Geographic Disparities in Vaccine Clinical Trial Access in the Mid-West: Impact of COVID-Era Clinical Trial Reform

Direct Original Research

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Open Access

Published: January 24, 2025

Research in Health and Medicine: *2025, Volume 5 (Issue 1): 2*

ISSN: 2768-492X

Abstract

Introduction: The COVID-19 pandemic prompted numerous vaccine studies. The Food and Drug Administration (FDA) also modified research regulatory guidelines, such as allowing virtual visits, in March 2020 that could make clinical research in rural areas more feasible. This study evaluates the effect of 2020 clinical trial reform on vaccine trial access in rural/underserved regions of the mid-West.

Methods: Clinicaltrials.gov data was accessed from 1/1/2018-9/30/2022 for vaccination studies conducted in Kentucky, Tennessee, Illinois, Indiana, and Ohio. Trial locations were categorized by Rural-Urban Commuting Area codes (urban, suburban, small town and isolated rural) and identified as pre- vs. post-pandemic regulations. Trial locations from pre- and post-pandemic regulation dates were analyzed by paired t-test. Comparison of trial location category by state was analyzed by one-way ANOVA with pairwise multiple comparisons.

Results: Pandemic-era deregulation had no impact on vaccine trial geographic availability ($p=0.8637$). Overall, 95% of study locations were in urban/metropolitan areas, 4% in suburban/micropolitan areas, 0.5% in small town/rural areas, and 0.1% in isolated rural areas. Results varied by state ($p<0.0001$) with Kentucky offering the most suburban and rural trial availability (31%).

Conclusions: While modifications in the FDA's regulatory guidelines may have increased flexibility for patients, these changes did not improve access to vaccine clinical trials at community sites in suburban, small town, and rural areas as measured by RUCA code. Increasing geographic diversity in vaccine clinical trials is critical for the development of more effective and equitable vaccines, as well as enhancing public trust in vaccination programs.

Key Words: Underserved, COVID-19 pandemic, Telemedicine.

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Introduction

Clinical research is the driver of innovation in modern medicine; hence, ensuring diversity in access to clinical trials is crucial. Despite repeated calls from federal governing agencies for better representation in clinical research, we continue to see that women, individuals from varied racial and cultural backgrounds, older adults, and individuals residing in rural communities are underrepresented. While 60 million people, 20% of the U.S. population, reside in rural areas,[1] rural residents are commonly cited as a group significantly underrepresented in medical research.[2,3]

The impact of social determinants of health on treatment outcomes must be considered with some minority groups being more susceptible to certain conditions or experiencing barriers that are not present in other communities. For example, rural residents encounter obstacles in accessing routine healthcare, including geographic distance, insufficient public transportation, and severe shortages of providers.[4] Diverse representation in trials broadens our understanding

of social determinants of health or genomic variations that may impact an intervention, drug metabolism, or treatment response.

The COVID-19 pandemic brought about drastic change in the research enterprise in a short time. First, public health measures to control the pandemic, such as mandatory lockdowns and restrictions in healthcare delivery, dramatically slowed research.[5] Secondly, there was unprecedented collaboration to launch new research to test vaccines and therapeutics for COVID-19.[6] By April 2020, more than 200 COVID-19 clinical trials were launched.[6] Regulatory authorities responded quickly to provide emergency guidance to ensure safety, compliance, and quality of clinical trials. This guidance resulted in the deregulation of clinical trials, which increased flexibility for patients by allowing telemedicine and virtual visits, decreased testing frequency, and provided the ability to have lab and imaging tests done locally.[7] This study sought to determine whether 2020 clinical trial reform improved access to vaccination clinical trials in rural/underserved geographic areas of the mid-West.

Scientific Methods

Data was accessed from clinicaltrials.gov for the time period of January 1, 2018 to September 30, 2022. Publicly available data retrieved included all interventional vaccine clinical trials for the states of Kentucky, Tennessee, Illinois, Indiana, and Ohio. The address and Zip Code for each location where the clinical trial was offered were used to identify the corresponding Rural-Urban Commuting Area (RUCA) code. The 10 primary codes provide a clear and comprehensive classification of metropolitan and nonmetropolitan areas based on the size and direction of primary commuting patterns. For our study purposes, each trial location was categorized as urban/metropolitan (RUCA 1-3), suburban/micropolitan (RUCA 4-6), small town/rural (RUCA 7-9) and isolated/rural (RUCA 10) using it's corresponding RUCA code. Trials were also categorized as pre- vs. post-pandemic regulations. Those trials starting prior to the date March 18, 2020, when regulatory guidelines from the FDA were modified,[7] were categorized as "pre-pandemic" and those starting on or after March 18, 2020 were categorized as "post-pandemic." Trial locations from pre- and post-pandemic time periods were compared by paired t-test. Analysis of trial location category (i.e., urban/metropolitan, suburban/micropolitan, small town/rural, and isolated rural) by state was conducted via one-way ANOVA with pairwise multiple comparisons made using the Tukey HSD/Tukey Kramer method.

Results

Data from 604 vaccine trials offered across the five states was exported from clinicaltrials.gov for the study time period. These 604 clinical trials constituted nearly 870 study locations. Overall, 825 (95%) of study locations were in urban/metropolitan areas, 38 (4%) in suburban/micropolitan areas, 4 (0.5%) in small town/rural areas, and 1 (0.1%) in isolated rural areas. Pandemic era deregulation had no impact on vaccine trial availability as measured by RUCA category (p=0.8637). Unsurprisingly, the number of vaccine studies increased dramatically, by 93%, after March 18, 2020. For pre-pandemic studies, 94% were in urban/metropolitan areas, 5% were in suburban/micropolitan areas, and 1% in small town/rural areas. Comparatively, post-pandemic studies had 96% in urban/metropolitan areas, 4% in suburban/micropolitan areas, and less than 0.4% in small town/rural areas (see Table 1).

Table 1: Comparison of pre- vs. post-COVID-era regulations on vaccine clinical trial location by rural-urban category.

Rural-Urban Category		Study Locations	% of Locations		Study Locations	% of Locations
Urban/Metropolitan Area	Pre-COVID-19 Regulations	279	94%	Post-COVID-19 Regulations	546	96%
Suburban/Micropolitan Area		14	5%		24	4%
Small Town/Rural		3	1%		1	0.2%
Isolated Rural Area		0	0%		1	0.2%
Total		296	100%		572	100%

For the reporting period, there were 211 trial locations in Illinois, 160 in Tennessee, 116 in Kentucky, 46 in Indiana, and 335 in Ohio. Similar to the overall data, regulatory changes had no impact on vaccine trial availability as measured by RUCA category within each state. Trial location urban/rural categories varied by state ($p<0.0001$) with Kentucky offering the most suburban, small-town, and isolated rural trial availability (31%) compared to Indiana, Ohio, Tennessee, and Illinois (4%, 4%, 1%, and 0.5% respectively, see Figure 1). Of the pairwise comparisons by state, Kentucky's trial geographic location mix was statistically significant ($p<0.0001$) when compared to all other states (i.e., Indiana, Ohio, Tennessee, and Illinois, see Figure 2). No other state location comparisons approached significance ($p>0.69$).

Figure 1: Vaccination clinical trial location rural-urban category by state.

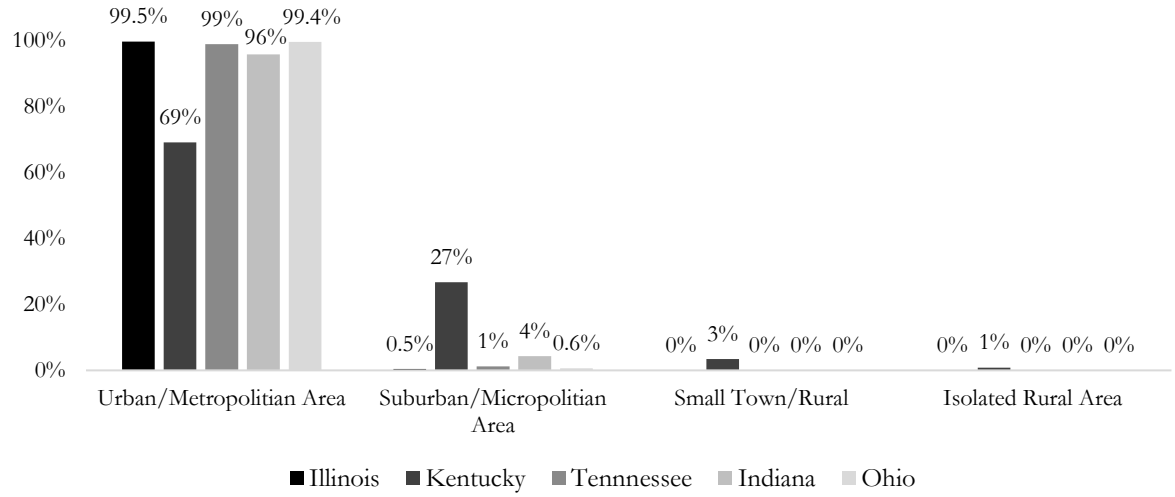
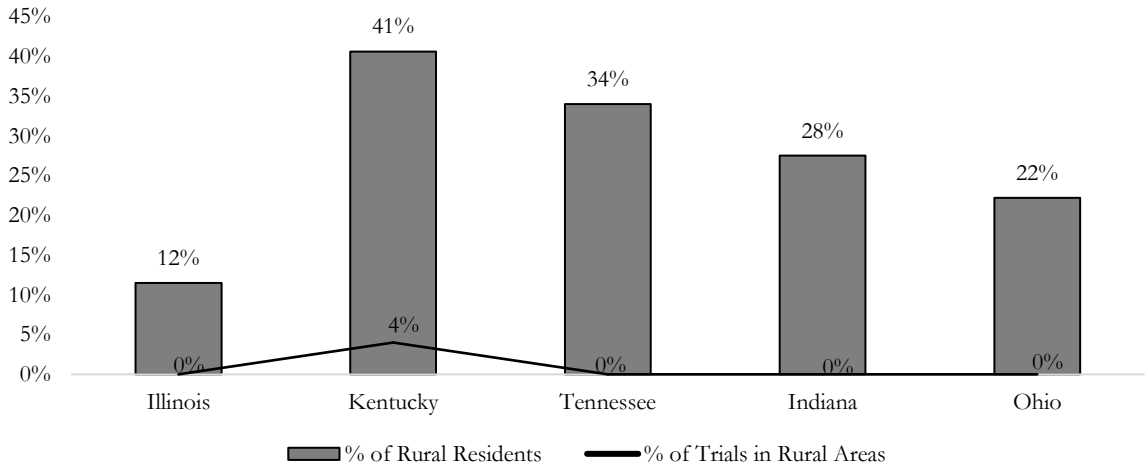


Figure 2: Comparison of rural population to proportion of vaccination clinical trials in rural areas by state.



Discussion

The COVID-19 pandemic propelled clinical research into a new era, giving patients more flexibility (allowing telemedicine, fewer testing sessions, etc.).[7] It also spurred the opening of hundreds of studies focused on vaccine research, recruiting thousands of participants from around the globe.[4] While data indicate that many of these early COVID-era vaccine studies recruited more diverse patient populations than we have seen historically,[8] research regulatory changes and concentrated recruitment efforts had no impact on vaccine trial geographic availability, notably in suburban and rural areas of the mid-West. While 25.7% of mid-West residents live in rural communities,[1] only 0.6% of vaccine clinical trials in this analysis were offered in rural communities. Although, Kentucky has the highest percentage of trials offered outside of urban areas (27% in suburban and 4% in rural), it also has the largest rural

population, at 40.6%, of the states studied. Figure 2 provides a dramatic comparison of the proportion of rural residents by state to the proportion of rural vaccine clinical trial locations.

There is a major misconception that rural residents do not want to be included in clinical research.[9] However, the key barrier remains that the vast majority of trials are not offered near residents outside of metropolitan areas. Community sites face unique challenges when conducting research, such as inadequate infrastructure, support staff, training, and dedicated physician time for research.[10] The 2020 pandemic highlighted a practical solution to help address these barriers: telemedicine. Telemedicine platforms can bring together physicians and research infrastructure from academic research sites with willing participants in small town America.

Telemedicine can help overcome the challenges with research infrastructure faced in community settings and address burdens placed on rural residents. Virtual visits reduce the time spent traveling to academic centers for study visits, along with the financial burden of transportation costs and possible overnight lodging. While use of telemedicine lags behind in rural compared to urban areas, it is used by a significant portion of the population. A 2021 Medicare Telemedicine Snapshot reported that between March 1, 2020, and February 28, 2021, 44% of rural Medicare users used a telemedicine service compared to 55% of urban Medicare users.[11] When promoting telemedicine for research purposes, however, consideration must be made of the digital divide. In some rural areas, internet and cellular signals are not always available or reliable. It is estimated only 75% of non-urban households have broadband internet access, compared to 87% of urban households.[12] Data on use of telemedicine by clinical trial is not available and represents an important consideration for future collection and exploration.

While telemedicine can address logistic barriers for rural patients, recruitment plans must also consider effective strategies for this population. Utilizing community pharmacists to make referrals, partnering with local community organizations and businesses, and encouraging participant referrals (i.e., snowball sampling) have been successful in recruiting diverse rural study participants.[13] In addition, Cooperative Extension agents can be good collaborators to gain insights into the community.[14] It is also key to enhance research capacity at rural healthcare facilities, which may lack experience and infrastructure in this area. Lastly, researchers should close the loop by partnering with the community to share findings, demonstrating that the research benefits everyone involved.[14] Information about the diversity of participants in clinical trials and the findings on safety and efficacy for traditionally underrepresented groups could play a vital role in outreach and education campaigns to help reduce disparities in vaccination rates.[8] Especially considering higher COVID-19 incidence and mortality rates in rural compared to urban areas, while rural counties had lower COVID-19 vaccination coverage (58.5%) compared to urban counties (75.4%).[15]

Limitations

Data for this study was retrieved from the publicly available clinicaltrials.gov database. Data on trial enrollment is not available, hence study authors could not assess impacts to vaccine study enrollment. This data limitation underscores the need for dynamic public data reporting systems for clinical research.

Conclusions

Increasing geographic diversity in clinical trials is crucial not only for the development of more effective vaccines, but also for enhancing public trust in vaccination programs. Rural communities face considerable health disparities, including lower vaccination rates, making it essential to include rural participants in research to better understand their unique experiences and develop targeted solutions to address their specific healthcare needs.[13] We must ensure that vaccines are rigorously tested across diverse populations, thereby optimizing their safety and effectiveness for all individuals, building trust across communities, and ultimately advancing public health equity.

Acknowledgements

The author would like to recognize the contribution made by Anjel Echols towards the analysis and interpretation of data for this study.

No conflict of interest to report.

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