)
	Infrequent exacerbations	9967 (59.1)	4890 (29.0)	1549 (9.2)	459 (2.7)	16,865 (100; 28.7)
	Recurrent exacerbations	2905 (39.6)	2653 (36.2)	1246 (17.0)	525 (7.2)	7329 (100; 12.5)
	Frequent exacerbations	566 (18.3)	912 (29.6)	803 (26.0)	805 (26.1)	3086 (100; 5.2)
UK	No exacerbations	675 (84.1)	105 (13.1)	20 (2.5)	3 (0.4)	803 (100; 55.5)
	Infrequent exacerbations	202 (60.3)	78 (23.3)	40 (11.9)	15 (4.5)	335 (100; 23.2)
	Recurrent exacerbations	61 (30.8)	71 (35.9)	40 (20.2)	26 (13.1)	198 (100; 13.7)
	Frequent exacerbations	10 (9.0)	34 (30.6)	25 (22.5)	42 (37.8)	111 (100; 7.7)

Note: <sup>a</sup>The darker the green shading in a cell, the higher the percentage.

Abbreviation: COPD, chronic obstructive pulmonary disease.



The pre-pandemic category of “exacerbation” was a predictor of those who were unlikely to experience an exacerbation during the pandemic. Most patients with no exacerbations before the pandemic continued to have no exacerbations during the pandemic. This trend is evident from the consistency in the proportion of patients with no exacerbation over the years 2020 and 2021 across all countries ([Supplementary Tables 3–7](#))

## Seasonal Exacerbation Analysis in the COPD and Exacerbation Cohorts

In each country, the proportion of patients with exacerbation in the COPD and exacerbation cohorts increased between the autumn and winter periods in the pre-pandemic years (black arrows and grey bars in [Figure 2](#)); however, this seasonal peak was absent during the first year of the pandemic (areas shaded pink in [Figure 2](#)). Decreases in the proportions of patients with exacerbation in 2020 were early, steep and deep. Although there was a slight increase from late 2020 to early 2021 (blue arrows in [Figure 2](#)), the number of events and patients with exacerbation remained lower than those in the pre-COVID window in Germany, Italy, the UK and the US. In France, the proportion of patients with exacerbation in both cohorts rebounded to 2019 levels in winter 2022.

## Treatment Analysis for the Continuous Follow-Up Cohort

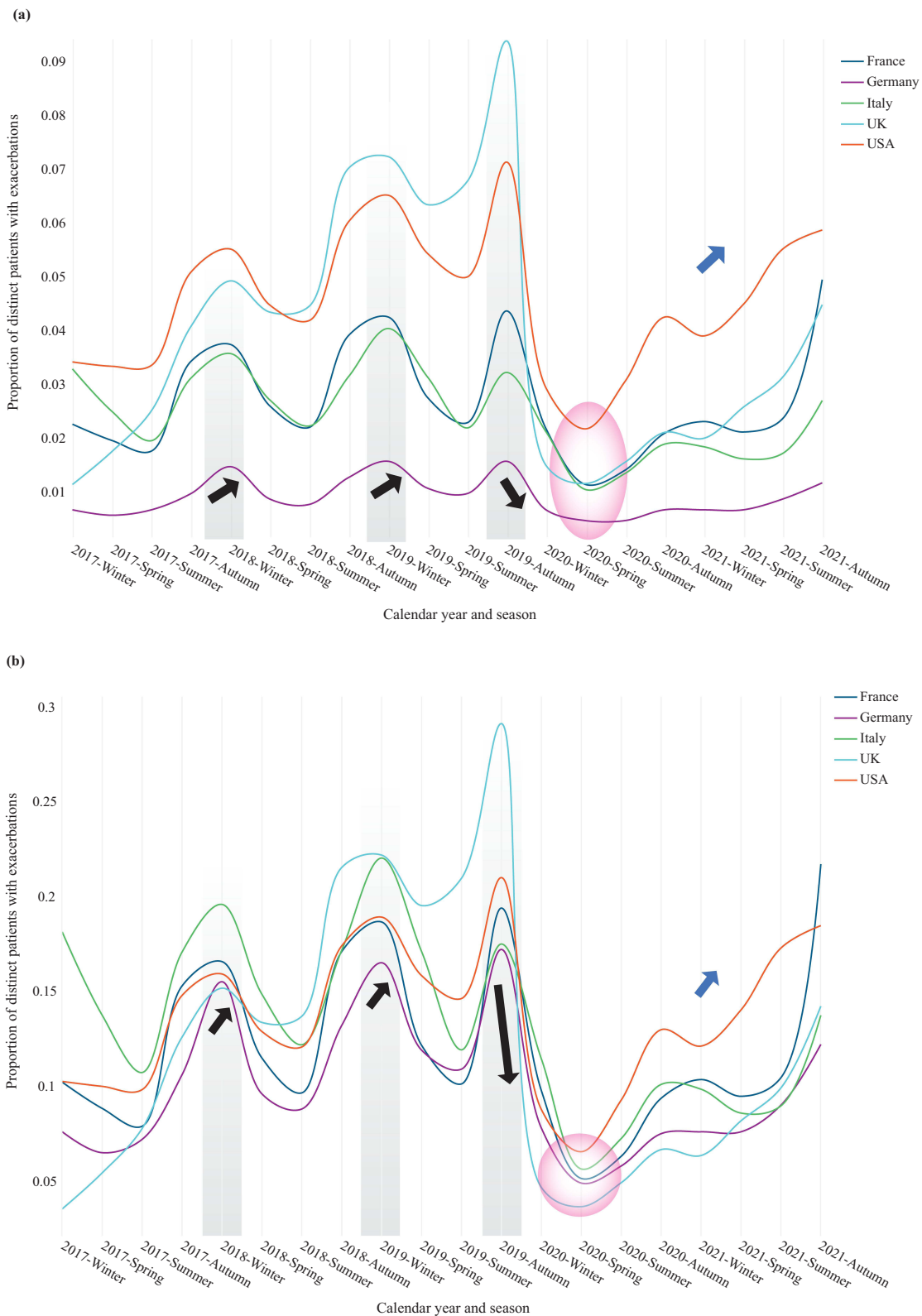
From 2019 through 2020, the percentages of patients who filled their prescriptions for stable maintenance therapy, including filling a prescription for fixed-dose triple therapy, increased in each country ([Supplementary Table 8](#)). A fixed-dose combination of inhaled corticosteroids (ICS)/long-acting beta agonist (LABA) was the most frequently prescribed treatment regimen except in the UK, where the fixed-dose combination of LABA/long-acting muscarinic antagonist (LAMA) was more frequently prescribed. Patients with more frequent exacerbations were also more likely to be on treatments such as ICS/LABA and triple therapy, but a large proportion remained untreated.

## Discussion

To our knowledge, the present study is the largest multinational study to compare COPD exacerbation rates and the concomitant change in percentage of patients filling prescriptions of COPD medications during the COVID-19 pandemic with those before the pandemic (2017–2019). A reduction in the rate of admissions due to COPD exacerbation during the initial months of the pandemic has been documented in the literature, with the reduction ranging from 27% to 78% among different nations.<sup>10,13–16</sup> In the present study, there was an early, steep and deep reduction in the number of exacerbation events during the peak of the COVID-19 pandemic. The decline in the proportion of patients with at least one exacerbation during the study period ranged from 45% to 78% among France, Germany, Italy, the UK and the US in 2020. The exacerbation events began to increase in 2021; this increase may have been due, in part, to changes in prescribing recommendations and patient behaviour—at the beginning of the COVID-19 pandemic, COVID-19-associated respiratory symptoms in patients with COPD were not considered to indicate an exacerbation, but this practice evolved later in the pandemic.<sup>19</sup> If antibiotic and OCS prescribing increased as a result, an increase in exacerbation would have been detected in our analysis. Despite the increase in exacerbation events in 2021, the rates remained lower than those in 2019. Overall, more patients had fewer exacerbations during the pandemic than before it. These observations were consistent across all three cohorts in the study.

Multiple plausible causes may account for the large reduction in the number of exacerbation events during the pandemic. Mask-wearing and social distancing are thought to have reduced the spread of seasonal viral respiratory infections, which can trigger exacerbations.<sup>20,21</sup> Reductions in air pollution, another potential promoter of exacerbation, may have resulted from nationwide lockdowns and thus may have led to fewer exacerbations. Increased medication adherence<sup>21,22</sup> and increased influenza vaccination rates for patients with COPD during the pandemic<sup>23</sup> might also have contributed to the decline in exacerbation rate. It remains unknown whether the reduction in the exacerbation events is due to a true reduction in exacerbations, to altered healthcare-seeking behavior during the pandemic or to other factors.<sup>24</sup> Therefore, recommendations regarding patients’ actions to reduce exacerbations would benefit from further investigations based on our findings.

Seasonal fluctuations in pre-pandemic exacerbation rates have been well documented,<sup>25,26</sup> and the seasonal patterns confirmed in the years before the COVID-19 pandemic in our study further validate the algorithm used to define a COPD exacerbation. Some studies have demonstrated a distortion or loss of the seasonal pattern of exacerbation during the



**Figure 2** Seasonal exacerbation trends for the (a) COPD population and (b) exacerbation population in France, Germany, Italy, the UK and the US. The pink circles indicate the nadir in the number of exacerbations during spring 2020. The black arrows indicate the autumn/winter trends and the blue arrows indicate an upward trend in exacerbation later in 2020 and 2021. Winter = January to March, spring = April to June; summer = July to September; autumn = October to December. An exacerbation was indicated by any of the following: a COPD exacerbation diagnostic code; prescriptions for a COPD-specific antibiotic and an oral corticosteroid (OCS) within 7 days; or two or more respiratory symptoms of exacerbation (eg cough, sputum production, breathlessness) with COPD-specific antibiotics or OCS within the next 7 days. **Abbreviation:** COPD, chronic obstructive pulmonary disease.

COVID-19 pandemic.<sup>19,26</sup> Results from the present study are consistent with those which previously reported altered seasonal variations in COPD exacerbation events during the pandemic.

A major strength of our study is the presentation of real-world evidence regarding exacerbation rates and seasonality data from multiple nations, representing diverse populations across Europe and the US. The exacerbation trends were very similar between countries, and this similarity provides reassurance of data robustness.

There were a few inherent limitations to the study. Our study is limited to those data that are reported. As such, any data not reported may include both the true absence of a condition (eg, no exacerbation) and missing information (eg, an exacerbation that was not recorded). Furthermore, the combined use of antibiotics and prednisolone for exacerbation diagnosis, along with the exclusion of courses lasting <30 days, may have resulted in an underestimation of the true rate of decline in COPD exacerbations. Comparison of results between countries should take into consideration possible heterogeneity of the data content and collection methodologies driven by differences in healthcare systems, national guidelines and clinical practice.<sup>27</sup>

## Conclusions

In conclusion, our study presents the long-term trend of exacerbation events before and during the COVID-19 pandemic in France, Germany, Italy, the UK and the US. We report an early, steep and deep decline in exacerbation events in 2020. The seasonal pattern of the exacerbation events was lost during the first pandemic year. In addition, more patients experienced less frequent exacerbations during the pandemic than before it. These findings could affect the feasibility of population-enrichment strategies in COPD trials started in Europe and the US in the period immediately after the COVID-19 pandemic started. Future studies are required to evaluate the impact of pandemic-associated changes in exacerbation trends and to assess the evolution pattern of these events in the post-pandemic period.

## Data Sharing Statement

IQVIA analysed the data on behalf of Chiesi and provided summarized insights; however, because of data confidentiality, the supporting data cannot be made publicly available.

## Ethics Approval

The study used de-identified data from five commercial databases described in this article. As per the LMMS Act (January 26, 2016), and the Ordinance No. 2018-1125 (12 December 2018) that amended the Data Protection Act (6 January 1978), IQVIA gained authorization by CNIL (France) to process EMRs used in this study (IQVIA<sup>®</sup> LPD France) for approved uses (Deliberation 2021-015 provided on 4 February 2021); therefore, IQVIA can conduct analyses for those pre-approved purposes without Ethics Committee approval on a per project basis. Studies of Disease Analyzer Germany data and IQVIA<sup>®</sup> LPD Italy data did not need Ethics Committee approval as these data are fully de-identified and thus comply with European Regulation 679/2016 (GDPR). The use of IQVIA Medical Research Data (UK) for the purpose of medical and public health research has received ethics approval by the NHS Health Research Authority (NHS Research Ethics Committee ref 18/LO/0441 and ref 23/EM/0151). The IQVIA PharMetrics Plus dataset (US) in this study complies with the US Health Insurance Portability and Accountability Act to ensure patient anonymity; therefore, approval from an institutional review board was not necessary.

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## Author Contributions

GG, DVG, AG, SP, RH, and JI led the design and implementation of the study. All authors were involved in data analysis and interpretation. All authors had access to the study results and participated in drafting or writing or substantial revisions or critical reviews of the article. All authors reached a consensus on the journal to which the manuscript is

submitted. Before submission, during revisions, and upon acceptance of the final version for publication, all authors reviewed and agreed on all versions of the article. Additionally, they collectively accepted any significant changes introduced during the proofing stage. Finally, all authors acknowledged their responsibility and accountability for the content of the article.

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