Examining the Inclusivity of US Trials of COVID-19 Treatment

J Gen Intern Med 36(5):1443–5
DOI: 10.1007/s11606-020-06566-8

INTRODUCTION

The urgency of the COVID-19 pandemic has increased attention on the need to include patients traditionally underrepresented in research, especially people with comorbid diseases, racial/ethnic minorities, pregnant/lactating women, and children.[1–4] We characterized the inclusion and exclusion criteria of US COVID-19 treatment trials to understand their applicability to highly affected populations and groups traditionally underrepresented in research.

METHODS

We conducted a cross-sectional analysis of all US COVID-19 treatment trials registered on ClinicalTrials.gov as of June 21, 2020, using two separate queries with the search terms "coronavirus" and "COVID". US studies were defined by the study or sponsor having at least one US location, or prior US study. Studies were excluded if they were observational, examined a vaccine or non-COVID-19 treatment, did not include COVID-19 patients, or only evaluated expanded drug access. All data were extracted in duplicate; discrepant results were resolved by discussion with a second reviewer. Included studies were reviewed for inclusion/exclusion criteria.

To analyze recruitment of patients with chronic diseases, we denoted conditions mentioned in inclusion and/or exclusion criteria and if studies excluded people based on disease severity. In a subanalysis, we used census block group-level data of Centers for Medicare & Medicaid Services–accredited hospitals from the 2015 American Community Survey 5-year estimate for each trial's recruitment hospitals' local geographic catchment area, in order to estimate the proportion of Blacks and Hispanics who may be recruited for US COVID-19 treatment trials. We assumed that each hospital would recruit patients in proportion to their catchment size and that they would recruit Blacks and Hispanics in the same proportion as their catchment area.

Received October 2, 2020
Accepted December 22, 2020
Published online January 27, 2021

RESULTS

The search yielded 303 unique, active US COVID-19 treatment trials, which would potentially recruit 92,112 patients. About 60% of trials excluded pregnant women and/or required contraception ($n = 187$, 62%); about half of trials excluded lactating women ($n = 142$, 47%) (Fig. 1). Only 5% ($n = 16$) of trials included children less than 18 years old. In contrast, 97% of trials ($n = 295$) did not exclude people older than 65 years. Most trials included adults > 75 years ($n = 291$, 96%) and > 85 years ($n = 260$, 86%). Half of trials ($n = 156$, 51%) excluded patients with non-severe comorbid disease, and 30% of trials ($n = 91$) permitted investigators to decide additional exclusion criteria as necessary (Table 1). Overall, the US COVID-19 treatment trials were estimated to include 17% Black ($n = 12{,}243$) and 14% Hispanic ($n = 9662$) patients, based on hospital catchment areas.

DISCUSSION

We found that about half of US COVD-19 treatment trials excluded people with high-risk chronic conditions, and most trials excluded children, pregnant women, and lactating women. Exclusion of patients with comorbid conditions can lead to several problems with the evidence-base for treating COVID-19 infections, including treatments that will likely be less effective in diverse patients and delayed study results because of slow patient recruitment.

Additionally, pregnant/lactating women and children were excluded from most US COVID-19 treatment trials. The absence of trial data validated in these physiologically and metabolically distinct populations will translate to little evidence about COVID-19 treatment for these populations and increase the risk of experiencing potentially severe adverse drug reactions. It is important to consider that the protected status of these groups is likely a large contributing factor to the hesitation about including these populations in clinical trials. However, because of the time-sensitive nature of the COVID-19 pandemic, alternative strategies (e.g., allowing inclusion for compassionate use) should be considered.

Furthermore, our subanalysis showed that the US COVID-19 treatment trials are being conducted at study locations that do not typically care for high proportions of Black and Hispanic patients. Re-consideration of exclusion criteria and inclusion of study locations with high proportions of minority patients would increase the generalizability of results.

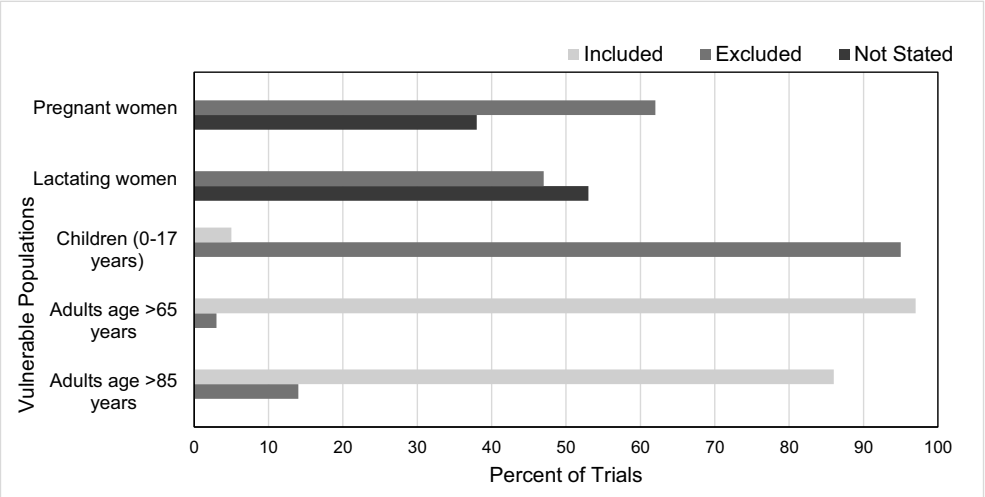

Figure 1 Inclusion and exclusion of vulnerable populations in US COVID-19 treatment trials, $N = 303$. ClinicalTrials.gov records ($N = 303$) for US COVID-19 treatment trials were characterized by the inclusion of pregnant or lactating women, children (0–17 years), adults age > 65 years, adults age > 85 years, prisoners, and nursing home residents. Light gray indicates the percentage of trials that included the population. Dark gray indicates the percentage of trials that excluded the population. Black indicates the percentage of trials that did not mention inclusion or exclusion of the population.

Our study has several limitations. Trials were only included if they had at least one US hospital location or a sponsor who had previously completed US-based research. Additionally, details available on ClinicalTrials.gov may be incomplete and are changing.

Our analysis of COVID-19 treatment trials found that patients with comorbidities, racial/ethnic minorities, pregnant/lactating women, and children would likely be underrepresented in ongoing COVID-19 treatment trials. Re-consideration of recruitment criteria would increase the generalizability of results. With more generalizability, clinical trials and their results about the effectiveness of treatments will be better realized in real-world US populations.

Table 1 Inclusion and Exclusion Criteria for US COVID-19 Treatment Trials, by Comorbidity and Vulnerable Populations, $N = 303$

	Inclusion criteria		Exclusion criteria	
Characteristic	**Definition**	**Trials, *n* (%)**	**Definition**	**Trials, *n* (%)**
High-risk subpopulations	Per trial	20 (7)	Investigator allowed to exclude based on unspecified criteria	92 (30)
Comorbidities				
Any comorbidity[a]	Any	29 (10)	Any non-severe	156 (51)
Lung disease	Any	15 (5)	Any not requiring home oxygen	27 (9)
Hypertension	Any	16 (5)	Controlled	0 (0)
Ischemic heart disease	Any	17 (6)	Not in last 6 months	10 (3)
Ischemic stroke	Any	8 (3)	Not in last 6 months	7 (2)
Heart failure	Any	11 (4)	New York Heart Association class 1 or 2, asymptomatic	26 (9)
Type 2 diabetes	Any	18 (6)	Controlled	5 (2)
Kidney disease	Any	8 (3)	Stage 3 only (glomerular filtration rate 30–59 mL/min)	23 (8)
Liver disease	Any	1 (0)	Child-Pugh class A, non-active hepatitis B/C, cirrhosis, no portal hypertension	36 (12)
Cancer	Active	12 (4)	History (> 1 year prior)	5 (2)
Autoimmune disease or chronic immunosuppression	Any	16 (5)	Any	77 (25)
HIV	Any	4 (1)	Stable, not AIDS	38 (13)
Dementia	Any	1 (0)	Any	15 (5)
Vulnerable populations				
Pregnant women	-	0 (0)	-	187 (62)
Lactating women	-	0 (0)	-	142 (47)
Nursing home residents	-	2 (1)	-	3 (1)
Children (0–17 years)	-	16 (5)	-	287 (95)
Adults age > 65 years	-	295 (97)	-	8 (3)
Adults age > 85 years	-	260 (86)	-	43 (14)
Prisoners	-	0 (0)	-	25 (8)

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome
[a]*Any comorbidity refers to all comorbidities included in the table*

Acknowledgments: *We would like to thank John Fahrenbach and Elizabeth Tung for their contribution of hospital catchment data for our racial subanalysis. We would also like to thank Brinda Doshi and Alexandra Knitter for assistance with generation of tables and figures.*

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