ORIGINAL ARTICLE

International Differences in the Frequency of Chronic Obstructive Pulmonary Disease Exacerbations Reported in Three Clinical Trials

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Abstract

Rationale: Exacerbations of chronic obstructive pulmonary disease (COPD) are an important endpoint in multinational clinical treatment trials, but the observed event rate is often lower than anticipated and appears to vary between countries.

Objectives: We investigated whether systematic differences in national exacerbation rates might explain this observed variation.

Methods: We reviewed data from three large multicenter international randomized trials conducted over an 18-year period with different designs and clinical severities of COPD, comparing bronchodilator and/or inhaled corticosteroids with bronchodilators alone and/or placebo. Exacerbations were defined by antibiotic and/or oral corticosteroid use (moderate) or need for hospitalization (severe). We calculated crude exacerbation rates in the 30 countries contributing 30 or more patients to at least two trials. We grouped data by exacerbation rate based on their first study contribution.

Measurements and Main Results: For the 29,756 patients in 41 countries analyzed, the mean exacerbation rate was two- to threefold different between the highest and lowest tertiles of the recruiting nations. These differences were not explained by demographic features, study protocol, or reported exacerbation history at enrollment. Of the 18 countries contributing to all trials, half of those in the highest and half in the lowest tertiles of exacerbation history remained in these groups across trials. Severe exacerbations showed a different rank order internationally.

Conclusions: Countries contributing to COPD trials differ consistently in their reporting of healthcare–defined exacerbations. These differences help explain why large studies have been needed to show differences between treatments that decrease exacerbation risk.

Keywords: chronic obstructive pulmonary disease; exacerbations; bronchodilators; inhaled corticosteroids

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At a Glance Commentary

Scientific Knowledge on the Subject: Chronic obstructive pulmonary disease (COPD) exacerbation rates in clinical trials are often lower than anticipated. The reasons for this remain unclear.

What This Study Adds to the Field: This study shows that the mean rate of COPD exacerbations differs substantially between countries irrespective of the study protocol and time when the study was conducted. Certain countries report consistently fewer exacerbations than others, which can compromise the ability of a trial to clearly answer questions about treatment efficacy.

Randomized controlled clinical trials (RCTs) are the cornerstone of evidence-based treatment. It is now customary to conduct large, complex studies to identify therapies that reduce the incidence of clinically important but infrequent events like death, hospitalization, or symptomatic deterioration. In chronic obstructive pulmonary disease (COPD), exacerbations are important because they drive clinical and physiological deterioration as well as healthcare costs (1). However, the interpretation of exacerbation data in clinical trials has proven to be very complex. Exacerbations are not normally distributed over time (2), and their occurrence can lead to behavioral changes such as leaving the trial (3). Further, the operational identification of an exacerbation's presence and severity relies on the *post hoc* determination of a new therapeutic intervention (4). The determinants of this therapeutic decision have not been studied in detail, and physicians in different countries might choose to manage the same event differently. Moreover, exacerbations may be under or overreported when determined only by patient-reported symptom variability and the specific treatment initiated (5).

Although some studies have relied on complex statistical models that address the problem of the patient's individual propensity to exacerbate (6), other studies have focused on identifying differences in the time to first exacerbation (7). Even when using these approaches, large numbers of patients are needed to provide sufficient statistical power for a proper test of the null hypothesis when exacerbation is an outcome. Indeed, the numbers involved in exacerbation studies have risen substantially in the last two decades (8, 9). In part, this reflects the falling exacerbation rates seen in the comparator arms of large RCTs, usually attributed to better background therapy. The strongest predictor of the likelihood of an exacerbation is previous exacerbation history (10), which is often used as a study enrichment entry criterion. However, the observed event rate is commonly lower than that anticipated from the patient's history before randomization (8, 10). Moreover, patients in efficacy trials commonly have lower rates of exacerbation than seen in studies with less strict inclusion criteria (11).

Large trials commonly recruit patients from multiple countries, assuming that patients with COPD and an exacerbation history will have a similar exacerbation risk, irrespective of their geographic location. On the basis of observations made while participating in several large COPD RCTs, we suspected this might not be true and that differences among reported exacerbation rates among countries could be contributing to the variability of exacerbation rates as a trial outcome. We tested this concept using data from three large international RCTs (TORCH [TOwards a Revolution in COPD Health], SUMMIT [Study to Understand Mortality and Morbidity in COPD], and IMPACT [Informing the Pathway of COPD Treatment]) (9, 12, 13) of different design conducted in the last 18 years where COPD exacerbations were reported as an outcome measure.

Methods

We performed *post hoc* analyses of data from three large multinational, randomized, double-blind, parallel-group trials supported by GlaxoSmithKline plc. (TORCH, SUMMIT, and IMPACT) published between 2007 and 2018, which the authors helped organize and direct. Complete details of the trial design and primary outcomes, including exacerbation rates, have been published previously (9, 12, 13), and their key features are summarized in Table E1 in the online supplement. Exacerbation rate was the primary outcome in the IMPACT trial and a prespecified key secondary outcome in the TORCH and SUMMIT trials. Exacerbations were defined similarly in all three trials as events in which symptomatic deterioration required additional treatment with antibiotics and/or oral corticosteroids (moderate events) or resulted in hospitalization (severe events). The patient's history of exacerbations in the year before study entry was available in all trials. The trials recruited symptomatic patients who met the current criteria for a diagnosis of COPD and had spirometric evidence of airflow obstruction with an absolute postbronchodilator ratio of FEV_1/FVC of less than 0.7 together with a smoking history of at least 10 pack-years of tobacco. All the trials were approved by the relevant ethical review boards. SUMMIT (NCT01313676) and IMPACT (NCT02164513) were registered with Clinicaltrials.gov; the TORCH trial was conducted before the registration system was introduced.

The three trials differed in several important areas (Table E1). TORCH and SUMMIT compared an inhaled corticosteroid in combination with a long-acting inhaled β-agonist (LABA) and each individual component with a placebo, whereas IMPACT compared combination inhaled corticosteroid/LABA/long-acting inhaled antimuscarinic with combination inhaled corticosteroid/LABA and long-acting inhaled antimuscarinic/LABA. Additional differences among the three trials and details regarding statistical

Data sharing statement: Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

power calculations are outlined in the supplementary methods.

Patients were recruited from multiple centers over five different continents. The same centers and countries did not necessarily contribute patients to each trial.

Data Management

Using the trial data from TORCH, SUMMIT, and IMPACT, patients were grouped by country irrespective of study therapy. Within each trial, countries were excluded if *1*) they had fewer than 30 patients to provide a more stable estimate of exacerbation numbers in that country or *2*) they participated in only one of the three trial, thereby precluding comparisons over time. Individual country exacerbation rates were calculated for each trial by dividing the total number of on-treatment COPD exacerbations in all subjects by the total exposure to study treatment in years.

For each trial, countries were ranked from highest exacerbation rate to lowest and then divided into even-numbered tertiles: high exacerbating countries within the trial (red), middle exacerbating countries within the trial (yellow), and low exacerbating countries within the trial (green) (ties were placed into the higher group). For the rest of the analysis, the countries were grouped by TORCH exacerbation rates, described in more detail in the supplementary methods.

No *a priori* assumptions were made about the normality of the distribution of national exacerbation rates. Simple descriptive statistics, including mean, standard deviation, median, and interquartile range, are reported for the baseline demographic data.

Results

Overall, 32,952 patients were recruited across the three trials, and the demographic data for the total patient population in each trial are presented in Table 1. By design, the postbronchodilator FEV_1 and body mass index were higher in SUMMIT than in TORCH or IMPACT, and the percentage of patients with a previous history of exacerbations was greatest in the IMPACT trial. Despite these prespecified differences, the gender mix, ethnicity, and smoking habits of the three trials were similar. The proportional reduction in exacerbation rate attributable to therapy was similar in each trial (*see* Figure E1).

Data from 29,756 (90.3%) patients in 41 different countries randomizing more than 30 patients per trial and in countries

Table 1. Baseline Demographic Characteristics of the Trial Populations of the Three Trials

	TORCH	SUMMIT	IMPACT
N (ITT)	6,112	16,485	10,335
Age, yr			
Mean (SD)	65.0 (8.3)	65.2 (7.9)	65.3 (8.3)
Gender, *n* (%)			
Female	1,481 (24)	4,196 (25)	3,485 (34)
Race, *n* (%)			
White	5,006 (82)	13,357 (81)	7,983 (77)
Black	95 (2)	258 (2)	264 (3)
Asian	769 (13)	2,723 (17)	1,679 (17)
Other	242 (4)	147 (<1)	428 (2)
BMI, kg/m^2			
Mean (SD)	25.4 (5.18)	28.0 (5.92)	26.6 (6.09)
Smoking status, *n* (%)			
Former smoker	3,482 (57)	8,807 (53)	6,768 (65)
Current smoker	2,630 (43)	7,678 (47)	3,587 (35)
Total pack-years			
Mean (SD)	48.5 (27.4)	40.8 (24.4)	46.6 (26.6)
Prior moderate COPD exacerbations*			
Mean (SD)	1.0 (1.3)	0.5 (0.8)	1.4 (0.9)
Median (Q1, Q3)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	1.0 (1.0, 2.0)
Prior severe COPD exacerbations†			
Mean (SD)	0.2 (0.6)	0.2 (0.4)	0.3 (0.6)
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)
Prior moderate*/severe† COPD exacerbations			
Mean (SD)	1.2 (1.6)	0.6 (1.0)	1.7 (0.7)
Median (Q1, Q3)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	2.0 (1.0, 2.0)
Post-BD FEV_1, L			
Mean (SD)	1.2 (0.42)	1.7 (0.40)	1.3 (0.49)
%Predicted post-BD FEV_1			
Mean (SD)	44.0 (12.4)	59.7 (6.1)	45.5 (14.8)
FVC, L	(Pre-BD)	(Post-BD)	(Post-BD)
Mean (SD)	2.3 (0.75)	3.0 (0.74)	2.7 (0.82)
FEV_1/FVC ratio (%)	(Pre-BD)	(Post-BD)	(Post-BD)
Mean (SD)	48.6 (10.80)	58.4 (8.32)	47.0 (11.96)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; COPD = chronic obstructive pulmonary disease; IMPACT = Informing the Pathway of COPD Treatment; ITT = intent-to-treat; Q = quarter; SUMMIT = Study to Understand Mortality and Morbidity in COPD; TORCH = Towards a Revolution in COPD Health.

*Requiring antibiotics and/or oral corticosteroids.

†Requiring hospitalization.

	TORCH	SUMMIT	IMPACT
Patients in ITT Pop	6,112	16,485	10,355
Patients in Analysis	5,704	13,985	10,067
High Exacerbating Group			
Patients in Group	2,663	4,171	4,410
United Kingdom	1st 1.73 [2.5%]	5th 0.67 [0.9%]	1st 2.10 [1.5%]
Philippines	2nd 1.64 [2.5%]	15th 0.39 [6.4%]	27th 0.59 [1.1%]
Viet Nam		2nd 0.86 [1.3%]	29th 0.48 [1.0%]
Hong Kong	3rd 1.60 [1.5%]		3rd 1.79 [0.3%]
Korea, Republic of		3rd 0.73 [1.3%]	17th 1.05 [3.2%]
Brazil	4th 1.60 [0.9%]		11th 1.38 [1.1%]
New Zealand	5th 1.36 [2.2%]		2nd 2.00 [0.6%]
Chile	6th 1.35 [1.3%]	11th 0.44 [0.5%]	19th 1.01 [3.7%]
Israel		6th 0.62 [0.5%]	20th 0.92 [2.0%]
Finland	7th 1.25 [3.1%]		8th 1.57 [0.8%]
Sweden	8th 1.19 [1.8%]		7th 1.57 [0.9%]
Denmark	9th 1.18 [2.2%]		5th 1.75 [0.9%]
Belgium	10th 1.12 [1.2%]		14th 1.25 [1.1%]
Australia	11th 1.11 [3.2%]	4th 0.70 [0.3%]	13th 1.29 [1.7%]
United States	12th 1.10 [24.3%]	16th 0.38 [18.5%]	15th 1.19 [23.9%]
Middle Exacerbating Group			
Patients in Group	1,606	3,871	3,215
Croatia	13th 1.07 [1.2%]	18th 0.36 [2.1%]	
Japan		13th 0.41 [1.0%]	21st 0.89 [3.8%]
South Africa	14th 1.06 [3.1%]	10th 0.47 [3.0%]	16th 1.18 [2.8%]
Canada	15th 1.05 [2.8%]	12th 0.44 [0.4%]	9th 1.55 [2.1%]
Argentina	16th 1.05 [1.1%]	14th 0.41 [3.6%]	26th 0.71 [9.7%]
Austria	17th 1.05 [2.2%]	9th 0.52 [0.9%]	18th 1.01 [1.2%]
Colombia		17th 0.36 [0.8%]	28th 0.57 [0.5%]
Mexico	18th 0.91 [1.3%]	26th 0.26 [0.6%]	
France	19th 0.89 [4.1%]		4th 1.75 [1.3%]
Romania	20th 0.87 [1.2%]	24th 0.27 [4.5%]	32nd 0.19 [1.0%]
Netherlands	21st 0.87 [1.9%]		12th 1.36 [3.0%]
Norway	22nd 0.84 [2.9%]		6th 1.60 [0.8%]
Spain	23rd 0.84 [4.3%]	1st 1.00 [0.8%]	10th 1.41 [5.0%]
Poland	24th 0.81 [2.3%]	21st 0.30 [10.1%]	30th 0.45 [0.9%]
Low Exacerbating Group			
Patients in Group	1,435	5,943	2,442
Czech Republic	25th 0.79 [3.2%]	27th 0.26 [3.8%]	25th 0.77 [1.4%]
Thailand	26th 0.69 [1.7%]	7th 0.61 [1.0%]	23rd 0.85 [1.4%]
Greece	27th 0.69 [3.1%]	19th 0.35 [0.3%]	
China	28th 0.66 [4.2%]	25th 0.27 [3.6%]	22nd 0.89 [5.3%]
Germany	29th 0.64 [2.6%]	20th 0.34 [3.8%]	24th 0.83 [11.8%]
Latvia	30th 0.62 [1.3%]	31st 0.12 [2.9%]	
Hungary	31st 0.61 [2.5%]	22nd 0.29 [2.1%]	
Taiwan	32nd 0.53 [1.8%]	8th 0.56 [0.3%]	
Ukraine	33rd 0.34 [0.6%]	29th 0.19 [9.8%]	33rd 0.15 [1.1%]
Bulgaria	34th 0.32 [1.8%]	30th 0.14 [4.6%]	
Slovakia	35th 0.27 [1.4%]	23rd 0.28 [0.9%]	
Russian Federation	36th 0.26 [1.0%]	28th 0.20 [9.3%]	31st 0.41 [3.2%]

Figure 1. Ranking of countries according to the observed rate of moderate and severe exacerbations (countries with fewer than 30 patients or only participating in one of the three trials are excluded). For each country, the figure shows the within-trial exacerbation rate ranking (first and highest rate to last and lowest rate), the within-trial exacerbation rate (exacerbations/years of exposure), and, in square brackets, the percentage contribution of patients to this analysis from that trial and country. Colors represent within-trial exacerbation tertile grouping (red: high; yellow: middle; green: low); however, the overall high, middle, and low exacerbating groups in this table, based mostly on TORCH, are used for this analysis. The number (*n*) of patients in each subgroup participating in each tertile of the exacerbation rate distribution is shown within a box above each trial group. COPD = chronic obstructive pulmonary disease; IMPACT = Informing the Pathway of COPD Treatment; ITT = intent-to-treat; Pop = population; SUMMIT = Study to Understand Mortality and Morbidity in COPD; TORCH = Towards a Revolution in COPD Health.

Table 2. Mean Moderate and Severe Exacerbation in Each Third of the National Distribution

	TORCH		SUMMIT		IMPACT	
	Mean Exacerbation Rate/yr	Previous Exacerbation Frequency/yr	Mean Exacerbation Rate/yr	Previous Exacerbation Frequency/yr	Mean Exacerbation Rate/yr	Previous Exacerbation Frequency/yr
High exacerbating group	1.23	1.2	0.43	0.4	1.19	1.7
Middle exacerbating group	0.93	1.2	0.37	0.5	1.03	1.8
Low exacerbating group	0.59	1.3	0.23	0.7	0.75	1.6

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; IMPACT = Informing the Pathway of COPD Treatment; SUMMIT = Study to Understand Mortality and Morbidity in COPD; TORCH = Towards a Revolution in COPD Health.
Data are provided on the basis of the rank order shown in Figure 1 together with mean number of exacerbations reported in the year before randomization.

included in at least two of the three trials were included in this analysis. The reasons for the inclusion of countries involved in the trials in this analysis are presented in Figure E2.

National Differences in Combined Exacerbation Rates

The mean annual exacerbation rate (moderate and severe events combined) observed in each country for all participants, irrespective of therapy, is tabulated for each trial in Figure 1. There were 18 countries that contributed more than 30 patients to all three trials. The relative contribution of each country to the total analysis population is also shown. The mean exacerbation rate of countries in each third of the exacerbation range is shown in Table 2. In TORCH, the lowest exacerbating countries reported events at half the rate of the highest ones; in SUMMIT and IMPACT, there was a threefold difference between the highest and lowest group. Low exacerbating countries contributed 25.2–32.8% of patients to each trial.

In general, countries where the exacerbation rates were high remained in the highest third of exacerbation frequency. Thus, 7 of 12 in the red zone in TORCH remained in that group in the other trials (mean exacerbation rate, 1.42 events/yr), as did 7 of 12 in the green zone (mean exacerbation rate, 0.46 events/yr), with less consistency in the yellow zone. The mean exacerbation rates of the 18 countries involved in all three trials are shown in Table 3 and show a 12-fold difference in rate between the highest and lowest contributing countries. The IMPACT trial had a prespecified exacerbation rate of at least 0.9 events per year, which was met by all of the 11 participating countries that had previously had high exacerbation rates, by all except one of those with intermediate values, and by none of those with a low rate of observed exacerbations.

Demographic characteristics of all three trials separated by observed exacerbation rate are shown in Tables E2–E4. Individuals with a low exacerbation rate across the trials did not differ in their baseline history of exacerbations from those who reported more frequent events at baseline. Individuals with lower observed event rates were less likely to have used inhaled corticosteroids and, in SUMMIT, had smoked less tobacco than the other groups, but all the groups had similar lung function impairment. As expected, the reported history of exacerbations in the year before the trial varied with the protocol. In all trials, there was a gradient of exacerbation frequency, with the low exacerbating countries having only a third of the events seen before the trial (Table 2).

In general, Western European and North American nations reported higher exacerbation rates than those in Central and Eastern Europe or Asia. However, this was not true in every country, with both Brazil and Austria being exceptions to this rule (Table 3).

The number of investigators contributing patients varied between countries with the trial design and size (Table E5). There was no evidence of substantial overlap in personnel between TORCH and the other trials. In total, 178 investigators were involved in both SUMMIT and IMPACT, representing 14.4% and 18.9% of the total number of trialists in each trial, respectively.

National Differences for Severe Events

Severe exacerbations requiring hospitalization were less frequent in all trials than moderate exacerbations, with a mean rate per year in this analysis of 0.19, 0.09, and 0.19 for TORCH, SUMMIT, and IMPACT, respectively. However, the rank order of nations reporting severe exacerbations was different from that based on total events, as shown in Figure 2, and for countries that contributed to all the trials in Table 3. Again, there were substantial differences between the severe exacerbation rate in the highest and lowest reporting countries, which differed from those in the data based on total exacerbation numbers.

Table 3 is ordered in terms of the mean rate of moderate and severe exacerbations for all the countries that contributed to all three trials. Clearly, the proportion of hospitalized exacerbations varies significantly between countries. There was no simple geographic explanation for these differences in exacerbation rate, although the four countries with the lowest rate of exacerbations all come from Eastern Europe.

Discussion

Multiple potential biases can affect the interpretation of RCTs in COPD (14). Our analysis adds further to the list of variables to be considered when designing, implementing, and interpreting these studies. In this analysis, we found that the rate of COPD exacerbation varies from country to country and that these differences persist over time. Similar differences exist in the likelihood of experiencing a severe exacerbation defined by hospitalization but did not

Table 3. Mean Number of All Exacerbations and Severe Exacerbations Across the Three Trials by Country

Country	Moderate + Severe Exacerbations/yr	Severe Exacerbations/yr	Severe-to-Total Exacerbations Ratio	Geographic Region
United Kingdom	1.51	0.20	0.13	Western Europe
Spain	1.07	0.23	0.21	Western Europe
Canada	1.09	0.11	0.10	North America
Australia	1.09	0.21	0.20	Southern Hemisphere
Republic of South Africa	0.78	0.10	0.12	Southern Hemisphere
United States	0.79	0.13	0.16	North America
Chile	1.05	0.17	0.17	South America
Austria	0.85	0.18	0.21	Central Europe
Thailand	0.69	0.35	0.51	Asia
Argentina	0.61	0.06	0.10	South America
Philippines	0.67	0.13	0.20	Asia
Czech Republic	0.44	0.05	0.12	Central Europe
Germany	0.60	0.08	0.13	Central Europe
China	0.60	0.16	0.26	Asia
Poland	0.36	0.06	0.16	Eastern Europe
Romania	0.34	0.12	0.35	Eastern Europe
Russia	0.23	0.09	0.39	Eastern Europe
Ukraine	0.19	0.04	0.21	Eastern Europe

Data are provided on the basis of countries contributing to all three trials and presented together with geographic region.

follow the same pattern as differences in the total exacerbation rate. This international variation is not explained by study design, recruiting physician selection of patients, or objective differences in the baseline characteristics of the patients recruited. Recent OECD (Organization for Economic Co-operation and Development) data (15) indicate that age-standardized admission rates for COPD vary 15-fold across OECD countries. However, these rates are imprecise owing to issues with data reporting, were not based on objectively diagnosed COPD as in our trials, and had a more limited geographic distribution than we report. Although large studies were able to identify differences in the effectiveness of different treatments, the selection of centers with a lower than anticipated exacerbation rate could affect the ability of the study to detect a treatment effect. These findings have implications for our understanding of COPD exacerbations and the conduct of future treatment trials where exacerbation rate is an endpoint.

Investigators involved in international clinical trials have long been aware of national differences in COPD exacerbation rates, but these have been attributed to variation in the selection of study sites and the relative severity of patients recruited. The observational ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) cohort based in Western Europe and North America defined a series of predictive factors for exacerbation risk, which confirmed the role of baseline lung function but emphasized that prior exacerbation history was the strongest predictor of future events (10). More recent data from both observational studies and clinical trials suggest this distinction is less reliable than first thought (16, 17). However, there is evidence that patients have an intrinsic exacerbation rate that varies significantly in a study population (18), a finding in keeping with our observed transnational differences in exacerbation frequency. In all the trials we report, fewer exacerbations were seen than anticipated from the exacerbation history, possibly reflecting the impact of the withdrawal of sickest patients (3, 14) and regression to the mean during the trial period. Although the prior history of treated exacerbations was similar at study entry across all countries with an absolute event rate in keeping with the respective study protocols, the observed event rate was substantially lower than expected in the mid- and lower range of exacerbation-reporting nations. This difference was substantially larger than the observed effect of treatment that appears to produce similar proportionate reductions in exacerbations, irrespective of the background event rate.

We found an average two- to threefold difference in the exacerbation rate between the highest and lowest exacerbating countries. These differences were seen irrespective of whether exacerbation rate was the primary study outcome and were present over the 18-year period when trials took place and irrespective of the trial design. The baseline characteristics of trial participants varied by design between the trials, but within each trial, there were no substantial differences between countries in baseline spirometry, smoking status, or reported history of previous events, which would identify groups at low or higher risk of subsequent exacerbation. The magnitude of these differences was substantially greater than those seen with any of the treatments studied and was not explained by differences in gender, a known determinant of exacerbation reporting (19), between groups.

The mean rate of severe (hospitalized) exacerbations varied substantially between countries, but the rank order of international difference did not correspond to that seen with the total exacerbation rate. Severe exacerbations accounted for between 10% and almost 40% of all exacerbations, suggesting significant differences in healthcare behavior and care access across the globe. These discrepancies highlight the limitations of a definition of exacerbation based solely on healthcare usage. Recent

	TORCH	SUMMIT	IMPACT
Patients in ITT Pop	**6,112**	**16,485**	**10,355**
Patients in Analysis	**5,704**	**13,985**	**10,067**
High Exacerbating Group			
Patients in Group	**1,339**	**3,691**	**3,746**
Hong Kong	1st 0.71 [1.5%]		1st 0.57 [0.3%]
Romania	2nd 0.42 [1.2%]	15th 0.07 [4.5%]	22nd 0.14 [1.0%]
Viet Nam		2nd 0.23 [1.3%]	10th 0.23 [1.0%]
Thailand	3rd 0.40 [1.7%]	1st 0.25 [1.0%]	2nd 0.49 [1.4%]
Latvia	4th 0.37 [1.3%]	29th 0.03 [2.9%]	
United Kingdom	5th 0.30 [2.5%]	14th 0.08 [0.9%]	25th 0.12 [1.5%]
Israel		5th 0.17 [0.5%]	23rd 0.14 [2.0%]
Austria	6th 0.29 [2.2%]	16th 0.07 [0.9%]	28th 0.10 [1.2%]
Korea, Republic of		6th 0.17 [1.3%]	13th 0.19 [3.2%]
Philippines	7th 0.29 [2.5%]	10th 0.09 [6.4%]	32nd 0.06 [1.1%]
Chile	8th 0.27 [1.3%]	28th 0.03 [0.5%]	21st 0.15 [3.7%]
Japan		8th 0.13 [1.0%]	15th 0.18 [3.8%]
Brazil	9th 0.24 [0.9%]		24th 0.13 [1.1%]
Colombia		9th 0.10 [0.8%]	20th 0.15 [0.5%]
Spain	10th 0.23 [4.3%]	4th 0.21 [0.8%]	8th 0.23 [5.0%]
Argentina	11th 0.22 [1.1%]	24th 0.04 [3.6%]	33rd 0.05 [9.7%]
Finland	12th 0.22 [3.1%]		3rd 0.33 [0.8%]
Middle Exacerbating Group			
Patients in Group	**2,824**	**6,804**	**3,742**
Australia	13th 0.21 [3.2%]	7th 0.16 [0.3%]	5th 0.26 [1.7%]
Mexico	14th 0.21 [1.3%]	31st 0.01 [0.6%]	
Taiwan	15th 0.21 [1.8%]	3rd 0.21 [0.3%]	
Denmark	16th 0.20 [2.2%]		19th 0.15 [0.9%]
New Zealand	17th 0.18 [2.2%]		6th 0.24 [0.6%]
Poland	18th 0.18 [2.3%]	22nd 0.04 [10.1%]	31st 0.07 [0.9%]
Greece	19th 0.17 [3.1%]	12th 0.08 [0.3%]	
United States	20th 0.17 [24.3%]	20th 0.06 [18.5%]	12th 0.20 [23.9%]
China	21st 0.15 [4.2%]	11th 0.09 [3.6%]	7th 0.24 [5.3%]
Croatia	22nd 0.14 [1.2%]	25th 0.04 [2.1%]	
South Africa	23rd 0.14 [3.1%]	17th 0.07 [3.0%]	27th 0.11 [2.8%]
Ukraine	24th 0.14 [0.6%]	26th 0.03 [9.8%]	30th 0.08 [1.1%]
Low Exacerbating Group			
Patients in Group	**1,541**	**3,490**	**2,579**
Slovakia	25th 0.13 [1.4%]	19th 0.06 [0.9%]	
Sweden	26th 0.13 [1.8%]		11th 0.20 [0.9%]
Norway	27th 0.13 [2.9%]		17th 0.18 [0.8%]
France	28th 0.12 [4.1%]		4th 0.33 [1.3%]
Belgium	29th 0.12 [1.2%]		9th 0.23 [1.1%]
Hungary	30th 0.12 [2.5%]	21st 0.05 [2.1%]	
Canada	31st 0.10 [2.8%]	30th 0.02 [0.4%]	18th 0.18 [2.1%]
Czech Republic	32nd 0.10 [3.2%]	27th 0.03 [3.8%]	29th 0.10 [1.4%]
Bulgaria	33rd 0.09 [1.8%]	18th 0.06 [4.6%]	
Germany	34th 0.08 [2.6%]	23rd 0.04 [3.8%]	26th 0.11 [11.8%]
Netherlands	35th 0.07 [1.9%]		16th 0.18 [3.0%]
Russian Federation	36th 0.02 [1.0%]	13th 0.08 [9.3%]	14th 0.19 [3.2%]

Figure 2. Ranking of countries according to the observed rate of severe exacerbations (*n*, %). Color coding and other data are as described in Figure 1. For definition of abbreviations, see Figure 1.

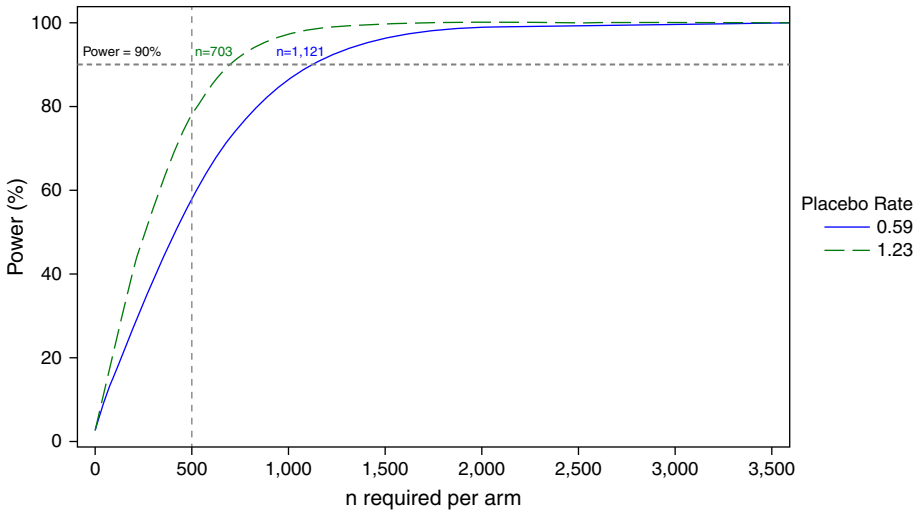

Figure 3. Power curves for different exacerbation rates to detect a difference assuming a 20% reduction in the rate from the comparator. The statistical power of the trial is shown on the *y*-axis and the number of participants per arm on the *x*-axis. Representative power curves are shown for trials with a mean exacerbation in the placebo arm of the rates seen in the highest and lowest thirds of participating countries in the TORCH (Towards a Revolution in COPD Health) trial (*see* Table 2). COPD = chronic obstructive pulmonary disease.

attempts at defining these events more rigorously may help reduce the extent of these international differences (20).

The reason for these international differences merits further study. Although all participants had a significant history of tobacco smoking, exposure to biomass fuels in countries like China (21) and many other Asian countries or heavy industrial atmospheric pollution in Eastern Europe earlier in life may have affected the balance of airway and parenchymal damage, causing COPD and hence the propensity to exacerbate, as might differences in the airway microbiome and the uptake of immunization programs (22). Systematic investigations using more sophisticated imaging and microbiological techniques should resolve these issues (23, 24). Alternatively, there could be problems in access to healthcare or with the subjective nature of the exacerbation definition itself. Differences in symptom interpretation, social custom, or the response by healthcare providers in terms of therapeutic interventions could influence the reporting of those events. Local customs about indications for hospitalization and differences in the availability and use of healthcare systems are additional potential explanatory factors.

There are strengths and limitations to our descriptive analysis of these data. We report data from trials using several different designs of well-characterized patients with COPD using the same exacerbation definition. We focused on exacerbations as an important COPD outcome available in all participants. The exacerbation rates are those calculated arithmetically rather than using complex modeling that takes into account the patient's inherent likelihood of experiencing an exacerbation (25). In our analysis, control for multiple confounders was not required as we were not comparing differences within a population but between populations, differences that occurred irrespective of the treatment allocation. One reason such complex modeling approaches are needed is the very heterogeneous nature of exacerbation data, which is in part because of the national differences we have observed. Unfortunately, we lack information about individual access to medical care during these trials, which might further influence the chances of treatment for a symptomatic event. There is evidence that the prescription of oral corticosteroids to treat exacerbations has increased over time, at least in the United Kingdom (26), but we do not believe this would impact our overall conclusions. Similarly, a Hawthorne effect related to participation in a clinical trial is likely to contribute to a reduction in exacerbations during the trial period. However, we anticipate that this effect would be similar in all participating countries.

Our data have implications for future trial design and interpretation. One implication for trial design is outlined graphically in Figure 3, where the relationships between study size, observed exacerbation rate, and statistical power are explored. In countries with an exacerbation rate similar to the average of the highest third of our sample, 703 patients per study arm would be needed to establish a 20% decrease in exacerbations with 90% statistical power compared with 1,121 patients per arm if recruiting was from countries in the lowest third of our sample. Thus, when testing a new intervention in exacerbation prevention, it would be prudent and more economical to recruit from countries where the exacerbation rate is usually high. Similarly, a different choice of sites would be helpful when prevention of hospitalization is the trial goal. Our observations help explain some of the discrepancies in exacerbation rate between studies with similar entry criteria (8, 27–29) and emphasize the need for caution when using a single number needed to treat derived from a heterogeneous patient population to evaluate the worth of treatment. The number needed to treat (or harm) is often derived in health economic studies from the mean data presented in a manuscript. Our data suggest that this metric would be better related to the exacerbation rate that applies in a particular nation. There are advantages to recruiting patients from primary care where more exacerbations have been identified compared with rates in multinational studies (30) and hence a potentially clearer treatment outcome identified (11), although the magnitude of this benefit may be influenced by national propensity to report exacerbations.

Conclusions

Our data suggest that the design of future trials of COPD exacerbations should take into account geographic differences in exacerbation rates. Further confirmation of our findings and a better definition of the factors that explain these differences would help us understand the impact of COPD globally and inform the interpretation of clinical trials intended to test our treatment strategies. ■

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References

1. Ritchie AI, Wedzicha JA. Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. *Clin Chest Med* 2020;41:421–438.
2. Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;179:369–374.
3. Calverley PM, Spencer S, Willits L, Burge PS, Jones PW; IOSLDE Study Group. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. *Chest* 2003;124:1350–1356.
4. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019;53:1900164.
5. Donaldson GC, Seemungal TA, Patel IS, Lloyd-Owen SJ, Wilkinson TM, Wedzicha JA. Longitudinal changes in the nature, severity and frequency of COPD exacerbations. *Eur Respir J* 2003;22:931–936.
6. Keene ON, Calverley PM, Jones PW, Vestbo J, Anderson JA. Statistical analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited. *Eur Respir J* 2008;32:17–24.
7. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM, *et al.*; POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093–1103.
8. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, *et al.*; TRial of Inhaled STeroids ANd long-acting β2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449–456.
9. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al.*; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–1680.
10. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, *et al.*; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128–1138.
11. Woodcock A, Boucot I, Leather DA, Crawford J, Collier S, Bakerly ND, *et al.* Effectiveness *versus* efficacy trials in COPD: how study design influences outcomes and applicability. *Eur Respir J* 2018;51:1701531.
12. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, *et al.*; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356:775–789.
13. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, *et al.*; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817–1826.
14. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, *et al.* Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. *Clin Respir J* 2011;5:44–49.
15. Health at a Glance 2019: facts and figures. Organization for Economic Co-operation and Development; 2019 [accessed 2022 Apr 26]. Available from: https://www.oecd-ilibrary.org/sites/4dd50c09-en/index.html?itemId=/content/publication/4dd50c09-en.
16. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, *et al.*; SPIROMICS investigators. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017;5:619–626.
17. Calverley PM, Tetzlaff K, Dusser D, Wise RA, Mueller A, Metzdorf N, *et al.* Determinants of exacerbation risk in patients with COPD in the TIOSPIR study. *Int J Chron Obstruct Pulmon Dis* 2017;12: 3391–3405.
18. Sadatsafavi M, McCormack J, Petkau J, Lynd LD, Lee TY, Sin DD. Should the number of acute exacerbations in the previous year be used to guide treatments in COPD? *Eur Respir J* 2021;57:2002122.
19. Celli B, Vestbo J, Jenkins CR, Jones PW, Ferguson GT, Calverley PM, *et al.*; Investigators of the TORCH Study. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience. *Am J Respir Crit Care Med* 2011; 183:317–322.
20. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, *et al.* An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal. *Am J Respir Crit Care Med* 2021;204:1251–1258.
21. Guan WJ, Zheng XY, Chung KF, Zhong NS. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. *Lancet* 2016;388:1939–1951.
22. Paget J, Spreeuwenberg P, Charu V, Taylor RJ, Iuliano AD, Bresee J, *et al.*; Global Seasonal Influenza-associated Mortality Collaborator Network and GLaMOR Collaborating Teams. Global mortality associated with seasonal influenza epidemics: new burden estimates and predictors from the GLaMOR Project. *J Glob Health* 2019;9: 020421.
23. Bhatt SP, Washko GR, Hoffman EA, Newell JD Jr, Bodduluri S, Diaz AA, *et al.* Imaging advances in chronic obstructive pulmonary disease. Insights from the genetic epidemiology of chronic obstructive pulmonary disease (COPDGene) study. *Am J Respir Crit Care Med* 2019;199:286–301.
24. Keir HR, Dicker A, Lonergan M, Crichton M, Miller BE, Tal-Singer R, *et al.* Clinical endotypes of exacerbation are associated with differences in microbial composition and diversity in COPD. *Eur Respir J* 2020;56: 2000391.
25. Keene ON, Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, *et al.* Methods for therapeutic trials in COPD: lessons from the TORCH trial. *Eur Respir J* 2009;34:1018–1023.
26. James GD, Donaldson GC, Wedzicha JA, Nazareth I. Trends in management and outcomes of COPD patients in primary care, 2000-2009: a retrospective cohort study. *NPJ Prim Care Respir Med* 2014; 24:14015.
27. Calverley PM, Kuna P, Monsó E, Costantini M, Petruzzelli S, Sergio F, *et al.* Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. *Respir Med* 2010;104:1858–1868.
28. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, *et al.* Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018;391:1076–1084.
29. Martinez FJ, Vestbo J, Anderson JA, Brook RD, Celli BR, Cowans NJ, *et al.*; SUMMIT Investigators. Effect of fluticasone furoate and vilanterol on exacerbations of chronic obstructive pulmonary disease in patients with moderate airflow obstruction. *Am J Respir Crit Care Med* 2017; 195:881–888.
30. Vestbo J, Leather D, Diar Bakerly N, New J, Gibson JM, McCorkindale S, *et al.*; Salford Lung Study Investigators. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. *N Engl J Med* 2016;375: 1253–1260.