Temporal and Spatial Patterns in Distemper Virus Carnivore Cases Diagnosed at the Southeastern Cooperative Wildlife Disease Study (SCWDS), 1975-2019

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## Abstract

Canine distemper is an important infectious disease that can affect many mammal species, particularly carnivores, and is responsible for substantial carnivore population declines. Analysis was conducted on passive surveillance diagnostic data of canine distemper (CDV) positive wild mammal cases that were submitted to the Southeastern Cooperative Wildlife Disease Study (SCWDS), Athens, GA, USA between January 1975 and December 2019. Overall, 964 cases were submitted to SCWDS from 17 states that were identified as CDV positive, comprising raccoons (n=646), gray foxes (n=254), striped skunks (n=33), coyotes (n=18), red foxes (n=4), gray wolves (n=3), black bears (n=3), two mink, and one long-tailed weasel. Raccoon and gray fox case data from the state of Georgia (n=441) were selected for further analysis based on these forming the considerably greater part of the data set. An auto regressive integrated moving average model used the numbers of gray fox CDV cases from the previous two months and of raccoon cases in the current month to predict the numbers of gray fox cases in the current month. There were temporal trends in CDV cases for both species, with cases more likely to occur during the breeding season. Spatial clustering of cases was more likely to occur in areas of medium to high human population density and fewer cases in both the most densely populated and sparsely populated areas. This pattern was most prominent for raccoons, which may correspond to high transmission rates in suburban areas, where population densities are highest, possibly due to a combination of suitable habitat and supplemental resources.

## Introduction

Canine distemper is a significant infectious disease affecting a wide range of wild and domestic mammals, principally carnivores. It has the second highest case fatality rate of canine diseases after rabies (Swango, 1995). The causative agent, Canine morbillivirus (CDV) is an enveloped, single stranded, negative sense RNA virus in the Morbillivirus family. The major route of transmission is through aerosolization of virus from respiratory secretions (Deem, Sharon L.; Spelman, L. H.; Yates, R. A.; Montali, 2000). CDV is a highly infectious virus that may be shed for 60-90 days post infection (Greene, C. E. & Appel, 1990). CDV results in a highly immunizing, acute infection that typically requires high densities and large populations of hosts for long‐term persistence (ES., 2001). The virus is maintained among wild carnivores by multi-host transmission, which overcomes the obstacles of population size and host density (Almberg, Cross, & Smith, 2010). There is evidence of CDV infection in all terrestrial carnivore families and some marine carnivore families (Deem, Sharon L.; Spelman, L. H.; Yates, R. A.; Montali, 2000). The Mustelidae family is among the species with the highest fatality rate, while the domestic dog (*Canis lupus familiaris*) can be a subclinical carrier (Deem, Sharon L.; Spelman, L. H.; Yates, R. A.; Montali, 2000). CDV has been responsible for substantial population declines in the African lion (*Panthera leo*) (Roelke-Parker et al., 1996) and Amur tigers (*Panthera tigris altaica*) (Seimon et al., 2013) and the endangered black-footed ferret (*Mustela nigripes*) in the US (Williams, Thorne, Appel, & Belitsky, 1988). In North America, raccoons (*Procyon lotor*), foxes (*Vulpes vulpes* and *Urocyon cinereoargenteus*), coyotes (*Canis latrans*), wolves (*Canis lupus*) , skunks (*Mephitis mephitis*), badgers (*Taxidea taxus*), mink (*Mustela vison*) and ferrets (*Mustelidae spp*) are among the wild species susceptible to CDV infection (Kapil et al., 2008). CDV is endemic in the eastern U.S. raccoon population and raccoons are thought to be a reservoir for other wild animals and domestic dogs (Roscoe, 1993). CDV is also a major cause of disease among gray foxes in the southeastern US, with 78% of animals undergoing diagnostic evaluation from1972 to 1989 being diagnosed with the disease in one study (Davidson, Nettles, Hayes, Howerth, & Couvillion, 1992). CDV has been found to persist in areas like Yellowstone National Park, which has a diverse carnivore population, and has experienced multiple outbreaks in the wolf, coyote, and cougar (*Puma concolor*) populations (Almberg et al., 2010; Almberg, Mech, Smith, Sheldon, & Crabtree, 2009). While there is a large body of work identifying distemper outbreaks in wild carnivores in the US, there has been more limited work on the spatio-temporal dynamics of CDV, particularly in raccoon populations. Further, most studies have been short term and often have focused on the Yellowstone National Park system, which differs from the southeast in a number of ways, including the absence of major urban centers (Almberg et al., 2010, 2009). The primary objective of this study was to identify long-term spatial and temporal patterns in CDV cases in wildlife reported to the Southeastern Cooperative Wildlife Disease Study (SCWDS) at the University of Georgia. In addition, we aimed to identify how outbreaks in two different species may be related, as raccoons are thought of the primary wild reservoir, and epizootics in this species may be followed by epizootics in others. Finally, we identified spatial patterns of infection within the southeastern US including potential associations with human activity.

## Methods

### Data acquisition and overview

We acquired data from wild mammals submitted to SCWDS between 1975 and 2019 that were diagnosed with CDV on postmortem examination. Cases of CDV were identified as CDV positive by fluorescent antibody testing (Fairchild, Steinberg, & Cohen, 1971) or immunohistochemistry (Palmer, Huxtable, & Thomas, 1990) and had characteristic histopathology (including intranuclear and intracytoplasmic inclusions). Many of the animals submitted were found dead or moribund and subsequently euthanized. The data set contained the following variables: case number, state, county, area, sex, species, age, and collection year.

Human population and land area data for Georgia counties from 1975-2019 was accessed and downloaded from census.gov (Bureau, 2019). Data were imported into R Studio (version 1.3.1056). Detailed description of data analysis and cleaning is contained in the processing scripts within the project repository in the “processing\_code” subfolder (<https://github.com/JJWilson1991/CDVGA_Project_JJW>). All analyses were conducted in the program R (version 3.5.3.). Exploratory analyses performed are in the “CDV19\_Exploration” file within the project repository.

### Spatial Analysis

Mapping data for US states and counties is available through the *ggplot2* (Wickham, 2016) package. As the CDV data only contained county level location information, county centroid coordinates were used for plotting case points. Individual cases were mapped for entire dataset and presence of CDV in raccoons and gray foxes were mapped at the county level in Georgia. Presence was defined as at least one CDV diagnosis in raccoon or gray fox in a particular county in Georgia in a particular year. Analysis of spatial clustering of cases in Georgia was performed using Ripley’s K from the *spatstat* package (A. Baddeley & R.Turner., 2015).

### Temporal Analysis

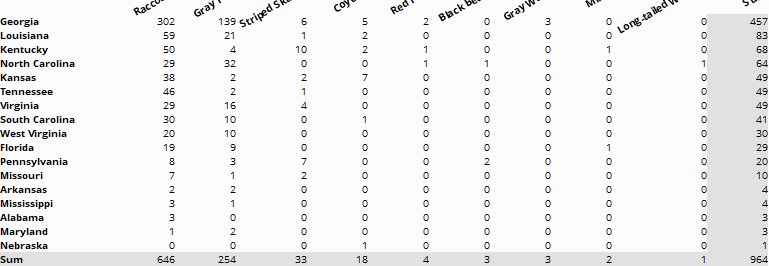
Cases were also analyzed in relation to the raccoon and gray fox reproduction cycle, defined as the breeding season being January to March, lactation as April to June and non-breeding for the remainder of the year (Zeveloff & Dewitte, 2002). Chi-square test (McHugh, 2013) was performed on these data as well as used to produce generalized linear models for each species and stage of breeding cycle.

Time series analysis and auto regressive integrated moving average (ARIMA) model construction was conducted using the *fpp2* package (Hyndman, R.J., & Athanasopoulos, 2018). The three components of an ARIMA model are auto-regression, differencing, and the moving average. Autoregression uses previous data in the time series from n number of previous time points to predict future data; differencing computes the difference between observations in non-stationary data to remove the influence of trends or seasonality, and the moving average uses the past forecast errors in the model to make future predictions. In addition to these basic components of the ARIMA model, lagged predictors were included in model building. In the case of the raccoon predictive model, the lagged predictors were comprised of current and past gray fox cases, and vice versa for the gray fox model.

For time series analysis, the data were pooled into raccoon or gray fox distemper cases in Georgia per month from April 1975-December 2019. For training and testing of the ARIMA models, the sequence of months from April 1975-December 2019, n=524 time points, was divided approximately 80:20 into the training set (up to n=423 i.e. July 2011) and the testing set (n=423 to n=524, i.e. August 2011-December 2019). The training set is used for building the model and the testing set is used for testing the accuracy of the model’s predictions compared to the real data. The stationarity of the time series was confirmed using both the augmented Dickey–Fuller test (Dickey & Fuller, 1979) and the Kwiatkowski–Phillips–Schmidt–Shin test (Kwiatkowski, Phillips, Schmidt, & Shin, 1992). The best fit models for each species were evaluated using the Akaike Information Criterion (AIC) (Akaike, 1981). The best model from each species was tested using the later part of the data set, and the root mean squared error (RMSE) was used to evaluate model performance.

## Results

A total of 964 cases diagnosed with canine distemper including 9 species were submitted from 17 states over the 45-year period (Table 1). There was a mean of 21.42 cases diagnosed with distemper submitted per year with a standard deviation of 16.96.

 **Table 1: Summary table of the species and state of wildlife cases diagnosed with canine distemper submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

Canine distemper cases in all species most often originated in southeastern states, with cases tending to occur in the same or adjacent counties to those with raccoon cases (Supplementary Materials). Georgia submitted most cases throughout all years of study, but Louisiana submitted the most from 2010 to 2019.

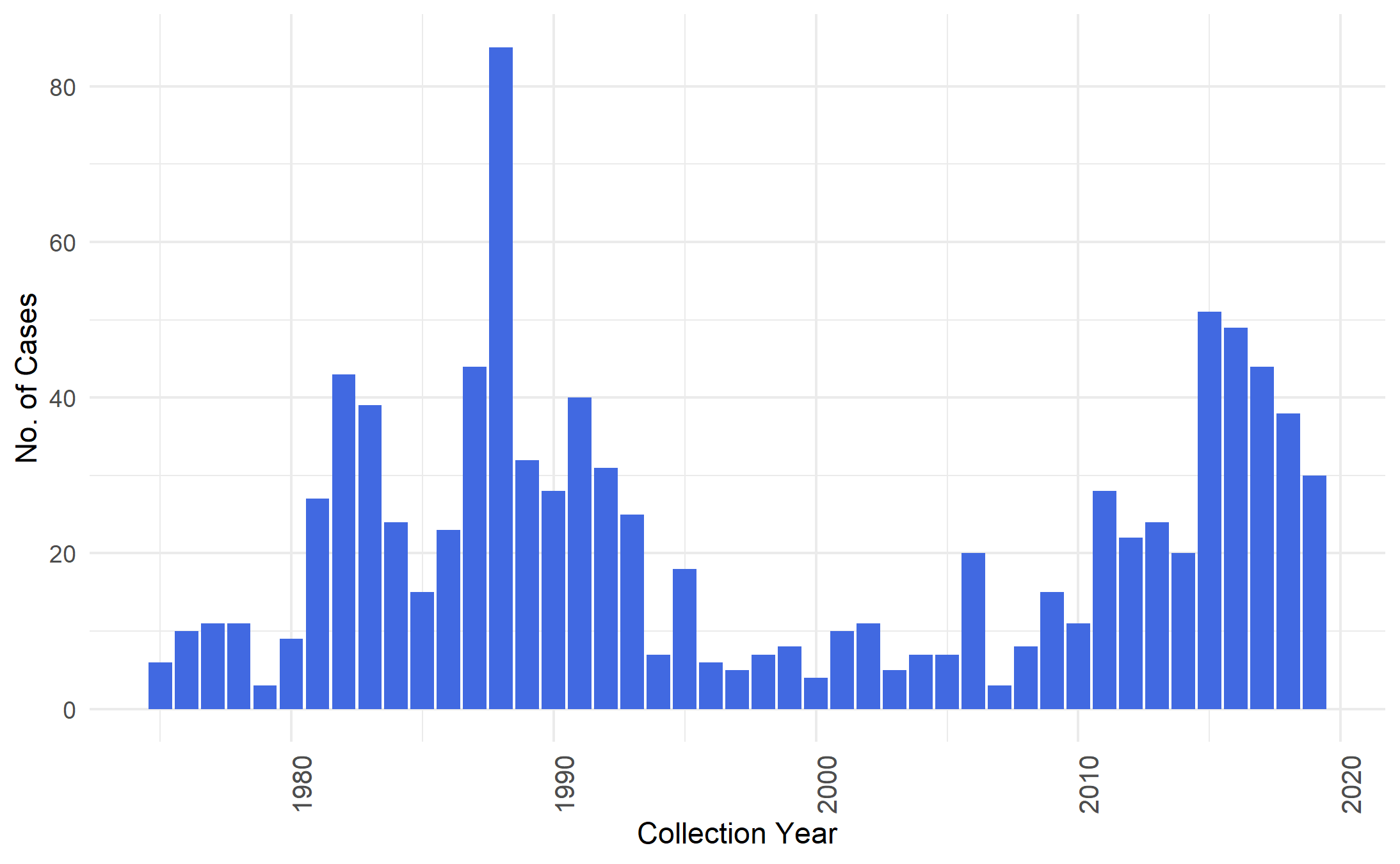


Figure 2: **Total number of wildlife cases diagnosed with canine distemper for all species and all states per year submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

As the greatest proportion of the cases came from gray foxes and raccoons in Georgia, further spatial and temporal analyses were limited to these cases. From 1975 to 2019, numbers of raccoon and gray fox distemper cases varied significantly over time, with the 1980s having the greatest numbers per year for both species (n=441 mean=9.8 SD=11.82371). The years 2000, 2007, 2008 and 2010 had no reported cases in gray foxes or raccoons in Georgia.

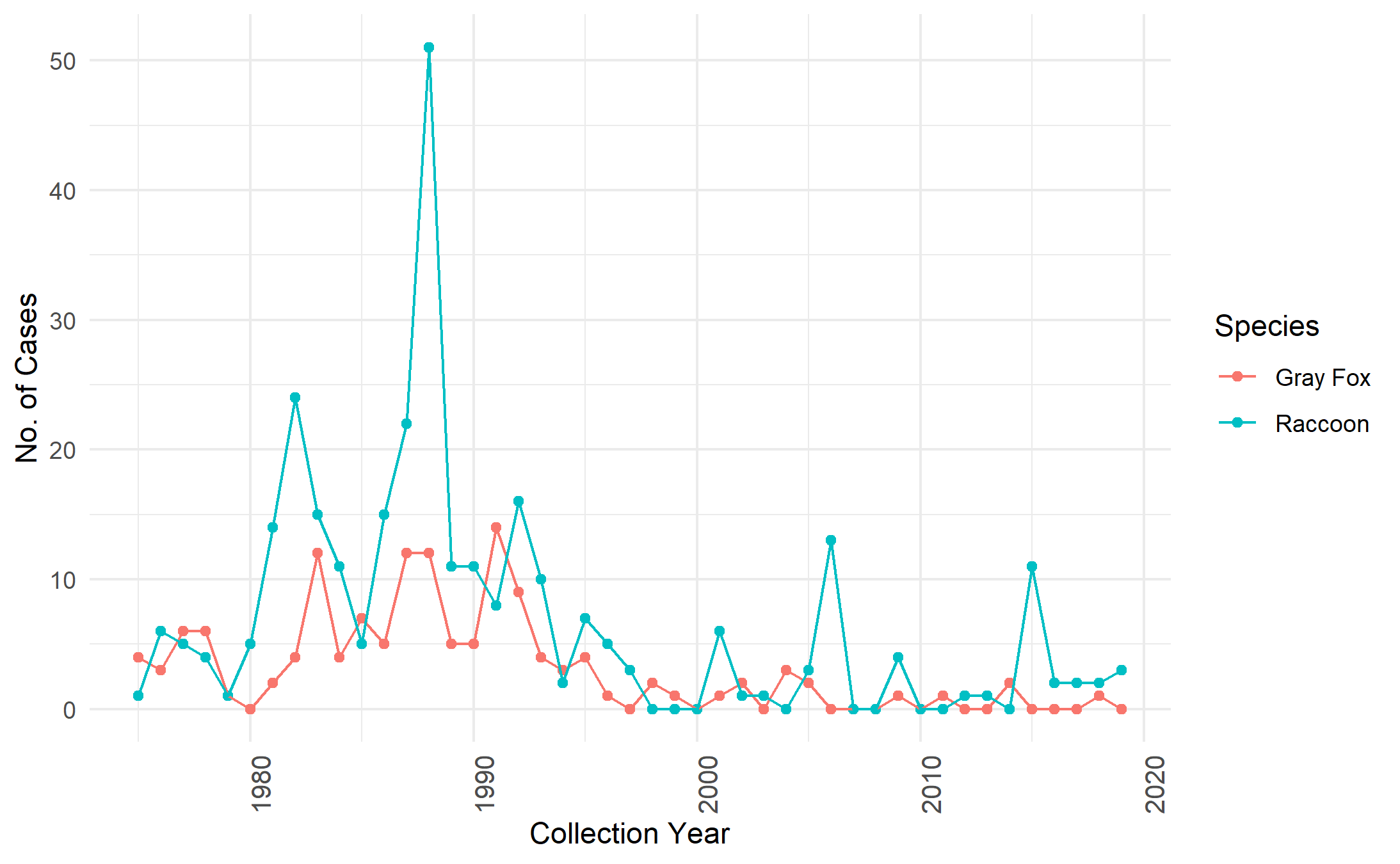


Figure 3: **Total number of raccoons and gray foxes diagnosed with canine distemper per year from Georgia that were submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

Most of the raccoon and gray fox cases in Georgia were received during the respective breeding seasons for these species (Zeveloff & Dewitte, 2002). There was a significant association between breeding season and the number of cases, particularly in raccoons (**Figure 3**).

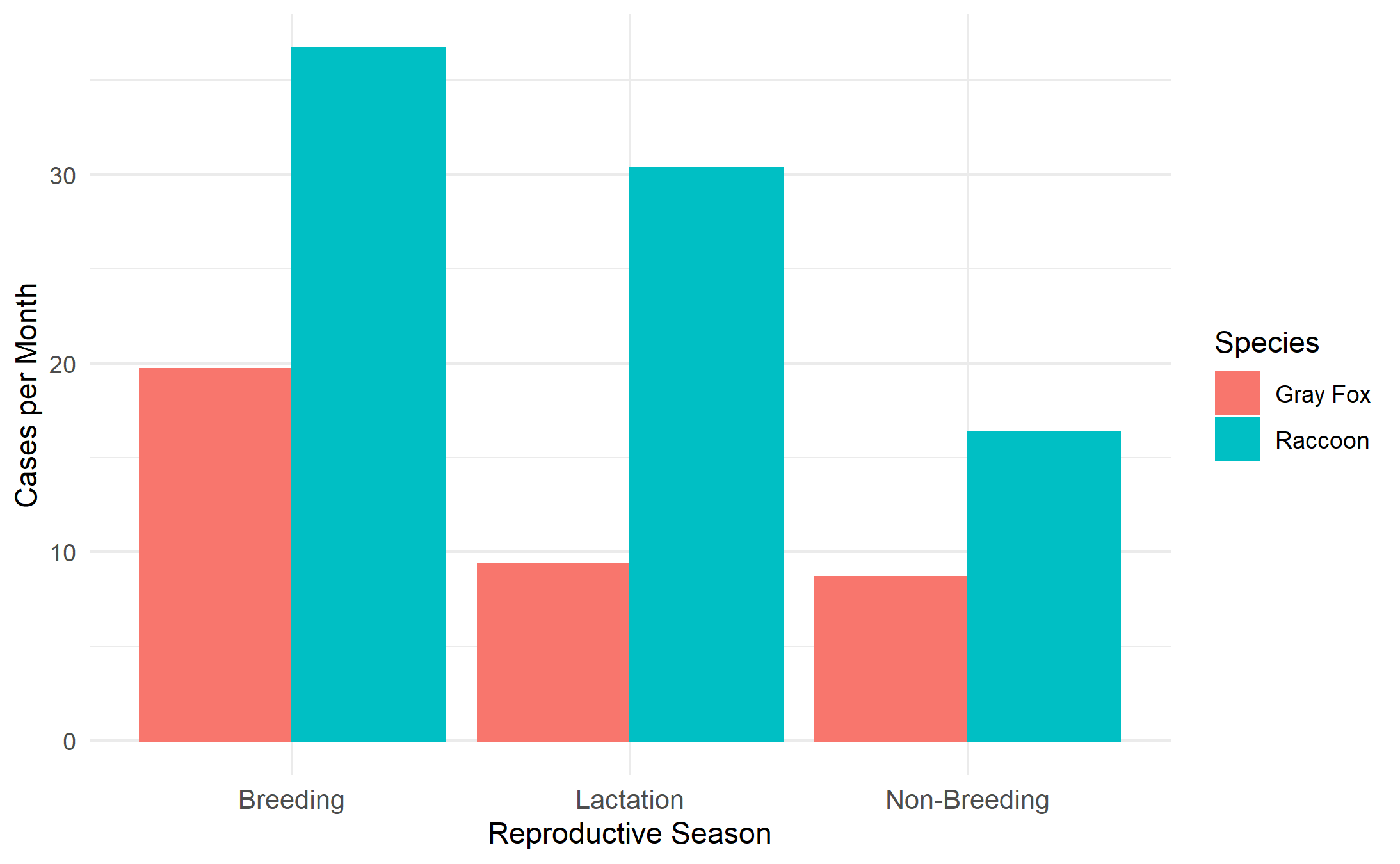


Figure 4: **FTotal number of raccoon and gray foxes diagnosed with canine distemper per month, from Georgia, in each part of the species reproductive cycle, submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

Chi-square test revealed a significant association between breeding season and number of distemper cases in both raccoons (χ2=21.20, p=2.49e-05) and gray foxes (χ2=11.46, p=0.003) in Georgia. Generalized linear models for raccoon and gray foxes, using number of cases as the dependent variable and stage of reproductive cycle as the independent variable, revealed a significant negative association between lactation or non-breeding season and the number of distemper cases reported in both species.

### Spatial Analysis

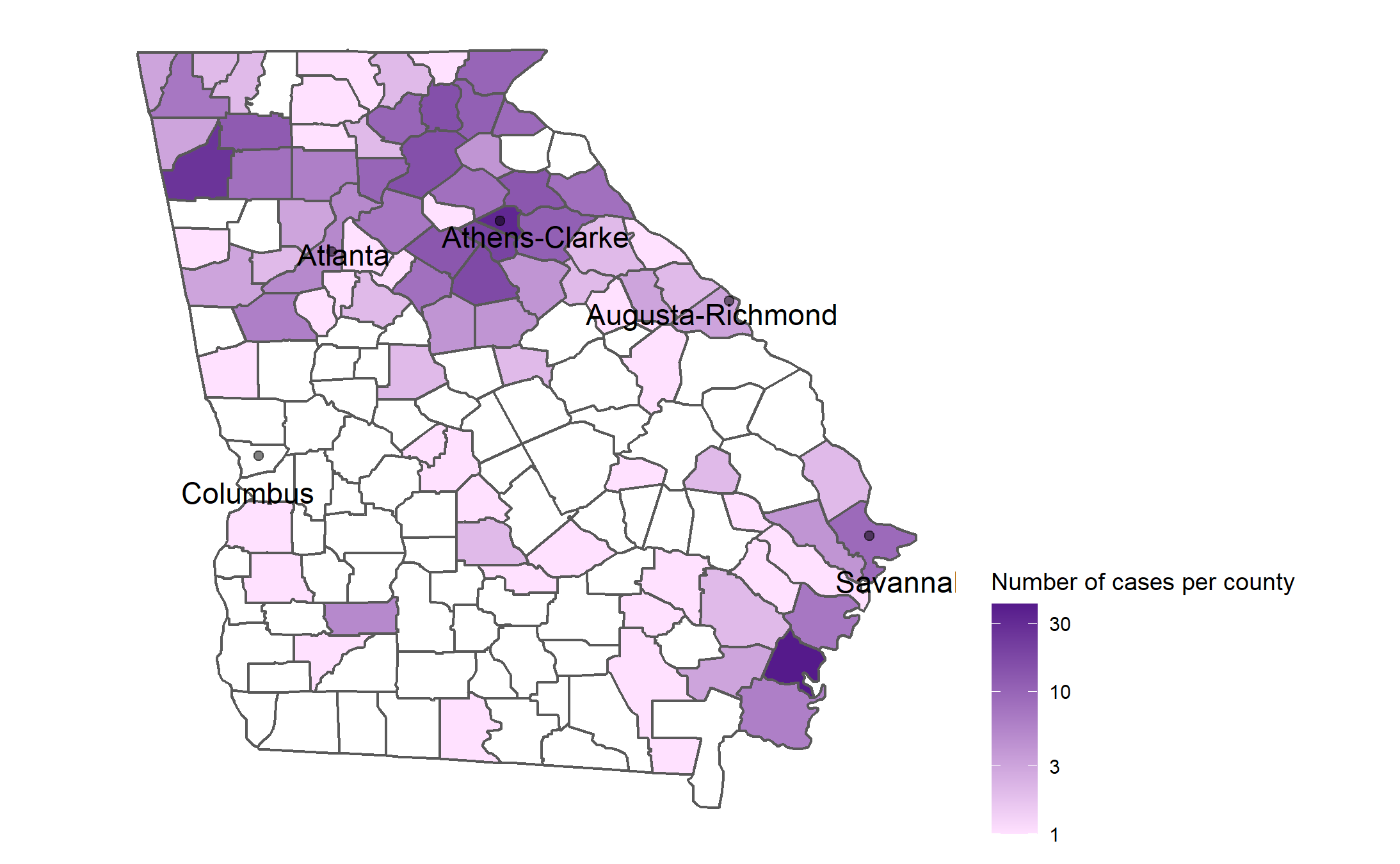


Figure 5: **Total number of raccoons and gray foxes diagnosed with canine distemper per county in Georgia, that were submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

The general pattern over the entire study period tended to be with most cases occurring in counties in the northern part of the state around the population centers of Atlanta, Athens and Augusta, Georgia. Additionally, there is a second area with high case numbers in the southeastern part of the state, around Savannah and Brunswick. Ripley’s K analysis of CDV cases in Raccoons and Gray Foxes in Georgia showed that these cases are significantly clustered. This pattern is shown again in the presence data by year (**Figure 5**) with cases occurring near these population centers, particularly in the 1980s. The northern part of the state has a cluster of cases involving many counties during the 1980s and early 1990s, with a smaller number of counties involved in the southeast.

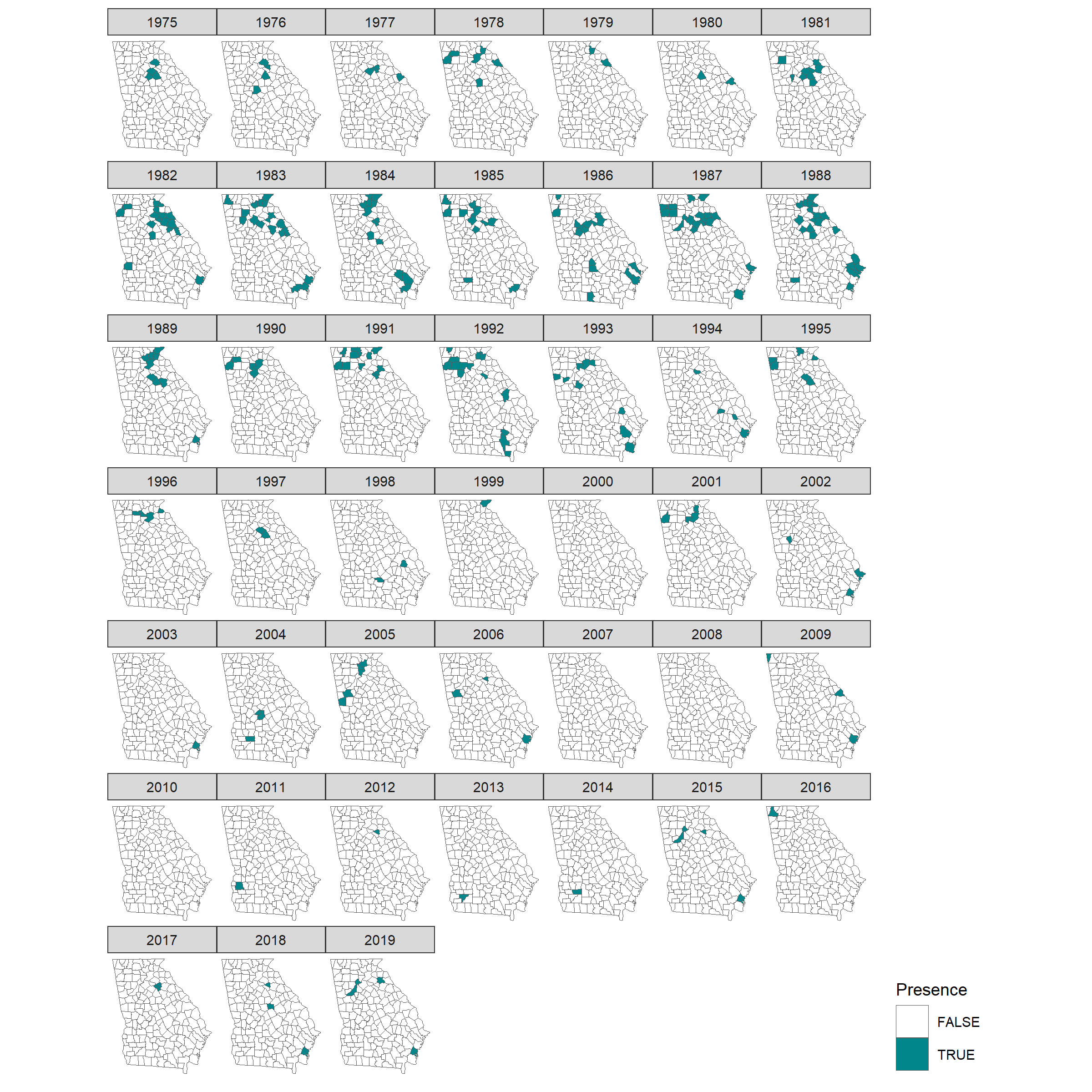


Figure 6: **Presence of raccoons or gray foxes diagnosed with canine distemper per county in Georgia per year that were submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

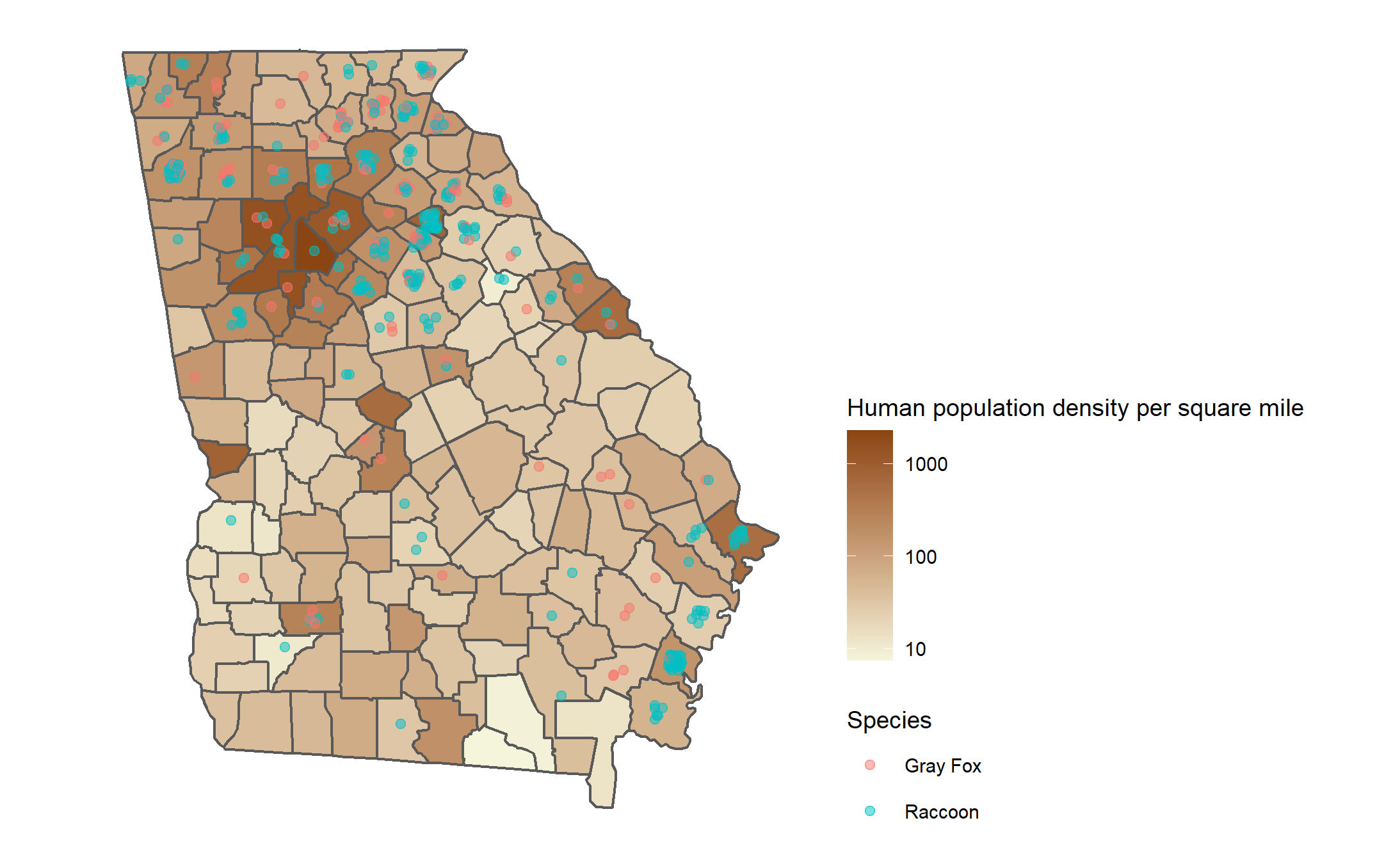


Figure 7: **The average human population density per square mile for each county in Georgia from 1975-2019 and the raccoons and gray foxes diagnosed with canine distemper, plotted as a county centroid coordinate, submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.**

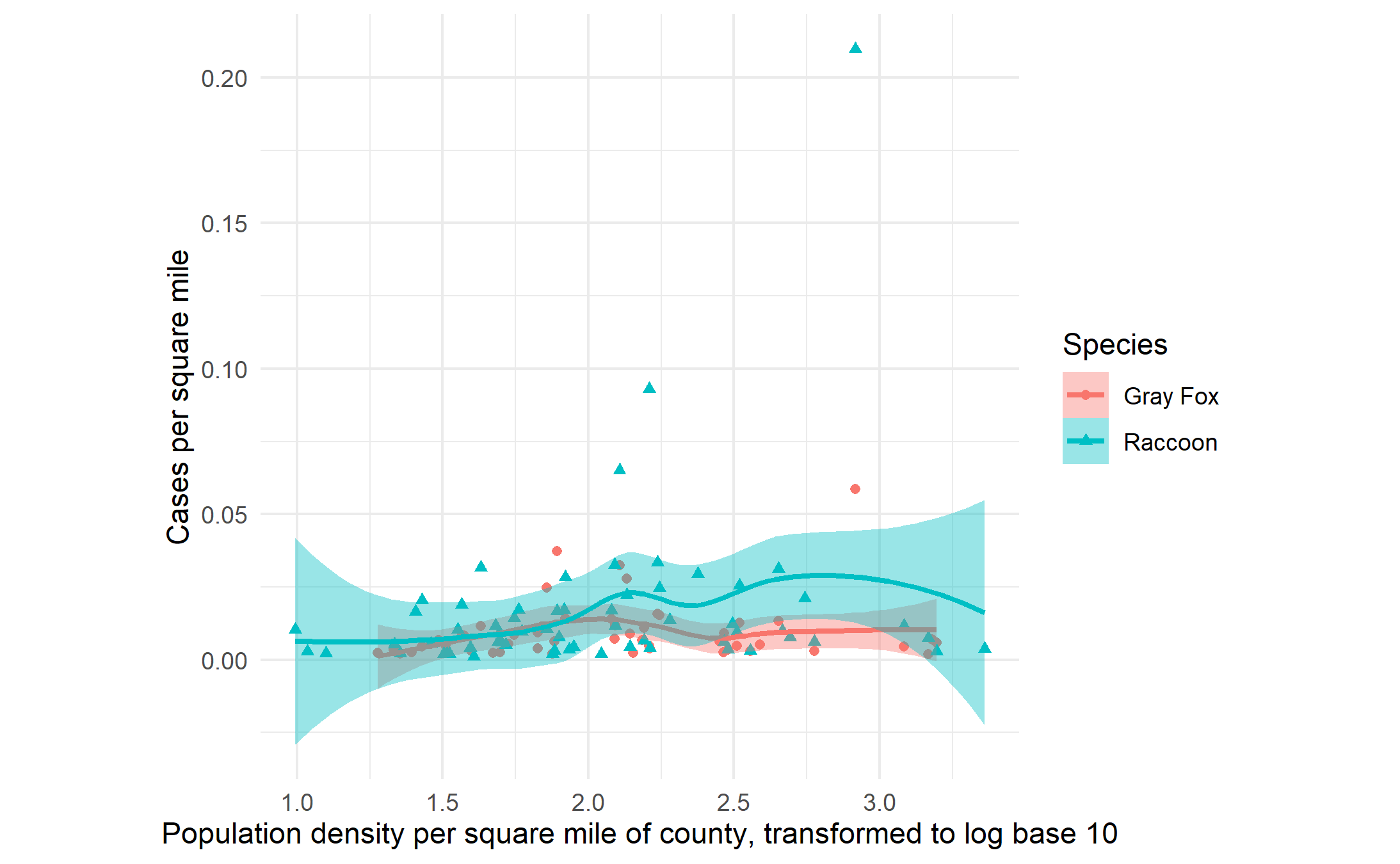


Figure 8: **Number of raccoons and gray foxes diagnosed with canine distemper per square mile of each county, which submitted cases to the Southeastern Cooperative Wildlife Disease Study, 1975-2019, plotted against average human population density per square mile in the county from 1975 to 2019.**

The data indicate increased frequency of submitted distemper cases in the medium to medium-high human population density counties, with fewer cases diagnosed in very high and very low human density counties. This relationship is more noticeable for raccoons than gray fox (**Figures 6 and 7**).

### Predictive Model development

The most accurate model for predicting the number of gray fox cases used the previous two months gray fox case numbers, the previous month’s predictive error, and the current month’s raccoon cases. Predictors were considered significant if the coefficient was more than two standard errors from zero.

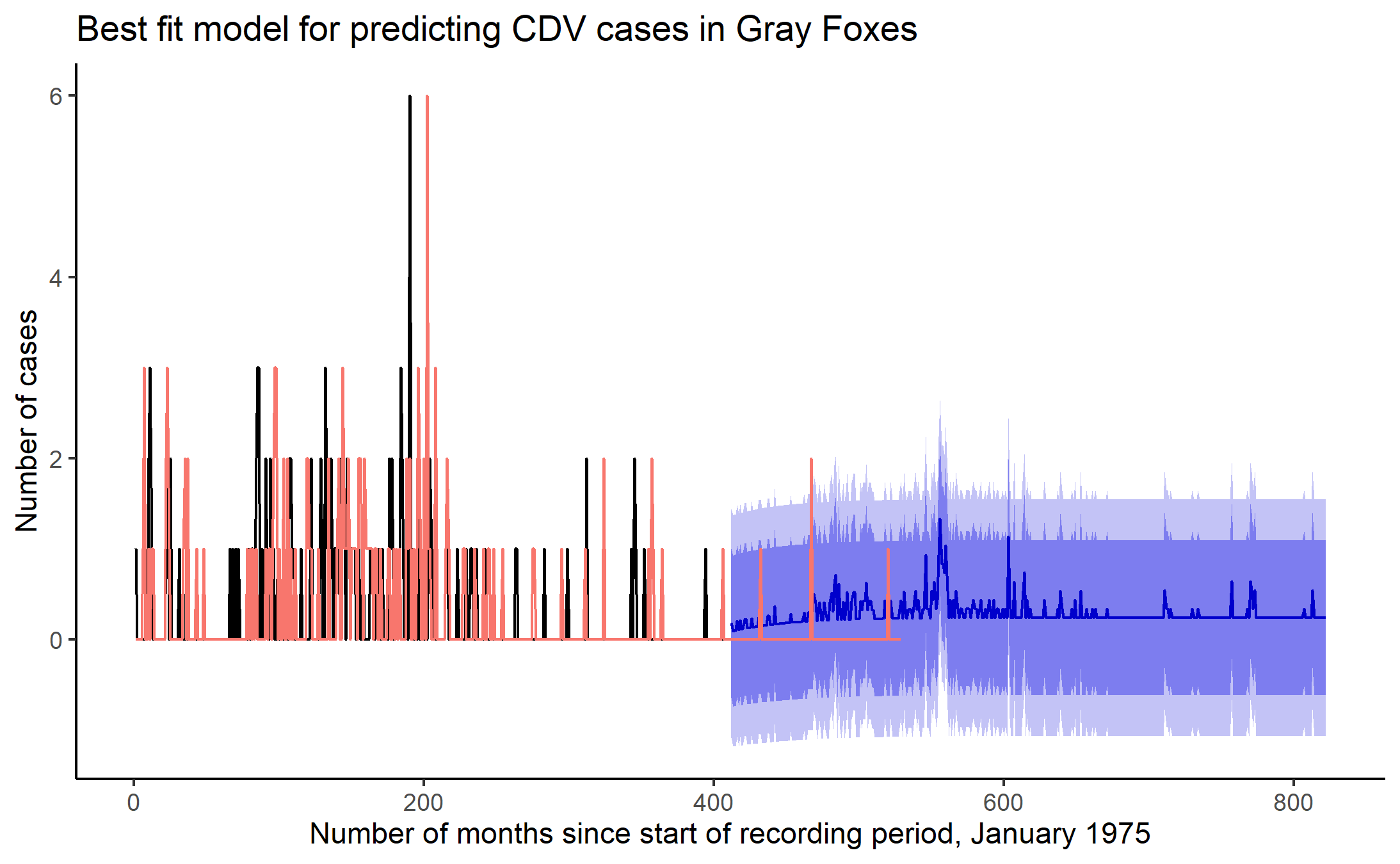


Figure 9: **Best fit auto regressive integrated moving average model for predicting canine distemper cases in gray foxes in Georgia, using the numbers of raccoons and gray foxes diagnosed with canine distemper per month, which were submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.** *The case data for gray foxes are shown by the red line, with the model prediction for the training period in black and the predictions for the test period and beyond in blue, with 80% and 95% prediction intervals.*

In the best performing model, differencing was not a useful predictor. As model error was useful in prediction, this means that if there was a significant change in the number of cases in the previous month, then that is likely to be followed by another significant change. In addition to the base model, the number of cases of raccoons in the current and previous months were used as predictors. The strongest model for predicting raccoon cases used the previous month’s raccoon cases and predictive error in addition to the number of gray fox cases in the current and previous two months.

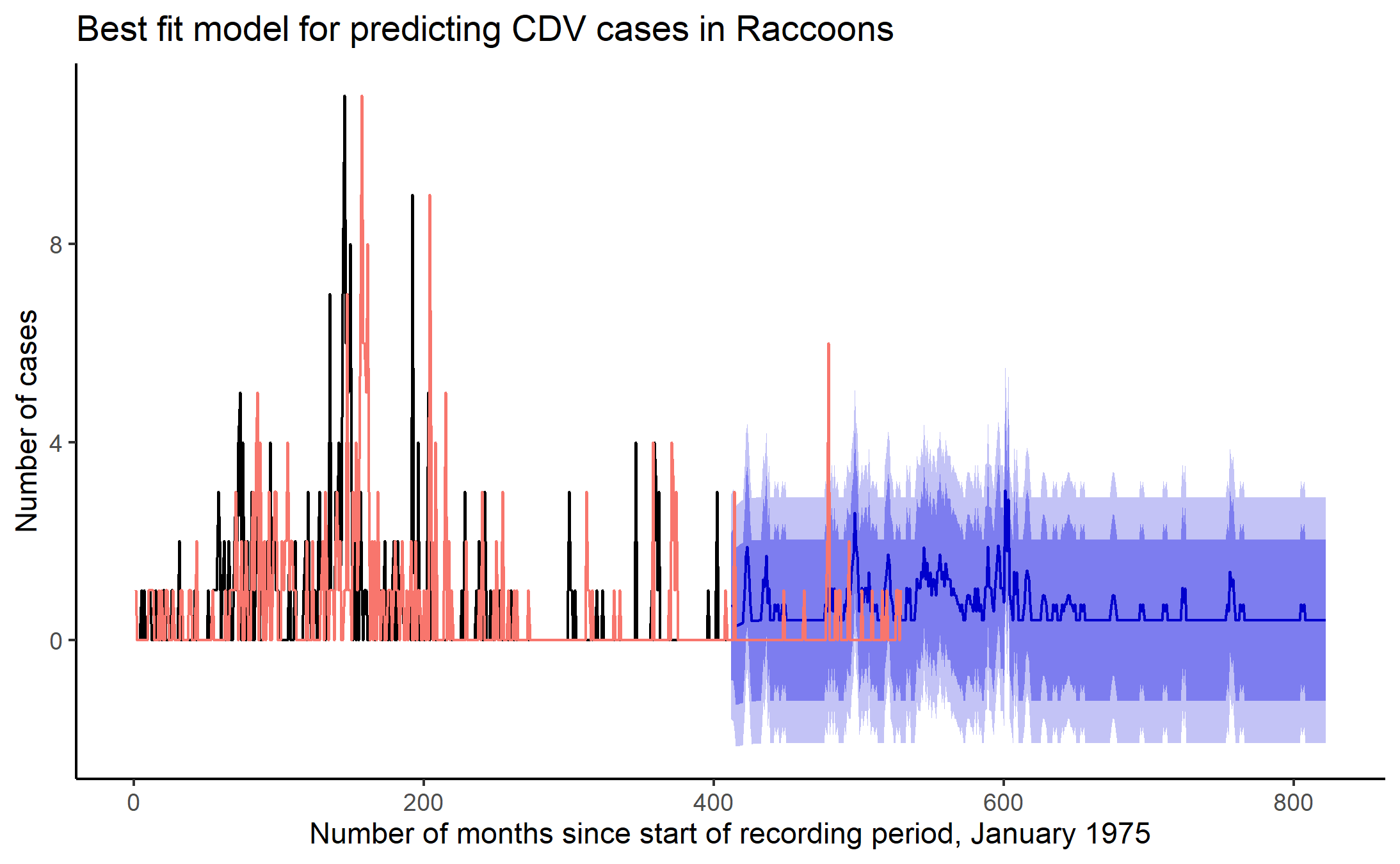


Figure 10: **Figure 9: Best fit auto regressive integrated moving average model for predicting canine distemper cases in raccoons in Georgia, using the numbers of raccoons and gray foxes diagnosed with canine distemper per month, which were submitted to the Southeastern Cooperative Wildlife Disease Study, 1975-2019.** *The original data for raccoon cases is shown by the red line, with the model prediction for the training period in black and the predictions for the test period and beyond in blue, with 80% and 95% prediction intervals.*

The gray fox predictive model is the most accurate model with an RMSE of 0.2669 for the test data, meaning it more accurately predicted gray fox distemper cases from these data. The raccoon prediction had a higher RMSE (0.7290).

## Discussion

A 45-year necropsy data set of wild carnivores diagnosed with distemper at SCWDS was analyzed for spatial and temporal trends. This included 17 states and 9 species, which were primarily concentrated in the southeastern US. Distemper cases in different species tended to spatially cluster. Further analysis was carried out on raccoon and gray fox data from Georgia. Ripley’s K analysis showed significant clustering of cases and there appeared to be an association between human population density and number of cases in raccoons, with fewer cases occurring in counties with very low and very high human population densities. There was a significant temporal association with the breeding season of foxes and raccoons with higher numbers of cases diagnosed.

Georgia reported most cases among the 17 states with distemper cases, especially in the 1980s, probably in part due to the proximity to SCWDS. Interestingly, Louisiana submitted the most cases in the 2010s, but whether this is due to an actual increase in CDV epizootics or other factors related to detection or reporting is unknown.

Spatial analysis showed significant clustering of distemper cases, which likely reflects the ecology of the virus which generally requires dense populations of susceptible hosts to facilitate viral spread, leading or contributing to epizootics (ES., 2001). The primary mode of CDV infection is aerosol inhalation, suggesting habitat overlap and contact is important in transmission (Hoff, Bigler, Proctor, & Stallings, 1974). The immunizing nature of this disease is useful for spatial and temporal analysis, as cases in the same area a number of years later are likely to be due to anew outbreak that has spread back into the area after an increase in the susceptible population to above the threshold required for an outbreak. Disease presence can be used for analysis in this scenario, as one can assume that a case corresponds to an outbreak.

There may be a parabolic relationship between human population density and the number of distemper cases in raccoons, with very high and very low population densities experiencing lower numbers of cases. This may be due to suburban areas being a hotspot for disease circulation with these areas being attractive to raccoons and gray foxes due to the available habitat and easy scavenging opportunities. Raccoons can maintain higher density populations within urban and suburban environments (Prange, Gehrt, & Wiggers, 2003). A similar pattern was seen in a studies in Germany of red foxes with prevalence of CDV higher in suburban and urban foxes compared to their rural counterparts, but with CDV risk being reduced in highly urbanized areas in Berlin (Frölich et al., 2000; Gras et al., 2018). This is of particular relevance as the disease is suggested to spillback from raccoons into domestic dogs (Kapil & Yeary, 2011). There appeared to be a much greater number of distemper cases in the northern part of Georgia. There are numerous possible reasons for this. Reporting biases may have played a role. For example, the northern part of the state is more densely populated by humans, is in closer proximity to SCWDS and thus more convenient to deliver carcasses and may have more suitable habitat and thus more robust populations of raccoons and gray foxes. In addition, results in detection of distemper cases in our study are skewed towards those that involved obvious illness or death of wildlife. For example, in one study, gray foxes and raccoons in Tennessee (Nov. 2013 – Aug. 2014) were known to be frequently infected, but passive surveillance only captured those with clinical signs. This failed to account for subclinically infected animals, with 55% of subclinically infected animals testing positive by real-time RT-PCR assay (Pope, Miller, Riley, Anis, & Wilkes, 2016).The data suggest a correlation between breeding season and the number of distemper cases diagnosed in raccoons and gray foxes, with cases more likely to occur during the breeding season.. This could be due to a number of reasons. There may be more contact between individual animals as they search for mates, thereby promoting aerosol spread of virus. Contact structure of a raccoon population can significantly impact disease transmission with raccoon contact networks changing depending on the season. For example, rabies virus infection can spread quickly among raccoons when the virus is introduced during the breeding season (Reynolds, Hirsch, Gehrt, & Craft, 2015). In addition, the physiological stress of reproduction may leave animals more susceptible to the virus or, as the cases in this study were from animals found moribund or dead, it could be that the increased movement during the breeding season leads to higher mortality rates from a variety of causes, such as vehicular collision, for which CDV may have contributed, but was not the primary cause of death.

The ARIMA model for predicting monthly distemper cases in gray foxes could accurately predict this using the numbers of distemper cases in gray foxes from the previous two months and in raccoons from the current month, suggesting that there may be an association between cases in the two species.. Initial introduction of CDV into wild carnivores in the US in the 1960’s, was through gray foxes with subsequent spread to raccoons (Hoff et al., 1974). Similarly, a distemper outbreak in raccoons in Berlin, Germany appears to have originated in foxes, with transmission seeming to readily occur between the species (**???**).

The raccoon prediction model was also accurate in predicting raccoon distemper cases, albeit with a higher error than the gray fox prediction model. This suggests a possible association between gray fox cases in previous months and raccoon cases in the current month. However, as the data for the time series analysis and ARIMA model building are pooled for the whole state, it is possible that the cases contributing to the overall number per month could be separated by hundreds of miles and thus the cases may not be related to each other. There are also limitations to the robustness of the data in concurrently analyzing spatial and temporal trends. While this is a rare long-term data set, there are limitations to using such a large area (i.e. statewide across Georgia) to generate meaningful conclusions about temporal trends.

In both predictive models, the test data, which uses the more recent data to test the accuracy of the model, had a lower error than the model training data. This can be explained by the variability of the case submission data over time. For example, the year to year variation in distemper case numbers among raccoons and gray foxes in Georgia is higher prior to 1996. The training data ran from April 1975-July 2011, and so the model had to cope with more variability in case numbers than for the test data (August 2011-December 2019), which likely reduced accuracy of the output. The higher RMSE in the raccoon prediction model may be explained by the larger degree of variability in raccoon case numbers throughout the study.

## Conclusions

Results from this analysis suggest that CDV is widely spread with 9 different carnivore species represented from 17 states, with raccoon and gray foxes the most common species reported. The other species were generally reported in the same or adjacent counties to those with raccoon or gray fox cases. Cases are mostly reported in southeastern US states and within the most represented state, Georgia, there appears to be temporal and spatial patterns of CDV cases in raccoons and gray foxes. Our results also suggested that numbers of gray fox cases can be predicted using data on past cases in foxes and raccoons. Among wild carnivore species, raccoons are easy to capture and sample, and thus may serve as a useful predictor for other, less tractable species. There appears to be temporal trends in cases in both species, with cases more likely to occur during the breeding season. Spatially there tends to be clustering of cases of both species within the same areas, with cases with fewer cases in very densely and sparsely populated areas. Ultimately, there are enough potential relationships suggested from this passively collected data which would support a worthwhile study, with comprehensive sampling of wild carnivores over time and space to try to elucidate spillover trends between species, particularly in suburban areas. This could inform decision making regarding vaccination and other strategies aimed at reducing transmission among both domestic and wild animals.

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