Rabies Virus Neutralizing Antibody Levels in Veterinary Medical Professionals: A Cross Sectional Study from Samples Collected at U.S. Veterinary Continuing Education Conferences

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Abstract

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Rabies is a viral pathogen primarily spread by animal bites; the resultant infection is a nearly 100% fatal. The American Veterinary Medical Association recommends all veterinary team members should receive pre-exposure rabies vaccination. The World Health Organization recommends that Rabies Virus Neutralizing Antibody (RVNA) levels should stay at or above 0.5 IU/mL. The goal of this study was to leverage an existing data set to look at trends of rabies vaccine seropositivity in vaccinated veterinarians and begin to investigate duration of adequate titer.

This was a cross sectional study using data which the Kansas State University (KSU) Rabies Laboratory generated by recruiting participants at veterinary continuing education conferences between 2018-2020.

Of the 1788 participants this study, the majority (90%) of participants had RVNA titers which fell into the adequate range (>/= 0.5 IU/mL). The odds of women having inadequate RVNA was 56% lower (OR 0.44, 95% CI 0.31-0.63) than for men having inadequate RVNA. The odds of inadequate RVNA titers among participants from rabies endemic regions was 20% lower (OR 0.80, 95% CI 0.58–1.09) than for participants from non-endemic regions.

When exploring the duration of seropositivity, this study found that the odds of a participant having an adequate vaccine titer was 3% lower (95% CI, 2%-5% lower) for each year since last reported vaccination.

The odds of a participant having an adequate RVNA titer decreased by 4% (95% CI, 1%-6%) for every one-year increase in participants age at time of vaccination.

This study is reassuring. It demonstrates that rabies vaccination results in long lasting seropositivity for most individuals. We also observed that women seem to be more likely to respond well to the vaccine and that vaccine antibody titers do wane over time. These data indicate that re-vaccination or titer testing should be done for those who continue to be at risk due to time since vaccination sex and age.

Introduction

Rabies is a viral pathogen primarily spread by exposure of broken skin to saliva from infected animals. The resultant symptomatic infection is a nearly 100% fatal encephalitis. Worldwide human fatalities have been estimated to be around 59,000 deaths each year, though there is debate of the accuracy of this in the literature (1). This discrepancy exists in part due to barriers to rabies testing and surveillance in resource poor countries with a higher burden of disease (1,2). Diagnostic testing for rabies (in both animals and humans) remains expensive and inaccessible in more rural regions around the globe (2,3). Furthermore, despite rabies being enzootic in canine populations, for example in Chad and other countries both in Africa and Asia, there are only a few countries with official rabies death data reports (3). The majority of human rabies cases and deaths occur due to dog bites (1). Fortunately, several safe and effective human and animal vaccines are available. Unfortunately, cost and the intensive pre-exposure vaccine schedule (3 injections on day 0, 7, and 21 or 28) and cold chain requirements for the human vaccines mean that large scale human vaccination is not a viable solution (4). Barriers also exist to control of rabies in canine (and wild animal) populations, due to differences in animal management systems and access to routine rabies vaccinations (2).

The United States has established control over rabies in the domestic animal population in part due to effective pet management/vaccination strategies (4). However, rabies remains enzootic in wildlife populations throughout the U.S. resulting in exposure to both pets and humans. In 2018 in the U.S., 22,418 dogs and 21,764 cats were euthanized and submitted for rabies testing, of which 63 dogs and 241 cats tested positive (5). Therefore, individuals who work in close contact with wildlife and pets are at an increased bite risk and subsequently a higher risk of potential rabies exposure as compared to the general U.S. population (6).

Cases and deaths due to rabies in the U.S. are rare. Only 18 people were reported to have acquired and died due to rabies within the U.S. between 2009-2018. Possible exposure in the U.S. still occurs with some frequency, the CDC estimates that between 30,000 and 60,000 Americans receive post exposure prophylaxis each year (7). The estimated cost for post exposure rabies treatment varies from $1,200 - $6,500 not including wound care or hospital associated expenses (8). Part of post-exposure treatment requires use of the same products which are used as pre-exposure vaccinations, however, treatment protocols for those who have received pre-exposure vaccination requires fewer doses (4). Due in part to the cost associated with treatment and the mortality rate The American Committee on Immunization Practices (ACIP) recommends that persons at increased risk receive pre-exposure vaccination (4).

Pre-exposure rabies vaccination recommendations by the ACIP are based on 4 risk categories: continuous, frequent, infrequent, and rare risk (4). The highest risk level, continuous risk is defined as individuals in environments where the virus is continuously present in high concentrations. For these individuals exposures are likely to go unrecognized, for example those who work with the rabies virus for a research facility or rabies biologics production workers. Frequent risk includes individuals whose exposure levels are usually episodic, and exposure is likely to be recognized but may be unrecognized for example those who work with animals in an enzootic region and people who handle bats. Infrequent risk is defined as those who's exposure is nearly always episodic with source recognized such as those who work with animals where rabies is rare or those traveling to regions where rabies in enzootic. Rare risk includes the U.S. population at large, where exposure is always episodic and the source recognized. According to the American Veterinary Medical Association (AVMA) all veterinarians fall into the "Frequent Risk' category. This means that all veterinary staff who handle animals should follow the ACIP's recommendations of a primary pre-exposure vaccination, with titer checks every 2 years. Vaccinated individuals should receive a booster if their rabies virus neutralization antibody (RVNA) levels fall below the level of detection, a 1:5 serum dilution (9). The World Health Organization (WHO) has a more conservative recommendation, due in part to the aforementioned threshold being the limit of

detection for current testing methods, the WHO recommends keeping levels at or above a 1:50 serum dilution (10).

It is unclear how well the U.S. veterinary professional population follows either of these recommendations. A study from Australia, where there is no terrestrial rabies, shows that 35% of veterinarians had received their primary rabies vaccine series (11). In theory U.S. veterinary professionals, because there is terrestrial rabies in the U.S., should be more motivated to be proactive about their rabies vaccination habits than Australian veterinary professionals. A study on RVNA levels in veterinary medical students in the U.S. found that two years following pre-exposure vaccination nearly 30% had RVNA levels which were inadequate according the WHO's recommendations (12). Most reports showing inadequate RVNA levels following primary vaccination range from 11-30% failure after one to two years following primary vaccination, however, re-vaccination after one to two years seems to be correlated with long lasting immunity for most individuals (13–16). The primary aim of this study was to utilize a data set that already exists to look at a trend in rabies vaccine seropositivity in veterinary professionals in the U.S. and begin to investigate how durable seropositive may be.

Methods

Study Design

This was a cross sectional study which used de-identified data obtained from Kansas State University (KSU) Rabies Lab based on convenience sampling of attendees at veterinary professional conferences.

Participants

KSU staff recruited from U.S. veterinary continuing education conferences by providing a discounted and convenient onsite serology testing service. Recruiting occurred at the following conferences between 2018-2020: Western Veterinary Conference 2019 & 2020, Veterinary Meeting & Expo 2018, 2019, 2020, Fetch Kansas City 2018 & 2019, Fetch East 2018, Fetch Baltimore 2019, American Veterinary Medical

Association WCV 2019 & 2020, American Veterinary Medical Association 2018 & 2019 and American Association of Equine Practitioners 2019. Participants were conference attendees interested in having their Rabies Virus Neutralizing Antibody levels measured. Data collection occurred at the same time as sample collection through participants filling out a brief questionnaire. This questionnaire asked for participants name, age, sex, address and contact information. There was a single line where participants could report their rabies vaccine history.

Exposures

In this analysis several exposures and their effect on RVNA were explored. These exposures were sex, region, year of birth, time since last reported vaccination, rabies revaccination (or booster) reporting. Living in an endemic region was also explored as a potential exposure which may affect booster reporting. Data for these exposures all came from or were calculated based on information from the questionnaire.

To determine sex participants had the option to choose between male or female.

Region was reported as the U.S. Department of Health and Human Services (HHS) region in which a participants' address from the questionnaire belonged. HHS divides the country into 10 regions with a regional office located within each one (17). Regions are named after the state in which the regional office is located. For those who did not live in the U.S. an additional category, "other" was created, resulting in 11 regions for this study.

Regions were additionally grouped for analysis by endemicity. Endemic regions were defined as HHS regions which included one or more of the 6 states which accounted for more than half of all animals that tested positive for rabies in 2018 (5) all other regions were defined as non-endemic. By this definition

endemic HHS regions were Dallas, DC, Atlanta, Denver, and New York City. International participants were not included in this part of the analysis

The questionnaire asked for participants age, this was reported as participants year of birth. Year of birth was used to calculate all age-related variables and to confirm participants were 18-79 years old at the time of sample collection.

The year of the most recently reported vaccination date and year of sample collection was used to calculate a variable time since last reported vaccination. Since these were free text field responses, it was necessary to manually code the variable using some judgement to interpret responses. Illogical dates such as dates after the sample collection or dates which were before participants year of birth were set to missing. Date ranges greater than 2 years were also set to missing. If a date range of two years was reported the later of the two years was used. Participants who reported multiple discrete dates for vaccination or explicitly stated they had a received a booster vaccine were counted as having reported a booster vaccine.

Confounder

Time since last reported vaccination was treated as a confounder for when looking into how age at last reported vaccination affected RVNA levels. The passage of time effects the dependent variable, RVNA levels, as vaccine titers generally wane over time. The independent variable, age at time of last reported vaccination, may be influenced by individuals' previous decisions to re-vaccinate based on time passing since their last (non-reported) vaccination.

Outcomes

The outcome of interest was RVNA levels which were measured using blood samples collected from study participants at the conferences. These samples were analyzed at KSU Rabies Lab using a serum

neutralization assay; Rapid Fluorescent Focus Inhibition Test (RFFIT). Endpoint titers were calculated based on protection of eucaryotic cells following incubation of serum dilutions with the rabies virus. These titers were converted to International Units (IU) based on a reference serum, in general a sample titer value can be divided by 100 to get an estimate of the IU/mL value (a 1:50 titer is roughly equivalent to 0.5 IU/mL). The quantification test reported three separate levels as results: under the level of detection, <0.5 IU/mL, and >/= 0.5 IU/mL.

For this study RVNA levels were defined as adequate or inadequate based on WHO recommendations. "Adequate levels" were results >/= 0.5 IU/mL and "Inadequate levels" were all results <0.5 IU/mL (10). A small portion of samples was analyzed using a quantification test which evaluates additional serum dilutions. For the sake of this study, all quantified values were added to the appropriate screening level. Booster reporting was also treated as an outcome to explore if there was a difference in reporting for those in endemic regions.

Statistical Methods

Data cleaning and analysis was preformed using R Studio Version 1.1.456. Descriptive statistics were generated to evaluate the distribution of RVNA adequacy in participants based on variables of interest and to look for trends in the data. Odds ratios and Wald-type 95% confidence intervals were evaluated to investigate associations between RVNA inadequacy and sex, and for RVNA inadequacy and endemic region. The same test was done to examine the relationship between booster reporting and 'endemic' region. Logistic regression was used to explore the relationship between time since last reported vaccination, age, and RVNA adequacy.

Results

There were 1788 total participants in this study, nearly 90% of participants had RVNA levels which fell into the adequate range (>/= 0.5 IU/mL) and most participants did report an interpretable vaccine history

(14.85% missing). Of the 10% of individuals who had inadequate levels, 159 had detectable RVNA levels (< .5 to >/= 0.1 IU/mL) and only 20 participants (1% of all participants) had levels below the threshold of detection (<0.1 IU/mL) (Table 1).

Most study participants (82%) were female. There was more missing data regarding age at time of last reported vaccination than there was for age when sample was collected (14.8% vs 0.5%). Most participants belonged to HHS regions Philadelphia, Atlanta, Chicago, and San Francisco. Only 12.5% (223) of participants reported a vaccine booster (Table 1).

The mean age of participants at the time of sampling was 42.9 years of age and the average age at the time of last reported vaccination in this study was 27.6 years of age. The mean number of years since last reported vaccination was 14.2 years (range, 0-50 years). Participants who had adequate RVNA levels had a mean of 13.9 years since last reported vaccination while those who had inadequate RVNA levels had a mean of 16.2 years for those with detectible levels and 25.5 years for those with levels under the limit of detection (Table 1).

Female participants tended to be younger than male participants (Figure 1). The odds of women having inadequate RVNA was 0.44 (95% CI 0.31-0.63) times that of men having inadequate RVNA (Table 2). The odds of inadequate RVNA levels among participants from endemic HHS regions was 0.80 (95% CI 0.58–1.09) that of participants from non-endemic regions (Table 2). The odds of participants from endemic regions reporting a rabies vaccine booster was 1.32 (95%CI 0.98-1.77) times greater than participants from non-endemic regions (Table 3).

The odds of a participant having an adequate vaccine titer was 3% lower (95% CI 2%-5%) for each year since last reported vaccination (Table 4). RVNA adequacy independent of sex seems to peak around 10 years since last reported vaccination while RVNA inadequacy peaks at around 10 years and just after 20

years since last reported vaccination (Figure 2). The odds of a participant having an adequate RVNA titer decreased by 4% (95% CI 1%-6%) for every one-year increase in participants age, when controlling for time since last reported vaccination (Table 4).

Discussion

This analysis highlights trends in accord with previous studies. Rabies vaccination results in long lasting immunity, as nearly 90% of participants had adequate levels. Women are more likely to respond favorably to the vaccine and age at time of vaccination may play a role in response. This study did not evaluate to what degree the difference in age may have played in women's decreased odds of an inadequate RVNA levels.

Exploratory analysis did not show any significant difference between RVNA levels or booster reporting by endemic regions as the confidence intervals for this exploratory testing did include the null hypothesis. This may be in part due to the lack of specificity for how we were able to define endemicity. It does appear that participants from endemic regions may be more likely to have inadequate RVNA levels than those from non-endemic regions. Additionally, participants from endemic regions may be more likely to report having received a booster. The expectation was that participants living in endemic regions would be more likely to have proactive rabies vaccination habits due a perceived increased change of exposure and/or different state and school requirements. For example, veterinary schools have different rules regarding pre-exposure rabies vaccination requirements. Washington State Universities' College of Veterinary Medicine does not require that students receive pre-exposure rabies vaccination. However, Cornell Universities' College of Veterinary Medicine located in one of the endemic states New York, does require vaccination. To further explore this concept and rule in or out the hypothesis that endemicity makes a difference in rabies vaccination, additional data describing habits of veterinarians are needed. Specifically, more granular data regarding region and more accurate reporting of rabies vaccination history. This would not account for individuals who re-locate throughout their career, which may require

a longitudinal study to thoroughly evaluate. As it stands in this study multiple states are included in the endemic category which have significantly lower rates of rabies positive animals than the 6 most endemic states (5) and the questionnaire did not ask explicit questions regarding rabies vaccination history.

The significant duration of RVNA level adequacy following last reported vaccination is demonstrated in part in by the density plot in Figure 2 and by the results of the simple logistic models. As seen in Figure 2 there are two peaks for inadequate RVNA. The second peak occurs after shortly after 20 years. It is possible that this reflects individual variability it may also be a reflection of the population sampled. As men in this study were generally older, and men were more likely have an inadequate response. Using a simple logistic regression model to further explore the relationship between time since last reported vaccination and RVNA adequacy we found that the odds of a participant having an adequate RVNA level was slightly, but still significantly, decreased for each year since last reported vaccination (Table 4).

We found that age at time of last reported vaccination may have a role in the duration of response to pre-exposure rabies vaccination, consistent with lower vaccine response (and shorter duration of protection) with older age. Although we were able to control for time since vaccination, other potential sources of variation in response, such as type of vaccine and vaccine schedule, were not known .

In this study the average age of vaccination was estimated to be 27.6 years which is very similar to the average age (27 years old) for students graduating from veterinary professional programs (18). This suggests that most veterinarians are receiving their rabies vaccinations around the time they are in school or at the start of their careers. And, based on these simple models it is likely that this is sufficient to result in long lasting seropositivity for most individuals. Unfortunately, there are few studies evaluating RVNA levels beyond 10 years following pre-exposure vaccination. This study suggests that RVNA levels may remain adequate beyond 10 years. However, levels do start to wane with age and as other studies have indicated they may drop off more quickly for older adults (15). Having more specific information

regarding participants vaccine history in a similarly structured study may allow for better evaluation of long term duration of immune response to rabies vaccination.

In a future longitudinal study, we suggest that more detailed information regarding vaccine history and geographic location of participants be obtained. Those data paired with repeated quantitative titer testing over time would allow researchers to better analyze the duration of vaccine response. Ideally such a study would also include regularly quantifying RVNA levels testing once participants were enrolled, in addition to tracking what states participants worked in over time. However, such a study would likely be cost prohibitive. A less costly future direction may be to modify a similar cross-sectional study by adding: a comprehensive questionnaire regarding vaccination history, improved granularity regarding location, and quantitative titer testing with active recruitment of veterinary professionals. This may not eliminate recall bias but it would provide for more consistent reporting of vaccine history from participants and decrease some misclassification.

Strengths and Limitations

The strength of this cross sectional study combined self-reported data with RVNA testing, but limitations in the questions asked led to bias and misclassification. It is likely that the further removed in time an individual may be from their last rabies vaccination, the less likely they are to accurately recall the date. For this study, we sought to minimize misclassification by excluding responses that were vague (for example, if a response to vaccine history: were "in the 80's" their response was treated as if they had not reported). How participants reported their history may also have been influenced by non-standardized data collection, which may not have been consistent across every conference.

Participants in this study were predominately women, and while veterinary medicine is a female dominated filed, this study was more skewed than expected. Demographics of the field from 2019 showed that roughly 63% of veterinarians were women (19) while 82% of participants in this study were women.

This could be due to a variety of factors; ranging from women being more likely to get the rabies vaccine to women being more likely to attend large continuing education conferences and participate in this study. Future studies may need to consider how to enroll participants so that sample size is adequate to evaluate if there is a difference in rabies vaccination adherence and RVNA levels by gender.

Generalizability, of this sample is problematic as well. We can see sex does not align with general demographics in the field. There may also be differences in veterinarians who attend large conferences vs those who do not. Individuals with families may be less likely to travel to attend these conferences which may affect the age range of those participating in the study. Often large conferences are more focused on small animal medicine (cats and dogs) and those who predominately work with large animals, pocket pets, wildlife or exotics may be less likely to attend. Additionally, there is no way tell if the same individuals attended and had their RVNA levels tested at multiple conferences and is represented in the data more than once. This study was unable to account for possible differences in RVNA response based on vaccine schedule, type of vaccine given, if individuals received the full primary course of vaccinations, or effects pre-existing medical conditions that could impact host response to the vaccine.

This study demonstrates that rabies vaccination results in long lasting seropositivity for most individuals. We also observed that women seem to be more likely to respond well to the vaccine and that vaccine antibody titers do wane over time. These data suggest that re-vaccination or titer testing should be done for those who continue to be at risk due to time since vaccination, sex and age.

Tables and Figures

	Rabies Virus Neutralizing Antibody Levels			
	Adequate	Inadequate		
	>/= 0.5 IU/mL (N=1609)	< 0. 5 to >/= 0.1 IU/mL (N=159)	< 0.1 IU/mL (N=20)	Total (N=1788)
Sex				
Female	1348 (83.8%)	113 (71.1%)	12 (60.0%)	1473 (82.4%)
Male	259 (16.1%)	46 (28.9%)	8 (40.0%)	313 (17.5%)
Missing	2 (0.1%)	0 (0%)	0 (0%)	2 (0.1%)
Region				
Boston	63 (3.9%)	10 (6.3%)	0 (0%)	73 (4.1%)
New York+	91 (5.7%)	5 (3.1%)	1 (5.0%)	97 (5.4%)
Philadelphia+	304 (18.9%)	30 (18.9%)	3 (15.0%)	337 (18.8%)
Atlanta+	285 (17.7%)	19 (11.9%)	2 (10.0%)	306 (17.1%)
Chicago	211 (13.1%)	11 (6.9%)	3 (15.0%)	225 (12.6%)
Dallas+	158 (9.8%)	14 (8.8%)	0 (0%)	172 (9.6%)
Kansas City	80 (5.0%)	11 (6.9%)	0 (0%)	91 (5.1%)
Denver+	149 (9.3%)	21 (13.2%)	5 (25.0%)	175 (9.8%)
San Francisco	182 (11.3%)	28 (17.6%)	3 (15.0%)	213 (11.9%)
Seattle	74 (4.6%)	10 (6.3%)	3 (15.0%)	87 (4.9%)
Other	12 (0.7%)	0 (0%)	0 (0%)	12 (0.7%)
Age When Sample Collected				
Mean (SD)	42.3 (11.3)	47.6 (13.2)	54.6 (14.1)	42.9 (11.7)
Missing	7 (0.4%)	2 (1.3%)	0 (0%)	9 (0.5%)
Reported Booster*				
No	1399 (86.9%)	147 (92.5%)	19 (95.0%)	1565 (87.5%)
Yes	210 (13.1%)	12 (7.5%)	1 (5.0%)	223 (12.5%)
Age at Last Reported Vaccination*				
Mean (SD)	27.4 (7.45)	29.8 (9.35)	29.7 (5.50)	27.6 (7.63)
Missing	227 (14.1%)	33 (20.8%)	4 (20.0%)	264 (14.8%)
Time Since Last Reported Vaccination (years)*				
Mean (SD)	13.9 (8.91)	16.2 (10.3)	25.5 (14.1)	14.2 (9.19)
Missing	222 (13.8%)	31 (19.5%)	4 (20.0%)	257 (14.4%)

Table 1.
Summary statistics for rabies virus neutralizing antibody levels >/= 0.5 IU/mL, <0.5 to >/= 0.1 IU/mL and <0.1 IU/mL by participants sex, US Department of Health & Human Services (HHS) Region, age at time of sample collection, reported booster, age at last reported vaccination and years since last reported vaccination.
* These results are derived an open-ended question “Rabies Vaccine History” and were not directly asked on the questionnaire.
+ Regions which contain at least one of the 6 states that accounted for nearly 50% of animals which tested positive for rabies in 2018.

RVNA Inadequacy by Sex and Region
The effect of a one-year increase in time on the odds of a participants RVNA results being adequate

	OR	CI (95%)
Female	0.44	0.31-0.63
Endemic	0.80	0.58-1.09

Table 2.
Odds ratios for the relationship between RVNA inadequacy and being female and for RVNA inadequacy and being from Endemic Regions.
[+] Regions were separated into endemic and non-endemic groups. Endemic refers the HHS regions which include states which accounted for nearly 50% of rabid animal cases in 2018.

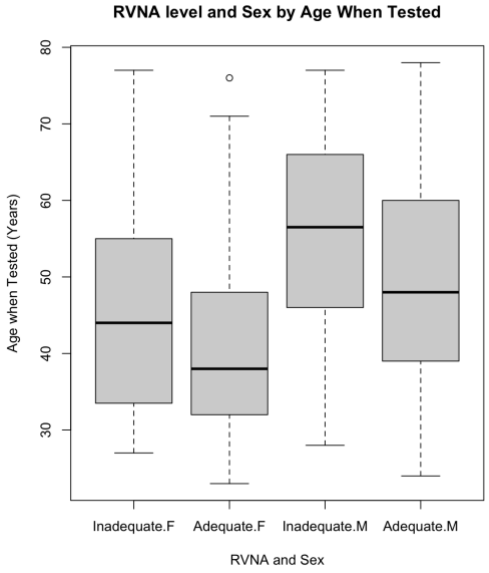

Figure 1.
Box plot showing how RVNA adequacy differs by age and sex when tested. In the labels .F stands for female & .M for male.

Booster Reporting by Region		
	OR	**CI (95%)**
Reported Booster	1.32	0.98-1.77

Table 3.
Odds ratio for booster reporting by region. Endemic is defined as HHS regions which contain at least one of the 6 states that accounted for nearly 50% of animals which tested positive for rabies in 2018.

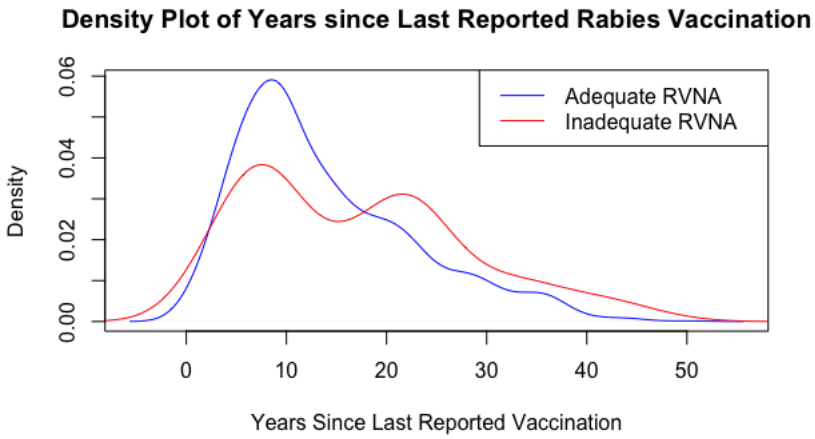

Figure 2.
Density plot displaying the difference in distribution of years since last reported vaccination by RVNA adequacy. The blue line is the distribution for those who had adequate RVNA levels and the red line represents those who had inadequate RVNA levels. The inadequate group has two peaks the second peak shows that around 20 years after last reported vaccination, inadequate results become more frequent.

Logistic Regression Results
The effect of a one-year increase in time on the odds of a participants RVNA results being adequate

	OR	CI (95%)
Time Since Last Reported Vaccine	0.97	0.95-0.98
Age at Last Reported Vaccine*	0.96	0.94-0.99

Table 4.
Logistic regression was used to evaluate how a one-year increase in time since…would affect the odds of a participant's RVNA levels being adequate
*The model for age at last reported vaccination controlled for time since last reported vaccination.

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