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Spatial epidemiology of carbapenem-resistant Enterobacteriaceae (CRE) in Tennessee, 2015-2018

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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

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Abstract

Spatial epidemiology of carbapenem-resistant Enterobacteriaceae (CRE) in Tennessee, 2015-2018

By Kyle E. Winston

Carbapenem-resistant Enterobacteriaceae (CRE) is an emerging public health threat. Bacteria in this group are difficult to treat and readily share resistance genes. Because CRE was traditionally viewed as a hospital-acquired infection, most studies have investigated risk factors and transmission dynamics associated with healthcare settings. However, community spread of CRE is also an important and understudied threat. Beef cattle production is a potential driver of community transmission. Cattle have been shown to carry CRE organisms and cattle farms regularly spread bacteria into the surrounding environment. Analyses presented here examine the spatial structure of beef cattle farming, CRE rates, and covariates at the county level in Tennessee from 2015 to 2018. CRE case counts were collected by the Tennessee Department of Health through its mandatory disease reporting surveillance system. These counts, and yearly populations, were pooled at the county level across the four-year study period, and rates per 100,000 person-years were calculated for each county. Three potential exposures were evaluated—the number of beef cattle operations with 1-49 heads of cattle in each county, the number of beef cattle operations with 50 or more heads of cattle in each county, and the beef cattle counts in each county. Variable mapping, Moran’s I spatial autocorrelation tests, aspatial linear regression, and spatial Durbin regression were conducted to determine the association between beef cattle and CRE rates at the county level. These analyses demonstrated a weak but statistically significant protective effect between beef cattle and CRE rates, as well as a strong spatial autocorrelation in CRE rates between neighboring counties. These ecological findings provide insight into the utility of using spatial regression methods to understand community transmission of diseases and demonstrate there is community transmission of CRE demonstrate inter-county community spread of CRE.

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1. Introduction

1.1 Antimicrobial Resistance

In March 1942, Anne Miller, a 33-year-old mother from New Haven, Connecticut, was facing a grave threat. Streptococcal bacteria had invaded her bloodstream and none of the treatments her doctors had tried were able to clear the infection. That is when, through the determination of her doctors and a stroke of luck, they were able to obtain a small vial of penicillin. She received her first dose on March 14, and, by the next day, her fever had already broken. Miller is the first person to have been saved by penicillin, which was regarded by many as a miracle drug (Yale New Haven Health, 2017).

Penicillin was the first of many antibiotics that helped revolutionize modern medicine. Diseases that were difficult to survive suddenly became easy to treat, and many common infections no longer invoke fear in the minds of the public like they used to. However, pathogens have not been idle. Over time, resistance has evolved against many antibiotics, and resistance genes can rapidly spread through bacterial populations. The World Health Organization defines antimicrobial resistance (AMR) as occurring “when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death” (World Health Organization, 2020). There are many mechanisms through which a pathogen can become resistant to antimicrobials, which include restricting access of the antimicrobial into the cell, getting rid of the antimicrobial through pumps in the cell wall, creating enzymes to destroy the antimicrobial, change the molecules that the antimicrobial targets, and bypassing the mechanism that the antimicrobial disrupts. These mechanisms all follow the same general evolutionary pathway. Bacteria and other pathogens are ubiquitous in people, animals, and the environment and, through random chance, some of them have mutations that make them resistant to an antimicrobial. Then, they encounter an antimicrobial which kills the susceptible germs, but not the resistant ones. These resistant germs then multiply and spread. Some can even pass on resistance genes directly to other germs (US Centers for Disease Control and Prevention, 2020). Thus, antimicrobial resistant strains begin to propagate and spread.

Drug-resistant pathogens are an international threat. They can spread rapidly across the globe. Further, resistant populations of pathogens can take over and become the predominant strain that causes infections. For example, the rate of resistance to ciprofloxacin, a common antibiotic used to treat urinary tract infections, is as high as 92.9% for *Escherichia coli* and 79.4% for *Klebsiella pneumoniae* in some countries. In many countries, over half the patients treated for these do not respond to traditional first-line treatments (World Health Organization, 2020).

This threat is not just a global one. Here in the United States, best estimates from the Centers for Disease Control and Prevention (CDC) indicate that more than 2.8 million antibiotic-resistant infections occur in the US each year and more than 35,000 people die each year as a result. Additionally, resistance extends hospital stays, undermines medical treatments, disrupts food production, and shortens life expectancies (US Centers for Disease Control and Prevention, 2019). As germs develop new resistance mechanisms and spread to new populations, the threat of AMR continues to increase. It is an urgent public health issue.

1.2 The Enterobacteriaceae Family of Bacteria

The Enterobacteriaceae family is a large family of rod-shaped, Gram-negative bacteria that are facultative anaerobes, meaning they grow with or without the presence of oxygen. Many organisms in this family are part of the normal gut flora in the intestines of humans and animals. Others can be found in the environment or as parasites growing on animals and plants (Martinson et al., 2019; Woodford et al., 2014). The common genera that are relevant to antibiotic resistance in this family are *Escherichia*, *Enterobacter*, and *Klebsiella*. Other common genera include *Citrobacter*, *Morganella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, and *Shigella*, as well as dozens of less common genera. These bacteria can cause a wide range of infections in respiratory, wound, urinary tract, invasive, tissue, other sites. They are also a major source of nosocomial, or hospital-acquired, infection (Lerner et al., 2013).

Members of the Enterobacteriaceae family often carry resistance genes, and they can transfer these genes between organisms through a process known as conjugation. Further, there are different levels of resistance. One class of resistant Enterobacteriaceae is known as extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. The beta-lactam class of antibiotics contains many narrow- and broad-spectrum antibiotics, such as penicillins, cephalosporins, and carbapenems. ESBL-producing Enterobacteriaceae produce an enzyme that breaks down many antibiotics in this class, but not the broad-spectrum carbapenems, which remain one of the few antibiotics that are effective against ESBL-producing bacteria. The CDC classifies these resistant bacteria as a serious threat (US Centers for Disease Control and Prevention, 2019).

Even more concerning is the class of bacteria known as carbapenem-resistant Enterobacteriaceae (CRE), which the CDC classifies as an urgent threat, the highest threat level. There are very few, if any, remaining antibiotics available to treat these bacteria (US Centers for Disease Control and Prevention, 2019). These bacteria can be resistant to carbapenem in multiple ways. Some genera, such as *Proteus* and *Providencia*, are naturally more resistant to some carbapenems. Others gain resistance through a mix of chromosomal and acquired mutations that make it harder for carbapenems to be effective, such as a modification of the porin gene that limits antibiotic entry into the cell. Finally, the most concerning cause of carbapenem resistance is the production of carbapenemase enzymes. These enzymes specifically target and inactivate carbapenem antibiotics, as well as other beta-lactams. Unlike non-carbapenemase resistance mechanisms, the presence of just one carbapenemase gene is generally enough to confer carbapenem resistance. Further, these genes are usually located on mobile genetic elements called plasmids that are easily passed between different Enterobacteriaceae bacteria. The five most common carbapenemases are Klebsiella pneumoniae carbapenemase (KPC), New Delhi Metallo-beta-lactamase (NDM), Verona Integron-Encoded Metallo-beta-lactamase (VIM), Imipenemase (IMP), and Oxacillinase-48 (OXA-48). These were historically associated with healthcare exposure outside the US, but now are often linked to US healthcare and community-acquired sources (US Centers for Disease Control and Prevention, 2019, 2021a).

In 2001, the first KPC-producing bacteria were identified in the US. KPC-producing and other carbapenemase-producing CRE organisms then rapidly spread across the country (US Centers for Disease Control and Prevention, 2021a). In 2017, there were approximately 13,100 cases of patients who were hospitalized due to CRE in the US, a slight increase over previous years. Further, there were an estimated 1,100 deaths and an estimated $130 million in attributable healthcare costs (US Centers for Disease Control and Prevention, 2019).

Because CRE was traditionally viewed as a nosocomial infection, hospital-associated risk factors are the best known. The most prominent ones are prolonged contact with an index patient; mechanical ventilation; exposure to an intensive care unit; carriage or co-infection with another multidrug-resistant organism; and prior exposure to several antibiotics, including carbapenems, cephalosporins, fluoroquinolones, and vancomycin (Schwartz-Neiderman et al., 2016; US Centers for Disease Control and Prevention, 2021b). Risk factors for community-acquired CRE is far less well-known. One study identified history of lung disease, nursing home residence, and recent antibiotic exposure as prominent risk factors for this type of CRE (Blatt et al., 2017). Due in part to the higher prevalence of ESBL-producing Enterobacteriaceae, more studies have been conducted to determine risk factors for community-acquired infections of this class of resistant organisms. These studies have identified recent antibiotic use, the use of medical devices, recurring urinary tract infections, and international travel as risk factors. However, many of these studies used medical records as their source of risk factor data and thus did not include a focus on environmental and animal reservoirs (Goyal et al., 2019; Karanika et al., 2016; Kizilca et al., 2012). In a population-based modelling study that collected prevalence and genetic data for ESBL-producing *E. coli* in the Netherlands from human, farm and companion animal, food, surface freshwater, and wild bird sources, non-human sources were found to be attributable for a significant portion of overall carriage, at around one-third. Food accounted for 18.9% (7.0–38.3) of carriage, companion animals for 7.9% (1.4–19.9), farm animals (non-occupational contact) for 3.6% (0.6–9.9), and swimming in freshwater and wild birds (environmental contact) for 2.6% (0.2–8.7). The model did not include carriage that was attributable to occupational contact with farm animals. Further, the authors identified 6,275 occurrences of ESBL-producing *E. coli* in non-human sources, of which 4,026 were identified in farm animals (Mughini-Gras et al., 2019). Thus, while medical exposures are the most well-studied for CRE and similar antibiotic-resistant organisms, animal and environmental contacts are an important and understudied potential source of CRE exposure.

1.3 Cattle as a Possible Source of CRE

Antibiotic resistance is a One Health problem. One Health is a disease framework that recognizes the link between human and animal health, and how diseases can threaten food supplies and economies (Mackenzie & Jeggo, 2019). According to the CDC, doctors' offices and emergency departments in the US prescribe 47 million antibiotic courses—30% of all antibiotics that are prescribed by these sources—for infections that do not need them. Antibiotics are also sometimes applied to crops, and they can enter the environment through waste. Finally, they are often given to pets and food animals, including livestock, often with little oversight. All these lead to increased encounters between antibiotics and bacteria, and, through natural selection, drive the proliferation of antibiotic resistance. Further, these sources are all interconnected as resistant bacteria spread between them (US Centers for Disease Control and Prevention, n.d.-b, 2019). Antibiotic resistance in non-human sources is still a threat to human health.

Enterobacteriaceae regularly colonize the guts of many animals, including cattle. This is significant since most beef cattle are raised on feedlots that present conditions that promote the evolution of antibiotic resistance. Feed lots have high densities of cattle; routine, intensive, and often unregulated antibiotic use; and unsanitary conditions. Additionally, many of the antibiotics that are used are considered medically important in protecting human health. The US in particular is at high risk of antibiotic resistance arising in cattle populations because it has one of the largest cattle industries in the world and the industry's use of antibiotics is particularly intense (McDaniel et al., 2014; Wallinga, 2020). These resistant bacteria can then spread to humans.

Zoonosis is the process where pathogens pass from animals to infect humans. Bovine zoonosis is a well-known and commonly studied issue. Geographically, it occurs worldwide, and transmission routes include ingestion and contact. A systematic review identified 45 pathogens than can pass from cattle to humans, many of which are in the Enterobacteriaceae family (McDaniel et al., 2014). Additionally, drug-resistant strains of bacteria have been found on beef in grocery stores and on livestock and workers in processing plants. Environmental contamination is also significant, with drug-resistant bacteria being detected in air, soil, and water samples. Coming into contact with any of these sources poses a risk of infection. The environmental contamination can spread even farther from feed lots through the sale of manure as fertilizer and through natural disasters such as flooding (Wallinga, 2020). Cattle farming and processing practices present plenty of opportunities for infection by resistant bacteria.

Enterobacteriaceae are among the most common bacteria that can be passed from cattle to humans (McDaniel et al., 2014). Furthermore, CRE and other antibiotic-resistant strains of Enterobacteriaceae have been detected living commensally in cattle, demonstrating the potential for zoonotic transmission. A systematic review of CRE in wildlife, food-producing, and companion animals found that many studies detected CRE in seafood, wildlife, pets, and livestock. There was no study that used a selective screening approach for cattle included in the systematic review, but multiple included studies did find CRE in cattle isolates (Köck et al., 2018; Sawant et al., 2007). In a study of two cattle farms in the High Plains region of the US, CRE was detected in several isolates. These included multiple resistant Enterobacteriaceae species as well as a variety of carbapenemase and other resistance genes, including a novel carbapenemase (*bla*$_{\text{OXA-497}}$) (Webb et al., 2016). Finally, a CRE prevalence study in beef cattle in South Africa found that resistance to various carbapenem antibiotics ranged from 28% to 42%, indicating that CRE can become widespread in beef cattle populations (Tshitshi et al., 2020). While the above studies did not examine transmission of CRE from cattle to humans, other studies have found evidence of ESBL-producing Enterobacteriaceae passing between humans and cattle through genetic analyses (Adler et al., 2015; Subramanya et al., 2021).

1.4 Spatial Analysis as an Opportunity to Understand Community-Acquired CRE Transmission

Most studies on the transmission of CRE focus on nosocomial infections. In general, there is a gap in the literature on the transmission dynamics of community-acquired CRE. It did not become a nationally notifiable disease in the US until 2018, meaning national data is limited. However, some states, such as Tennessee, implemented reporting requirements as early as 2011, with the current case definition being implemented in 2015. That case definition follows the standard CDC case definition, which is “Enterobacterales that test resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase” (APIC Governmental Affairs, 2014; Tennessee Department of Health, 2018; US Centers for Disease Control and Prevention, n.d.-a, 2021a).

Tennessee is also notable because of the importance of cattle farming to its agricultural industry. Beef cattle rank among the state’s top three agricultural commodities, and the state is home to more than two million cattle and 45,000 cattle operations (Tennessee Department of Agriculture, n.d.). Due to the known risk of environmental contamination with drug-resistant bacteria by cattle feedlots, studying spatial patterns of CRE prevalence in Tennessee is likely a helpful tool for understanding the transmission patterns of community-acquired CRE and the risk to the community presented by cattle feedlots.

2. Methods

2.1 Study Population and Outcome Data

Carbapenem-resistant Enterobacteriaceae is classified as a reportable disease for both healthcare providers and laboratories in the state of Tennessee. The state requires all healthcare providers, laboratories, or other persons knowing of or suspecting a reportable disease to report it to the health department. For CRE specifically, healthcare providers and laboratories must call in a case report within a day and submit a general reporting form within a week. Further, laboratories must submit an isolate to the state health department (Tennessee Department of Health, 2021a, 2021b). The state follows the 2015 CDC case definition where a case is considered to be any species of "Enterobacterales that test resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase" (US Centers for Disease Control and Prevention, 2021a).

The study population for this project is the entire population of Tennessee from 2015 to 2018. The outcome is the rate per 100,000 person-years of CRE cases reported from the start of the newest case definition (2015) to the latest year of data that is available (2018), aggregated at the county level. Both CRE case counts and yearly population data were pooled across four years for each county, then the overall county-level rate was calculated. The yearly CRE case data and the yearly population data were obtained from the Tennessee Department of Health's interactive data portal, which provides a county-level breakdown of population and CRE case data for each year from 1995 to 2018 (Tennessee Department of Health, n.d.).

2.2 Exposure and Covariate Data

Every five years, the US Department of Agriculture's National Agriculture Statistics Service (NASS) conducts a national census of agriculture. The goal of that census is to reach all farms in the country, which are defined as "any place from which $1,000 or more of agricultural products were produced and sold, or normally would have been sold, during the census year" (USDA NASS, 2019a). In the 2017 Census of Agriculture, NASS sent census forms to 2,259,750 agriculture operations that were thought to meet the farm definition and 739,348 operations that were potential farms. In that census, Tennessee had a response rate of around 75%, above the national average (USDA NASS, 2019a, 2019b). Exposure data were obtained from the 2017 Census of Agriculture using the NASS Quick Stats portal (USDA NASS, n.d.). County-level beef cattle inventories and county-level beef cattle operation counts, subdivided by number of heads of cattle, were retrieved to be evaluated as potential exposure variables.

The CDC National Center for Health Statistics (NCHS) has developed an urbanicity scale that categorizes counties into six urbanicity levels using data from the Office of Management and Budget's metropolitan and micropolitan statistical areas. This scale was designed with the intention to be more useful in analyzing health data. Counties are classified as large central metro, large fringe metro, medium metro, small metro, micropolitan, and non-core (see Table 1). Counties classified in the first four levels on this scale are metropolitan, while levels 5 and 6 are non-metropolitan. The 2013 NCHS Urban-Rural Classification Scheme for Counties that was used in this analysis was retrieved from the NCHS website (CDC NCHS, 2017).

Table 1: Definition of 2013 NCHS Urban-Rural Classification Scheme for Counties.

Coding	Definition
1	Large central metro
2	Large fringe metro
3	Medium metro
4	Small metro
5	Micropolitan
6	Non-core

Finally, because this was a spatial analysis, geography data were needed to add the spatial component. Data for the geography of Tennessee’s counties were retrieved from the US Census Bureau using the Tigris package in the R statistical analysis program (Walker, 2020).

2.3 Statistical Analysis

Statistical analyses were conducted using R version 4.0.2 (R Core Team, 2020). The exposure, outcome, and covariate datasets were imported into R. To create an analytic dataset, the four years of numerator (CRE case counts) and denominator (population) were pooled across the four years included in this study for each county and the CRE rate per 100,000 person-years was calculated for each county (see Appendix). Then CRE case counts, population, CRE rate, and covariates were merged together by county FIPS ID. Three potential exposure variables were evaluated: county-level cattle counts, county-level number of cattle operations with fewer than 50 heads of cattle, and county-level number of cattle operations with greater than or equal to 50 heads of cattle. First, the three potential exposures were mapped at the county level to understand their overall distribution across the state of Tennessee. Then, CRE rates per 100,000 person-years were calculated for each county and smoothed using non-spatial Empirical Bayes smoothing. Non-spatial smoothing was used because CRE was a rare event in some counties, which was the cause for rate instability. However, there was still good stability in the crude data. Both the crude and smoothed CRE rates were mapped. Finally, the 2013 NCHS urbanicity score, which was included as a confounder, was mapped to understand its distribution.

Next, Pearson correlation coefficients were calculated for the three potential exposure variables to assess degree of collinearity and to understand the spatial structure of cattle within each county. Because of collinearity issues between the exposure variables, only the county-level number of cattle operations with fewer than 50 heads of cattle was used as an exposure variable in regression analyses. Then, a series of aspatial linear regression models was conducted assessing exposure-outcome associations and fit statistics were calculated to determine the best-fitting model. Linear regression was used because it is more compatible with spatial analysis. The distribution of the county-level CRE rates was checked to ensure it was normal, satisfying the assumption of a normal distribution for linear regression models. Residuals were then mapped and a Moran's I was calculated to determine the spatial autocorrelation of the residuals. The autocorrelation of residuals indicates the degree to which the spatial structure—or spatial dependence—in CRE rates was explained by the aspatial linear regression. Next, a spatial Durbin model was run. An aspatial linear regression model allows for dependence between the covariates and outcome within a county, but it assumes that the covariates and outcomes in neighboring counties are independent of one another. In situations where there is spillover of the covariates or the outcome between counties, a spatial regression model can be run. The spatial Durbin model is the only model that remains unbiased in scenarios where there is spillover in both the covariates and the outcome, and it provides measures to estimate the exposure-outcome associations within and between counties, as well as the outcome-outcome relationships between counties. Because there is potential spatial spillover in covariates and in the outcome, a spatial Durbin model was used. Finally, impact measures were calculated. A p-value of less than 0.05 was considered significant.

3. Results

3.1 Geographic Context of Tennessee

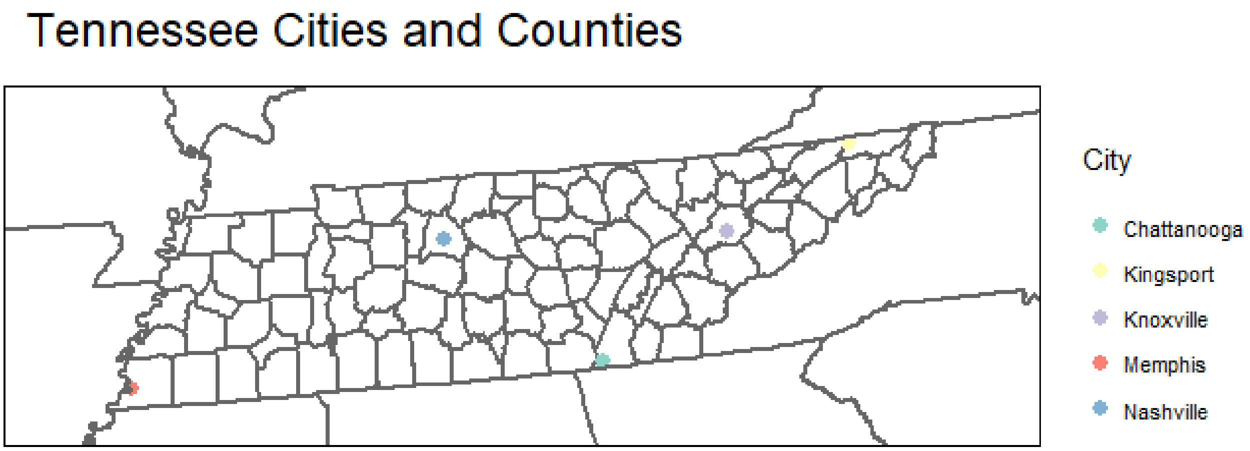

Figure 1: Map of the surrounding states, 95 counties, and five largest metropolitan areas of Tennessee.

The neighboring states, counties, and five largest metropolitan cities of Tennessee were mapped (Figure 1). Tennessee is a state in the Southeastern United States. It is surrounded by eight other states: North Carolina to the east; Georgia, Alabama, and Mississippi to the south; Arkansas and Missouri to the west; and Kentucky and Virginia to the north. Its five largest metropolitan areas are spread across the state. The largest, Memphis, is located on the state's western border. Next is Nashville in central Tennessee, and then Knoxville, Chattanooga, and Kingsport, which are all located in the eastern part of the state. Tennessee is home to 95 counties, which are approximately equal in size.

3.2 Spatial Structure of Covariates

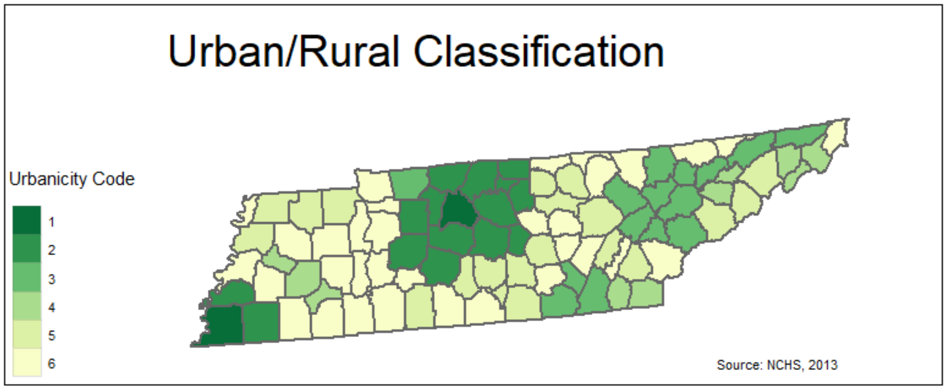

Figure 2: Map of the urbanicity codes for each county in Tennessee. The color palette ranges from the lightest colors representing the most rural counties to the darkest colors representing the most urban counties.

The 2013 NCHS urbanicity codes for each county in Tennessee were mapped (Figure 2). Urbanicity is potentially associated with the exposure, beef cattle production, as this agricultural activity is more likely to be conducted in rural areas than urban areas. Additionally, urbanicity is potentially associated with the outcome, CRE, as more urbanized communities present opportunities for the rapid spread of infectious diseases, including those in the Enterobacteriaceae family (Neiderud, 2015). Therefore, urbanicity was included as a confounder in this analysis. Shelby and Davidson Counties, home to Memphis and Nashville, are the most urbanized, with urbanicity codes of one. There is a stretch of counties in eastern Tennessee from Hamilton County, home to Chattanooga, to Sullivan County, home to Kingsport, that have moderate levels of urbanization. The rest of the counties in the state are generally the most rural.

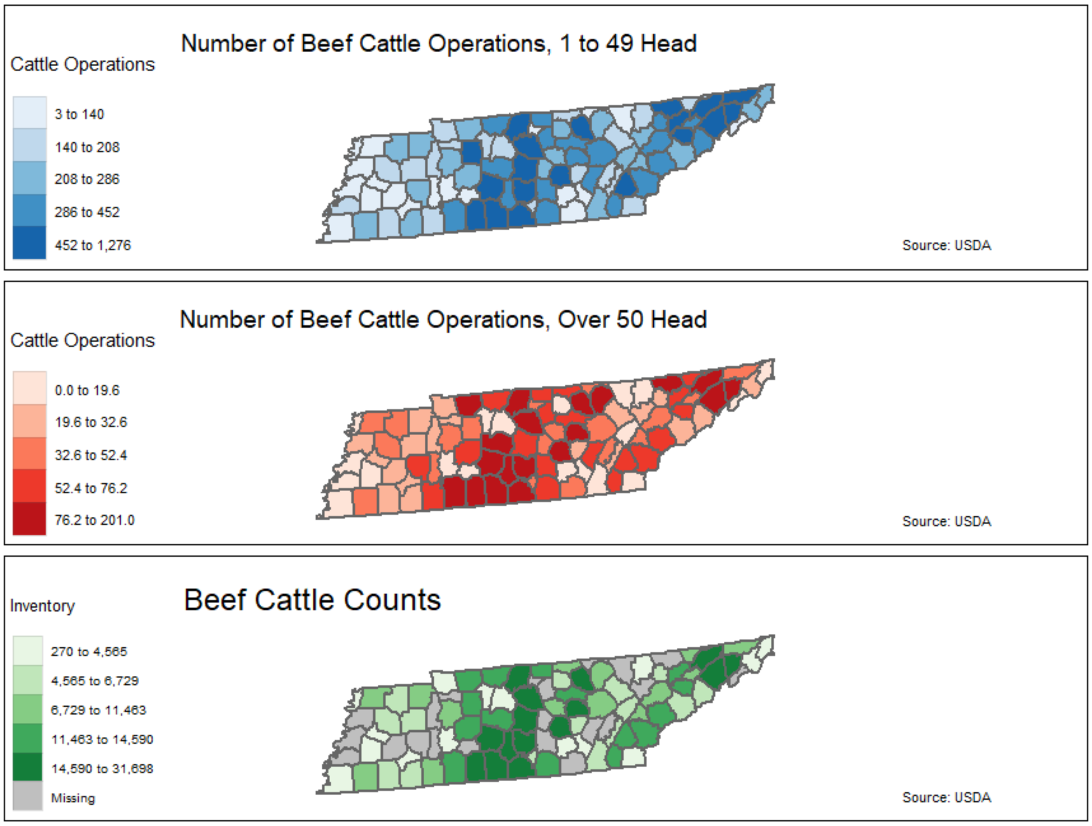

Figure 3: Maps of the county-level distributions of three possible exposure variables: number of beef cattle operations with 1-49 heads of cattle, number of beef cattle operations with 50 or more heads of cattle, and beef cattle counts in Tennessee. Cutpoints were determined by dividing the counties into five quantiles. The color palette ranges from the lightest colors representing the counties with the fewest cattle counts or operations to the darkest colors representing counties with the most.

The number of beef cattle operations with 1-49 heads of cattle, the number of beef cattle operations with 50 or more heads of cattle, and the beef cattle counts, all at the county level, were mapped to understand their spatial structures (Figure 3). All three have similar distributions of high and low values across the state of Tennessee. Counties in central and northeastern Tennessee have high levels of beef cattle production using all three metrics, while counties in western Tennessee have low levels of beef cattle production. Shelby and Davidson Counties, the two most urbanized counties in the state, have among the lowest beef cattle production, but elsewhere it appears to be grouped based more on geography than urbanicity. Counties with high numbers of small operations generally also have high numbers of large operations, indicating that there are distinct regions in the state where cattle production occurs. These maps demonstrate that cattle production is spatially structured, with heterogeneity between counties. Further, there appears to be some spatial autocorrelation, as counties with high and low production are often grouped together.

3.3 Spatial Structure of Outcome

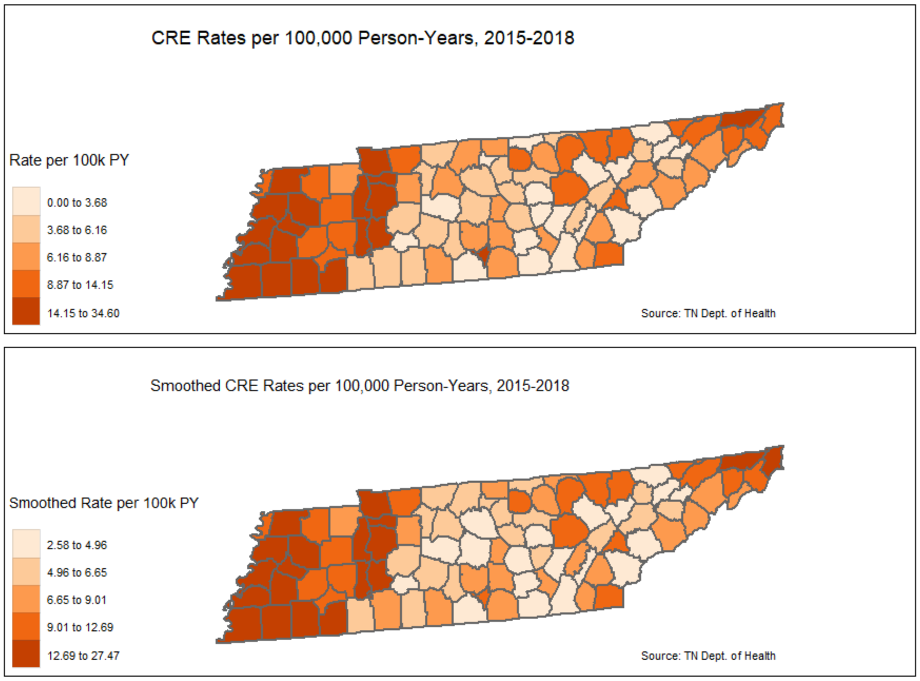

Figure 4: Maps of the county-levels distributions of crude and Empirical Bayes non-spatially smoothed CRE rates per 100,000 person-years from 2015-2018 in Tennessee. Cutpoints were determined by dividing the counties into five quantiles. The color palette ranges from the lightest colors representing the counties with the lowest CRE rates to the darkest colors representing counties with the highest.

The county-levels rates of CRE, both crude and Empirical Bayes non-spatially smoothed, were mapped to understand the spatial distribution of the outcome in this study (Figure 4). In the four-year study period, there were 2,415 cases of CRE across Tennessee, ranging from 391 to 679 per year. The state population at risk varied from 6,600,211 to 6,768,611 people for an overall statewide CRE rate of 9.03 cases per 100,000 person-years across the study period (Table 2). The crude county-level CRE rates ranged from 0.00 to 34.60 cases per 100,000 person-years, while the smoothed county-level rates ranged from 2.58 to 27.47 cases per 100,000 person-years.

As with the distributions of beef cattle production across Tennessee, there is also spatial structure in this variable, where counties with the highest CRE rates are generally grouped together. The region with the highest CRE rates was western Tennessee. It was high in both the rural counties of this area and the more urbanized ones around Memphis. Additionally, the counties in the far northeast corner of the state around Kingsport have high rates of CRE in both maps. The patterns in spatial structure persisted after the aspatial smoothing, indicating that there was good stability in the crude data and the spatial patterns did not appear to be spurious due to sparse counts in some counties.

Table 2: Statewide CRE case counts and population by year in Tennessee.

Year	2015	2016	2017	2018	Pooled
Cases	391	678	679	667	2415
Population	6600211	6651130	6715862	6768611	26735814

3.4 Selecting an Exposure Variable

The USDA NASS provides county-level for beef cattle counts and beef cattle operations for the state of Tennessee. Because of data suppression out of concern for farm privacy, the cattle counts for 21 of the 95 Tennessee counties were suppressed. The number of beef cattle operations was available for all counties. Additionally, the county-level number of operations from the NASS was subdivided into seven categories based on the number of heads of cattle in each operation, which were aggregated into two variables based on herd size, number of small operations (1-49 heads of cattle) and number of large operations (greater than 50 heads of cattle). A cut-off of 50 heads of cattle was chosen because farms with fewer than 50 cattle are often hobby farms that do not have cattle production as a primary income source. These farms generally have less use of technology, less vaccination, and fewer safe antibiotic practices than farms with 50 or more heads of cattle (Lhermie et al., 2019). After preparing the data, the distributions of the three variables were checked using Q-Q plots, and all three were approximately normally distributed.

To better understand the distribution of cattle within each county, the correlations between the three variables were assessed by calculating Pearson correlation coefficients. The Pearson correlation coefficient between number of small operations and cattle count was 0.91 [0.86, 0.94] ($p < 2.2e-16$), and the Pearson correlation coefficient between number of large operations and cattle count was 0.97 [0.95, 0.98] ($p < 2.2e-16$). This means cattle count was very strongly correlated with both the number of small and number of large operations variables. Additionally, the correlation was also strong between the number of small and number of large operations variables ($r = 0.83$ [0.75, 0.88], $p < 2.2e-16$). These results indicate that the density of cattle within each county was consistent regardless of operation size. There were no counties that had high counts of cattle due to many small operations and no large ones, or due to having some large operations and no small ones. Further, counties with large numbers of small operations also generally had many large ones, and vice versa. This means that the three exposure variables were good proxies for each other.

Because of the strong correlations between the three potential exposure variables, only one could be included in the regression analysis out of concern of running into collinearity issues. Because of the missing data in the cattle count variable and the research that shows smaller farms tend to be poorer antibiotic stewards and lower users of technology—and thus potentially presenting a higher risk of spreading CRE—the number of small operations (1-49 heads of cattle) was chosen as the exposure variable for this analysis.

3.5 Description of Study Population

Table 3: Characteristics of Tennessee counties (n = 95).

	Beef Cattle Operations (1 – 49 Heads of Cattle)		
	Tertile 1 3 – 173 Operations	Tertile 2 173 – 330 Operations	Tertile 3 346 – 1276 Operations
Counties (n)	32	32	31
CRE Rate per 100,000 PY (mean ± SD)	13.09 ± 9.91	9.13 ± 5.85	6.15 ± 3.33
Nonmetropolitan (%)	62.5	59.4	45.2

All 95 Tennessee counties were included in this analysis. To understand the distribution of the CRE rates and urbanicity of the counties, they were broken into tertiles based on their number of small beef cattle operations. The first tertile, which included 32 counties, had between 3 and 173 operations per county, had a mean smoothed CRE rate of 13.09 cases per 100,000 person-years (SD: 9.91), and had 62.5% of its counties classified as nonmetropolitan. The middle tertile, with 32 counties, had between 173 and 330 operations per county, had a mean smoothed CRE rate of 9.13 cases per 100,000 person-years (SD: 5.85), and had 59.4% of its counties classified as nonmetropolitan. Finally, the third tertile, with 31 counties, had between 346 and 1,276 operations per county, had a mean smoothed CRE rate of 6.15 cases per 100,000 person-years (SD: 3.33), and had 45.2% of its counties classified as nonmetropolitan.

From looking at these characteristics alone, it is possible to see a potential dose response between number of small beef cattle operations and CRE rate, where counties that have more operations have a lower CRE rate. There is also evidence of a potential dose response relationship between number of operations and urbanicity, where counties with more cattle operations are less likely to be nonmetropolitan (rural).

3.6 Aspatial Linear Regression

First, an aspatial linear regression model was constructed and run with the smoothed CRE rate as the outcome, the number of small operations as the exposure, and urbanicity as a confounder. Interaction between the number of operations and urbanicity was assessed. However, the interaction term was not statistically significant ($p = 0.50$), so it was dropped from the model. Therefore, the following aspatial linear regression model was used to evaluate the relationship between the county-level CRE rate and the number of small beef cattle operations per county:

$$Y = \beta_0 + \beta_1 \text{ (number of small operations)} + \beta_2 \text{ (urbanicity code)} + \varepsilon.$$

There was a statistically significant relationship between the rate of CRE and the number of small beef cattle operations. The rate of CRE per 100k PY decreased by 0.84 for every 100-operation increase in the number of beef cattle operations with 1-49 heads of cattle in the county ($p = 0.003$), controlling for urbanicity.

3.7 Spatial Linear Regression

CRE is an infectious disease that can easily spread across county borders. Additionally, environmental contamination due to beef cattle operations can also easily spill across county lines. Therefore, each county in the analysis is likely not independent of the others, and there is

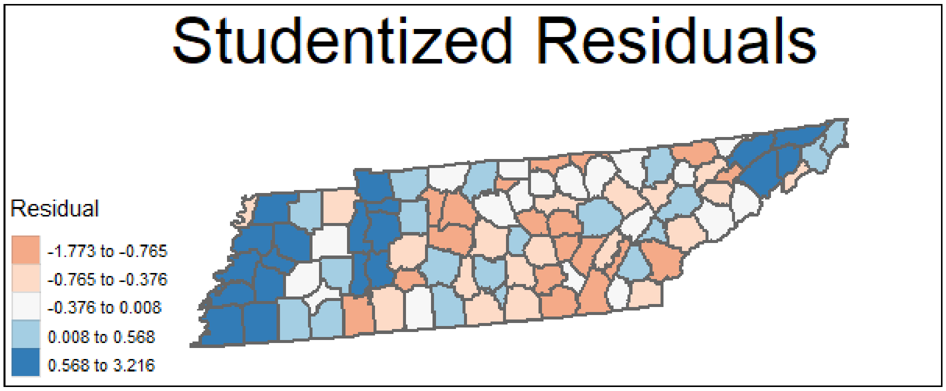

Figure 4: Map of studentized residuals from the aspatial linear regression model for each county in Tennessee. Cutpoints were determined by dividing the counties into five quantiles.

likely a spatial component in the disease generating process. To assess how well the exposure variable accounted for the spatial structure in the CRE rate data, the studentized residuals from the aspatial linear regression model were mapped (Figure 6). Additionally, Queen contiguity neighbors were created and a Moran's I statistic was calculated to assess the spatial autocorrelation of the residuals. With a Moran's I statistic of 0.44 ($p < 0.001$), there was moderately strong spatial autocorrelation in the residuals, indicating that a significant portion of the spatial structure in CRE rates was unexplained by the aspatial linear regression model.

Because of the spatial spillover of both the exposure and the outcome, as well as the spatial autocorrelation of the residuals, a spatial Durbin regression model was run. It is the only spatial regression model that remains unbiased when there is spillover in both the exposure and the outcome. The lower AIC (542.33 compared to 567.84) and the lower log-likelihood ratio (-256.17 compared to -285.78) indicate that the spatial Durbin model had a better fit than the aspatial linear regression model. The within-county effect of the number of small beef cattle operations on CRE rate was -0.0036, but this effect was not statistically significant ($p = 0.08$). The spatial Durbin model also provides spatially lagged parameter estimates. The γ parameter, which is the effect on the rate of CRE due to a change in the number of small beef cattle operations in neighboring counties, was -0.0008. Again, this parameter was not statistically significant ($p = 0.82$). Because of the spatial lag, the values in each county are not independent, so the above parameters cannot be interpreted as they would be for normal linear regression. Therefore, impact measures were calculated. Bayesian Markov Chain Monte Carlo simulations ($n = 199$) were run to quantify the bounds of these impacts to determine if they appear to be statistically significant from zero.

The direct impact is the effect of the number of small cattle operations in a given county on the CRE rate of that county, which was equal to -0.0042 (95% credible interval: [-0.0085, -0.0003]). This means the rate of CRE per 100k PY decreased by 0.42 for every 100-operation increase in the number of beef cattle operations with 1-49 heads of cattle in the county, controlling for urbanicity, and the effect appeared to be statistically significant, as the 95% credible interval did not contain zero. The indirect impact is the effect of the number of small beef cattle operations in neighboring counties on the CRE rate of a given county, and the total effect combines the direct and indirect effects. In this analysis, the indirect impact was -0.0074 (95% credible interval: [-0.0224, 0.0100]) while the total effect was -0.0117 (95% credible interval: [-0.0287, 0.0081]), but neither of these appeared to be statistically significant after running Monte Carlo simulations.

Next, the ρ parameter was 0.62 ($p < 9.8\text{e-}12$), indicating that there was statistically significant strong correlation of CRE rates between a given county and its neighboring counties after controlling for the spatially lagged covariates. Finally, a Lagrange Multiplier test, which is a hypothesis test used to test model fit based on adding parameters, was conducted to test for the significance of spatial autocorrelation of the residuals. The test statistic of 0.004 was not statistically significant ($p = 0.95$), indicating that there was not spatial autocorrelation in the residuals and the spatial Durbin model did an effective job accounting for the spatial structures of the disease generating process.

While there was not autocorrelation in the error, the exposure variable, or the confounder variable in the spatial Durbin model, there was autocorrelation in the outcome variable, CRE. This ecological result is consistent with inter-county community spread. Thus, it is worthy of further evaluation and more in-depth analysis of community transmission dynamics. However, the number of small beef cattle operations in a county and the urbanicity of a county do not explain this spatial process. Instead, there is some unknown process that is leading to the spatial structure of CRE. Additionally, even though there was a statistically significant protective relationship between the number of small beef cattle operations and the rate of CRE in each county, it does not make logical sense that the number of cattle operations would be protective for CRE. Therefore, there is some unknown factor in counties with high numbers of small beef cattle operations that is protective for CRE for which the number of operations acted as a proxy.

4. Discussion

4.1 Limitations

This study has several limitations. First, because the CRE case data were collected through a passive surveillance system, it is likely that cases were missed. A survey of healthcare providers in Tennessee found that, while providers recognized their responsibility to comply with disease reporting (98.4%) and most acknowledged that they had cared for a patient with a reportable disease (83.2%), fewer than half said they had actually reported a disease to health authorities (43.3%). A lack of knowledge of which diseases are reportable and uncertainty about the logistics to report a disease were the largest barriers (Fill et al., 2017).

Another limitation is the limited data for CRE cases. The Tennessee Department of Health only provided the county case counts and county populations for each year, but additional information would be helpful in determining patterns in CRE cases. For example, information about whether a case was hospital-acquired or community-acquired would improve the quality of analyses that focus on one source and help unmask underlying trends. This analysis was limited by the fact that such information was unavailable.

4.2 Conclusions and Public Health Implications

CRE is an emerging public health threat that has rapidly spread across the United States in the past couple decades. The CDC recognizes these bacteria to be an urgent threat, its highest threat level (US Centers for Disease Control and Prevention, 2019). Yet little is known about its risk factors, especially for community-acquired CRE. Gaining an increased understanding of how CRE spreads in the community is important step in containing this public health threat.

Additionally, cattle have been recognized as a potential source of zoonotic transmission for many pathogens, including Enterobacteriaceae (McDaniel et al., 2014). Poor antibiotic stewardship in agricultural practices, such as the overuse of antibiotics, contributes to antibiotic-resistant strains of bacteria arising in cattle populations, especially beef cattle populations, which can then be passed on to humans through environmental and other contamination (Wallinga, 2020). Several studies have also detected CRE in cattle populations and demonstrated that it can quickly become widespread within them (Köck et al., 2018; Sawant et al., 2007; Tshitshi et al., 2020; Webb et al., 2016). Thus, it was hypothesized that beef cattle could be an important contributor to the community spread of CRE.

However, the results of this study are not what was hypothesized. The regression analyses demonstrated a small statistically significant protective relationship between the number of small beef cattle operations and CRE rates. It could be the case where having a larger number of beef cattle operations is protective for CRE. But, after accounting for the fact that research shows cattle operations generally contribute to zoonotic transmission of pathogens rather than protect against them, it is likely that the protective relationship is one where beef cattle farming acts as a proxy for a different, unknown factor. Further, cattle are potentially not drivers in of carbapenem resistance in Enterobacteriaceae, which could explain the small effect size detected in this study. Finally, there could be masking of the true effect due the lack of data on the source of infection, which makes it difficult to disentangle hospital-acquired infections, which are largely not related to cattle, with community-acquired infections, which are potentially related to cattle. The strong autocorrelation in CRE rates between counties indicates that CRE is spread between neighboring counties, but without source data, it is hard to say how indicative of community spread the spatial autocorrelation is.

This study shows that gaps still persist in the understanding of risk factors for the community spread of CRE. There is potentially some unknown factor that is protective against CRE at the county level. Identifying this factor could guide future public health interventions by helping identify where they are needed, where they could be the most effective, and potentially even what components should be included in the intervention. CRE is an urgent public health threat and understanding its transmission dynamics and risk factors is the first step in protecting against it.

4.3 Future Directions

The findings of this study help identify the importance of comprehensive data collection and the fact that reporting case counts alone is not enough to provide detailed understandings of disease transmission dynamics. Efforts should be taken to improve the breadth of CRE case and covariate data, while still protecting patient privacy. Additionally, further analyses should be conducted to examine transmission dynamics and risk factors of community-acquired CRE. In particular, they should include information about the source of CRE infection. Finally, attempts should be made to better understand the spatial structure of CRE rates in Tennessee to identify protective factors that could be used in future interventions.

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6. Appendix

Table 3: County-Level CRE Data

County	2015 Cases	2015 Population	2016 Cases	2016 Population	2017 Cases	2017 Population	2018 Cases	2018 Population	Pooled Cases	Pooled Population	Rate per 100,000 PY
Anderson	2	75760	4	75937	2	76262	3	75478	11	303437	3.625134707
Bedford	1	47185	4	47492	6	48117	4	49045	15	191839	7.819056605
Benton	1	16132	4	16019	7	15991	1	16183	13	64325	20.20987175
Bledsoe	0	14477	1	14675	0	14722	0	14767	1	58641	1.70529152
Blount	5	127260	0	128666	6	129933	5	131341	16	517200	3.09358082
Bradley	12	104095	8	104484	9	105563	5	106738	34	420880	8.078312108
Campbell	1	39758	2	39716	8	39647	6	39579	17	158700	10.71203529
Cannon	1	13844	0	14047	3	14222	1	14473	5	56586	8.836107871
Carroll	1	27909	2	28100	4	27859	4	28022	11	111890	9.8310841
Carter	5	56485	7	56490	9	56479	4	56345	25	225799	11.07179394
Cheatham	0	39741	4	39879	2	40334	1	40446	7	160400	4.364089776
Chester	2	17475	1	17454	4	17126	0	17273	7	69328	10.09693053
Claiborne	0	31710	2	31773	1	31621	1	31746	4	126850	3.153330706
Clay	0	7779	0	7740	0	7714	1	7731	1	30964	3.229556905
Cocke	2	35164	1	35214	4	35556	3	35779	10	141713	7.056515634
Coffee	0	54282	7	54689	4	55027	4	55706	15	219704	6.827367731
Crockett	5	14605	3	14403	5	14476	7	14319	20	57803	34.60028026
Cumberland	2	58237	10	58665	8	59074	6	59695	26	235671	11.03232897
Davidson	21	678888	45	684415	62	691239	44	692590	172	2747132	6.261075187
Decatur	2	11662	2	11779	6	11751	5	11710	15	46902	31.98157861
DeKalb	0	19190	1	19373	1	19836	1	20133	3	78532	3.820098813
Dickson	1	51483	5	52187	3	52854	5	53439	14	209963	6.667841477
Dyer	3	37887	5	37721	7	37460	9	37317	24	150385	15.95903847
Fayette	8	39159	8	39598	6	40042	8	40510	30	159309	18.8313278
Fentress	3	17915	1	18023	3	18129	1	18214	8	72281	11.0679155
Franklin	0	41440	2	41686	4	41655	5	41887	11	166668	6.5999472

Gibson	5	49404	3	49414	11	49110	23	49052	42	196980	21.32196162
Giles	1	28929	2	29304	4	29401	1	29504	8	117138	6.829551469
Grainger	0	22844	2	23093	0	23148	0	23137	2	92222	2.168679925
Greene	3	68585	10	68612	5	68800	3	69089	21	275086	7.633976284
Grundy	0	13433	0	13366	0	13370	0	13322	0	53491	0
Hamblen	0	63400	2	63786	3	64267	3	64570	8	256023	3.124719264
Hamilton	20	354104	6	357745	7	361613	8	364286	41	1437748	2.851681936
Hancock	1	6552	0	6565	1	6579	1	6532	3	26228	11.43815769
Hardeman	6	25703	2	25434	2	25449	5	25227	15	101813	14.73289266
Hardin	1	25761	2	25673	1	25846	1	25778	5	103058	4.851636942
Hawkins	1	56472	5	56555	10	56463	7	56526	23	226016	10.17627071
Haywood	2	18019	2	17847	5	17567	8	17339	17	70772	24.02079919
Henderson	3	28016	4	27825	4	27751	3	27840	14	111432	12.56371599
Henry	0	32152	3	32315	5	32454	2	32362	10	129283	7.734969021
Hickman	0	24370	2	24288	0	24863	3	25048	5	98569	5.072588745
Houston	0	8164	2	8121	4	8219	4	8269	10	32773	30.51292222
Humphreys	1	18134	4	18351	7	18491	2	18498	14	73474	19.05435937
Jackson	0	11492	2	11533	1	11683	2	11756	5	46464	10.76101928
Jefferson	2	53250	6	53534	0	53810	3	53996	11	214590	5.126054336
Johnson	1	17828	6	17743	2	17680	1	17777	10	71028	14.07895478
Knox	17	451323	31	456117	26	461860	46	465293	120	1834593	6.540960311
Lake	2	7575	0	7571	0	7470	1	7403	3	30019	9.993670675
Lauderdale	7	26937	8	26775	8	25271	11	25825	34	104808	32.44027173
Lawrence	0	42572	1	43094	7	43399	2	43740	10	172805	5.786869593
Lewis	0	11847	0	11907	1	12026	0	12092	1	47872	2.088903743
Lincoln	0	33757	0	33637	3	33747	1	34126	4	135267	2.957114448
Loudon	1	51130	5	51461	8	52158	6	53054	20	207803	9.624500128
McMinn	5	52647	6	52857	2	52884	5	53284	18	211672	8.503722741
McNairy	0	26070	5	25951	6	26009	4	25827	15	103857	14.44293596
Macon	1	23176	2	23442	1	24074	2	24262	6	94954	6.318849127
Madison	10	97607	7	97668	7	97646	18	97606	42	390527	10.75469814
Marion	1	28494	0	28450	1	28429	1	28588	3	113961	2.632479532
Marshall	0	31551	2	31914	3	32933	1	33681	6	130079	4.612581585

Maury	0	87772	11	89974	8	92162	3	94342	22	364250	6.039807824
Meigs	0	11825	0	12000	0	12064	0	12298	0	48187	0
Monroe	1	45783	1	45969	1	46228	3	46366	6	184346	3.254749222
Montgomery	10	193479	18	195729	26	200177	18	205953	72	795338	9.052754929
Moore	2	6313	2	6322	0	6377	0	6421	4	25433	15.727598
Morgan	1	21485	0	21548	2	21630	0	21572	3	86235	3.47886589
Obion	3	30644	6	30580	6	30376	9	30256	24	121856	19.69537815
Overton	1	22129	2	22041	2	22003	1	22072	6	88245	6.799252082
Perry	1	7930	2	7958	3	7984	1	8057	7	31929	21.92364308
Pickett	0	5132	0	5129	1	5060	0	5060	1	20381	4.906530592
Polk	1	16770	3	16765	1	16754	1	16900	6	67189	8.93003319
Putnam	1	74555	6	75943	1	77676	6	78840	14	307014	4.560052636
Rhea	0	32529	1	32444	4	32695	3	33040	8	130708	6.120512899
Roane	2	52755	3	52880	2	53032	4	53127	11	211794	5.193725979
Robertson	0	68564	5	69175	6	70177	6	71014	17	278930	6.094719105
Rutherford	7	298606	14	308257	19	317165	18	324896	58	1248924	4.643997553
Scott	0	21935	2	21936	5	21985	3	22039	10	87895	11.37721145
Sequatchie	1	14803	1	14883	1	14736	1	14872	4	59294	6.746045131
Sevier	3	95948	8	96672	9	97629	12	97894	32	388143	8.244384157
Shelby	112	938072	219	934612	178	936954	170	935767	679	3745405	18.12888059
Smith	1	19288	1	19420	1	19634	0	19937	3	78279	3.832445483
Stewart	0	13262	6	13175	4	13347	3	13563	13	53347	24.36875551
Sullivan	21	156793	34	156669	26	157161	29	157671	110	628294	17.50772727
Sumner	2	175987	16	180073	11	183546	16	187147	45	726753	6.191924904
Tipton	19	61866	12	61306	7	61374	13	61594	51	246140	20.7199155
Trousdale	1	8035	0	8266	0	10077	0	11009	1	37387	2.674726509
Unicoi	1	17851	2	17730	2	17753	1	17746	6	71080	8.441193022
Union	0	19089	2	19133	0	19430	2	19685	4	77337	5.172168561
Van Buren	0	5636	0	5663	0	5711	0	5752	0	22762	0
Warren	0	40444	3	40522	3	40655	0	40871	6	162492	3.692489476
Washington	21	126301	17	127438	17	127800	10	128605	65	510144	12.74150044
Wayne	0	16741	0	16715	2	16563	2	16562	4	66581	6.00771992
Weakley	6	33962	6	33500	0	33336	6	33413	18	134211	13.41171737

White	0	26523	1	26661	1	26767	1	27110	3	107061	2.802140836
Williamson	2	211674	4	219105	7	226249	8	231373	21	888401	2.363797429
Wilson	2	128910	9	132764	4	136436	5	140632	20	538742	3.712352109