

ANAMNESTIC RESPONSE TO RABIES VACCINE:
COMPARING THE RESPONSES IN CURRENTLY
VACCINATED VS. OUT-OF- DATE DOGS AND
CATS.

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Thanks

Dr. Cathy Hanlon

Dr. Sue Nelson

Dr. John Teeter

Dr. Don Dinges

RABIES

- 1) Viral Disease
- 2) Zoonotic
- 3) Reportable
- 4) 100% fatal
 - there is no treatment
- 5) 100% preventable in humans
 - with prophylactic vaccination and passive antibody

Each year in the United States thousands of domestic cats and dogs are exposed to rabies. Primarily from the bite of a rabid wild animal.

Because of the zoonotic nature of rabies, and the severity of the disease, public health is charged with the task of making sure that a human exposure is not the end game of these exposures.

Each state has its own laws that govern how these exposed animals are handled.

Most Public Health Officers use the guidelines from the National Association of State Public Health Veterinarians (NASPHV). They along with the Centers of Disease Control (CDC) and other rabies experts, publish the Compendium of Animal Rabies Prevention and Control (Compendium) to provide guidance on the disposition of exposed animals.

Exposed animals are broken down into 3 categories.

- 1) Currently vaccinated
- 2) Out of Date
- 3) Non-Vaccinates

The Compendium recommendations for currently vaccinated and non-vaccinates are clear cut.

The recommendations for out of date animals are intentionally vague so they can be evaluated on an individual basis.

Compendium states that the disposition of out of date dogs and cats exposed to rabies should be decided by these criteria.

- 1) Severity of exposure.
- 2) Time elapsed since last vaccination.
- 3) Number of previous vaccinations.
- 4) Current health status.
- 5) Local rabies epidemiology.

Vagueness

- 1) Current
- 2) Out of date
- 3) Non vaccinate

How this study came to be:

2009 - 2010

- Calls from veterinarians and pet owners to run titers

2010 - 2012

- Pilot study

2012 -2013

- Cross Sectional Study / with pilot included

Vaccine Response Study Represents

- 1) 75 dogs
- 2) 33 cats
- 3) 13 States
- 4) 3 years 9 months

Materials and methods:

- 1) Two ml serum samples were harvested upon initial presentation of the animal (day 0) and then again 5-7 days later.
- 2) Booster at day 0
- 3) Shipped fresh KSU/DL
- 4) Run by RFFIT – same set
- 5) Antibody titer of 0.5 IU/ml or greater was considered an adequate vaccine response
- 6) Titer determination (12)
- 7) Determination of Vaccine status
- 8) Data Analysis
 - proportional hazard model to test for non-inferiority.

Pilot Cohort Study

Exposed

Assession	Species	State	Birth date	Previous Vaccine	Previous Vaccine	Product Used	Exposure	Day 0 draw	Results	Booster date	Product Used	Day 5-7 draw	Results	Mos. From	Exposure Description	Current	Out of Date	6 Month	Survived
									IU/ml				IU/ml	Last Vacc.		Biological		Quarantine	
R10-4727	dog	NM	9/25/2005	yes	12/19/2006	3-year	3/17/2010	3/18/2010	9.7	3/18/2010	Imrab 3TF	4/2/2010	12	39.0	contact with skunk		X	X	X
R10-5663	cat	TX	5/16/2001	yes	1/1/2007	Defensor 3	3/?/10	3/25/2010	0.3	3/23/2010	Rabdomun3	3/30/2010	12	38.7	exposed to wild racoon (puncture wounds)		X	X	X
R10-14117	cat	MD	?/?/1999	yes	10/29/2006	3-year	7/?/10	7/27/2010	12	7/27/2010	3-year	8/4/2010	12	44.9	exposed to bat		X	X	X
R11-5757	dog	VA	?/?/2006	yes	7/1/2010	unknown	3/30/2010	4/1/2011	0	4/1/2011	Defensor 3	4/8/2011	12	9.0	killed (+) skunk	X			X
12-201967	dog	FL	10/10/2001	yes	7/31/2008	Merial K3	1/11/2012	1/12/2012	12	1/12/2012	Imrab 3TF	1/19/2012	12	41.4	racoon bite		X	X	X
12-205146	dog	KS	?/?/2002	yes	8/13/2010	Defensor 1	2/13/2012	2/14/2012	0.7	2/14/2012	Defensor 3	2/24/2012	3.4	18.1	bitten by racoon	X		X	X
12-207675	dog	KS	12/?/2008	no	3/19/2009	Defensor 3	3/15/2012	3/19/2012	0.6	3/19/2012	Defensor 3	3/26/2012	12	36.0	tangled with positive skunk		X	X	X
12-208012-1	dog	TX	?/?/2009	yes	12/2/2010	Imrab 3TF	3/19/2012	3/21/2012	12	3/21/2012	Imrab 3TF	3/29/2012	12	15.6	exposed to positive skunk	X			X
12-208012-2	dog	TX	?/?/2010	no	12/2/2010	Imrab 3TF	3/19/2012	3/21/2012	0.2	3/21/2012	Imrab 3TF	3/29/2012	12	15.6	exposed to positive skunk		X	X	X
12-210273	dog	NE	?/?/2008	no	12/29/2010	Defensor 3	4/3/2012	4/9/2012	0.6	4/9/2012	Defensor 3	4/19/2012	12	15.4	exposed to positive skunk		X	X	X
12-210560	dog	MO	?/?/2001	yes	10/1/2009	Pfizer (1 yr)	4/17/2012	4/17/2012	1.8	4/17/2012	Imrab 3TF	4/23/2012	12	30.5	bite on nose by racoon (not tested)	X		X	X
12-211068	dog	GA	?/?/2007	yes	4/1/2010	Imrab 1TF	4/?/2012	4/25/2012	0.5	4/25/2012	Nobivac 1	5/7/2012	12	24.8	bite by wild animal	X		X	X
12-215340	dog	KS	6/?/2006	yes	7/11/2011	Defensor 3	5/29/2012	6/2/2012	3.1	6/2/2012	Defensor 3	6/9/2012	12	10.7	exposed to (+) skunk	X			X

Anamnestic Titers

Assession	Species	State	Birth date	Previous Vaccine	Previous Vaccine	Product Used	Exposure	Day 0 draw	Results	Booster date	Product Used	Day 5-7 draw	Results	Mos. From	Exposure Description	Current	Out of Date	6 Month	Survived
									IU/ml				IU/ml	Last Vacc.		Biological		Quarentine	
R10-4727	dog	NM	9/25/2005	yes	12/19/2006	3-year	3/17/2010	3/18/2010	9.7	3/18/2010	Imrab 3TF	4/2/2010	12	39.0	contact with skunk		X	X	X
R10-5663	cat	TX	5/16/2001	yes	1/1/2007	Defensor 3	3/3/10	3/25/2010	0.3	3/23/2010	Rabdomun3	3/30/2010	12	38.7	exposed to wild racoon (puncture wounds)		X	X	X
R10-14117	cat	MD	?/?/1999	yes	10/29/2006	3-year	7/?/10	7/27/2010	12	7/27/2010	3-year	8/4/2010	12	44.9	exposed to bat		X	X	X
R11-5757	dog	VA	?/?/2006	yes	7/1/2010	unknown	3/30/2010	4/1/2011	0	4/1/2011	Defensor 3	4/8/2011	12	9.0	killed (+) skunk	X			X
12-201967	dog	FL	10/10/2001	yes	7/31/2008	Merial K3	1/11/2012	1/12/2012	12	1/12/2012	Imrab 3TF	1/19/2012	12	41.4	racoon bite		X	X	X
12-205146	dog	KS	?/?/2002	yes	8/13/2010	Defensor 1	2/13/2012	2/14/2012	0.7	2/14/2012	Defensor 3	2/24/2012	3.4	18.1	bitten by racoon	X		X	X
12-207675	dog	KS	12/?/2008	no	3/19/2009	Defensor 3	3/15/2012	3/19/2012	0.6	3/19/2012	Defensor 3	3/26/2012	12	36.0	tangled with positive skunk		X	X	X
12-208012-1	dog	TX	?/?/2009	yes	12/2/2010	Imrab 3TF	3/19/2012	3/21/2012	12	3/21/2012	Imrab 3TF	3/29/2012	12	15.6	exposed to positive skunk	X			X
12-208012-2	dog	TX	?/?/2010	no	12/2/2010	Imrab 3TF	3/19/2012	3/21/2012	0.2	3/21/2012	Imrab 3TF	3/29/2012	12	15.6	exposed to positive skunk		X	X	X
12-210273	dog	NE	?/?/2008	no	12/29/2010	Defensor 3	4/3/2012	4/9/2012	0.6	4/9/2012	Defensor 3	4/19/2012	12	15.4	exposed to positive skunk		X	X	X
12-210560	dog	MO	?/?/2001	yes	10/1/2009	Pfizer (1 yr)	4/17/2012	4/17/2012	1.8	4/17/2012	Imrab 3TF	4/23/2012	12	30.5	bite on nose by raccoon (not tested)	X		X	X
12-211068	dog	GA	?/?/2007	yes	4/1/2010	Imrab 1TF	4/?/2012	4/25/2012	0.5	4/25/2012	Nobivac 1	5/7/2012	12	24.8	bite by wild animal	X		X	X
12-215340	dog	KS	6/?/2006	yes	7/11/2011	Defensor 3	5/29/2012	6/2/2012	3.1	6/2/2012	Defensor 3	6/9/2012	12	10.7	exposed to (+) skunk	X			X

6 Month Quarantine

Assession	Species	State	Birth date	Previous Vaccine	Previous Vaccine	Product Used	Exposure	Day0 draw	Results	Booster date	Product Used	Day 5-7 draw	Results	Mos. From	Exposure Description	Current	Out of Date	6 Month	Survived
									IU/ml				IU/ml	Last Vacc.		Biological		Quarantine	
R10-4727	dog	NM	9/25/2005	yes	12/19/2006	3-year	3/17/2010	3/18/2010	9.7	3/18/2010	Imrab 3TF	4/2/2010	12	39.0	contact with skunk		X	X	X
R10-5663	cat	TX	5/16/2001	yes	1/1/2007	Defensor 3	3/?/10	3/25/2010	0.3	3/23/2010	Rabdomun3	3/30/2010	12	38.7	exposed to wild racoon (puncture wounds)		X	X	X
R10-14117	cat	MD	?/?/1999	yes	10/29/2006	3-year	7/?/10	7/27/2010	12	7/27/2010	3-year	8/4/2010	12	44.9	exposed to bat		X	X	X
R11-5757	dog	VA	?/?/2006	yes	7/1/2010	unknown	3/30/2010	4/1/2011	0	4/1/2011	Defensor 3	4/8/2011	12	9.0	killed (+) skunk	X			X
12-201967	dog	FL	10/10/2001	yes	7/31/2008	Merial K3	1/11/2012	1/12/2012	12	1/12/2012	Imrab 3TF	1/19/2012	12	41.4	racoon bite		X	X	X
12-205146	dog	KS	?/?/2002	yes	8/13/2010	Defensor 1	2/13/2012	2/14/2012	0.7	2/14/2012	Defensor 3	2/24/2012	3.4	18.1	bitten by racoon	X		X	X
12-207675	dog	KS	12/?/2008	no	3/19/2009	Defensor 3	3/15/2012	3/19/2012	0.6	3/19/2012	Defensor 3	3/26/2012	12	36.0	tangled with positive skunk		X	X	X
12-208012-1	dog	TX	?/?/2009	yes	12/2/2010	Imrab 3TF	3/19/2012	3/21/2012	12	3/21/2012	Imrab 3TF	3/29/2012	12	15.6	exposed to positive skunk	X			X
12-208012-2	dog	TX	?/?/2010	no	12/2/2010	Imrab 3TF	3/19/2012	3/21/2012	0.2	3/21/2012	Imrab 3TF	3/29/2012	12	15.6	exposed to positive skunk		X	X	X
12-210273	dog	NE	?/?/2008	no	12/29/2010	Defensor 3	4/3/2012	4/9/2012	0.6	4/9/2012	Defensor 3	4/19/2012	12	15.4	exposed to positive skunk		X	X	X
12-210560	dog	MO	?/?/2001	yes	10/1/2009	Pfizer (1 yr)	4/17/2012	4/17/2012	1.8	4/17/2012	Imrab 3TF	4/23/2012	12	30.5	bite on nose by raccoon (not tested)	X		X	X
12-211068	dog	GA	?/?/2007	yes	4/1/2010	Imrab 1TF	4/?/2012	4/25/2012	0.5	4/25/2012	Nobivac 1	5/7/2012	12	24.8	bite by wild animal	X		X	X
12-215340	dog	KS	6/?/2006	yes	7/11/2011	Defensor 3	5/29/2012	6/2/2012	3.1	6/2/2012	Defensor 3	6/9/2012	12	10.7	exposed to (+) skunk	X			X

The average increase in titer 5-7 days following booster vaccination for current and out of date dogs and cats is summarized in table 2.

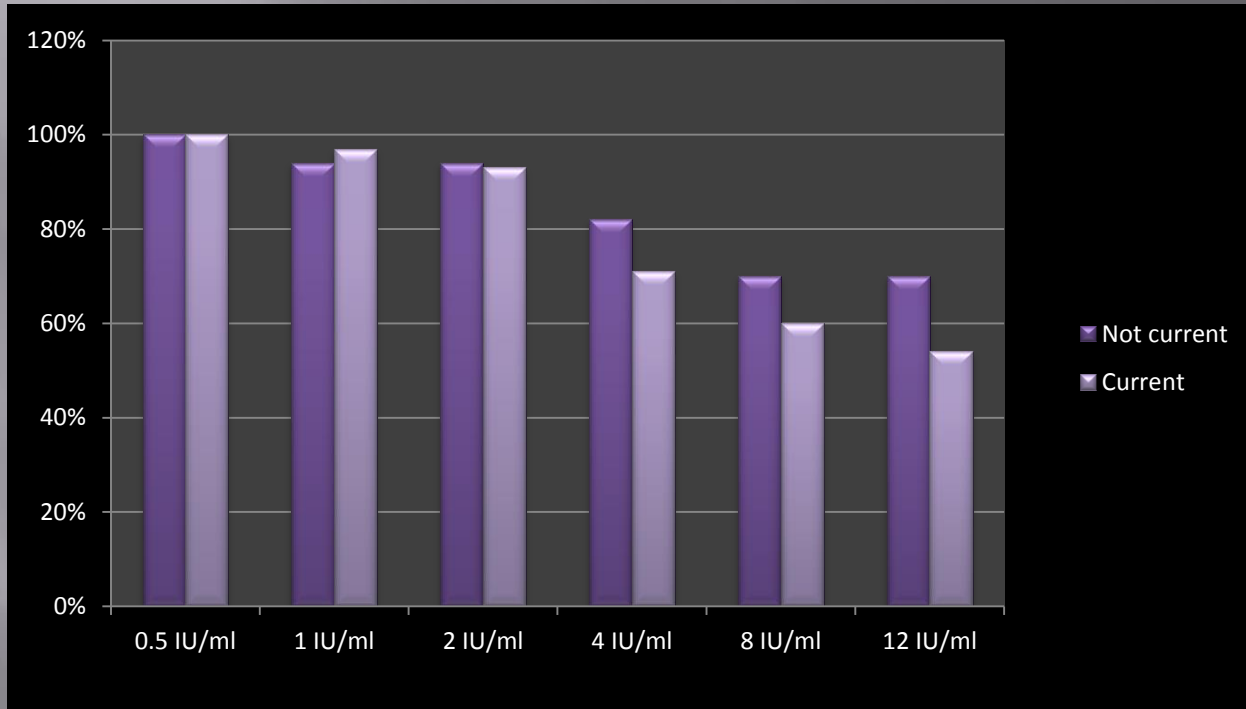
(Table 2)

			Ave. Start	Ave. End	Ave. Change	Ave. Fold rise
			IU/ml	IU/ml	IU/ml	
Dog (n=56)	current		4.1	8.3	4.2	1.3
Dog (n=19)	out of date		3.1	9.4	6.3	2.1
Cat (n=7)	current		3.5	10.7	7.3	2.1
Cat (n=26)	out of date		7	10.9	3.9	0.8

All animals in the study reached a 0.5 IU/ml titer following booster vaccination. The percentage of dogs and cats in each vaccine category that obtained fold rises above 0.5 IU/ml titers are shown in Table 3.

(Table 3)

		0.5 IU/ml	1.0 IU/ml	2.0 IU/ml	4.0 IU/ml	8.0 IU/ml	12.0 IU/ml
				% reached			
Dog (n=56)	current	100%	96%	91%	73%	62%	48%
Dog (n=19)	out of date	100%	94%	94%	84%	68%	68%
Cat (n=7)	current	100%	100%	100%	85%	85%	85%
Cat (n=26)	out of date	100%	100%	100%	88%	88%	76%



Fourteen dogs (9 current and 5 out of date) and 2 cats (1 current and 1 out of date) had titers below 0.5 IU/ml on day 0. All of these animals reached or exceeded a titer of 0.5 IU/ml within 8 days following booster vaccination (table 4).

(Table 4)

				Starting		Ending
				IU/ml		IU/ml
12-208012-2	dog	out of date	3/21/2012	0.2	3/29/2012	12
13-200389	dog	out of date	12/26/2012	0.2	1/2/2013	12
13-211925	dog	out of date	4/17/2013	0	4/22/2013	12
13-217935-7	dog	out of date	6/10/2013	0.4	6/17/2013	2.4
13-221941	dog	out of date	7/22/2013	0	7/30/2013	0.5
					Ave. End	7.8
R11-5757	dog	current	4/1/2011	0	4/8/2011	12
12-224778	dog	current	9/26/2012	0.4	10/3/2012	4.4
13-211605-1	dog	current	4/12/2013	0.3	4/17/2013	11.1
13-217935-9	dog	current	6/12/2013	0.4	6/19/2013	0.5
13-217935-11	dog	current	6/7/2013	0.1	6/14/2013	1.3
13-220131-7	dog	current	7/1/2013	0.1	7/8/2013	6.1
13-222033-1	dog	current	7/24/2013	0	7/31/2013	2
13-225691	dog	current	9/6/2013	0.1	9/11/2013	4
13-231389	dog	current	11/7/2013	0.3	11/13/2013	0.5
					Ave End	4.7
R10-5663	cat	out of date	3/25/2010	0.3	3/30/2010	12
13-208466	cat	current	3/20/2013	0.1	3/26/2013	12

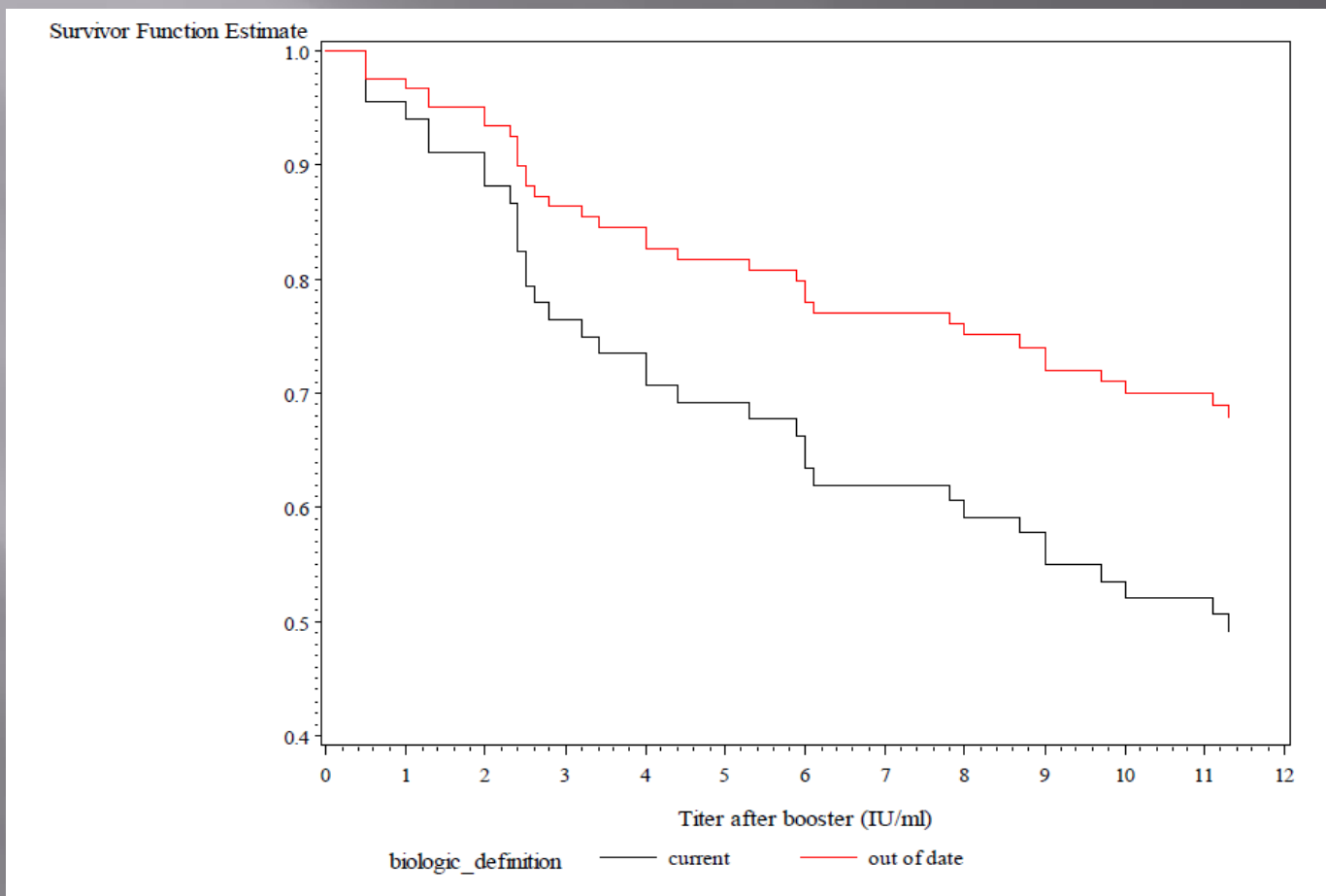
The average rise in titer for out of date animals was greater for those receiving only 1 prior vaccination compared to those receiving 2 or more prior vaccinations. These are arranged by length of time out of date in months (table 5).

(Table 5)

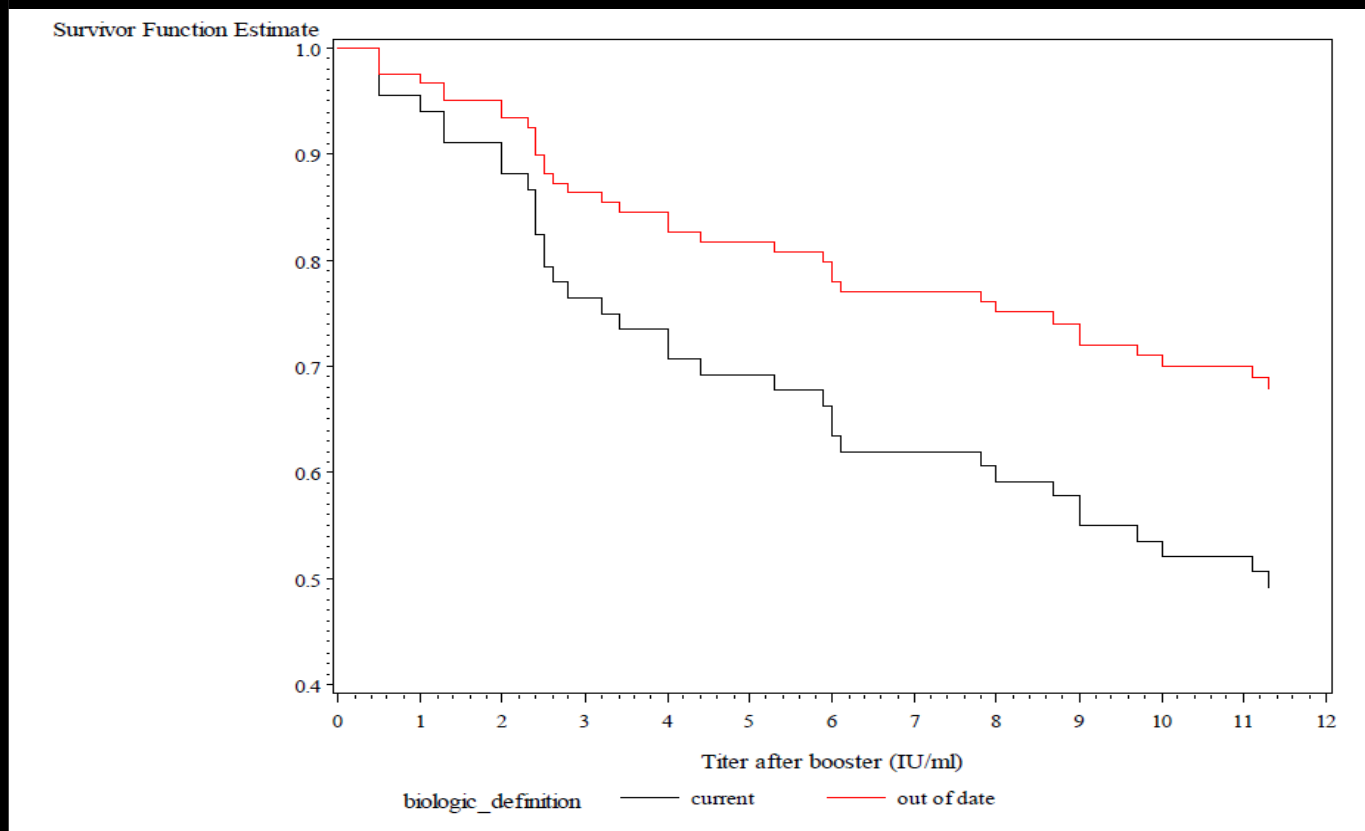
Vaccines Received	Accession	Species	Day 0 draw	Result	2nd draw	Result	Months	
Before Booster				IU/ml		IU/ml	Overdue	
2 or more	12-231786	dog	12/20/2012	0.6	12/26/2012	2.8	0.2	
2 or more	13-217935-7	dog	6/10/2013	0.4	6/17/2013	2.4	0.3	
2 or more	R10-4727	dog	3/18/2010	9.7	4/2/2010	12	3	
2 or more	13-233970	dog	12/6/2013	4	12/13/2013	5.9	4.8	
2 or more	13-206021	dog	2/25/2013	12	3/3/2013	12	7.5	
2 or more	13-219218-1	dog	6/24/2013	3.9	7/1/2013	12	10.6	
2 or more	13-218316-3	dog	6/17/2013	2.9	6/24/2013	7.8	14.9	
2 or more	13-221941	dog	7/22/2013	0	7/30/2013	0.5	19.7	
2 or more	13-219218-3	dog	6/24/2013	2	7/1/2013	12	22.8	
			Ave. Start	3.9	Ave. End	7.5	Ave Rise	3.5
1	13-224801-1	dog	8/15/2013	3.4	8/22/2013	12	0.3	
1	12-210273	dog	4/9/2012	0.6	4/19/2012	12	3.4	
1	12-208012-2	dog	3/21/2012	0.2	3/29/2012	12	3.6	
1	13-211925	dog	4/17/2013	0	4/22/2013	12	5.9	
1	12-207675	dog	3/19/2012	0.6	3/26/2012	12	24	
1	13-200389	dog	12/26/2012	0.2	1/2/2013	12	36.1	
			Ave. Start	0.8	Ave. End	12	Ave Rise	11.2

Vaccines Received	Accession	Species	Day 0 draw	Result	2nd draw	Result	Months	
Before Booster				IU/ml		IU/ml	Overdue	
2 or more	13-218316-5	cat	6/13/2013	12	6/21/2013	12	0.1	
2 or more	13-219978-5	cat	6/24/2013	6.1	7/1/2013	11.3	0.1	
2 or more	13-203255	cat	1/29/2013	12	2/5/2013	12	0.1	
2 or more	13-226978	cat	9/17/2013	3.4	9/24/2013	12	0.2	
2 or more	13-220131-9	cat	7/1/2013	12	7/8/2013	12	0.2	
2 or more	13-220131-17	cat	7/5/2013	5.4	7/11/2013	12	0.9	
2 or more	13-206233	cat	2/28/2013	6.4	3/6/2013	9	1.1	
2 or more	13-232141-1	cat	11/13/2013	12	11/20/2013	12	2.3	
2 or more	13-219978-9	cat	6/26/2013	12	7/3/2013	12	2.5	
2 or more	R10-5663	cat	3/25/2010	0.3	3/30/2010	12	2.7	
2 or more	13-222033-5	cat	7/13/2013	3.4	7/20/2013	3.7	2.9	
2 or more	13-217462	cat	6/7/2013	12	6/14/2013	12	2.9	
2 or more	13-218081	cat	6/14/2013	8.9	6/21/2013	12	3.2	
2 or more	13-217935-1	cat	6/8/2013	12	6/15/2013	12	3.7	
2 or more	13-213409	cat	5/1/2013	12	5/8/2013	12	5.6	
2 or more	13-213415	cat	5/1/2013	2.5	5/8/2013	12	5.6	
2 or more	13-219978-11	cat	6/26/2013	2.4	7/3/2013	12	8.4	
2 or more	R10-14117	cat	7/27/2010	12	8/4/2010	12	8.9	
2 or more	13-220131-15	cat	7/5/2013	2.4	7/11/2013	12	15.9	
2 or more	13-218316-9	cat	6/11/2013	3	6/17/2013	3.3	34.6	
2 or more	13-218316-1	cat	6/17/2013	0.6	6/24/2013	2.9	46.1	
			Ave. Start	7.3	Ave. End	10.6	Ave Rise	3.3
1	13-208465	cat	3/20/2013	0.6	3/26/2013	12	4.9	
1	13-220131-13	cat	7/5/2013	9.6	7/11/2013	12	21.2	
1	12-223557	cat	9/5/2012	2.7	9/11/2012	12	38.5	
			Ave. Start	4.3	Ave. End	12	Ave Rise	7.7

This is the graph of the survivor function analysis for the non-inferiority test. It compares (survival) of current and out of date dogs at a titer above the adequate response to vaccine level of 0.5 IU/ml. The out of date dogs were non-inferior ($p=.0325$).



The two populations (current and out of date) were compared by modelling their reverse cumulative distributions with respect to the observed titer. At a fixed titer value, this can be thought of as the proportion of animals in the population with a titer value at least as large as the given titer.



Discussion

Titer comparison:

- 1) Fold rise
- 2) Delta, or rise in titer
- 3) End point (5-7 days)

End Point Titer Comparison

Using a proportional Hazard Model to test for non-inferiority, out of date dogs anamnestic response to booster is equal to or greater than a currently vaccinated dog ($p=.0325$).

Our cats were not statistically significant. Probably because of lower numbers and higher titers.

With this study in mind, let's revisit the Compendium's criteria for evaluating out of date dogs exposed to rabies.

- 1) Severity of exposure.
- 2) Time elapsed since last vaccination.
- 3) Number of previous vaccinations.
- 4) Current health status.
- 5) Local rabies epidemiology.

Conclusion

The compendium states “because a rapid anamnestic response is expected, an animal is considered currently vaccinated immediately after a booster vaccination”. This statement coupled with the results of this study should warrant a policy change to booster healthy dogs and cats, which are overdue and exposed to rabies, and observe for 45 days instead of euthanasia or 6 month quarantine.

Four potential ways to handle this policy change would be:

- 1) Allow out of date animals and current animals to go home after a booster for a 45 day observation.
- 2) Do day 5-7 titers, after booster, on all exposed dogs and cats to determine if they reach an endpoint of pre-determined acceptance. If they do not, booster again and proceed with a 6 month quarantine.
- 3) Do day 5-7 titers, after booster, on biologically out of date animals exposed to determine if they reach an endpoint of pre-determined acceptance. If they do not, booster again and proceed with a 6 month quarantine.
- 4) Do day 5-7 titers , after booster, on by label out of date animals exposed to determine if they reach an endpoint of pre-determined acceptance. If they do not, booster again and proceed with a 6 month quarantine.