Demographic Characteristics of Participants in Trials Essential to US Food and Drug Administration Vaccine Approvals, 2010–2020

BACKGROUND AND OBJECTIVE

Vaccines are a cornerstone of the strategy to address the COVID-19 pandemic. Given disparities in morbidity and mortality from COVID-19 among US populations, calls have been made to ensure representation of those most affected by the disease in trials of new vaccines. Prior research has shown that older adult, Black, and Hispanic participants have historically been underrepresented in clinical trials, including pivotal trials for new drug and device approvals.[1, 2] However, no comparable evaluation of representation in vaccine approvals has been done. This study examines the inclusion of age, sex, racial, and ethnic subgroups and participants with comorbidities in trials essential to new vaccine approvals in the USA.

METHODS

We identified all novel vaccine products licensed by the US Food and Drug Administration (FDA) between January 2010 and June 2020 for diseases endemic to the USA.[3] We identified all trials identified as essential to FDA approval of those products in FDA clinical reviews, including efficacy, safety, and lot-to-lot consistency trials.[4] Using data in clinical reviews, or if not available, in corresponding registration and results reported on ClinicalTrials.gov or publications, we identified the inclusion and exclusion criteria for each trial, then determined the number of participants in each trial and characterized their age, sex, race, and ethnicity. We aggregated trial participants by vaccine approval and, for those trials with subgroup data available, determined the proportions of participants in age, sex, race, and ethnicity subgroups supporting each approval. Participants in pre-2016 trials described as being of Hispanic race were designated as unknown race and Hispanic ethnicity, to allow comparison with trials following more recent guidance on reporting, which specifies Hispanic as an ethnic category. We then characterized the demographic composition of participants, presented in relation to

demographic characteristics of the US population.[5] Analyses were conducted using R version 3.5.1 (R Foundation for Statistical Computing).

FINDINGS

From 2010 through 2020, the FDA approved 17 vaccines for diseases endemic to the USA, supported by a total of 40 trials considered essential to approval. Each vaccine was supported by a median of 3 (IQR, 2–4) essential trials with 5241 total participants (IQR, 4281–10423). While no trials used inclusion or exclusion criteria based on sex, race, or ethnicity, age was a common exclusion criteria, with 58.6% of trials excluding adults 65 or older (95% CI, 39.6–77.7), as were conditions such as pregnancy or lactation (92.9%, 95% CI, 82.7–100%) and comorbidities such as cardiovascular, renal, or hepatic disease (Table 1).

Distributions of participants' age were reported for 32 (80.0%) trials. Overall, 24.7% (95% CI, 0–50.1%) of participants were children and 8.5% (95% CI, 0–20.7%) were adults aged 65 years or older, the latter suggesting underrepresentation when compared to the general US population (Table 2). All trials reported participants' sex; 44.8% (95% CI, 37.8–51.8%) of participants were male, 55.2% (95% CI, 48.2–

Table 1 Exclusion Criteria in Trials Considered Essential to US Food and Drug Administration Approval of New Vaccines, 2010–2020

	Trials excluding, % (95% CI)
Age-based exclusions	
Pediatric (<18 years)*	37.8 (21.4–54.2)
Older Adult (≥65 years)†	58.6 (39.6–77.7)
Pregnancy or lactation-based exclusions	92.9 (82.7–100)
Comorbidity-based exclusions	
Immunodeficiency	90.0 (80.3–99.7)
HIV infection	37.5 (21.8–53.2)
Current/past alcohol or drug abuse	22.5 (9.0–36.0)
Autoimmune conditions	30.0 (15.2–44.8)
Cardiovascular disease	20.0 (7.0–33.0)
Renal dysfunction	17.5 (5.2–29.8)
Hepatic dysfunction	7.5 (0–16.0)

*Among trials for vaccines expected to include pediatric participants (e.g., excluding vaccines for shingles)
†Among trials for vaccines expected to include older adult participants (i.e., excluding childhood vaccines)

Table 2 Characteristics of Participants in Aggregated Trials Considered Essential to US Food and Drug Administration Approval of New Vaccines, 2010–2020

	Aggregated trial participants, % (95% CI)		
	All vaccine trials essential to approval	**Including only essential trials intended for use among population subgroups***	**US population (%, 2019 US Census Estimate)**
Age subgroups†			
Pediatric (<18 years)	40.5 (16.1–64.8)	24.7 (0–50.1)	22.3
Adult (18–64 years)	41.7 (19.0–64.4)	66.7 (42.3–91.2)	61.2
Older Adult (≥65 years)	17.8 (0–36.4)	8.5 (0–20.7)	16.5
Sex subgroups			
Male	45.2 (39.0–51.4)	44.8 (37.8–51.8)	49.2
Female	54.8 (48.5–61.0)	55.2 (48.2–62.2)	50.8
Race subgroups‡			
White	70.5 (61.4–79.7)	–	76.3
Black	9.2 (6.1–12.4)	–	13.4
Asian	6.6 (0–13.3)	–	5.9
Other	5.2 (2.0–8.3)	–	4.3
Ethnicity subgroups§			
Hispanic	19.2 (11.7–26.8)	–	18.5
Non-Hispanic‖	80.7 (73.2–88.3)	–	81.5

*For age, this excludes trials supporting 5 childhood vaccine approvals and 1 shingles vaccine approval, leaving 21 essential trials supporting 11 vaccine approvals for analysis. For sex, this excludes 1 essential trial examining only the cervical cancer endpoint for Gardasil 9 approval, leaving 39 essential trials supporting 17 vaccine approvals for analysis
†Age subgroup data was available for 32 essential trials supporting 16 of 17 vaccine approvals
‡Race subgroup data was available for 39 essential trials supporting 17 vaccine approvals. Percentages may not sum to 100%, as data for participants with unknown race are not included in the table
§Including participants whose race was not explicitly defined, such as those participants in pre-2016 identifying as Hispanic in trials designating Hispanic as a racial category
‖Ethnicity subgroup data was available for 33 essential trials supporting 15 vaccine approvals.

62.2%) female. Information about participants' race and ethnicity was reported for 39 (97.5%) and 33 (82.5%) trials, respectively. Among these, 70.5% of participants identified as White (95% CI, 61.4–79.7%), 9.2% as Black (95% CI, 6.1–12.4%), and 6.6% as Asian (95% CI, 0–13.3%), suggesting underrepresentation among Black participants (Table 2); 19.2% identified as Hispanic (95% CI, 11.7–26.8%).

DISCUSSION

Among trials considered essential to FDA approval of 17 vaccines for diseases endemic to the USA from 2010 through 2020, we found that exclusion criteria based on older age and prevalent comorbidities were commonly used, and there was underrepresentation of Black and older adult participants, but not female or Hispanic participants. Our finding of disparities in participation and gaps in reporting in vaccine trials are consistent with those seen among recent FDA approvals of drugs and medical devices.[1, 2]

This study examined only demographic composition of vaccine trials essential to FDA approval and does not account for enrollment in other supportive pre-market trials that were ongoing or completed at the time of approval. While we reviewed all vaccine approvals over the past 10 years, there were a limited number of vaccines endemic to the USA on which to base our study. Nonetheless, as COVID-19 vaccine testing and evaluation proceeds, our study reinforces recent FDA guidance to include in COVID-19 vaccine trials diverse populations of participants from communities most affected by the disease—particularly racial and ethnic minorities, older adults, and individuals with comorbidities.[6]

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REFERENCES

1. **Downing NS**, **Shah ND**, **Neiman JH**, **Aminawung JA**, **Krumholz HM**, **Ross JS**. Participation of the Elderly, Women, and Minorities in Pivotal Trials Supporting 2011-2013 U.S. Food and Drug Administration Approvals. Trials. 2016;17:199–210.

2. **Dhruva SS**, **Mazure CM**, **Ross JS**, **Redberg RF**. Inclusion of Demographic-Specific Information in Studies Supporting US Food & Drug Administration Approval of High-Risk Medical Devices. JAMA Intern Med. 2017 Sep 1;177(9):1390–1.

3. Center for Biologics Evaluation and Research. Vaccines Licensed for Use in the United States. FDA [Internet]. 2020 Apr 24 [cited 2020 Oct 7]; Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

4. **Puthumana J**, **Egilman AC**, **Zhang AD**, **Schwartz JL**, **Ross JS**. Speed, Evidence, and Safety of Vaccines Approved by the US Food and Drug Administration. JAMA Intern Med. 2020 Nov 10;e207472. https://doi.org/10.1001/jamainternmed.2020.7472

5. U.S. Census Bureau Quick Facts: United States [Internet]. United States Census Bureau. 2020. Available from: https://www.census.gov/quickfacts/fact/table/US/PST045219

6. US FDA. Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry. 2020 p. 24.

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