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MAJOR ARTICLE

The Relationship Between Hepatitis C Virus Rates and Office-Based Buprenorphine Access in Ohio

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Background. The United States is experiencing an epidemic of hepatitis C virus (HCV) infections due to injection drug use, primarily of opioids and predominantly in rural areas. Buprenorphine, a medication for opioid use disorder, may indirectly prevent HCV transmission. We assessed the relationship of HCV rates and office-based buprenorphine prescribing in Ohio.

Methods. We conducted an ecological study of the county-level (n = 88) relationship between HCV case rates and office-based buprenorphine prescribing in Ohio. We fit adjusted negative binomial models between the county-level acute and total HCV incidence rates during 2013–2017 and 1) the number of patients in each county that could be served by office-based buprenorphine (*prescribing capacity*) and 2) the number served by office-based buprenorphine (*prescribing frequency*) from January–March, 2018.

Results. For each 10% increase in acute HCV rate, office-based buprenorphine prescribing capacity differed by 1% (95% CI: –1%, 3%). For each 10% increase in total HCV rate, office-based buprenorphine prescribing capacity was 12% (95% CI: 7%, 17%) higher. For each 10% increase in acute HCV rate, office-based buprenorphine prescribing frequency was 1% (95% CI: –1%, 3%) higher. For each 10% increase in total HCV rate, office-based buprenorphine prescribing frequency was 14% (95% CI: 7%, 20%) higher.

Conclusions. Rural counties in Ohio have less office-based buprenorphine and higher acute HCV rates versus urban counties, but a similar relationship between office-based buprenorphine prescribing and HCV case rates. To adequately prevent and control HCV rates, certain rural counties may need more office-based buprenorphine prescribing in areas with high HCV case rates.

Keywords. buprenorphine; HCV; Ohio; opioids.

The United States (US) is currently experiencing a hepatitis C virus (HCV) epidemic, spread primarily through the use of shared injection drug equipment by people with opioid use disorder (OUD) [1]. The US has seen a 133% increase in acute HCV infections (from 0.3 to 0.7 cases/100 000 person-years) concurrent with a 93% increase in admissions to substance use disorder treatment facilities for opioid injection from 2004 to 2014 [2]. Additionally, rural areas of the US, where access to evidence-based treatment for OUD is limited, have experienced the most pronounced increases in HCV case rates [3, 4]. The Drug Addiction and Treatment Act of 2000 allows buprenorphine to be prescribed by physicians in office-based settings following an 8-hour training for a "waiver" [5, 6]. Physicians' assistants and nurse practitioners began prescribing buprenorphine in 2017 following the Comprehensive Addiction and Treatment Recovery Act of 2016 [7]. Prior to 2000, methadone was the only medication for OUD that could be prescribed and could only be prescribed in highly regulated opioid treatment programs. At the individual level, prescribed buprenorphine may prevent incident HCV infection among people with OUD by reducing the frequency of opioid injections [8, 9]. This reduction in injection drug use may prevent and control the spread of HCV within the population.

Due to increases in unintentional drug overdose rates and OUD burden, office-based buprenorphine prescribing capacity has expanded [10, 11]. A similar expansion in office-based buprenorphine may have occurred in response to the rising rates of HCV [5]. Even with this expansion in office-based buprenorphine prescribing capacity, not all physicians with a waiver actually prescribe buprenorphine [10, 12, 13]. Therefore, the prescribing capacity may not equate to the prescribing frequency. Due to differences in levels of community-level stigma and differences in HCV case rates,

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these relationships may differ by urban/rural classification [5, 7, 14, 15].

Increasing office-based buprenorphine prescribing is a quick and effective practice that can be implemented to prevent and control HCV wherever there are health care professionals. Thus, we assessed the county-level relationship between acute and total HCV rates in 2013–2017 and office-based buprenorphine prescribing in 2018. We also assessed if this relationship varies between rural and urban counties. We hypothesize that office-based buprenorphine has a greater prescribing capacity and frequency in areas with higher rates of HCV in previous years.

METHODS

We conducted an ecological study to estimate the relationship between acute and total HCV rates and office-based buprenorphine prescribing capacity, and the relationship between acute and total HCV rates and office-based buprenorphine prescribing frequency for all 88 counties in Ohio. We obtained data in 2020 on acute and total HCV incidence by county from the Ohio Department of Health for 2013–2017 through publicly available data. In Ohio, incident HCV is classified as acute or chronic. Identifying acute HCV requires specialized testing and confirmation and is the only indicator available that designates an HCV infection that occurred within the past 6 months, whether symptomatic or asymptomatic [16]. Total HCV is a combination of acute and chronic HCV. The Ohio Department of Mental Health and Addiction Services (OMHAS) surveyed all physicians (MD or DO) with an active X-waiver certification through quarter 1 (31 March) of 2018. OMHAS X-waiver and buprenorphine prescribing data were self-reported by the physicians with an active X-waiver. We calculated the prevalence of patients (patients per 1000 population) in each county that could have potentially been treated by a prescriber with an X-waiver (office-based buprenorphine prescribing *capacity*) in January through March 2018. We also calculated the prevalence of patients (patients per 1000 population) in each county that physicians with an X-waiver were prescribing buprenorphine (office-based buprenorphine prescribing *frequency*) in January through March 2018. Buprenorphine prescribing data are privately held data that were provided by OMHAS through personal correspondence with an administrator in 2018. We assumed that if a physician with an X-waiver was prescribing buprenorphine, they were prescribing to the legal limit of their buprenorphine prescribing capacity. Rural and urban county categorization was gathered from the US Health Resources and Services Administration (HRSA) [17]. In HRSA's 2013 classification (based on 2010 US Census data), any county that is not a part of a metropolitan area (including micropolitan) is considered rural [18]. This research was deemed to be exempt from a full institutional review board (IRB) review by the Ohio State University Biomedical Sciences IRB.

Statistical Analyses

All statistical analyses were conducted in spring of 2020. We summarized variables in our analysis using the median and interquartile range. We fit 4 models (Figure 1) with all

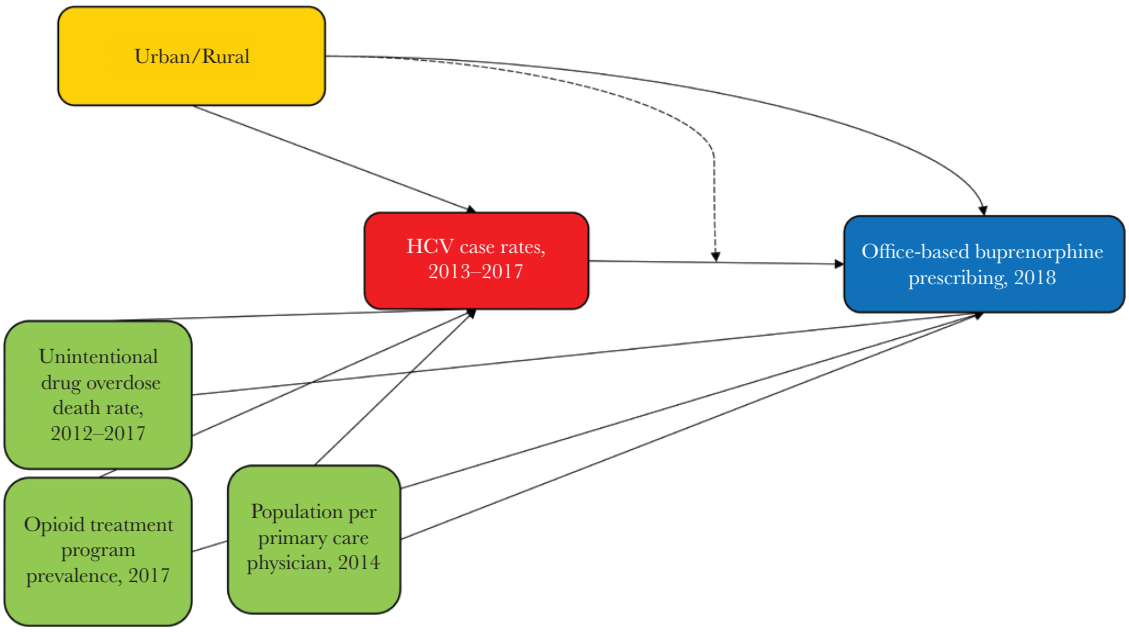

Figure 1. A theoretical model of the county-level relationship between the hepatitis C virus (HCV) rate during 2013–2017 and office-based buprenorphine prescribing in 2018 in Ohio. Red indicates our exposures and blue indicates the outcomes. Yellow indicates a confounder that was tested for effect measure modification (dashed arrow) and green indicates confounding factors.

combinations of our 2 exposures (total and acute HCV case rates, 2013–2017) and our 2 outcomes (office-based buprenorphine prescribing capacity and frequency in 2018). To allow for overdispersion, we fit unadjusted and adjusted negative binomial models to assess the relationship between HCV incidence rates during 2013–2017 and office-based buprenorphine capacity and prescribing in 2018. We averaged the values of the total and acute HCV incidence rates separately for 2013–2017 as our exposures and then log-transformed these values so that each prevalence ratio represents a percentage change in the office-based buprenorphine prescribing capacity and frequency per 10% higher HCV case rate. Using the Robert Wood Johnson Foundation County Health Rankings, we adjusted for the 2014 (most recent data available before 2018) county-level population per primary care physician [19]. The County Health Rankings use data from the Area Health Resource File, which is a collection of data from >50 sources, including: the American Medical Association, American Hospital Association, US Census Bureau, Centers for Medicare and Medicaid Services, Bureau of Labor Statistics, and National Center for Health Statistics. The American Medical Association maintains the Physician Masterfile, which contains information on nearly all the Doctors of Medicine and Doctors of Osteopathic Medicine in the nation. We also obtained the age-adjusted unintentional drug overdose rate for 2012–2017 through the Ohio Department of Health. Four counties (Holmes, Monroe, Noble, and Paulding) had suppressed age-adjusted unintentional drug overdose death rates for 2012–2017 because their unintentional drug overdose counts for 2012–2017 were <10. For these 4 counties we hand-calculated the non-age-adjusted unintentional drug overdose death rate using the unintentional drug overdose death count divided by the county population size estimate. Finally, we adjusted for the 2017 opioid treatment programs per 100 000 population using data from the Substance Abuse and Mental Health Administration's Opioid Treatment Program Directory [20]. To assess for effect measure modification, we included an interaction term for county rural/urban status based on the HRSA categorization. We considered the interaction term to be statistically significant at the $\alpha = .05$ level. We used Stata IC 16.1 software for all analyses (StataCorp, College Station, Texas) and all mapping was done in ArcGIS Pro 2.7.1 software (Esri, Redlands, California).

RESULTS

All 38 urban and 50 rural counties were included in the analyses (N = 88). In total, 1828 physicians were certified to prescribe office-based buprenorphine, with 859 actively prescribing buprenorphine through 31 March 2018. In 2018, 66 counties in Ohio had an active waivered physician and 22 did not. Four urban counties (10.5%) and 11 rural counties (22%) had no physicians certified to prescribe office-based buprenorphine. Seven rural counties had physicians who had a certification to prescribe office-based buprenorphine but did not actually prescribe office-based buprenorphine in 2018. Eight urban (16%) and 3 rural (8%) counties had no reported acute HCV cases during 2013–2017. All 88 counties reported at least 1 case of total HCV during 2013–2017.

The overall median acute HCV rate in Ohio during 2013–2017 was 5.46 per 100 000 population (Table 1). The median acute HCV rate in rural counties during 2013–2017 (10.72 per 100 000 population) was larger than in urban counties (4.16 per 100 000 population). The overall median total HCV rate in Ohio during 2013–2017 was 566.75 per 100 000 population. Median total HCV rates in urban (577.36 per 100 000 population) and rural (550.65 per 100 000 population) counties were similar.

The overall county-level office-based buprenorphine prescribing capacity was 6.78 patients per 1000 population. Overall

Table 1. Summary Statistics of Hepatitis C Virus Incidence and Office-Based Buprenorphine Prescribing in Ohio

	Median (IQR)		
Variable	Total (N = 88)	Urban (n = 38)	Rural (n = 50)
Average acute HCV rate per 100 000 population, 2013–2017	5.46 (2.30–14.93)	4.16 (1.40–7.56)	10.72 (3.64–19.54)
Average total HCV rate per 100 000 population, 2013–2017	566.75 (380.84–862.74)	577.36 (408.22–833.50)	550.65 (379.80–929.74)
County-level office-based buprenorphine prescribing capacity per 1000 population, 2018	6.78 (2.32–11.83)	10.25 (5.98–13.77)	3.95 (0.74–9.30)
County-level office-based buprenorphine prescribing frequency per 1000 population, 2018	5.06 (0.29–9.33)	6.63 (4.21–10.22)	1.76 (0–7.16)
County-level office-based buprenorphine prescribing frequency/ county-level office-based buprenorphine prescribing capacity	0.75 (0.59–0.82)	0.75 (0.68–0.81)	0.77 (0.40–0.87)
County-level age-adjusted unintentional drug overdose death rate, 2012–2017	22.00 (16.20–31.20)	23.25 (18.80–32.50)	21 (13.20–29.60)
Population per primary care physician, 2014	46.98 (37.25–65.71)	81.50 (28.00–193.00)	41.83 (31.60–53.93)
Opioid treatment program per 100 000 population, 2017	0 (0–0)	0 (0–0.23)	0 (0–0)

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range.

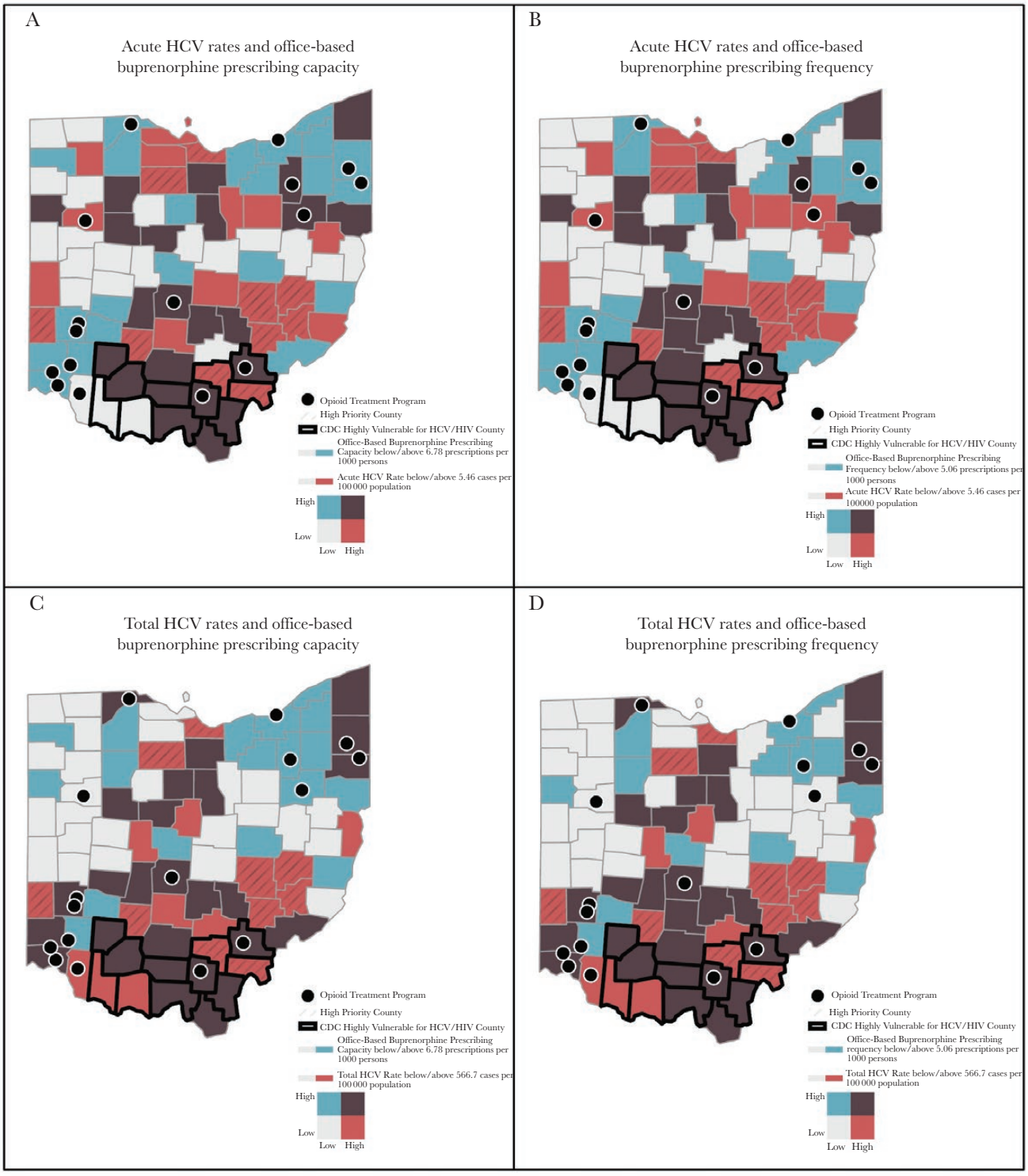

Figure 2. Bivariate choropleth maps of hepatitis C virus (HCV) case rates, 2013–2017, and office-based buprenorphine prescribing capacity and frequency, 2018. *A*, Acute HCV rates and office-based buprenorphine prescribing capacity. *B*, Acute HCV rates and office-based buprenorphine prescribing frequency. *C*, Total HCV rates and office-based buprenorphine prescribing capacity. *D*, Total HCV rates and office-based buprenorphine prescribing frequency. Abbreviations: CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

county-level office-based buprenorphine prescribing frequency was 5.06 patients per 1000 population. Urban counties had a larger office-based buprenorphine capacity (10.25 patients per 1000 population) and more prescribing frequency (6.63 patients per 1000 population) than rural counties (capacity: 3.95 patients per 1000 population, frequency: 1.76 patients per 1000

Table 2. Crude and Adjusted Relationship Between the County-Level Hepatitis C Virus Rate in 2013–2017 and Office-Based Buprenorphine Prescribing Capacity in Ohio in 2018

	Prescribing Capacity		Prescribing Frequency	
HCV Rate	Unadjusted PR (95% CI)	Adjusted PR (95% CI)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)
Acute HCV rate, 2013–2017	1.01 (.98–1.03)	1.01 (.99–1.03)	1.01 (.98–1.03)	1.01 (.99–1.03)
Total HCV rate, 2013–2017	1.09 (1.04–1.14)	1.12 (1.07–1.17)	1.10 (1.05–1.16)	1.14 (1.07–1.20)

Adjusted for the population per primary care physician in 2014, age-adjusted unintentional drug overdose deaths in 2012–2017, and opioid treatment programs per 100 000 population in 2017.
Abbreviations: CI, confidence interval; HCV, hepatitis C virus; PR, prevalence ratio per 10% increase in the hepatitis C virus rate.

population). Urban and rural counties had similar prevalence of office-based buprenorphine prescribing frequency per capacity (75% of prescribing capacity vs 77% of prescribing capacity).

Counties in Ohio with high HCV case rates and low office-based buprenorphine prescribing were primarily concentrated in the northwest and western (Appalachia) region of Ohio (Figure 2). Ten of these counties are above the median HCV rates (both total and acute) and below the median office-based buprenorphine prescribing (both capacity and frequency). All of these 10 counties are rural. Two of these counties are among the 220 counties that were highlighted by the Centers for Disease Control and Prevention (CDC) to be particularly vulnerable to human immunodeficiency virus (HIV)/HCV by the CDC [21]; however, 8 of these counties were not among the vulnerable counties.

For each 10% increase in acute HCV rate during 2013–2017, office-based buprenorphine prescribing capacity differed by 1% (95% confidence interval [CI], –1% to 3%) in 2018 (Table 2). For each 10% increase in total HCV rate during 2013–2017, office-based buprenorphine prescribing capacity was 12% (95% CI, 7%–17%) higher in 2018. For each 10% increase in acute HCV rate during 2013–2017, office-based buprenorphine prescribing frequency was 1% (95% CI, –1% to 3%) higher in 2018. For each 10% increase in total HCV rate during 2013–2017, office-based buprenorphine prescribing frequency was 14% (95% CI, 7%–20%) higher in 2018. We did not identify effect measure modification by rural or urban status.

DISCUSSION

We investigated urban/rural differences in the ecological relationship between the county-level HCV case rates and office-based buprenorphine prescribing in Ohio. For January–March 2018, urban counties had a median office-based buprenorphine prescribing capacity and frequency that was 2.6 times higher and 3.8 times higher than rural counties, respectively, while rural counties had acute HCV case rates that were 2.6 times higher than urban counties for 2013–2017 (total HCV was relatively equal). Roughly 75% of the office-based buprenorphine capacity was prescribed in both rural and urban counties, but whereas 89% urban counties had the capacity to prescribe any office-based buprenorphine, only 78% of rural counties had any office-based buprenorphine prescribing capacity. Therefore, the biggest barrier for rural counties may be the office-based buprenorphine prescribing capacity. The prescribing frequency to capacity ratio does not differ by rural/urban designation.

In this investigation, we observed no evidence that office-based buprenorphine prescribing frequency and capacity are associated with acute HCV case rates; however, office-based buprenorphine prescribing frequency and capacity are associated with total HCV case rates. We also observed that the association between office-based buprenorphine prescribing frequency and capacity and HCV case rates did not meaningfully differ between urban and rural counties in Ohio.

These associations demonstrate 3 key points. First, potential office-based buprenorphine prescribing is only associated with total HCV cases, whereas acute HCV cases are those most strongly associated with drug use [2, 22]. However, we believe that this association may reflect a bias in HCV surveillance data in Ohio. HCV primarily affects vulnerable and hidden populations such as people who inject drugs and have limited access to the health care system, many of whom reside in rural areas in the current opioid syndemic. Rural Ohio is an especially vulnerable region, with limited access to health care services that may serve as testing and treatment facilities for HCV infection [4]. Ohio is also a "home-rule" state that relegates confirmatory testing responsibilities to self-funded county health departments [23]. Therefore, completing the requirements to categorize an infection as acute HCV may be dependent upon the local health department's capacity, which varies across the state. Rural health departments are often underfunded and may not have the capacity to test all those in need. Thus, HCV public health data are likely missing a significant amount of data from people who are currently using drugs and do not participate in the health care system or have never been tested. Bias in HCV surveillance may also extend to physician classification of disease since Ohio Medicaid prior approval also requires HCV treatment to be overseen by infectious disease (ID) or gastroenterology (GI) specialists. Primary care physicians, who do not typically treat HCV in Ohio, may be less aware of the particular requirements that need to be met for diagnosing acute vs chronic HCV. This is especially true in rural areas where many counties do not have ID or GI specialists. These

results could also indicate that increased access to office-based buprenorphine may have a stronger relationship with the prevalence of HCV actually seen in the health care system than with cases of acute HCV most associated with the opioid syndemic. Total HCV better reflects the burden of all cases of HCV seen in the health care system as it contains both acute and chronic cases. Chronic cases of HCV may be associated with other causes of HCV infection (blood transfusion prior to 1992 or sexually transmitted), but these likely represent a minority of HCV cases detected in the US [2]. Additionally, publicly available surveillance data reflect HCV tests conducted in their entirety, which likely included many tests conducted, including outside of the traditional health care system such as through public health or syringe service programs.

Second, our results show that urban counties appear more equipped to prevent HCV cases because they have more office-based buprenorphine prescribing. Historically, drug use has been an urban public health problem [24]. In the current substance use epidemic, drug use has significantly affected rural populations, particularly in states like Ohio, Kentucky, West Virginia, and New Hampshire [24]. Rural areas may have substantial stigma toward medication for OUD compared to urban areas [25]. This stigma of addiction may decrease the willingness of physicians to obtain the waiver to prescribe office-based buprenorphine in the absence of a significant epidemic [14, 15]. While stigma against drug use exists in urban areas, urban areas may already have relatively more health care professionals willing to treat addiction. Office-based buprenorphine prescribing has also changed dramatically over the course of the opioid syndemic, including over the years 2012–2018 [10, 12], but this change, especially in rural areas, is primarily driven by non-physician health care professionals [7]. Still, office-based buprenorphine prescribing in 2018 likely does not reflect prescribing in 2013. Therefore, this investigation's descriptive ecological association between office-based buprenorphine prescribing in 2018 should not be interpreted as causally related to the HCV rates in 2013–2017. Alternatively, areas with more office-based buprenorphine may also be areas with higher health care service access in general, leading to more detection of HCV infection [26]. We adjusted for the ratio of population to primary care physicians as a proxy for health care service access, but this adjustment may have been insufficient to fully account for all aspects of what influences an individual to be tested for HCV infection.

Third, this investigation has highlighted 10 counties in Ohio that have high HCV case rates and that may be insufficiently supplied with office-based buprenorphine. Eight of these counties were not included in the CDC's list of 220 counties at risk of an HIV or HCV outbreak due to injection drug use [21]. This investigation highlights that focused research on individual features of county-level vulnerability may uncover regions that were otherwise missed by our public health infrastructure.

Prior studies have examined county-level vulnerability to HIV and HCV using myriad public health ecological predictors [21, 27]; however, the interpretation of the estimates of these studies represents a table 2 fallacy [28]. These county-level vulnerability studies provide adequate information for policy-level geographic interventions, but they do not provide a method for examining the relationship between each individual predictor and HCV case rates [21, 27]. The relationship between HCV and medication for OUD, more generally, has been studied [8, 29–31], but the specific relationship between urban and rural differences in this relationship is unknown. Additionally, our study expands upon analyses that have used unintentional drug overdose deaths as a predictor of office-based buprenorphine access [32]. Unintentional drug overdose deaths may not accurately reflect the entire population of people who use drugs in a given region [32]. Using HCV rates as a predictor provides a new perspective on the burden of injection drug use within a region [21, 27]. In Ohio, people who inject drugs are primarily injecting opioids [33]. The population of people with HCV and those who experience an unintentional drug overdose death may represent overlapping, but not identical, populations. As the overdose reversal drug naloxone increases in availability and theoretically decreases the relative proportion of opioid overdoses that lead to death, other factors, such as HCV case rates, may serve as useful markers of opioid burden to track this syndemic [34].

We assumed that all physicians who did prescribe office-based buprenorphine did so to their full X-waiver patient capacity. This assumption is likely incorrect and may represent a source of bias for this analysis. We also assumed that physicians are knowledgeable about the HCV rates in the county in which they registered for their X-waiver. We also assumed that each physician only prescribed office-based buprenorphine in the county in which they registered. These assumptions may be incorrect as physicians may list a county other than the one that they work in on their X-waiver paperwork or may work in multiple counties. Finally, stigma against buprenorphine appears to be a significant problem, particularly in rural areas [35, 36]. This stigma may represent a particular barrier to increasing office-based buprenorphine prescribing.

We used all cases of HCV in our model as a proxy for the cases of HCV associated with the opioid syndemic. Likely, not all of these cases of acute HCV were caused by injection use and some may not be associated with the opioid syndemic. CDC investigations found that around 80% of acute HCV cases were associated with injection drug use [2, 22]. We believe that this estimate likely reflects Ohio's HCV epidemic and may underestimate the burden of acute HCV cases associated with injection drug use due to social desirability bias.

We used only 1 classification of rurality, and results might vary when other rurality definitions are used. Different definitions of rurality may be particularly impactful in counties that are primarily rural but border a metropolitan area and

thus can be reclassified as nonrural. Ohio has several counties that border the Ohio River with metropolitan areas in neighboring states that may fall into this category. An analysis at a smaller areal unit such as a zip code or census tract may more accurately reflect these nuances and provide a less confounded relationship.

In summary, rural counties in Ohio have less office-based buprenorphine and higher acute HCV rates compared to urban counties, but a similar relationship between office-based buprenorphine prescribing and HCV case rates compared to urban counties. To adequately prevent and control HCV outbreaks, rural counties may need more office-based buprenorphine prescribing in areas with high HCV case rates.

Notes

Data availability. Data are not publicly available.

Author contributions. D. L. B.: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, visualization, writing. A. T. H.: Investigation, methodology, formal analysis, validation, visualization, writing. S. R. C.: Investigation, methodology, formal analysis, validation, writing. C. A. S.: Conceptualization, writing—review and editing. A. L. S.: Conceptualization, writing—review and editing. K. E. L.: Conceptualization, funding acquisition, supervision. V. F. G.: Conceptualization, supervision. W. C. M.: Conceptualization, funding acquisition, supervision, writing—review and editing. D. M. K.: Supervision, funding acquisition, methodology, writing—review and editing.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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