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# Longitudinal analysis of raccoon rabies in West Virginia, 2000-2015

K. Bert Plants <sup>Corresp., 1</sup>, Sijin Wen <sup>1</sup>, Jeffrey Wimsatt <sup>2</sup>, Sarah Knox <sup>1</sup>

<sup>1</sup> School of Public Health, West Virginia University, Morgantown, West Virginia, United States

<sup>2</sup> Unaffiliated, Morgantown, WV, United States

Corresponding Author: K. Bert Plants  
Email address: kbplants@mix.wvu.edu

Animal borne rabies is a source of infection in humans, and raccoons (*Procyon lotor*) are the primary terrestrial reservoir in West Virginia (WV). To assess the behavior and status of raccoon variant rabies virus (RRV) in WV, a longitudinal analysis for the period 2000-2015 was performed, using data provided by the state Bureau of Public Health. Analytic approaches included linear-mixed, Poisson, and zero inflated Poisson regressions. Each of these approaches indicated that there had been a reduction in numbers of RRV positive animals over the study period, predominantly due to a decrease in raccoon infections. Non-raccoon species did not appear to have a similar decline, however. This has implications for the preventive measures currently being implemented. Spatial analyses of RRV and further examination of the virus in non-raccoon species are warranted.

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5

6 <sup>1</sup> School of Public Health, West Virginia University, Morgantown, WV, USA

7

8 Corresponding Author:

9 Bert Plants<sup>1</sup>

10 PO Box 9190, Morgantown, WV, 26506-9190 USA

11 Email address: [kbplants@mix.wvu.edu](mailto:kbplants@mix.wvu.edu)

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## 13 Longitudinal Analysis of Raccoon Rabies in West Virginia, 2000-2015

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15

### 16 Abstract

17 Animal borne rabies is a source of infection in humans, and raccoons (*Procyon lotor*) are  
18 the primary terrestrial reservoir in West Virginia (WV). To assess the behavior and status of  
19 raccoon variant rabies virus (RRV) in WV, a longitudinal analysis for the period 2000-2015 was  
20 performed, using data provided by the state Bureau of Public Health. Analytic approaches  
21 included linear-mixed, Poisson, and zero inflated Poisson regressions. Each of these approaches  
22 indicated that there had been a reduction in numbers of RRV positive animals over the study  
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25 currently being implemented. Spatial analyses of RRV and further examination of the virus in  
26 non-raccoon species are warranted.

### 27 Introduction

28 Rabies causes an almost invariably fatal infection in any mammal, including humans.  
29 This neurotropic virus is a lyssavirus, within the *Rhabdoviridae* family.(Prevention 2011a)  
30 Rabies induced fatal encephalomyelitis is endemic throughout the Americas, with higher  
31 numbers of human deaths in Mexico, Central America and South America.(Prevention 2011c)

32 Over the past 100 years, the species distribution of rabies and risk of human exposure in  
33 the United States have changed dramatically because of coordinated vaccination efforts in  
34 domestic animals, especially dogs and cats.(Prevention 2011b; Prevention 2011c) More than

35 90% of all animal cases reported annually to the CDC now occur in wildlife; whereas before  
36 1960, the majority were in domestic animals.(Prevention 2011b) The principal rabies hosts in the  
37 U.S. today are wild mesocarnivores and bats,(Prevention 2017) and most human exposures  
38 remain from carnivores. Although rabies kills thousands of people each year worldwide, human  
39 deaths have decreased dramatically in the United States, (Lozano et al. 2012) primarily due to  
40 successful preventive efforts.

41 Affected wildlife animals, including raccoons (*Procyon lotor*), often lose their fear of  
42 humans and become active during daylight hours, drastically increasing the potential for human  
43 and domestic animal exposures.(Kappus et al. 1970) When a dog or cat is reported to have bitten  
44 a human, the animal is quarantined for an established observation period of 10  
45 days.(webmaster@wvlegislature.gov 2017) In the event of a wild animal bite, if the animal in  
46 question is deceased, or the quarantine period is not established, the brain of the animal is  
47 submitted for rabies confirmation.(Brown et al. 2016) Often, the person bitten must undergo a  
48 post exposure prophylactic (PEP) regimen that entails an injection of anti-rabies immunoglobulin  
49 in addition to three doses of human rabies vaccine.(Prevention 2015) In the US, 40,000 to 50,000  
50 PEP treatments are given to people annually, suggesting rabies remains a significant  
51 problem.(Prevention 2015) In the event of a local outbreak, or when the disease becomes  
52 established in a region, the number of PEP treatments administered increases to meet the local  
53 need, putting a burden on local resources. While costs vary, a course of rabies immunoglobulin  
54 and three doses of vaccine typically exceed \$3,000.(Prevention 2015)

55 There are a number of strains of rabies virus, with many being associated with a specific  
56 host species, although spillover into other hosts frequently occurs.(Wallace et al. 2014) In fact,  
57 the labelling of the strains by host species (raccoon, bat, fox, etc.) is only reflective of the species

58 that acts as the primary reservoir for that strain of virus at that time.(Baer 1991) Either bat or  
59 carnivore origin rabies infection can be transmitted to any other mammalian host. It is almost  
60 always lethal in all species, including humans, once symptoms have developed.

61 In the United States, effective rabies vaccination protocols for domestic animals have  
62 resulted in near elimination of the disease in that population.(Prevention 2011b) However, non-  
63 domesticated animals are still a problem and effective prevention does not come without an  
64 economic burden. The cost of rabies prophylaxis, treatment and control programs is estimated to  
65 be between \$250 and \$500 million dollars annually.(Prevention 2011b) This includes  
66 prophylaxis for both domestic and wild animals. Additionally, rabies infection in agricultural  
67 settings has significant cost burdens for animal producers.(Chipman et al. 2013)

68 In West Virginia (WV), the viral strains known to be present are the bat and raccoon  
69 rabies virus variants.(WV Dept of Health and Human Services 2017) Bat strain rabies virus has  
70 caused sporadic cases reported in all counties. Even so, bat cases represent less than 5% of the  
71 animals found to be positive for virus.(West Virginia Department of Health and Human Services  
72 2017) Raccoon strain rabies virus (RRV) is currently enzootic in the Southeast United States,  
73 and it has expanded its range in the eastern part of WV subsequent to the inadvertent  
74 introduction of translocated rabid raccoons along the WV – Virginia border near Greenbrier  
75 County in the late 1970s.(Nettles et al. 1979) Since then, RRV infection has expanded  
76 geographically at a rate between 30 and 60 km/yr.(Sternner et al. 2009) This has become a major  
77 issue because, despite the success of immunization programs in domestic animals, rabies  
78 infection is on the rise in WV wildlife, particularly in raccoons.(West Virginia Department of  
79 Health and Human Services 2017) Raccoons are of special concern since they readily coexist in

80 peridomestic settings close to humans; for example, they commonly raid refuse containers and  
81 pet food left outdoors, along with other food sources such as bird feeders around homes.

82 Prior to the introduction of RRV in WV, there were a handful (5-10) of rabies positive  
83 raccoons reported annually, all of which were infected with bat strain virus.(West Virginia  
84 Department of Health and Human Services 2017) Once the RRV front moved through, numbers  
85 of RRV positive raccoons increased dramatically, peaking in 2002 with 126 positive  
86 animals.(West Virginia Department of Health and Human Services 2017) Moreover, spillover  
87 species added 37 positive animals (23% of the total positives) in that year, including eight  
88 domestic animals (cats, horses and cows).(West Virginia Department of Health and Human  
89 Services 2017) RRV is especially associated with spillover into other species, and has been  
90 described as a “super spreader” organism.(Wallace et al. 2014) There has been some suspicion  
91 that RRV has the potential to undergo host shifts more readily than other viruses, because it  
92 easily adapts to a new host species and begins independent circulation within that  
93 species.(Wallace et al. 2014) This tendency could result in establishment of a viral reservoir in  
94 previously uncontaminated species, and potentially even in domestic animals, if vaccination and  
95 control practices are not maintained. The importance of RRV in WV is highlighted by the fact  
96 that over 95% of rabies positive animals identified from 2000-2015 were infected with  
97 RRV.(West Virginia Department of Health and Human Services 2017)

98 Of particular interest are cats which represent roughly 5% of the RRV positives identified  
99 in peridomestic settings in WV.(West Virginia Department of Health and Human Services 2017)  
100 This is of particular concern, because many remain unvaccinated for rabies, even though rabies  
101 prophylaxis is mandatory in WV.(webmaster@wvlegislature.gov 2017) In addition, cats have a  
102 propensity to establish viable feral populations.(Rupprecht et al. 2006) These factors, and others,

103 contribute to the current situation, where over 2500 animal bites and other potential rabies  
104 exposures are reported annually in WV.(WV Dept of Health and Human Services 2017)  
105 Unfortunately, data are not available regarding how many of these are true exposures (defined as  
106 a bite or a scratch), nor is a complete species breakdown of the animals involved available.

107 In order to assess the public health risk of rabies to humans in WV and the current state  
108 of rabies prevention efforts, the aim of this paper is to determine whether there has been a  
109 significant change in the number of RRV cases over the period 2000-2015 in WV. The novel  
110 software techniques employed evaluate the data accounting for the uneven distribution of rabid  
111 animals, in addition to including all types of affected animal species in the analysis.

112

## 113 **Materials and Methods**

### 114 *Data collection and database structure*

115 Data used here were from the annual state rabies cases of RRV by county, provided by  
116 the WV State Bureau of Public Health.(West Virginia Department of Health and Human  
117 Services 2017) This is a complete dataset, including all cases of RRV identified in the state  
118 during the study period and the county where they were collected, as well as the species of  
119 positive animals and viral strain. Disease was diagnosed by submission of the heads of suspect  
120 animals to the state diagnostic laboratory by veterinarians and animal control personnel. Positive  
121 animals were then submitted to the CDC for viral strain identification. Unfortunately, the  
122 database does not provide location data more specific than county. Only those cases specifically  
123 identified to have RRV infection were retained for evaluation, with cases showing unspecified  
124 viral strain or bat strain excluded. All data were compiled in Microsoft Excel spreadsheets.



## 125 **Data analyses**

126           The open source statistical programming platform R was used to evaluate the data,  
127 employing the glmmADMB package (version 0.8.3.3). (Skaug et al. 2016; Team 2017) Initial  
128 analysis involved generating descriptive statistics. Next, linear mixed models were developed to  
129 optimize the longitudinal nature of the data and examination of the data distribution revealed that  
130 it was not normally distributed (Figure 1). The data were seen as following a Poisson  
131 distribution, so a Poisson model was fit. However, Poisson modelling requires an offset, to  
132 permit different weighting of the data clusters. The offset is the variable used to denote the  
133 population at risk in each cluster for the Poisson regression. Although the preferred offset would  
134 be total raccoon population in each county, these data are not readily available. Several other  
135 factors were considered as possible offsets, and potential offsets evaluated in exploratory  
136 analyses. Offsets examined were area (in square kilometers) of individual counties, county  
137 population and county human population density. It became evident that these potential offsets  
138 were essentially equivalent, both in coefficient value as well as p-value. Given the known  
139 behavior of raccoons and their propensity to inhabit areas in close proximity to human activity,  
140 human population density was selected as the offset, as it was believed to be most likely to be  
141 proportional to actual raccoon populations. (Erb et al. 2012) Finally, due to the large number of  
142 zero case entries in many counties, an analysis incorporating a zero inflated Poisson (ZIP)  
143 approach was performed. The ZIP approach allows for separation of the two components of the  
144 distribution for separate analyses, separating out excess zero outcomes for analysis under a  
145 binomial distribution, while non-zero outcomes are evaluated using a Poisson  
146 distribution. (Lambert 1992) All models were run using  $\alpha = 0.05$  as the significance threshold.

## 147 **Results**

148                   There were 1464 RRV positive animals during the study period from 2000-2015.  
149   These were comprised of 962 raccoons, 391 nondomestic non-raccoons (NDNR) (predominantly  
150   striped skunks (*Mephitis mephitis*) and red foxes (*Vulpes vulpes*)), and 111 domestic animals.  
151   Preliminary examination of the state RRV data from 2000-2015 seems to show a decreasing  
152   trend in absolute number of animal cases over that timeframe, as shown in Figure 2.

153                   The mixed linear modeling provided a regression coefficient of -0.061, with a p-value of  
154   0.0024, a highly significant result. The Akaike Information Criterion (AIC) for the linear-mixed  
155   model was 4432.4 however, indicative of a poor fit of the model to the data. Linear mixed  
156   models assume normally distributed data, which was not true in this study, and the AIC likely  
157   reflects this. Examination of the data histogram (Figure 1) bears this out, as previously discussed.

158                   The Poisson model was fit using log human population density as the offset, yielding a  
159   regression coefficient of -0.050 with a p-value of <0.001 and an AIC of 2377.5, as shown in  
160   Table 1. This indicates that there is a significant negative trend in RRV numbers and that the  
161   model provides an improved fit to the data as compared to the linear mixed model.

162                   The data appeared highly right skewed, as shown in Figure 1, with substantial numbers of  
163   zero values. Once the ZIP model was fit, a regression coefficient of -0.044 was obtained, with a  
164   p-value of <0.001 and a 2260.2 AIC. This result was highly significant and resulted in an AIC  
165   that indicated improved model fit. In the ZIP model, the coefficient can be interpreted as follows:  
166   the mean number of cases in log-scale was reduced by 0.044 per year for 16 years, which is  
167   equivalent to a reduction of 1.045 cases per year for 16 years.

168                   Finally, ZIP models were fit for each of the three animal types in this study, and the  
169   results are shown in Table 2. Raccoons were found to have a regression coefficient of -0.053,

170 with a p-value of  $<0.001$  and an AIC of 1924.3, all of which are comparable to the results  
171 obtained for the total numbers of RRV positive animals. Nondomestic, non-raccoon (NDNR)  
172 species had a regression coefficient of -0.007, p-value of 0.55 and an AIC of 1057.1. Domestic  
173 animals had a regression coefficient of 0.002, p-value of 0.93 and an AIC of 584.6. These results  
174 indicate that while there was a significant ( $p<0.001$ ) reduction in raccoon infection, no such  
175 significant reduction was detected in non-raccoon species, both nondomestic and domestic  
176 ( $p=0.55$  and  $0.93$ , respectively).

## 177 **Discussion**

178           An examination of the current literature indicates that there have been several  
179 studies regarding rabies infection, with many specific to RRV. Rabies is frequently reported in  
180 the Eastern United States, where the primary reservoir for the virus is the raccoon. Raccoons  
181 represented 32% of the positive animals nationwide in 2012, 2013 and 2014, although there was  
182 a reduction in total numbers of positive raccoons detected of 1.4%, 2.8% and 4.0%,  
183 respectively.(Dyer et al. 2013; Dyer et al. 2014; Monroe et al. 2016) Prior studies have focused  
184 on cases in raccoons, while disregarding cases in domestic and non-raccoon, non-domestic  
185 animals. The study includes a novel examination of all species affected with RRV. There is a  
186 relative paucity of published studies regarding longitudinal analysis of RRV. This is unfortunate,  
187 since such information is useful for determining the optimum allocation of limited resources for  
188 rabies prevention and control.

189           Since the inadvertent introduction of RRV into the Mid-Atlantic States, the disease has  
190 spread throughout the region and into New England and Canada. There have been few studies  
191 published that examine the numbers of RRV positive animals over time, especially ones that  
192 consider all positive animals as opposed to raccoons alone. The primary finding of the current

193 analysis is that there has been a significant decline in all RRV positive animals in WV during the  
194 study period, with the bulk of the decline in positives occurring in raccoons. Substantial  
195 resources have been used in WV to control rabies in raccoons,(Nelson 2010; Slate et al. 2009)  
196 and have apparently been successful only with regard to raccoons. The decline does not extend to  
197 non-raccoon species. Control efforts have not deterred spread to, and among, other species. This  
198 suggests that the virus is becoming established in non-raccoon species, and may be beginning to  
199 circulate independent of the raccoon reservoir. This is plausible given the propensity of RRV to  
200 spillover into non-raccoon species and establish itself in new reservoir host animals.(Wallace et  
201 al. 2014)

202           These findings are consistent with the available literature. Ma et al noted a general  
203 reduction in numbers of RRV positive raccoons recovered in areas of WV where oral rabies  
204 vaccination (ORV) occurred, subsequent to the commencement of the ORV program.(Ma et al.  
205 2010) Their study was concerned only with raccoons and examined counties where ORV had  
206 been provided, however, and compared them to the eastern counties of the state, rather than the  
207 state as a whole. Likewise, their data only extended up through 2007. They did identify 2002 as  
208 the peak of RRV positives in the state, with a subsequent smaller peak in 2006, but their study  
209 period ceased prior to the peaks in 2009 and 2011 shown in Figure 1. Here we also considered  
210 disease in non-raccoon animals, both domestic and non-domestic.

211           There are several potential reasons for the reduction in RRV incidence over the study  
212 period. The ORV project is well established in the state, and may be having a significant effect  
213 on overall RRV numbers. Additionally, given the rapidly fatal progression of the infection in  
214 affected animals, it is possible that the disease is “burning itself out” and has reached, or is

215 reaching, a self-limiting steady state. Fluctuations in state and local human populations may be  
216 affecting raccoon numbers, with concomitant changes in animal contacts with affected animals.

217         The temporal pattern of RRV infection in non-raccoon animals may be cause for concern.  
218 One would anticipate that as numbers of RRV positive raccoons decline, numbers in non-  
219 raccoon species would experience a similar decline. This is not borne out by the data examined  
220 here. NDNR and domestic species had no significant changes in RRV positive animals. The fact  
221 that both are not declining tends to decrease the likelihood that this is simply a reflection of  
222 diminished domestic animal vaccination practices. This would indicate that RRV is not  
223 experiencing a decline in these animal species, and could be indicative of the virus becoming  
224 independently established in another reservoir where baits are not having an effect. This is of  
225 particular concern in the case of domestic animals, as these are most likely to have close contact  
226 with humans. Additionally, there were a number of cases in livestock species (such as horses,  
227 cows, sheep and goats). Although less frequently encountered than in domestic carnivores, these  
228 cases may actually represent higher risk to humans due to a lowered index of suspicion among  
229 farmers or veterinarians caring for these animals. This could cause significant delay in proper  
230 diagnosis of these infections, potentially allowing owners and others to have greater risk of  
231 infection.

232 *Limitations:* The data available constrain the current study. Given that the data provided are  
233 limited to county and year of collection and/or analysis, it is impossible to examine seasonal  
234 patterns or perform more detailed geographic analysis. Additionally, it is difficult to assess  
235 whether the animals submitted for testing are truly representative of the disease as it exists in the  
236 larger natural population of these species. It is possible that these animals represent a biased  
237 sample of the population as a whole. Finally, the limited number of submissions of non-raccoon

238 animals, both domestic and wild, may place constraints on accurate assessment of the  
239 longitudinal trend in these species. The analyses suggested the need for an analytic approach that  
240 accounts for the high number of zeros in the data. Thus, a ZIP model was more appropriate given  
241 the data distribution; correspondingly, the fitted model had a lower AIC.

## 242 **Conclusion**

243 This study demonstrates that numbers of RRV positive animals declined significantly  
244 over the study period throughout the state of WV, particularly in the primary viral reservoir host,  
245 raccoons. There is no reason to assume that diagnostic or recovery methods have changed during  
246 this same period. Further examination of RRV in non-raccoon species seems warranted to  
247 explain why these diverse groups are not trending down also. Future directions for this work  
248 include a spatial analysis of those factors that may be associated with RRV and raccoon  
249 populations, including land use, human population density and availability of surface water as  
250 well as ambient weather conditions. Additionally, cluster analysis of RRV positives would  
251 provide useful information to use as guidance for RRV control and other public health measures.

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**Table 1** (on next page)

Comparison of regression models fit for RRV in West Virginia, 2000-2015.

Comparison of the regression models evaluated in this study. All models showed significant reduction in RRV for the study period (2000-2015), with the ZIP regression providing the best fit to the data.

<sup>a</sup> Lower value indicates better fit

<b>Analysis type</b>	<b>Coefficient (SE)</b>	<b>p-value</b>	<b>AIC<sup>a</sup></b>
<b>Linear-mixed model</b>	-0.061 (0.02)	0.0024	4432.4
<b>Poisson model</b>	-0.050 (0.006)	<0.001	2377.5
<b>Zero inflated Poisson model</b>	-0.044 (0.006)	<0.001	2260.2

**Table 2** (on next page)

ZIP regression coefficients, p-values and AIC for the different animal types in this study, West Virginia, 2000-2015.

A comparison of the regression coefficients for the animal types during the study period, 2000-2015. Note the lack of significance of the regressions for the NDNR and domestic species. (NDNR = Nondomestic, non-raccoon)

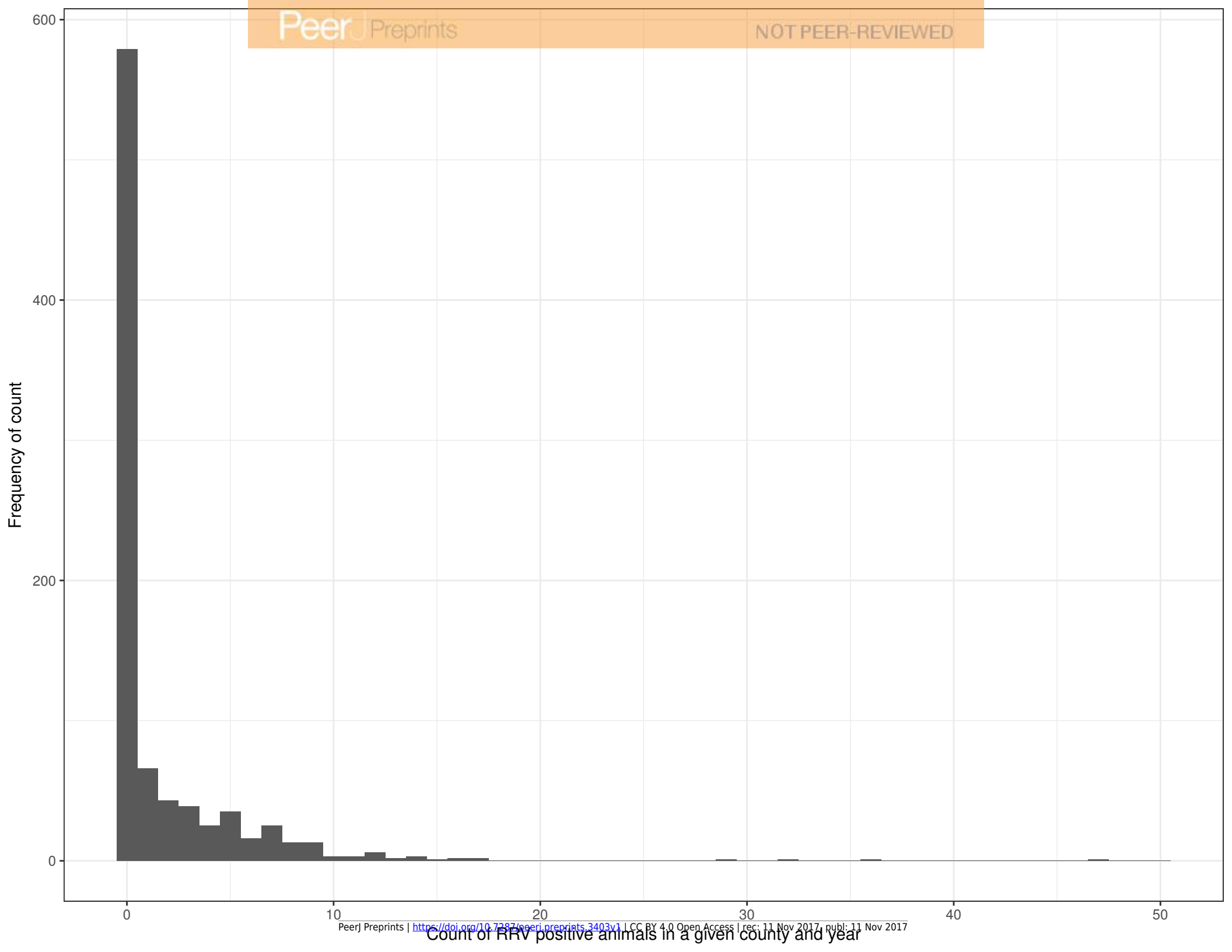
<i>Animal type</i>	<i>Regression coefficient (SE)</i>	<i>p-value</i>	<i>AIC</i>
<b>Raccoon</b>	-0.053 (0.008)	<0.001	1924.3
<b>NDNR</b>	-0.007 (0.012)	0.55	1057.1
<b>Domestic</b>	0.002 (0.024)	0.93	584.6

**Figure 1**(on next page)

Histogram of total RRV positives by county (n=55) in West Virginia, 2000-2015.

The histogram demonstrates the preponderance of zero count entries in the study period, necessitating zero inflated Poisson analysis.





Count of RRV positive animals in a given county and year

**Figure 2** (on next page)

Numbers of RRV positive animals by animal type, West Virginia, 2000-2015 .

Figure 2 depicts the decline of RRV in raccoons over the study period, 2000-2015. There was no concomitant decline in non-raccoon species.

