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Investigating Individual and Population Determinants of Rabies Exposure in Georgia Using a Comprehensive Bite Surveillance System

By

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Epidemiology

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By

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University of Maryland Baltimore County
2014

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Abstract

Investigating Individual and Population Determinants of Rabies Exposure in Georgia Using a Comprehensive Bite Surveillance System
By Trevor Hsu

Georgia's Animal Bites Module (ABM) is part of the Georgia Department of Public Health's State Electronic Notifiable Disease Surveillance System (SendSS) and is one of the most extensive animal bite reporting systems in the U.S [7]. Georgia's surveillance system is novel and arguably only 2 other states capture data on animal bites and rabies at a level similar to Georgia. This system was used in our study to help identify local-scale human population dynamics that affect the incidence animal bites. The local scale of our model is represented at the county level. This study was conducted to examine the extent that human population density and metropolitan versus non-metropolitan environment, and human characteristics such as race, gender, and age, affect the likelihood of being bitten as well as an individual's likelihood of specifically being bitten by animals that pose a 'high risk' of transmission. This study uses multilevel multivariable modeling to examine the how human population density and metropolitan environment affects the likelihood of individuals being bitten by animals and infected with rabies. Two statistical models were constructed using bite records. One examines potential factors that affect the risk of all animal bites in Georgia white the other examines potential factors that affect the risk of bites from animal species with a high known risk of rabies transmission based on cited literature. These models may provide useful insight for public health agencies to direct education and training efforts for rabies prevention and surveillance in the Southeastern United States.

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Epidemiology

Rabies, a disease that is nearly always fatal, contributes to more deaths worldwide than any other viral zoonotic disease [1]. Surveillance and monitoring of disease outbreak and human exposure is critical for prevention and control of rabies [2]. While annual rabies deaths in the United States have declined from over 100 cases per year at the turn of the 20th century to an average of 1-2 cases per year in the past decade, rabies still poses serious public health risk [3]. A comprehensive understanding of the full epidemiology of rabies is necessary to determine which preventive measures should be taken by federal, state, and local health departments to prevent rabies transmission.

Rabies is present on all continents, except Antarctica and Australia [4]. Though there are few documented cases of human rabies infection in the United States, rabies ranks roughly 11th for all infectious disease as a cause of deaths worldwide [4]. According to the World Health Organization, approximately 50,000-55,000 human deaths worldwide are attributable to rabies [2] [5] and approximately 95% of rabies cases occur in Asia or Africa [6]. Stray and domesticated dogs, particularly in developing countries, are still the most commonly documented species of animal responsible for human rabies infection; roughly 99% of rabies deaths in humans can be attributed to dog bites [5] [2].

Rabies contributes to approximately 30,000 deaths per year in Asia. The highest rate reported is in India, where over two-thirds of Asian rabies-attributable deaths occur [2] [5] [6]. Some estimates suggest there are as many as 30,000 annual cases of rabies in India alone, where there are approximately 15 million people bitten each year by

rapid animals [2]. Nepal and Sri Lanka also have high per capita rates of human rabies infections, with over 90% caused by unvaccinated dog bites [2]. Additionally, Bangladesh and Pakistan have high rates of rabies and dog bites for the continent [2]. Approximately 24,000 deaths in Africa occur as a result of rabies each year, and southern African countries are disproportionately affected [2]. Following Asia, most deaths from rabies occur in Africa, Latin America and Oceania [5].

While terrestrial rabies still exists in wildlife in the United States and Europe, there are very few human cases of rabies in these countries due to improved public health policy and vaccination efforts [2]. Primarily as a result of successful vaccination efforts, canine rabies has been eliminated in the United States and several other developed counties [6]. Vaccination campaigns have proven quite effective in decreasing the transmission rates of rabies from dogs to humans in the United States and Western Europe yet rabies still poses a public health threat worldwide.

Virology

Rabies is an enzootic disease caused by infection from a species of *Lyssavirus* genus under the *Rhabdoviridae* family, which attacks the host's nervous system. It is transmitted between mammals, including humans [5] [2]. The virus is bullet-shaped and contains a core with Ribonucleic acid (RNA), nucleocapsid protein, phosphoprotein and viral transcriptase [8].

Transmission

A prominent, and sometimes early, symptom of rabies, particularly in carnivorous mammalian species is the tendency to bite, which often results in transmission amongst these species [9]. Although theoretically rabies can be

transmitted through non-bite animal exposure and human to human transmission, inoculation almost always occurs through the bite of a diseased host [2]. In these instances, the virus is transmitted through the animal's saliva [9] [2]. Hosts of rabies tend to only transmit the virus when symptomatic, though transmission is possible as many as eight days earlier [9]. In 1969, researchers investigated a rabies epizootic that occurred on an island off the coast of Georgia. Researchers trapped and tested raccoons for rabies, and found that approximately 10% of the raccoons in the sample tested positive for rabies. The virus was present in their salivary glands yet these rabid animals were asymptomatic in behavior [10].

Despite rabid mammal bites being the most common catalyst of infection, there are other modes of transmission. Although very rare, another form of rabies transmission is aerosol transmission, which is unique to bats. Human to human transmission of rabies has been reported through solid organ transplantation, particularly corneal transplants; however, few documented instances have occurred [5]. While it is biologically possible for human to human transmission of rabies to occur through bites, no documented example of transmission has transpired.

Symptoms

The rabies virus replicates and travels from the site of exposure (i.e., the bite) to striated and connective tissue. It then enters the peripheral nervous system and spreads to the central nervous system, where it eventually manifests in the brain [2]. There are three clinical stages of rabies: (1) prodromal, (2) excitement, and (3) paralytic [2].

The incubation period for the disease is generally one to three months in most mammals but can range from a few weeks to over six months depending on species and

circumstance [9]. The incubation period for rabies in humans is typically from 20-30 days but can be as short as 5-6 days and as long as 6-9 months [5].

Curiously, no antibody response is generated from the immune system during the incubation period [8]. Initial symptoms of rabies may be vague, including pain, pruritus, fever, headache, anorexia and general malaise, and paresthesia at the exposure site due to viral replication. Symptoms may later progress to include anxiety, hallucination, hydrophobia, aerophobia, hyper-excitability, hyperventilation, hyper-salivation, autonomic dysfunction and viral encephalitis, which often results in paralysis, coma, cardio-respiratory failure, and death [2] [5] [8]. It is estimated that about 20% of human cases of rabies result in flaccid paralysis [4].

Active cases of rabies, where symptoms are present, are almost always fatal in humans, with cases resulting in death between two to ten days after the onset of illness, and most cases resulting in death five to six days after symptoms are manifest [9]. Essentially, once the rabies infection is past the incubation period and an infected human is symptomatic, death is eminent. There have only been 8 documented cases of rabies with victims surviving the infection without receiving vaccination prior to the onset of symptoms, and many of these cases are not well documented [11]. Damage to the brain is generally minor; most patients die from symptoms resulting from neuronal dysfunction, rather than neuronal tissue damage itself [8].

Due to the often vague prodromal and early neurological symptoms, as well as the variable presentation of the disease, rabies occasionally goes undiagnosed as the suspected agent until death, when laboratory tests confirm the presence of the disease [84-85]. Rabies should be considered as a potential diagnosis in the presence of any case

of encephalitis with the absence of coma, especially if the patient has a known history of an animal bite or neurological or psychological disturbances [8]. Rabies should also be more seriously considered in suspected cases of Guillain-Barré syndrome and poliomyelitis [8].

Diagnosis

Laboratory-confirmed diagnosis of an infected animal is conducted post-mortem by testing tissue from at least two parts of the brain, primarily the cerebellum and brainstem [2]. Using these tissue samples, a number of laboratory tests for the presence of the rabies virus can be conducted, including Direct Fluorescent Antibody Technique (DFA), Mouse Inoculation Technique (MIT), Tissue Culture Infection Technique (TCIT), or Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) [2]. While the presence of antibodies in the cerebrospinal fluid is useful in diagnosing the presence of rabies in humans and animals, the presence of the rabies virus in both humans and infected animals can only be confirmed by laboratory tests on tissue samples from the cranium, since it is possible that prior vaccination of a patient may result in positive antibodies [2] [8]. The gold standard for laboratory testing is fluorescent antibody testing, as antibody testing of the brain is highly sensitive and specific [5] [8].

Vaccines and Treatment

Rabies immunization vaccines have existed for over a century [2]. White nerve tissue vaccines were first introduced in the late 1800s; cell cultured vaccines have been used since 1967 and include both inactivated diploid cells of the Pitman-Moore L503 strain and the Wistar strain. Side effects of the rabies vaccines may include redness and soreness at the site of injection, and more rarely, headache, fever or muscular soreness.

Those professionals who are considered at high risk of coming in contact with rabies, such as veterinarians, laboratory workers, animal control workers, speleologists, or individuals whose jobs require them to come in contact with wild animals or unvaccinated domestic animals are recommended to receive pre-exposure prophylaxis [2]. Three types of vaccines are used in the United States: (1) HDCV, (2) purified chick embryo cell culture, and (3) feral rhesus cell culture. The most common rabies vaccine commercially available in the U.S. is IMOVAX, followed by RabAvert [5].

Individuals bitten by an animal suspected of carrying the rabies virus should seek medical attention immediately [8]. Efforts to prevent rabies after known exposure have become nearly 100% successful, if post-exposure prophylaxis is administered soon after exposure and prior to the appearance of symptoms [8]. Following exposure to the rabies virus through an infectious animal bite, the wound should be thoroughly washed with soap and water, followed by iodine or ethanol application in order to remove free rabies virus from the victim's tissue [2] [5] [5]. Rabies can be prevented following immediate exposure to the virus by administering post-exposure prophylaxis, which includes an injection of rabies immune globulin at the bite wound, in addition to a regimen of rabies vaccines [2]. Generally, five doses of rabies vaccine are administered to exposed individuals within a period 28 days following the exposure incidence. Immune globulin and rabies vaccinations should be administered no more than 7 days apart from each other [5]. Rabies immune globulin contains antibodies that help to prevent viral progression through the infected patient's nervous system. In the U.S., only human immune globulin is used; however, equine immune globulin may be used in other countries with equal success in preventing the progression of the disease. [8]. Tens of

thousands of potentially exposed individuals receive post-exposure prophylaxis in the U.S. each year [12]. Human rabies is preventable with proper wound care and timely, appropriate administration of human rabies immune globulin and the rabies vaccine series before onset of clinical symptoms. Post-exposure prophylaxis is recommended for all persons who have been bitten or scratched by an animal suspected to have the rabies virus and for all persons whose mucous membranes have been exposed to the virus.

Treatment of clinically present rabies (i.e., when a patient is symptomatic and clinical signs are manifest) is seldom effective, with nearly all cases resulting in death. No antiviral or immunomodulation drugs have been found effective; thus, care is usually limited to supportive, palliative measures [5]. The indications for post-exposure prophylaxis among health-care workers who care for patients with rabies include exposure of mucous membranes or open wounds to infectious body fluids or tissue (e.g., saliva, tears, cerebrospinal fluid, or neurologic tissue) from the patient. Adherence to standard infection-control precautions minimizes the risk for health-care workers' exposure to rabies [5] [9].

Rabies post-exposure prophylaxis can be costly and include adverse clinical reactions [12]. It is often considered over-utilized in the U.S. [12]. While national estimates of post-exposure prophylaxis use have been limited, there have been calls from the Public Health community for significant reduction in the use of post-exposure prophylaxis [12]. The increased incidence of rabies in raccoons of densely populated areas of the Southeast and Mid-Atlantic may be a partial reason for significant increased use of post-exposure prophylaxis in this region since the 1980s; however, it has been suggested that human population density and post-exposure prophylaxis are not

strongly correlated [12]. Cost for a five-dose treatment of post-exposure prophylaxis and immunoglobulin exceeds $1,000 [13].

The possibility of post-exposure prophylaxis use following an animal bite should be assessed based on the potential risk of rabies infection. Physicians and healthcare providers should consider if there is high suspicion that the biting animal has rabies based on its behavior and clinical signs [8]. Animal domestication, as well as history of vaccination, should also be acknowledged when evaluating the likelihood that a biting animal has rabies [8]. In the event that a person has been bitten by a wild animal with a high likelihood of transmitting rabies, such as a large carnivorous terrestrial mammal or a bat, laboratory testing for rabies by sampling the cranial tissue of the suspect animal should be performed. This is especially important if the animal has been captured or killed, particularly amongst species of animals most likely to have transmissible rabies, such as raccoons, skunks, foxes and bats [8]. If the biting animal is unavailable for testing, then veterinarians or public health experts should be consulted to determine if the species of biting animal poses a high risk of rabies contraction in the given geographic location [8].

Prevention and Control

In the United States and Europe, rabies in humans is well-controlled due to successful surveillance and control measures [2]. Since the 1980s, there has been a dramatic reduction in documented human rabies cases. This can be attributed in no small part due to an elimination strategy that began in 1983, which included vaccinating 44 million dogs and providing medical care to hundreds of thousands of people [5]. For control of rabies in the domestic animal population, the Centers for Disease Control and

Prevention and veterinarians recommend that pet owners on keep rabies vaccinations up-to-date for all cats, ferrets, and dogs; and owners keep cats and ferrets indoors and dogs under direct supervision. It is also recommended that stray animals be removed from neighborhoods by Animal Control agents as these animals may be unvaccinated and could potentially be ill. Monitoring and control of rabies in wildlife populations is primarily the task of public health, agricultural and wildlife agencies at the local to federal levels [14] [15].

Severely affected countries in Asia and Africa either fail to prioritize rabies as a disease of significant public health impact, lack sufficient surveillance systems, or require the resources to control rabies such as pre- and post-exposure prophylaxis [2]. Most human and domesticated animal cases of rabies can be prevented through avoiding contact with wild animals, vaccine programs, and education. Other useful tools for the prevention of rabies contact in human populations include animal habitat modification, wildlife vaccination programs, and population control efforts for vector populations [15].

Domestic Rabies

Rabies is an enzootic disease and can be found in wildlife all throughout the United States, with the notable exception of Hawaii [8]. Approximately 7,000 to 9,000 cases of rabies-positive animals in the U.S. are confirmed each year [16] with over 90% of these cases occurring in wildlife populations and the remainder occurring in domesticated animals [5] [12][16-19]. In the United States, rabies transmission amongst humans has significantly declined through the past century, particularly cases caused by domestic dogs and cats. Recent studies have even suggested that domestic dog rabies is

no longer enzootic in the United States [7]; the significant reduction in the prevalence of rabies in domestic dogs and cats is primarily attributed to the successful use of prophylactic vaccines [8]. Vaccination campaigns for domestic animals have led to an increase in the proportion of cases caused by wild animals [5]. Human rabies incidence closely reflects the prevalence of rabies in animals and with the decline in canine rabies in the developed world, rabies caused by wildlife, including bats, has made up a larger portion of all human cases [8].

Most cases of domestic U.S. human rabies infection in recent decades have undocumented animal exposure but are generally attributed to infection through 'cryptic', or unidentified, bat bites [5]. In these cases, a documented incident of bite exposure is never reported as the individual is unaware that he/she has been bitten by a rapid bat, but later antigenic testing reveals that the strain of rabies present in the human host is unique to bats. Although most domestic U.S. cases of rabies in humans are attributable to bats, the majority of confirmed cases of rabies transmission in animals are found in carnivorous mammals such as raccoons, skunks, and foxes [8]. This may be a result of trapping bias as many agencies which test for the rabies virus in wild animals are sent more terrestrial mammals than bats to test.

Bats

Bats are capable of carrying all species of lyssaviruses, and it is hypothesized that the rabies virus may have originated in bat species [8]. The most notable species of bats that contribute to the spread of rabies in the U.S. are the Silver-Haired (*Lasionycteris noctivagans)* and Eastern Pipistrelle bat (*Pipistrellus subflavus)* [8]. In fact, approximately 75% or unidentified rabies deaths and 70% of all human rabies cases in

the U.S. are attributed to virus variants associated with these two species of bats [17]. A significant number of human rabies attributable to bats may be unidentified because bites from the teeth of small bats may not be easily noticed or seen without careful examination, and therefore may go undetected [17]. Moreover, research suggests that rabies virus variants associated with *L. noctigagans* and *P. subflavus* may be more infectious through superficial exposure than other rabies variants [18]. It is estimated that <1% of wild bats in the U.S. population are infected with rabies [18]; however, 30% of bats submitted to health departments for biting people and 50% of bats found in houses by wakening individuals were found to have had rabies. The prevalence of rabies in the wild bat population may also be underestimated as the Silver-Haired bat and Eastern Pipistrelles bat both make up a small portion of all bats submitted to health departments for testing, <5% each [18].

Rabies in humans tends to cluster in the Northwestern and Northcentral United States, with cases attributable to bats occurring primarily in the Northwest [18]. This may be partially due to the high population density of the Silver-Haired bat in these regions [18]. Furthermore, the Eastern Pipistrelle is widely distributed throughout the Eastern United States [18].

Not only is post-exposure prophylaxis always recommended for bat bites, but it is common practice for certain individuals who may have come in contact with bats; such individuals include children, the elderly and immunocompromised. In many states with a high burden or bat rabies it is suggested these populations be provided post-exposure prophylaxis, even if it is unknown whether the individual was bitten or not [8]. Likewise, individuals found in a room with a bat who cannot be certain that they were

not bitten, such as children, mentally disabled persons, intoxicated persons or people who were sleeping are recommended to receive post-exposure prophylaxis [8].

Southeastern Raccoon Strain and Georgia

Although annual rates of rabies fluctuate in wildlife, once rabies is introduced into an environment, it tends to persist as an enzootic disease. There are several species of terrestrial mammals that are responsible for the majority of rabies cases in wildlife in the United States. Natural mutations in the virus in animal populations results in distinct antigenic and genetic variants. Variants are often closely associated with a specific animal species in which the virus primarily circulates within that geographic location and are often classified by this predominant host species. Thus, in Georgia and the rest of the United States east of the Appalachian Mountains, the predominant strain of terrestrial rabies found in wildlife is the raccoon strain [12] [1]. The spread of the raccoon variant of the virus thought eastern North America is the largest U.S. wildlife zoonotic on record [14].

Since the 1990s, raccoons have been the animal most reported to health departments for having rabies in the U.S., with most of these reports coming from the Mid-Atlantic and Northeast [19]. Currently, an estimated 50% of all reported wildlife cases of rabies occur in raccoons [20]. Rabies has been endemic in the wild raccoon population of the Southeast since the 1950s, with the incidence of rabies in raccoons increasing in Florida from 1950-1970 and spreading to Georgia, Alabama, South Carolina, and parts of North Carolina [21]. In the 1960s, a particularly notable epizootic of rabies spread northwards from Florida to Georgia [22].

In recent decades, a major concern amongst rabies researchers in the U.S. has been the growth and spread of raccoon rabies from the Southeast to mid-Atlantic and Northeastern states [8]. An epizootic of raccoon rabies is thought to have emerged in the 1970s, when the translocation of rabid raccoons from the Southeast to the mid-Atlantic resulted in a dramatic increase in the prevalence of the raccoon variant in the mid-Atlantic and Northeastern U.S. and some parts of Canada [1]. It is believed that this epizootic occurred when raccoons incubating the rabies virus were captured in Florida and introduced along the border of Virginia and West Virginia by humans [12] [1] [23]. The first reported case of rabies in raccoons in this region was reported in West Virginia in 1977 [20]. Cases continued to propagate outward at a rate of approximately 40-48 km per year [19][28-30], until the 1990s, where raccoon rabies had spread as far north as Southern Canada and North Carolina, converging with the historically enzootic Southeastern strain in 1994 [24]. Raccoon rabies now stretches from southwestern Alabama to southeastern Canada [20] [25].

Each antigenic variant of rabies, however, still possesses the ability to infect a variety of potential host species [1] and the geographic expansion of raccoon rabies in the Eastern U.S. has affected the rate of rabies in other terrestrial animals, as well. Research by Marta A. Guerra of the Division of Viral and Rickettsial Diseases at the CDC concluded that the epizootic spread of rabies in skunks in the Eastern U.S. mirrored that of raccoons. Moreover, the number of reported rabid raccoons can help predict the number of rabid skunks with a 1 month lag [23]. The epizootic of raccoon rabies is thought to have had an effect on lagomorphs and rodents, as well. There was a 62.3% increase in the number of rabid lagomorphs and rodents tested between 1995 and 2010,

compared to the number reported from 1979 to 1994. There was a large number of rabies cases in these species associated with the raccoon variant [26].

Interestingly, in the epizootic that occurred in the Eastern U.S. between the 1970s and 1990s, raccoon rabies spread slower in a southerly direction than in any other direction [27]. In a 2000 study, Andy Dobson from the Department of Ecology and Evolutionary Biology, Princeton University hypothesized that latitudinal differences in raccoon populations may have played a role in the slow southern spread of raccoon rabies by serving as a buffer, and called for future studies to examine how pathogen dynamics are affected by host species diversity [27]. In 2011, Duke-Sylverster et al., stressed the importance of seasonality in raccoon rabies by finding that the variability of timing of births in the southern raccoon population. Due to a longer breeding season, spatially synchronized epidemics resulted, as opposed to in Northern raccoon populations, where short pulses of births caused by succinct mating seasons contribute to irregular epidemics. The researchers also concluded that epidemics of rabies in raccoons in the South tend to be more spatially and temporally dispersed. These findings suggest that Southern states could reduce surveillance efforts relative to Northern states without minimizing the ability to detect potential epidemics [28].

Local habitat features may also play a significant role in the prevalence of rabies amongst the wild animal population, as well as disease exposure in humans [15]. Phenomenological algorithms for defining outbreaks and understanding periodicity of rabies outbreaks in raccoons have been conducted for several states, such as Virginia, Connecticut, and Maryland. Few studies unique to the Southeastern U.S. have identified environmental factors that affect rabies transmission patterns through time [1]. Despite

the expansion of raccoon rabies in the last quarter of the 20th century, there is only a single documented case of human rabies caused by the raccoon variant, which occurred in 2003 in Virginia [16]. The fact that only one case of rabies transmission from a raccoon has occurred in recent years is likely because raccoons are large animals; thus, individuals bitten by raccoons are more likely to seek immediate medical care. The increase in wild raccoon rabies throughout the Mid-Atlantic, however, has resulted in significantly more post-exposure treatments administered to humans [1]. In fact, prior to 1990, fewer than 100 persons per year, on average, received post-exposure prophylaxis in New York. Yet between 1990 and 1995, this figure increased roughly 20 fold [20]. While this increase in post-exposure prophylaxis treatments corresponds to the epizootic that existed in the region during that time, the extent to which post-exposure prophylaxis treatments increased is disproportionate to the actual increase in rabies cases experienced by New Yorkers. Additionally, Jenkins found in a 1982-1983 study on a rabies outbreak in the Mid-Atlantic states that nearly 50% of post-exposure treatments were administered to individuals with very low risk of exposure to rabies. While raccoons are still the most commonly reported species testing positive for rabies, since 2006 there has been a continuous decrease in the number of raccoon rabies cases reported each year [29].

Spatial Analysis of Rabies in the Environment

While the decline in documented rabies amongst domesticated animals in the United States is largely attributable to improved vaccination efforts, the steady rise in the percentage of rabies cases occurring in wildlife can be partially attributed to changes in human demographics, ecological alterations and human encroachment and

development [12]. Recognizing spatial, temporal, and environmental determinants of rabies transmission, particularly in primary reservoir species and other species with high rates of transmission to humans, is essential for effectively monitoring and preventing rabies transmission. Factors such as population density, land use, elevation, and the presence of roads, rivers and lakes tend to be associated with geographical clustering of rabies in certain regions [30].The ability to identify distinct variants of the rabies virus according to reservoir host species is a relatively recent breakthrough in epidemiological studies. With this, scientists and health professionals better understand which species are primarily responsible for transmitting rabies in an area [1]. Population dynamics of the dominant reservoir host is crucial in determining the spatial pattern of disease distribution [15]. According to an analysis of studies on red fox populations in Europe, incidence of rabies is often positively correlated to the population density of the primary reservoir species of that region [15]. The CDC's "Recommendations of a national working group on prevention and control in the United States" concluded that the role of reservoir host abundance and demography is poorly understood" [15].

Rabies is generally endemic in affected communities with the number of cases fluctuating in 'irregular' ways, although environment and seasonality strongly influence patterns of transmission and disease occurrence [9]. While the epizootic spread of rabies has been well defined for many mammalian hosts [1], very few models have been developed to characterize the population dynamics and spread of raccoon rabies in the United States [1]. Furthermore, it is reasonable to assume that environmental factors influencing the spread of rabies differ among predominant host species [23]. Case studies of environmental factors on rabies transmission conducted in areas where the

Southeastern Raccoon strain is not the predominant variant of the rabies virus may not be completely applicable to understanding the influence that environment and human encroachment has on the risk of animal rabies transmission to humans in Georgia and its neighboring states.

This section will attempt to discuss the current body of spatial and environmental research unique to raccoon rabies. Studies suggest that transmission rates of rabies vary depending on environmental factors such as vegetation type, population animal population density and major natural barriers [1]. Environmental risk factors and potential areas of disease occurrence have been identified using rabies mapping. One notable example was conducted in Chile in 2015, when public health investigators examined the ecological effect that vegetation had on bat-born rabies cases.

Reese et al., examined how landscape structure affects the spread of disease and antigenic drift of rabies [31]. Communities can sometimes be separated from a heavily rabies-infected area by natural barriers such as rivers and mountain ranges [20] [32]. In Connecticut, reported cases of rabies transmission were found to be 7 times lower in towns separated by a river [33]. Comparison of genetic variability among raccoons along the Niagara River and St. Lawrence River found that landscape configuration, specifically the peninsular shape of the Niagara basin that is bounded by Lake Ontario and Lake Erie, creates bottlenecking. This bottlenecking effect reduces the movement of raccoons and rabies in this area [31]. Genetic analysis of raccoons sampled along the Niagara River border reveals two distinct variants of rabies in raccoons on either side of the river [31]. Communities protected by an environmental barrier may find only a small number of cases but may be susceptible to sudden and severe epidemics if measures are

not affixed to protect against encroachment [9]. Communities are likewise susceptible to epizootics of rabies should these measures be insufficient. Reese et. al., also examined the effect of natural and artificial environmental barriers on the spread of rabies in raccoons and foxes in North America. The researchers found that high levels of vaccination were protective against rabies outbreaks; however, mild levels of vaccination could be counterproductive [34].

Within urban contexts, the relationship between rabies and micro-environmental conditions has been examined. A study that examined the number of raccoons captured or collected throughout Baltimore City, Maryland between 1984 and 1987 found fewer raccoons than expected in multi-unit residential and commercial-industrial-institutional areas while significantly more raccoons were found in single-unit residential areas [22]. Although there have been numerous studies on environmental factors that affect rabies transmission and how environment influences rabies transmission of the raccoon variant specifically, few studies on environment and the spread of rabies have been unique to the Southeastern United States. Specifically, it is generally agreed upon that agricultural activities, urbanization and human encroachment on wildlife increase the risk of exposure to animals infected with rabies. The majority of the studies investigating these relationships for areas where raccoons are the primary reservoir for rabies occurred in the Mid-Atlantic and Northeastern United States, and in Canada. These areas have been more recently affected by the spread of raccoon rabies.

Further research suggests that the relationship between artificial environments and animal species capable of transmitting rabies may be more complex than previously

believed [22]. Areas of moderate population and housing density may be more suitable for certain reservoir species, while areas of high commercial activity and population density may be no more habitable for wild reservoir species than wilderness areas [22].

Analysis of Rabies by Animal and Human Characteristics

Human interaction and exposure to mammalian wildlife is the single greatest risk factor for human rabies infection. The increase in the number of raccoons living in urban and suburban areas, in particular, has raised significant public health concern. Raccoons are considered well-adapted to living in these areas, with raccoon population density often greater in urban and suburban populations than other habitats [35],therefore posing significant risk for transmitting rabies to humans [23] [19] [35]. A 1997 report from the Centers for Disease Control and Prevention (CDC) explains that the rapid spread of raccoon rabies though the mid-Atlantic, particularly northward, may have been attributable to an abundance of food for raccoon populations in the unbroken urban and suburban environment of this region [20].

Although poorly understood, there is a hypothesized relationship between human industrial encroachment on wildlife habitat and rabies transmission. Studies on rabies in mid-Atlantic states have found that the following increased the odds of a given county experiencing a rabies epizootic: (1) large amount of agricultural land use, (2) less than or equal to 15% mixed forest coverage, (3) high water coverage along with low human population density, and (4) low water coverage with high human population density. Moreover, raccoon abundance was particularly high along edge habitats between farms and deciduous forests [19]. Jones et al., concluded that “A combination of land use and human population density measures provided the best model for determining epizootic

size and may be important predictors of epizootic behavior and risk of exposure to this reservoir species." [19] These findings are particularly relevant today because, coupled with the diminishing level of rabies in domesticated animals, human infection by wildlife may become an increasingly larger portion of rabies cases in humans due to increased human contact with wildlife in formerly rural areas [8] [36].

Characteristics of a given animal, such as species, age, sex, behavior and appearance, can be used to assess the level of potential risk of infection that human contact with that animal may pose. Assessing the likelihood that an animal has rabies is useful in determining probability that post-exposure prophylaxis is required to treat a bitten individual. An epidemiological study of an outbreak of rabies in raccoons in Loudoun County, Virginia in 1981-1982 made three primary discoveries: (1) female raccoons were more likely to be infected with rabies than males, (2) a 'skunky odor' was often associated with raccoons with rabies, and (3) analysis of rainfall data showed a causal effect on the occurrence of rabies-infected raccoons [37]. Jenkins found that raccoons identified in the daytime and raccoons that were killed by people or domestic dogs had significantly higher risk of testing positive for rabies than raccoons that were captured or raccoons that were found at night [38] [39]. Surveillance of raccoon populations in a target area allows public health forces to estimate health risk and develop disease control strategies [14].

While there is a body of knowledge on the characteristics of animals and risk of transmitting rabies, there has been significantly less research on whether human demographic characteristics, such as age, race, and gender, affect human risk of animal bites. Those that have examined human demographic features associated with rabies in

wild animals have not examined how these factors affect human exposure to reservoir species [19], with the exception of a few studies conducted in the Northeastern United States[40]. Additionally, researchers concerned with the expansion of raccoon rabies since the 1970s have focused primarily on how these factors affect rabies transmission in the Mid-Atlantic and Northeast and have not looked at whether this relationship is latitudinally consistent.

Surveillance

The CDC and Institute of Medicine have recently stressed the importance of continued development and improvement of surveillance strategies as intervention methods for controlling the transmission of reemerging diseases [33]. Successful control and elimination of zoonotic diseases relies heavily on effective surveillance systems for early detection and reporting of cases [41]. Surveillance also allows the generation of data and the ability to assess cost effectiveness of intervention efforts/campaigns. This information is essential for efficient implementation of control measures. Rabies surveillance typically consists of passive reporting of clinically suspected cases of human and animal rabies [41]. In past instances of zoonotic rabies outbreaks in wildlife, states and county public health efforts significantly diminished within a short period of time after the last reported rabies case, often within a few weeks. [9] This approach acutely undermines the significance of the disease's long incubation period; a key characteristic which lends itself to separate generations of the disease.

Historically, the primary use of rabies surveillance data has been to understand the temporal spatial patterns of rabies and to predict future epizootics, as well as to identify environmental and seasonal factors that uniquely affect the rates of rabies in

different species. Recent studies, using county-level reports of rabies in animals, have estimated an approximate lag time of 3-4 months from the initial detection of rabies to epizootic development in raccoons [33]. Accounting for environmental heterogeneity is essential when predicting the spread and development of rabies.

Understanding factors that affect the prevalence of rabies in the primary host species of a region highly pertinent in comprehending the ecological characteristics of rabies. In a 2003 study, Guerra explained that "scant information exists on the population densities and behavior patterns of skunks and raccoons in the eastern United States." [23]. While field studies to access the prevalence of rabies in wildlife populations have been conducted infrequently [23] due to prohibitive cost [19], passive surveillance is widespread through most of the United States. Animal bite incidences are recorded in public health records, allowing for an estimation of the burden of rabies relative to previous years. Surveillance in animal and human populations is an essential tool for rabies control and should be conducted in concert with evaluation of existing control practices. While many models have been developed to discern the population dynamics of rabies among wildlife, testing the predictive power of these models, with adequately large datasets in size and duration, is quite uncommon [42].

Rabies in humans and animals has been a nationally notifiable disease since 1944 [43] and is currently reported to the National Notifiable Disease Surveillance System, which is maintained by the CDC and the Council of State and Territorial Epidemiologists [44]. The national rabies surveillance network consists of over 125 county, state and agricultural agencies and labs, including university-based facilities [45]. Private veterinarians, animal control agencies, local and state governments all play

a role in rabies surveillance by capturing and testing animals that are suspected of carrying rabies. Technology-based surveillance systems will prove essential aspects of future rabies control programs, as they allow for consolidation of data across multiple agencies and districts, and rapid, cost-effective analyses through mapping and epidemiologic modeling. These tools allow for real time dissemination of data to stakeholders. In recent years, researchers have developed GIS-based rabies surveillance systems and open-source internet mapping applications, such as RabID [46].

From 2010 to 2012, the Georgia Department of Public Health developed an Animal Bite Module (ABM), which was pilot-tested in certain counties in 2012. The ABM was eventually adopted for use by the entire state in January 2013 [47]. Georgia's ABM is part of the Georgia Department of Public Health's State Electronic Notifiable Disease Surveillance System (SendSS) and is one of the most extensive animal bite reporting systems in the U.S [47]. Georgia's surveillance system is innovative; arguably only two other states capture data on animal bites and rabies at a level similar to Georgia. As with many disease surveillance systems, healthcare providers are the primary source of reporting animal bite exposure and suspected cases of animal rabies exposure in humans. This state-wide system is web-based and data can be filtered and downloaded into multiple formats, allowing for more comprehensive analyses. Rabies disease monitoring will become increasingly effective as surveillance databases and other data repository systems, such as Georgia's ABM, evolve [14].

Surveillance studies can produce biased estimates of the true prevalence of rabies in a natural population [17]; however, these efforts, along with retrospective examination of human rabies cases, often help researchers and public health officials to

better understand the risk that rabies poses to humans. While animal bites are not a nationally notifiable event, animal bites are notifiable in Georgia [47]. Although citizens are not required to report bite or exposure incidents to the Georgia Department of Public Health, healthcare providers, hospitals, and local health departments are required by law to report any exposure incident that they are aware of to the Georgia Department of Public Health. Therefore, animal exposure incidences, where the victim sought medical treatment or reported the incident to the county public health department officials, must be reported to the Georgia Department of Public Health. In Georgia, the primary responsibility of rabies control lies within Georgia's County Boards of Health [48].

Due to the mandatory reporting nature of animal bites and exposures in the state, Georgia's AMB likely captures nearly all animal bite incidents in which bitten individuals sought medical care. In regards to potential exposure to larger terrestrial mammals, such as raccoons, skunks, and foxes, it is reasonable to believe that most individuals bitten or injured by these animals would seek medical attention. Thus, ABM is believed to capture the majority of exposure incidences that involve high risk wildlife species, such as bites from large terrestrial wild animals. An exception to this assumption is in instances where an individual was bitten by or exposed to a bat, as individuals may be unaware of exposure to bats and therefore less likely to seek medical care.

Justification of Study

Georgia's relatively consistent and comprehensive reporting at the state level suggests that exposure data collected in this system may be a valuable asset in assessing

risk factors for potential rabies exposure. This study aims to identify local-scale human population dynamics that affect the incidence of animal bites. The local scale of our model is represented at the county level.

A major concern in dealing with rabies outbreaks is the overuse of post-exposure prophylaxis. In the U.S., approximately 1% of all injury related emergency department visits are due to animal bites [49]. Over 300 million dollars are spent on rabies control efforts each year in the United States [3] and an additional $15 million is spent on post-exposure prophylaxis for 18,000 to 20,000 potentially exposed individuals each year [27]. In 1997, when the raccoon rabies zoonotic reached its furthest extent, approximately 45,000 U.S. residents received post-exposure prophylaxis [1]. While post-exposure prophylaxis is not mandatorily reportable in Georgia, the Georgia ABM does allow public health officials to document whether post-exposure prophylaxis was recommended for each exposure incidence. The degree to which counties in Georgia reported recommending post-exposure prophylaxis varies dramatically, with some counties reporting recommending post-exposure prophylaxis treatment over 10 times as often per animal bite as other counties. Although post-exposure prophylaxis recommendations are not documented in every exposure event captured by the Georgia ABM and some counties more thoroughly document recommendations of post-exposure prophylaxis than others, findings from this study could help to guide rabies prevention practices at the county level and help to ensure a more appropriate allocation of funding for rabies prevention.

This study also seeks to examine how human characteristics, such as gender, race, and age, affect the likelihood of being bitten as well as an individual's likelihood of

specifically being bitten by animals that pose a 'high risk' of transmission. These findings could help to determine how best to target educational efforts that stress to the public how to avoid unfamiliar animals, and emphasize the importance of vaccinating pets against rabies, methods that the CDC has found to be the most effective in reducing human rabies exposure [50].

Methods

Georgia's Animal Bite Module (ABM)

The Georgia ABM covers a large geographic region, all of Georgia, and consists of comprehensive bite reports for multiple years. The ABM tool allows investigators the unique opportunity to examine animal bites records over multiple years and estimate the risk of rabies among human demographic groups. This information may be useful in determining where county health departments should focus education efforts.

Georgia's animal bite module contains not only incidents of animal bites but any incident where a human was potentially exposed to rabies through contact with an animal, such as scratches or blood contact. Therefore, this system also captures incidents other than bites; however, because the vast majority of animal exposures recorded by this system are bites and the primary mode of rabies transmission is through bites, any exposure incident captured by this system will be referred to by the author as a "bite".

This study uses multilevel multivariable modeling to examine the how human population density and metropolitan environment affects the likelihood of individuals being bitten by animals likely to be infected with and transmit rabies. A 2006 study

examining post-exposure prophylaxis in South Carolina from 1993-2002 found that the administration of post-exposure prophylaxis at the county level was inversely correlated with population density [51]. Population data at the county level were publicly sourced from the National Census Bureau's 2013 County Population Estimate and county metro status was classified using the U.S. Department of Agriculture's Rural-urban Continuum Code designations. These variables were used to quantify the population density and metropolitan environment in which animal bite incidence and potential exposure to rabies occurs.

Bites from different animal species were categorized based on expected risk of rabies. Bites from large carnivorous animals such as raccoons or skunks, along with bats, were classified as 'high risk' bites for the transmission of rabies; bites from dogs and cats were classified as 'moderate risk' and bites from lagomorphs and rodents were classified as 'low risk' [48]. Additionally, in any bite incidence that contained information on previous rabies vaccination of the biting animal, the animal risk groups was considered "low" regardless of species.

Multivariable analysis, using the statistical analysis program SAS 9.4, was conducted in order to construct two mathematical models for predicting bites in individuals. The first model was constructed using all animal bite incidences in the ABM that occurred between January 1, 2013 to November 23, 2015 in which information was documented for race, gender, age, and county of the bite incident. Information on the county's Rural Urban Continuum Code and estimated population data were tied to bites as additional predictor variables. County rural urban continuum codes were then condensed into 3 levels of metropolitan status, counties in metropolitan areas (RUCC 1-

3), suburban counties or counties in urban non-metro areas (RUCC 4-7), and completely rural counties (RUCC 8-9). This model examined how the potential risk factors -- race, gender, and age, as well as metropolitan status and population of county of residence -- affect the prevalence of animal bite. The second model used the same predictor variables to examine the risk of an individual being bitten by an animal with a 'high risk" of transmitting rabies. For this model, data on animal to human bite incidents from January 1, 2013 to November 23, 2015 involving a 'high risk' animal species and containing documented information on the individuals' race, gender, and age as well as county where the bite occurred were analyzed. Both models were constructed using the negative binomial distribution.

Assessment of multicollinearity was conducted for predictor variables; no extreme instances of multicollinearity among variables were identified. Population and metropolitan status, particularly rural classification, had the greatest measured variance inflation for both the model predicting all animal bites and the model predicting only high risk animals bites. The highest variance inflation of a first order variable for either model was below 1.25, indicating that multicollinearity was not a major issue.

Two-way interactions were assessed with likelihood ratio tests. Metropolitan status -- Metropolitan, Suburban, and Rural – w s categorized as a categorical variable instead of an ordinal variable as it was believed that suburban counties may be more protective or less protective than both rural and metropolitan counties. Therefore, treating metropolitan status as an ordinal variable may be inappropriate.

Results

All Bites Summary Tables:

There were 30,592 animal bites recorded by the Animal Bite Module during the study period (Table 1). Of these incidents, 10,413 bite events contained information on the species of biting animal, the county where the bite occurred, and the race, sex, and age of the individual who was bitten (Table 2). Individuals of minority races were significantly less likely to have reportedly been bitten with rates of 66.9 (RR = 0.44), 59.8 (RR = 0.36), and 27.6 (RR=0.18) bites per 100,000 individuals for Black, Hispanic and Asian individuals, respectively, versus 151.6 bites per 100,000 individuals for whites.

Males appeared slightly less likely to be bitten than females, with just 246.7 bites per 100,000 male residents versus 265.1 bites per 100,000 female residents, RR = 0.93 (95% CI 0.91-0.95). Individuals ages 15 years and older were significantly less likely to have reportedly been bitten, RR = 0.65 (95% CI 0.63-0.66. Finally, bite rates for Metro, Urban, and Rural counties (as defined by 2013 Rural-Urban Continuum classification) were compared for the study period. Suburban counties had a slightly higher bite rate than urban counties during the study period with 316.3 bites per 100,000 residents versus 312.8 bites per 100,000 residents, RR = 1.01 (95% CI 0.98-1.04), while rural counties had a slightly lower bite rate of 293.2 bites per 100,000 residents when compared with urban counties, RR = 0.94 (95% CI 0.86-1.01).

Of the 30,592 recorded bites in the study period, 10,413 records contained information on all variables used in analysis. These variables included gender, age, and race of the human victim, as well as the county where the exposure incident occurred. Although a substantial amount of bite incidents did not include information on all variables of interest, relative risk of bites among strata of race and gender appeared

more or less unchanged from what was observed by the full dataset of bite incidents, suggesting that omitting incomplete bite records did not substantially alter the observed relative risk by race and gender. Significantly more bite records containing information on bite victims age 15 years and older were found to be complete compared to bite records with victims age 14 years and younger, thus artificially increasing the observed relative risk of individuals ages 15 years and older from 0.65 (95% CI 0.63, 0.66) to 0.80 when retaining only records with complete information on all variables. Similarly, exposure incidents that occurred in rural counties were found to contain complete information (Figure 1), thus changing the observed relative risk of rural counties compared to metropolitan counties from 0.94 (95% CI 0.86, 1.01) to 1.46 when examining only complete records for analysis.

High Risk Bites Summary Tables:

When examining the number of exposure incidents to animals with a high risk of rabies, different trends emerged (Tables 3). Minorities were even less likely to have reportedly been bitten by high risk animals relative to white individuals , with observed relative risk of 0.31 (95% CI 0.24, 0.39), 0.22 (95% CI 0.14, 0.35) and 0.06 (95% CI 0.02, 0.26) for Black, Hispanic, and Asian individuals, respectively. Males and females appeared to have almost the same level of risk of bites by animals with high risk of transmitting rabies. The relative risk of males compared to females was 1.01 (95% CI 0.92, 1.12). Individuals ages 15 years and older also appeared to have a similar risk of high risk bites compared to individuals ages 14 years and younger, RR = 0.99 (95% CI 0.89, 1.11).

Finally, trends in reporting and the completion of records among high risk bites appeared similar to the trend noted among all bites with roughly proportional numbers of bites being retained among all races and gender groups (Table 4). Records for individuals ages 15 year and older and for exposure incidents in rural counties appeared to be more likely to contain information on Race, Age, Gender, and Metropolitan Status.

All Bite Model:

The complete multivariate negative binomial model constructed using all animal exposure incidents for which there was complete variable information contained two interaction terms -- gender*race, and age*gender. Although all 3 minority races were found to be less likely to be bitten than white individuals, after adjusting for confounding the model results indicate that adjusted relative risk for minority races was higher than the unadjusted observed relative risk when compared to white individuals. The risk of bites among male minority races was more similar to the risk of bites among white males than that of female minority races to males (Table 5). The adjusted relative risk of animal bites among Black, Hispanic, and Asian males compared to white males was 0.84 (95% CI 0.73, 0.98), 0.71 (95% CI 0.53, 0.95), and 0.60 (95% CI 0.39, 0.93) respectively, whereas the adjusted risk of animal bites among Black, Hispanic, and Asian females relative to white females was 0.57 (95% CI 0.49, 0.66), 0.32 (95% CI 0.24, 0.44), and 0.18 (95% CI 0.12, 0.29) respectively.

Males 15 years of age and older had an observed lower risk of bites relative to their female counterparts according to the model, RR = 0.83 (95% CI 0.76-0.91); however, males 14 years and younger had a greater risk of bites then females 14 and under RR = 1.18 (95% CI 1.03-1.35).

Increased county population was found to be a protective factor against bite prevalence; however, because the population of counties was right skewed, with a few counties in the Atlanta metropolitan area having significantly larger populations than the rest of the state, relative risk predictions comparing the largest counties to smaller counties appeared exaggerated by our model. The author chose not to log transform the variable for county population in order to preserve ease of interpretation for the reader. Relative risk of a county with 10,000 or more residents than another county was 0.96 (95% CI 0.96-0.97). One possible explanation for this finding could simply be that, on average, counties with higher populations have a smaller animal to human ratio, making the chance of an individual being bitten lower even if the propensity of an animal to bite a human is the same. It should be noted that human environment, the absence of human activity, or simply affluence may play a role in increasing or decreasing the risk of bites, as the difference in risk among counties of different metropolitan categories suggests.

Although a general increase in county population was a protective factor, the effect that human-built environment and human activity have on an individual's risk of bites appears to be more complex. While individuals from suburban counties appeared less at risk for bites that individuals from urban counties, RR = 0.72 (95% CI 0.53-0.99), individuals from urban counties appeared more at risk for bites, RR = 1.23 (95% CI 0.90-1.67).

<u>High Risk Bite Model:</u>

According to the high risk model, minority individuals were substantially less likely to report being bitten by animals with high risk of transmitting rabies than white

individuals with a relative risk of 0.46 (95% CI 0.25, 0.83), 0.21 (95% 0.06,0.70), 0.10 (95% 0.02, 0.58) for Black, Hispanic, and Asian individuals, respectively. This estimated disparity in the likelihood of high risk bites between white and minority races was greater than the disparity in the likelihood of all bites between these groups.

Gender and age affected the likelihood of high risk bites differently than all bites. Whereas females appeared more likely to be bitten by all types of animals, males appeared more likely to be bitten by high risk animals than females, RR = 1.22 (95% CI 0.96, 1.55). Similarly, whereas individuals ages 14 years and under were more likely to have reportedly been bitten by any type of animal, individuals ages 15 years and older appear more likely to be bitten by animals with a high risk of transmitting rabies, RR = 1.08 (0.81, 1.43).

As previously observed in the all bites model, increased county population was found to be a protective factor against high risk bites. Living in a county with 10,000 more residents than another county resulted in a reduction in one's risk of bites, RR = 0.97 (95% CI = 0.96, 0.99). One particular finding of interest was that residents from suburban counties (counties with a Rural Urban Continuum Code of 4 to 7) appeared less likely to experience animal bites than individuals from rural or urban areas. Individuals in suburban counties were significantly less likely to report high risk bites than individuals in metropolitan counties, RR = 0.53 (95% CI 0.32-0.89), while individuals in rural counties appeared more likely to reportedly be bitten than individuals in metropolitan counties, RR = 1.54 (95% CI 0.57-4.16).

Although many studies have found that urban environments are highly suitable environments for raccoons [23][25][41]the study by Anthony et al., which examined

human and raccoon encounters in Baltimore, MD found that the area of the city where most raccoons were caught and where most raccoon encounters occurred was in single unit residential areas [26]. In other words, raccoons were most often found in 'suburban like' neighborhoods. This finding – reported wild animal bites occur more commonly in urban counties than in suburban counties – does not necessarily contradict other research studies. Although raccoons may inhabit suburban environments in similar or higher numbers than in urban environments, their behavior may differ in a way that makes human encounters more common in urban environments. Secondly, the model for high risk bites includes bites from all animals that present high risk of rabies, including skunks, foxes, and coyotes; and these animals may not be as well suited to urban environments as raccoons.

Limitations

Approximating Risk using Risk-like Fraction

Not all individuals exposed to animal bites in Georgia are residents of Georgia. Therefore, the calculated fraction for number of bitten individuals over number of residents is not a true calculation or risk, since not all individuals who experienced an event are contained in the population at risk. It is believed that the majority of individuals bitten in Georgia are, in fact, residents. Thus, this risk-like fraction can be used to estimate the true risk of exposure in the population.

Incomplete 'at risk' population

The population used as individuals at risk in Georgia was constructed using 2013 estimates of Georgia residents who are Black, White, Hispanic, or Asian (n=9,746,355).

The actual estimated population of Georgia in 2013, including individuals who declined to identify as one of these racial groups, is 9,992,167. The author concluded that individuals in Georgia who identify as Black, White, Hispanic, or Asian, were a large enough portion of Georgia's entire population to be used to estimate the risk of animal bites for the entire state.

Approximation of Risk (Surveillance Missing Instances)

As with all surveillance systems, Georgia's Animal Bite Surveillance System does not capture every single bite incident or possible instance of rabies exposure through animal contact. Instead of examining the rate and relative risk of being bitten for exposure groups, this dataset allows us to approximate the rate and relative risk of a bite being reported by Georgia's surveillance system and entered into its bite module for exposure groups.

While the model presented here examines the relative risk of an exposure incidence being reported, our model cannot account for reporting errors. Differences in reporting rates among different age groups, racial groups, and genders may be partially explained by certain groups being more or less likely to seek medical treatment for a bite. For instance, the author suggests that while the reported exposure rate for females is higher than for males, the actual exposure rate for females may be the same or lower than males; however, females may be more likely to report exposures or seek medical treatment after an exposure occurs. The author speculates that this difference in the inclination to report an incident may occur among different age groups and racial groups and may account for some of the observed differences in the rate of exposure. If

this is true, then the risk of rabies in white individuals, individuals 14 years of age or younger, and females may be inflated by our model.

More complete records in rural counties

The percent of reported bites that included information on all potential risk factors – race, age, gender, and animal species – was significantly higher in rural counties than in non-suburban counties (see Figure 1). Due to analysis constraints, only bite observations where information on all risk factors of interest were used for statistical analysis in our model. This likely increases the estimated risk of both all animal bites and high risk bites in rural counties, as a larger portion of bites that occurred in rural counties contained complete documentation of all variables than bites that occurred in suburban or urban counties (Figure 1).

More animals likely vaccinated

In accordance with the national Compendium of Animal Rabies Prevention and Control, Georgia's Rabies Control Law-O.C.G.A-31-19 requires that all domestic cats and dogs owned by individuals be vaccinated against rabies [81]. As animal vaccination is required for all owned dogs and cats in Georgia, it is likely that in most dog and cat bite incidents captured in surveillance, where the animal was owned, the dog or cat involved was likely vaccinated even if surveillance records do not explicitly contain vaccination dates. Therefore, it is important to note that the number of dog and cat bites that were classified as of "medium risk" for rabies transmission (ANIMAL_RISK = 1) is likely to be inflated and the number of dog and cat bites classified as "low risk" for rabies transmission (ANIMAL_RISK = 0) is likely to be smaller than in reality.

The relationship between environmental factors and animal bites does not necessarily indicate a causal relationship between environment and rabies transmission. Animals may be more likely to bite out of self-defense when either coming in contact with humans in rural areas and locations of human encroachment or in urbanized areas. Based on literature, it is believed that the former is more likely and that a smaller portion of animal bites occurring in rural areas or areas of human encroachment are from infected animals than in urban areas or areas of high population density.

High population density has been found to increase the likelihood of rabid animals being detected [19]. Thus, in areas of low human population density, a greater number of rabid raccoons may have to be tested in order to detect an epizootic of similar magnitude [19]. Contrary to this assumption, the number of observed bites or animals submitted for testing in a county is not necessarily representative of the actual distribution of rabies in the wildlife population. Areas with high human population density may simply submit a larger portion of the animal population for testing, and may experience more bites per square mile although likely less bites per person. This is not to say, however, that the number of detected rabid animals is not a good estimate of the risk of human rabies exposure. Finally, seasonal variation in human activity may influence human contact with wildlife and domestic animals as well as the number of animals submitted to health departments for testing [36].

Conclusion

As discussed previously, the observed rate of all risk levels of animal bites may be artificially low for individuals ages 15 and over due to older individuals being less likely to seek medical treatment for bites. The increased rate of bites among individuals ages

14 and under may be primarily attributable to bites from domestic animals, such as cats and dogs, which make up the majority of all reported animal bites. The increased risk of dog bites among children relative to adults is well documented [49]. Although children appear less likely to reportedly be bitten by all animals, individuals ages 15 years and older appear significantly more likely to report being bitten by high risk animals. This is an important finding because it suggests that it may be beneficial for rabies education efforts to be directed towards adults and older adolescents.

Finally, stark differences in the rate of animal encounters were observed among different racial groups, with minority races being significantly less likely to be bitten or exposed than white individuals. Although this observed difference in bite risk may be, at least in part, the result of underreporting of animal bite exposures in minority races or systematic errors in reporting by the county or state, this observed trend is one of the first of its kind and further research should be conducted on the matter.

This model represents one of the only human and environmental bite models constructed in the Southeastern United States, where raccoons are the primary reservoir for terrestrial rabies. As a result, it may not be appropriate to use this model's findings to make conclusions or predictions outside of Georgia or its neighboring states. Its primary application may not be in predicting rabies events or animal bites but in assessing surveillance efforts and need for post-exposure prophylaxis throughout the state as post-exposure prophylaxis treatments constitute a major cost associated with rabies prevention and treatment. The author proposes that this model could be used by the Georgia Department of Public Health to calculate the number of bites expected for each county by entering into the model demographic features of each county. By

generating an "'expected' number of bites" for each county and comparing this to the true observed number of bites with information for each exposure variable, researchers could draw conclusions about the surveillance practices of each county. Counties with a significantly lower number of documented bites could be identified and targeted as areas where surveillance efforts could be improved. Counties with a significantly higher number of reported bites than expected may be identified with effective surveillance as these areas may capture a greater portion of actual animal exposure events. Either of these models developed and presented in this study may provide useful insight for public health agencies to direct education and training efforts for rabies prevention and surveillance in Georgia.

Figures and Tables

Table 1: *Human animal exposures captured by Georgia's Animal Bite Module (ABM) from January 1, 2013 to November 23, 2015.*

Characteristic	Bites (%)	Population[a]	Bites per 100,000 residents	RR (95% CI)	P-value
n	30592	9746355	313.9		
Race					
White	8261 (27.0)	5448717	151.6	(ref.)	
Black	2046 (6.7)	3056726	66.9	0.44 (0.42, 0.46)	<.0001
Hispanic	536 (1.8)	896717	59.8	0.39 (0.36, 0.43)	<.0001
Asian	95 (0.3)	344195	27.6	0.18 (0.15, 0.22)	<.0001
Other	157 (0.5)				
Missing	19497 (63.7)				
Gender	11095				
Female	13214 (43.2)	4984012	265.1	(ref.)	
Male	11751 (38.4)	4762343	246.7	0.93 (0.91, 0.95)	<.0001
Missing	5627 (18.4)				
Age	30592				
<= 14 years	8361 (27.3)	2004806	417.0	(ref.)	
>= 15 years	20907 (68.3)	7741549	270.1	0.65 (0.63, 0.66)	<.0001
Missing	1324 (4.3)				
Rural-Metro Status	30592				
Metro (RUCC 1-3)[b]	25004 (81.7)	7994303	312.8	(ref.)	
Suburban (RUCC 4-7)[b]	4925 (16.1)	1556960	316.3	1.01 (0.98, 1.04)	0.4685
Rural (RUCC 8-9)[b]	572 (1.9)	195092	293.2	0.94 (0.86, 1.01)	0.1258
Missing	91				

a.) Population refers to the study population used in the statistical model. This study population is the total number of residents in Georgia categorized as White, Black, Hispanic, or Asian

b.) 2013 County Rural-Urban Continuum Code as classified by the USDA Economic Research Service

Table 2: *Human animal exposures captured by Georgia's Animal Bite Module (ABM) from January 1, 2013 to November 23, 2015 in which complete information was documented for Race, Gender, Age, and Bite County.*

Characteristic	Bites (%)	Population[a]	Bites per 100,000 residents	RR (95% CI)	P-value
n	10413	9746355	106.8		
Race					
White	7879 (75.7)	5448717	144.6	(ref.)	
Black	1940 (18.6)	3056726	63.5	0.44 (0.42, 0.46)	<.0001
Hispanic	505 (4.8)	896717	56.3	0.39 (0.36, 0.43)	<.0001
Asian	89 (0.9)	344195	25.9	0.18 (0.15, 0.22)	<.0001
Gender					
Female	5519 (53.0)	4984012	110.7	(ref.)	
Male	4894 (47.0)	4762343	102.8	0.93 (0.89, 0.96)	0.0001
Age					
<= 14 years	2555 (24.5)	2004806	127.4	(ref.)	
>= 15 years	7858 (75.5)	7741549	101.5	0.80 (0.76, 0.83)	<.0001
Rural-Metro Status					
Metro (RUCC 1-3)[b]	8383 (80.5)	7994303	104.9	(ref.)	
Suburban (RUCC 4-7)[b]	1732 (16.6)	1556960	111.2	1.06 (1.01, 1.12)	0.0251
Rural (RUCC 8-9)[b]	298 (2.9)	195092	152.7	1.46 (1.30, 1.64)	<.0001

a.) Population refers to the study population used in the statistical model. This study population is the total number of residents in Georgia categorized as White, Black, Hispanic, or Asian

b.) 2013 County Rural-Urban Continuum Code as classified by the USDA Economic Research Service

Table 3: *Human animal exposures captured by Georgia's Animal Bite Module (ABM) from January 1, 2013 to November 23, 2015 in which information on biting animal species was documented, categorized into animal risk classes. Risk Ratios have been calculated for high risk bites.*

Characteristic	Low Risk Bites (%)	Med Risk Bites (%)	High Risk Bites (%)	Population[a]	RR High Risk Bites (95% CI)	P-value
n	2029	8188	606	9746355		
Race						
White	1655 (81.6)	5925 (72.4)	495 (81.7)	5448717	(ref.)	
Black	240 (11.8)	1655 (20.2)	85 (14.0)	3056726	0.31 (0.24, 0.39)	<.0001
Hispanic	86 (4.2)	421 (5.1)	18 (3.0)	896717	0.22 (0.14, 0.35)	<.0001
Asian	21 (1.0)	69 (0.8)	2 (0.3)	344195	0.06 (0.02, 0.26)	<.0001
Other	27 (1.3)	118 (1.4)	6 (1.0)			
Gender	3686	18004	1601			
Female	2004 (54.4)	9538 (53.0)	814 (50.8)	4984012	(ref.)	
Male	1682 (45.6)	8466 (47.0)	787 (49.2)	4762343	1.01 (0.92, 1.12)	0.8140
Age	3842	21764	1916			
<= 14 years	1079 (28.1)	5511 (25.3)	396 (20.7)	2004806	(ref.)	
>= 15 years	2763 (71.9)	16253 (74.7)	1520 (79.3)	7741549	0.99 (0.89, 1.11)	0.9153
Rural-Metro Status	3964	22737	2083			
Metro (RUCC 1-3)[b]	3264 (82.3)	18586 (81.7)	1729 (83.0)	7994303	(ref.)	
Suburban (RUCC 4-7)[b]	604 (15.2)	3780 (16.6)	272 (13.1)	1556960	0.95 (0.87, 1.04)	0.2489
Rural (RUCC 8-9)[b]	96 (2.4)	371 (1.6)	82 (3.9)	195092	1.21 (0.98, 1.48)	0.0710

a.) Population refers to the study population used in the statistical model. This study population is the total number of residents in Georgia categorized as White, Black, Hispanic, or Asian

b.) 2013 County Rural-Urban Continuum Code as classified by the USDA Economic Research Service

Table 4: *Human animal exposures captured by Georgia's Animal Bite Module (ABM) from January 1, 2013 to November 23, 2015 in which information on victim's race, gender, and age, as well as county where bite incidence occurred and biting animal species was documented. Biting animals were categorized into animal risk classes. Risk Ratios have been calculated for high risk bites.*

Characteristic	Low Risk Bites (%)	Med Risk Bites (%)	High Risk Bites (%)	Population[a]	RR High Risk Bites (95% CI)	P-value
n	1954	7885	574	9746355		
Race						
White	1618 (82.8)	5786 (73.4)	475 (82.8)	5448717	(ref.)	
Black	234 (12.0)	1625 (20.6)	81 (14.1)	3056726	0.30 (0.24, 0.38)	<.0001
Hispanic	81 (4.1)	408 (5.2)	16 (2.8)	896717	0.20 (0.12, 0.34)	<.0001
Asian	21 (1.1)	66 (0.8)	2 (0.3)	344195	0.07 (0.02, 0.27)	<.0001
Gender						
Female	1073 (54.9)	4158 (52.7)	288 (50.2)	4984012	(ref.)	
Male	881 (45.1)	3727 (47.3)	286 (49.8)	4762343	1.04 (0.88, 1.22)	0.6444
Age						
<= 14 years	529 (27.1)	1939 (24.6)	87 (15.2)	2004806	(ref.)	
>= 15 years	1425 (72.9)	5946 (75.4)	487 (84.8)	7741549	1.45 (1.15, 1.82)	0.0013
Rural-Metro Status						
Metro (RUCC 1-3)[b]	1560 (79.8)	6356 (80.6)	467 (81.4)	7994303	(ref.)	
Suburban (RUCC 4-7)[b]	316 (16.2)	1332 (16.9)	84 (14.6)	1556960	1.04 (0.92, 1.17)	0.5241
Rural (RUCC 8-9)[b]	78 (4.0)	197 (2.5)	23 (4.0)	195092	2.05 (1.63, 2.57)	<.0001

a.) Population refers to the study population used in the statistical model. This study population is the total number of residents in Georgia categorized as White, Black, Hispanic, or Asian

b.) 2013 County Rural-Urban Continuum Code as classified by the USDA Economic Research Service

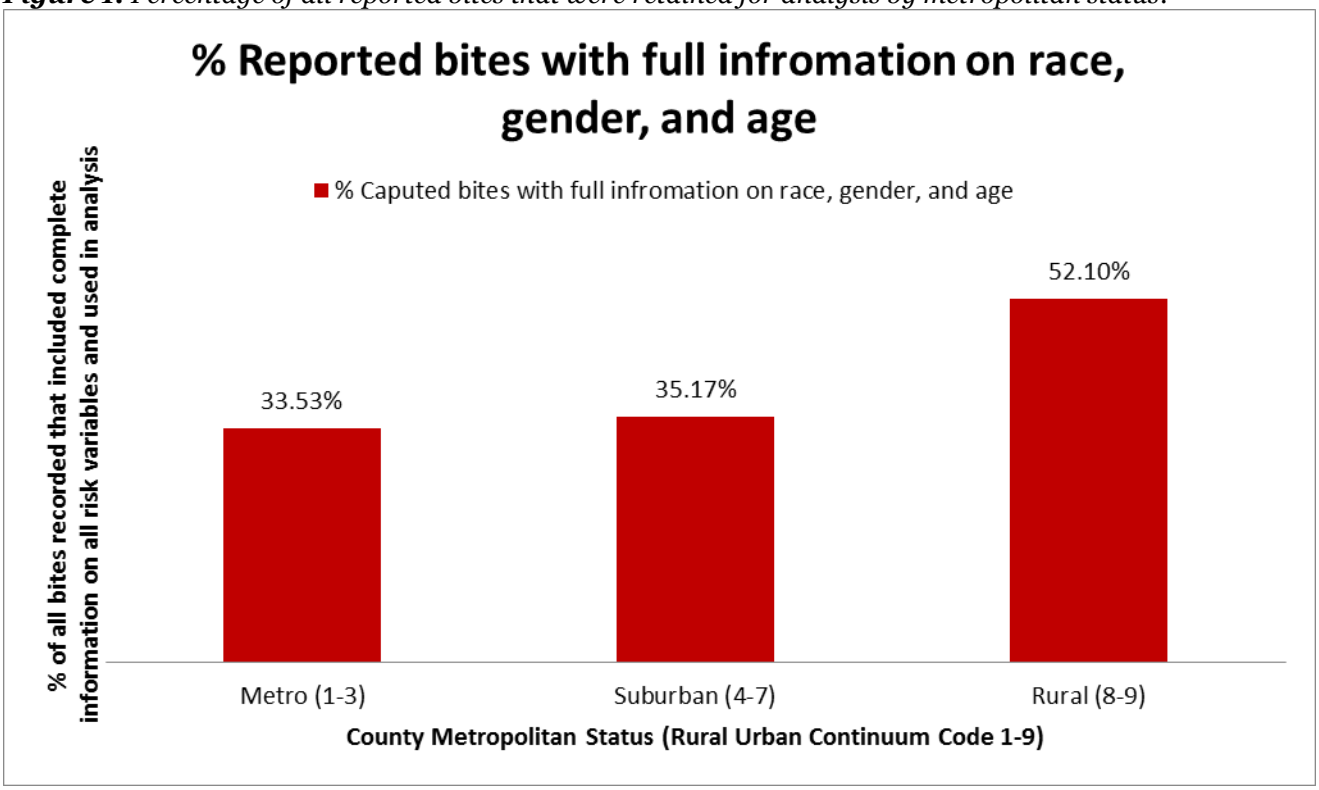
Table 5: *Estimated Relative Risk Results for All Animal Bites*

Exposure to Any Animal Capable of Rabies Transmission			
Strata	Risk Factor	RR (95% CI)	P-value
Male	White	(ref.)	0.022
	Black	0.84 (0.73,0.98)	
	Hispanic	0.71 (0.53,0.95)	
	Asian	0.60 (0.39,0.93)	
Female	White	(ref.)	<0.001
	Black	0.57 (0.49,0.66)	
	Hispanic	0.32 (0.24,0.44)	
	Asian	0.18 (0.12,0.29)	
<= 14 years	Female	(ref.)	0.020
	Male	1.18 (1.03,1.35)	
>= 15 years	Female	(ref.)	<0.001
	Male	0.83 (0.76,0.91)	
	Metro (RUCC 1-3)	(ref.)	
	Suburban (RUCC 4-7)	0.72 (0.53,0.99)	0.043
	Rural (RUCC 8-9)	1.23 (0.90,1.67)	0.198
	10,000 additional county residents	0.96 (0.96,0.97)	<0.001

Table 6: *Estimated Relative Risk for High Risk Animal Bites*

Exposure to Animal with High Risk of Rabies Transmission		
Risk Factor	RR (95% CI)	P-value
White	(ref.)	0.011
Black	0.46 (0.25,0.83)	
Hispanic	0.21 (0.06,0.70)	
Asian	0.10 (0.02,0.58)	
Female	(ref.)	0.097
Male	1.22 (0.96,1.55)	
<= 14 years	(ref.)	0.603
>= 15 years	1.08 (0.81,1.43)	
Metropolitan	(ref.)	
Suburban	0.53 (0.32,0.89)	0.019
Rural	1.54 (0.57,4.16)	0.019
10,000 additional county residents	0.97 (0.96,0.99)	<0.001

Figure 1: *Percentage of all reported bites that were retained for analysis by metropolitan status.*



The significantly higher percentage of bites from rural counties retained for analysis compared to bites from urban and suburban counties suggest that the statistical models may overestimate the risk of bites in rural counties relative to other counties.

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