Introduction

The US opioid crisis has evolved over time. Ciccarone\(^1\) posited a theory of 3 overlapping waves of opioid-involved overdose deaths (OODs) based on supply (iatrogenic and new illicit sources) and demand (social, cultural, and technological). Wave 1, in approximately 2000, was prompted by doctors overprescribing opioid painkillers, which was associated with mass addiction.\(^1\) Wave 2 involved heroin; OODs from heroin escalated in 2007 and surpassed those from prescription opioids by 2015.\(^1\) Wave 3 involved illicit synthetic opioids, such as fentanyl, the use of which escalated after 2013.\(^1\) Further evidence suggests a fourth wave, complicated by the addition of stimulants and the COVID-19 pandemic.\(^2\) To inform prevention and mitigation strategies, this cross-sectional study examined trends in OOD rates in urban and rural US counties during the 4 waves.

Methods

Data included OODs from January 1, 1999, to December 31, 2020, recorded in the Centers for Disease Control and Prevention’s WONDER database for 3147 counties and county equivalents categorized on a 6-point urbanicity scale (most urban to most rural) (Figure 1). OODs were defined using ICD-10 codes for underlying and multiple causes of death (Figure 1). We followed the STROBE reporting guide.
guideline. The institutional review board of Northwestern University exempted the study from approval and waived informed consent because publicly available data were used. We calculated OOD rates as OOD count within a given year and county type, divided by midyear population, multiplied by 100 000. Acceleration (relative change in OOD rate year over year) is expressed as a percentage. Data were analyzed with Microsoft Excel, version 16.61.

Results

Counties of every urbanicity type experienced statistically significant heterogeneous annual OOD rate growth (Figure 1). Differences in OOD rates by urbanicity were largest at the start and end of the study period. The initial rank order, with urban counties having the highest rates and rural the lowest, reemerged by 2020.

In waves 1 and 4, OOD rates were higher in the most urban counties but acceleration rates were higher in the most rural counties (Figure 2). Wave 2 was characterized by approximately linear growth in OOD rates, with diverse trends across urbanicity types. In wave 3, linear growth shifted to nonlinear growth, with 4 years of substantial acceleration across all urbanicity types; OODs from fentanyl increased by a factor of 12. In wave 4, there was marked growth across all urbanicity types.

Discussion

Overall, OOD rates increased steadily in counties of every urbanicity type, although there were distinct temporal wave patterns by urbanicity. Before 2010, OOD rates accelerated more quickly in rural counties than in urban counties; before 2000, OODs were rare in rural communities, which lacked resources to treat opioid use disorders associated with prescription opioids in wave 1.3

Restrictions on synthetic and semisynthetic opioids are associated with increased heroin use, which contributed to wave 2.4 OOD rates accelerated more quickly in urban counties during wave 2, beginning approximately in 2013.
From 2013 to 2019, OODs from fentanyl increased 12-fold. This third wave substantially impacted urban and rural counties. The COVID-19 pandemic coincided with a fourth wave marked by worsening of the opioid crisis in all county types.

These results are consistent with the wave theory of Ciccarone. The varied timing of acceleration by urbanicity suggests that policy makers should consider resources and socioeconomic and treatment needs of rural and urban communities as the opioid crisis evolves, particularly because urban outreach and treatment approaches may not work in rural areas.

A limitation is that the data may undercount OODs because death investigation systems vary by state. Not all individuals who die of opioid-involved overdose have opioid use disorder, and deaths in wave 4 are often a function of multiple drug interactions or inclusion of stimulants with synthetic opioids in the nonregulated nonopioid drug supply. Some OODs are the result of drug interactions or recreational use that may require nonrehabilitative interventions.

**ARTICLE INFORMATION**

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