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Temporal dynamics of rabies in a wildlife host and the risk of cross-species transmission

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SUMMARY

An epidemiological model was developed for rabies, linking the risk of disease in a secondary species (cats) to the temporal dynamics of disease in a wildlife reservoir (raccoons). Data were obtained from cats, raccoons, and skunks tested for rabies in the northeastern United States during 1992–2000. An epizootic algorithm defined a time-series of successive intervals of epizootic and inter-epizootic raccoon rabies. The odds of diagnosing a rabid cat during the first epizootic of raccoon rabies was 12 times greater than for the period prior to epizootic emergence. After the first raccoon epizootic, the risk for cat rabies remained elevated at levels six- to seven-fold above baseline. Increased monthly counts of rabid raccoons and skunks and decreasing human population density increased the probability of cat rabies in most models. Forecasting of the public health and veterinary burden of rabies and assessing the economics of control programmes, requires linking outcomes to dynamic, but predictable, changes in the temporal evolution of rabies epizootics.

INTRODUCTION

Epidemiological models of zoonoses linking risk of disease in humans or a sentinel species to increasing densities of reservoir host or vector populations, frequently rely upon an environmental trigger to precipitate a cascade of events resulting in higher rates of cross-species pathogen transmission. Models linking environmental events, trophic cascades, and increased risk of human disease include the impact of El Niño-Southern Oscillation (ENSO) on hantavirus pulmonary syndrome in the southwestern United States [1] and masting of oak trees and Lyme disease in the northeastern states [2, 3]. In addition to requiring complex causal chains, the occurrences of environmental triggers are temporally variable; ENSO every 2–10 years and masting every 2–5 years. In this report, an epidemiological model of cross-species transmission (spillover) of rabies was developed where the temporal dynamics of disease in a wildlife reservoir host, the raccoon (*Procyon lotor*), was directly associated with risk of incidental rabies spillover to domestic cats (*Felis catus*). Furthermore, the temporal dynamics of rabies in raccoon populations can be understood and modelled using characteristics inherent to the virus and the outcome of disease among raccoons without recourse to external triggers. Some knowledge of the molecular epidemiology of rabies virus, the role of reservoir hosts in virus transmission, and various methods developed for predicting and documenting patterns in rabies occurrence is a prerequisite to further discussion.

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The enzootic areas affected by rabies and its wildlife hosts are typically circumscribed, and the borders can be determined with reasonable accuracy [4]. Distinct variants of rabies virus (hereafter referred to simply as 'variant') are associated with and maintained by one or more closely related species of mammal [the reservoir host(s)]. The virus circulating among raccoons is an antigenically and genetically distinct variant [5, 6]. In addition to raccoons, other species of carnivores and insectivorous bats serve as wildlife reservoirs for distinct variants in the United States [4].

Since 1990, raccoons have been the animals most frequently reported rabid in the United States [5]. The raccoon variant was restricted to the southeastern United States, when unexpectedly in the late 1970s, it was identified from an outbreak of raccoon rabies along the West Virginia/Virginia border [5, 7]. This emergence was attributed to the translocation of rabies-infected raccoons captured in the southeast for restocking of local populations [8]. The subsequent spread of this variant has been heralded by unprecedented increases in raccoon rabies and spillover to cats and other animals [9, 10]. Since 2002, the raccoon variant is enzootic from Alabama to Ontario, Canada [11, 12].

As rabies spreads into naive populations of raccoons inhabiting defined areas (i.e. a county), the long-term temporal dynamics of disease can unfold with regular and predictable features. An algorithm discriminating time-intervals of increased (epizootic) and diminished (inter-epizootic) counts of rabid raccoons was developed for use with state-based rabies surveillance data [9]. In the 'typical' county, the epizootic wave-front of rabies arrives within 3–4 months after the initial detection of the raccoon variant, and the ensuing epizootic generates unprecedented numbers of rabid raccoons [10, 13]. A lull (inter-epizootic interval) follows the epizootic, and raccoon rabies is markedly reduced and may seem to disappear [9]. Typically, a second epizootic occurs within a period of 4–6 years after the initial epizootic. Successive smaller epizootics of raccoon rabies follow. As epizootics diminish in size and increase in frequency, patterns devolve into a background of sporadic disease. During epizootics of raccoon rabies, over 10% of the affected animals are not raccoons [14, 15]. In 1999, molecular typing of tissues from 308 rabid cats and dogs identified 307 (99%) of the cases as infections due to the dominant terrestrial wildlife variant in the home state. The exception was a single cat infected by a bat variant [16].

Cats are the domestic animal most frequently diagnosed with rabies in the United States [11]. Cases among cats are most common in the eastern United States [10], the region recently affected by an epizootic of rabies associated with raccoons. In 2001, rabid cats outnumbered rabid dogs by 3 to 1 (270 cats, 89 dogs) [14]. The numbers of rabid cats increased over the past decades in the United States before stabilizing at between 250 and 300 cases per year, even as the number of rabid dogs declined to an historically low count in 2001 [14]. Factors contributing to the resilience of rabies in cats include their increasing popularity as companion animals, a large subpopulation of feral and free-ranging cats [17, 18], and less stringent and poorer compliance with rabies vaccination laws [15, 19, 20].

The skunk variant is enzootic in California and the north and south central United States [21]. In Ontario, enzootic skunk rabies is thought to have started from an epizootic of red-fox variant rabies in the 1950s [16, 22]. As the raccoon variant epizootic has progressed, there has been an increase in the number of rabid skunks, with the number of rabid skunks exceeding the number of rabid raccoons in some counties. Massachusetts and Rhode Island each reported more rabid skunks than raccoons from 1996 to 2000 [21]. It is not known if the raccoon variant in the East is becoming established in the skunks and circulating independently [23]. Raccoon variant has been recovered in skunks and skunks may constitute an important secondary source of rabies among cats.

Reports of increases in rabies spillover coincident with epizootics of raccoon rabies have been largely descriptive [15, 24, 25]. Herein, methods previously developed to describe the temporal dynamics of rabies in raccoons were extended to explore how rabies spillover is associated with the course of disease in the reservoir host. Rabies spillover from raccoons to cats was modelled since cats are the domestic animals most commonly reported rabid in the United States and are a major cause of potential human exposure to rabies virus [26, 27].

METHODS

Surveillance data

Human and animal rabies cases are reportable diseases in all states, the District of Columbia and Puerto Rico. Each state submits monthly results of laboratory tests for rabies to the CDC; the results are

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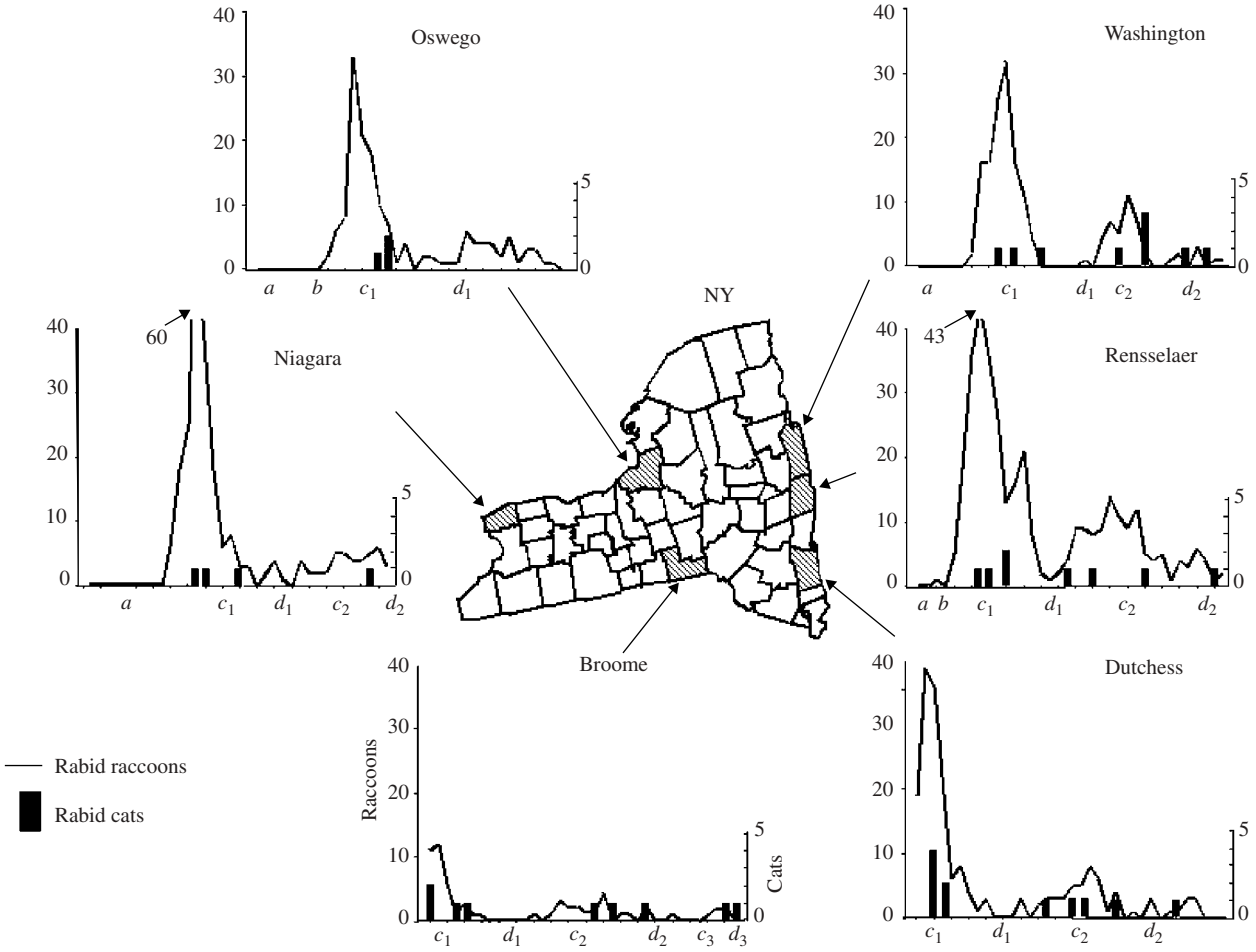

Fig. 1. Number of raccoons and cats reported rabid and epizootic temporal stages in Oswego, Washington, Rensselaer, Dutchess, Broome and Niagara counties, New York (NY), from 1992 to 2000. Stage *a*, pre-raccoon variant; stage *b*, sporadic raccoon variant; stage $c_{1–n}$, sequential epizootics; stage $d_{1–n}$, sequential inter-epizootics.

tabulated by animal tested and by county of origin. The standard diagnostic test is the direct fluorescent antibody test for detection of viral antigen in fresh brain tissue [28].

Since 1992, most states have reported the results of all rabies testing as positive, negative, or equivocal; equivocal results were not considered in these analyses. States were included only after they began reporting both positive and negative results. Data from 129 counties in Connecticut (8), Massachusetts (14), Maine (16), New Hampshire (10), New York (62), Rhode Island (5) and Vermont (14) were included in these analyses.

Definitions of temporal stages of the raccoon rabies epizootic

The epizootic wave-front of raccoon rabies spread in a northeasterly direction at approximately 30–46 km/year [13, 15, 29]; thus, counties were affected at different times by epizootics of various magnitudes (Fig. 1). The temporal course of raccoon rabies in each county was divided into discrete time-intervals, using an epizootic algorithm [9, 10]. The epizootic algorithm was used to distinguish intervals (months) of sustained high counts of rabid raccoons against the intervening intervals of sporadic disease [9, 10]. In previous studies, the temporal characteristics of raccoon rabies obtained by these methods were robust to changes in the algorithm defining epizootic and inter-epizootic intervals [9] and they were in agreement with those obtained using a mathematical model [30]. The median number of rabid raccoons reported per month was calculated from each county's time-series data, from the first month that the raccoon variant was detected to the end of this study (31 December 2000). An interval of epizootic raccoon rabies was defined as starting on

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the first month of a run of consecutive monthly counts exceeding the county median, and continued until 2 consecutive months with rabies counts below the median. In addition, an epizootic was required to have a minimum duration of 5 months. An inter-epizootic interval started on the first month ending an epizootic and continued until the next epizootic began. Successively numbered epizootic temporal stages, c_i, and inter-epizootic temporal stages, d_i, were defined, where $i=1, 2, \ldots, n$, where $n=$ the total number of stages for each county (Fig. 1).

The complete time-series of rabies among cats for 101 of 129 counties (78%) included negative and positive test results preceding the emergence of the first case of raccoon rabies. This interval was defined as the pre-raccoon temporal stage *a*. A total of 70 counties (54%) experienced sporadic cases of raccoon rabies before the first epizootic [5, 31]; this interval was defined as the sporadic raccoon variant temporal stage *b* (Fig. 1). Stages *a* and *b* were empirically defined after application of the epizootic algorithm had determined the starting month for the first epizootic [4, 5]. Temporal stages as defined by the epizootic algorithm were qualitative county-specific measures of rabies activity but contained no quantitative information on the number of rabid animals.

Data analysis

In the analyses that follow, risk for rabies in domestic cats was equated with risk for a cat testing positive for rabies (positive = 1, negative = 0). To reduce bias from excluding months in which no cat was submitted for testing, months with zero cat counts were assigned a value of 1 negative cat. The probability for a cat testing positive for rabies was modelled by using multivariate logistic regression analysis.

Seven classes of covariates were evaluated; three classes were coded as collections of indicator variables (temporal stage, human population density and season) and four were coded as continuous count variables (numbers of raccoons and skunks testing positive or negative). An indicator variable was included for the temporal stage of the raccoon epizootic in the county of origin for the month of testing. A second indicator variable designated levels of human population density, divided into quartiles based on the summary statistics for the 129 counties ($\leqslant 61{\cdot}5$, $>61{\cdot}5$ to $\leqslant 131{\cdot}6$, $>131{\cdot}6$ to $\leqslant 420{\cdot}2$, and $>420{\cdot}2$ persons per sq. mile) [32]. The third indicator variable indicated the season (January–March, April–June, July–September, October–December) for the month of testing. The level resulting in the lowest association with model outcome was coded as the referent value for each collection of indicator variables. The four continuous variables linked with each cat's record were the summed monthly counts of negative and positive test results for raccoons and skunks (in units of 10 animals tested).

Two models were developed using different groupings of temporal stages of raccoon rabies in a county. Three stages were used in the first analysis. The pre-raccoon variant and the sporadic raccoon variant stages were combined to increase model stability to form a pre-epizootic stage ($a+b$). Epizootic ($\Sigma_{i=1}^{n} c_i$) and inter-epizootic ($\Sigma_{i=1}^{n} d_i$) stages were grouped together to represent high and low levels of rabies activity.

In the second model, four temporal stages were used. The pre-epizootic stage ($a+b$), as previously described, was included in both models. The first epizootic stage (c_1) and first inter-epizootic stage (d_1) were separated into two individual groups. All the temporal stages that followed the first inter-epizootic ($\Sigma_{i=2}^{n} c_i + \Sigma_{i=2}^{n} d_i$) were considered one group coded as 0, 1. The first model had the advantage of grouping temporal stages by rabies activity, but does not consider the successive dampening of the cycles (Fig. 1). The second analysis, by separating the first epizootic and inter-epizootic, examines continued risk of rabies in cats after the initial cycle. In addition, this data-set was modified as described below.

Until recently, a focus of rabies caused by a red fox (*Vulpes vulpes*) variant of rabies virus in Ontario, Canada, was causing spillover infection among domestic and wild animals in the northern border counties of Maine, New Hampshire, New York and Vermont (Fig. 2) [33, 34]. However, rabies control efforts in Ontario eliminated spillover infection into the United States by 1997–8 [35]. Accordingly, logistic regression models were developed using the entire data-set and the modified data-set, which excluded rabies cases mis-classified as raccoon variant in eight counties bordering Canada. Logistic models that included red-fox variant rabies permitted the evaluation of the additive impact of the raccoon rabies epizootic when pre-existing enzootic rabies caused by a different virus variant was present. By removing rabies cases mis-classified as raccoon variant, the exclusive contribution of the raccoon rabies epizootic to risk of spillover infection in cats was shown.

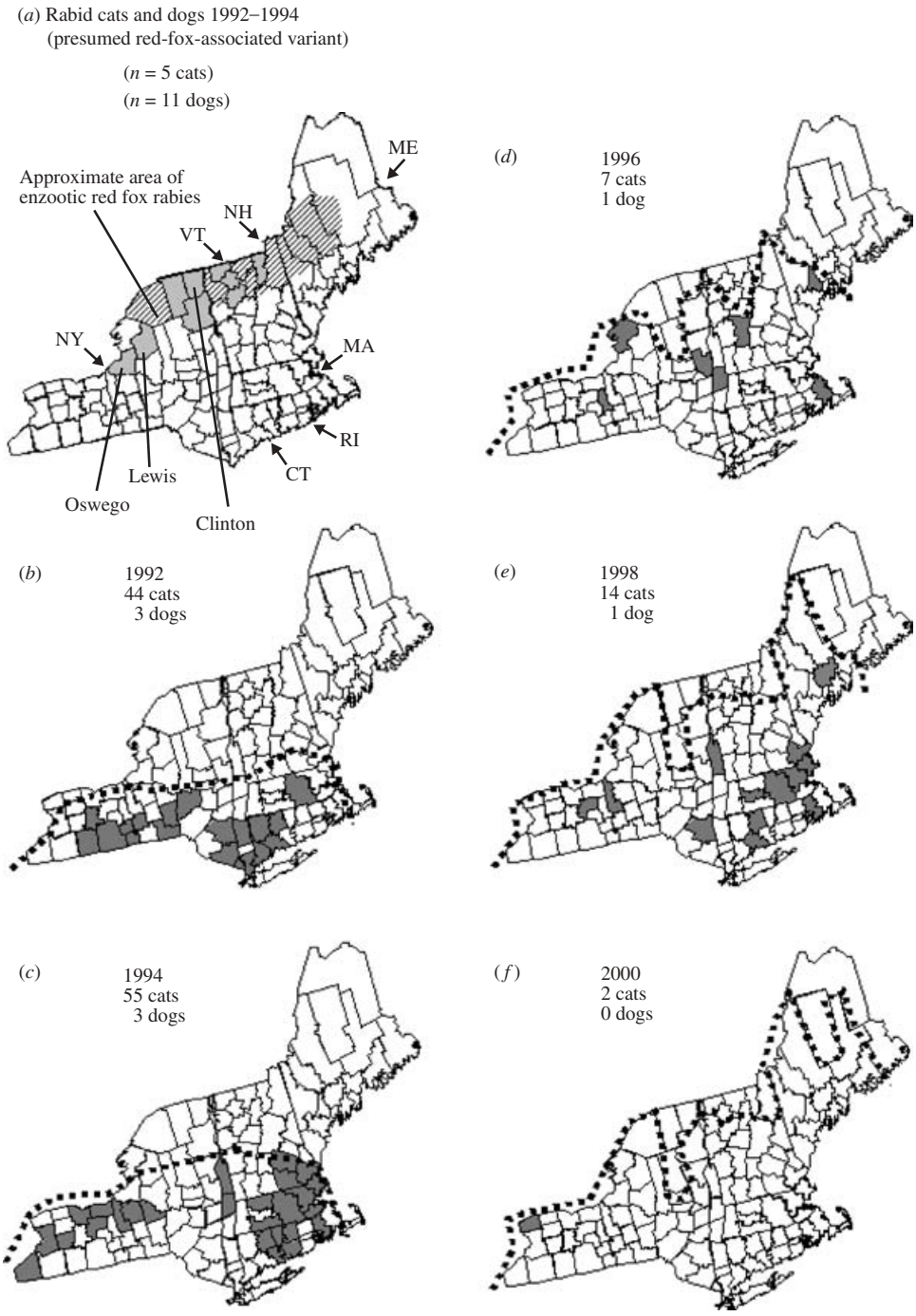

Fig. 2. Progress of the raccoon-associated rabies variant epizootic in the northeastern United States from 1992 to 2000. (*a*) Shaded counties reported a rabid cat or dog in the raccoon variant pre-epizootic stage. Striped counties are in area of red-fox-associated variant. (*b–f*) Shaded counties reported a rabid cat or dog. Broken line demarcates the extent of raccoon-associated variant in the corresponding year.

SAS software was used for analysing data [36]. The effect of repeated observations obtained for individual counties over time was controlled for in the analysis by using a generalized estimating equation [37]. Logistic models were constructed using a backwards selection procedure that eliminated non-significant variables until all remaining variables were significant at $P<0{\cdot}05$.

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Table 1. *County months of observation and numbers of positive (per cent of total tested) and negative rabies tests for cats, skunks and raccoons, northeastern United States, 1992–2000. The four strata for the temporal stages of the raccoon epizootic and human population density are indicated*

Variable	No. of observation months (no. of counties contributing)	Cats*†		Skunks*‡		Raccoons*§	
		No. (%) positive	No. negative	No. (%) positive	No. negative	No. (%) positive	No. negative
Epizootic stage¶							
Pre-raccoon variant (stage *a*)	3213 (101)	6 (0·2)	3530	30 (6·4)	437	0 (0·00)	3457
Sporadic raccoon variant (stage *b*)	1183 (70)	11 (0·5)	2395	103 (25·5)	318	414 (13·9)	2570
Epizootics (stage *c*)	2403 (104)	234 (1·6)	14 493	1866 (48·6)	1972	12 025 (62·7)	7153
Inter-epizootics (stage *d*)	6389 (105)	253 (1·0)	24 801	2330 (36·4)	4071	3732 (37·6)	6190
Total no. of months, animals	13 188 (129)	504 (1·1)	45 219	4329 (38·9)	6798	16 171 (45·5)	19 370
No. of persons per sq. mile							
⩽61·5	3276 (33)	54 (2·1)	2520	463 (47·0)	526	1497 (46·0)	1759
>61·5 to ⩽131·6	3360 (32)	94 (1·5)	6146	584 (43·4)	762	3503 (52·8)	3128
>131·6 to ⩽420·2	3108 (31)	153 (1·3)	11 444	1041 (47·0)	1172	4234 (52·8)	3786
>420·2	3444 (33)	203 (0·8)	25 109	2241 (34·1)	4338	6937 (39·3)	10 697

* Animals from counties with red-fox variant included.
† Number of cats excluded in data-set without red-fox variant counties: positive 5 (1·5), negative 320.
‡ Number of skunks excluded in data-set without red-fox variant counties: positive 25 (21·7), negative 90.
§ Number of raccoons excluded in data-set without red-fox variant counties: positive 91 (18·6), negative 398.
¶ Stages *a* and *b* combined in analysis.

RESULTS

During the 9 years of study, 92 391 records of cats, skunks and raccoons tested for rabies were reported from Connecticut (17 258), Massachusetts (17 695), Maine (3431), New Hampshire (3464), New York (46 525), Rhode Island (2351) and Vermont (1667). Rabies was confirmed among 504 (1·1%) cats, 4329 (38·9%) skunks and 16171 (45·5%) raccoons tested (Table 1). The highest monthly rates for rabies (number of rabid animals/number of months of observation; Table 1) among cats (0·1%), skunks (0·8%) and raccoons (5·0%), were observed during epizootic stages. The lowest rates among cats (<0·1%), skunks (<0·1%) and raccoons (0·1%) occurred during the pre-epizootic stage (Table 1).

Risk for rabies among cats was strongly linked to the temporal dynamics of raccoon rabies (Table 2). The risk for rabid cats associated with epizootic stages of raccoon rabies was seven-fold greater than before the emergence of the raccoon variant (Table 2). Risk for rabies in cats was greatest during the epizootic stages, followed by inter-epizootic, and the lowest risk was during the pre-epizootic stage. Independent of the temporal stage of raccoon rabies, the risk for rabies in cats increased with an increasing number of positive raccoons [odds ratio (OR) = 1·1 per 10 positive raccoons). Increased numbers of positive skunks also increased the risk for rabid cats (OR = 2·3 per 10 positive skunks). The risk for rabies among cats

Table 2. *Independent predictors of a cat testing positive for rabies using multivariate logistic regression, Northeastern United States, 1992–2000. Counties affected by the red-fox variant of rabies virus are included*

Variable	OR	95% CI	*P**
Intercept			<0·01
Epizootic stage			
Pre-epizootic	Referent		
Epizootics	7·4	4·2–13·0	<0·01
Inter-epizootics	5·1	3·0–8·9	<0·01
Raccoon positive ($\times 10^{-1}$)	1·1	1·0–1·2	<0·01
Skunk positive ($\times 10^{-1}$)	2·3	1·2–4·4	0·01
Human density†			
>420·2	Referent		
>131·6 to ⩽420·2	1·8	1·3–2·3	<0·01
>61·5 to ⩽131·6	2·0	1·5–2·8	<0·01
⩽61·5	2·6	1·6–4·1	<0·01

OR, Odds ratio; CI, confidence interval.
* Significant at alpha = 0·05.
† Persons per sq. mile.
Hosmer and Lemeshow goodness-of-fit test, $\chi^2 = 6{\cdot}50$, P value = 0·59.

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Table 3. *Independent predictors of a cat testing positive for rabies using multivariate logistic regression, Northeastern United States, 1992–2000. Counties affected by the red-fox variant of rabies virus excluded*

Variable	OR	95% CI	*P**
Intercept			<0·01
Epizootic stage			
Pre-epizootic	Referent		
Epizootics	9·7	5·0–18·9	<0·01
Inter-epizootics	6·7	3·5–12·8	<0·01
Raccoon positive ($\times 10^{-1}$)	1·1	1·0–1·2	<0·01
Skunk positive ($\times 10^{-1}$)	2·3	1·2–4·4	0·01
Human density†			
>420·2	Referent		
>131·6 to ⩽420·2	1·7	1·3–2·3	<0·01
>61·5 to ⩽131·6	2·0	1·4–2·7	<0·01
⩽61·5	2·7	1·3–2·3	<0·01

OR, Odds ratio; CI, confidence interval.
* Significant at alpha = 0·05.
† Persons per sq. mile.
Hosmer and Lemeshow goodness-of-fit test, $\chi^2 = 5{\cdot}16$, P value = 0·74.

Table 4. *Independent predictors of a cat testing positive for rabies using multivariate logistic regression, Northeastern United States, 1992–2000. Counties affected by the red-fox variant of rabies virus excluded. First epizootic and inter-epizootic considered separately from all later intervals*

Variable	OR	95% CI	*P**
Intercept			<0·01
Epizootic stage			
Pre-epizootic	Referent		
Epizootic 1	12·2	6·2–23·7	<0·01
Inter-epizootic 1	5·8	3·0–11·2	<0·01
All stages after inter-epizootic 1	7·5	3·9–14·3	<0·01
Skunk positive ($\times 10^{-1}$)	2·5	1·3–4·7	<0·01
Human density†			
>420·2	Referent		
>131·6 to ⩽420·2	1·7	1·3–2·2	<0·01
>61·5 to ⩽131·6	1·9	1·4–2·6	<0·01
⩽61·5	2·5	1·6–4·0	<0·01

OR, Odds ratio; CI, confidence interval.
* Significant at alpha = 0·05.
† Persons per sq. mile.
Hosmer and Lemeshow goodness-of-fit test, $\chi^2 = 7{\cdot}17$, P value = 0·62.

was significantly lower for the highest population density compared to the other quartiles. The risk for cat rabies exhibited a general increase with decreased population density although the ⩽61·5 quartile did not significantly differ from the >61·5 to ⩽131·6 and >131·6 to ⩽420·2 categories. Interaction terms combining positive raccoons or positive skunks with the temporal stage were not significant. Season, and the monthly number of raccoons and skunks testing negative were not significantly associated with risk of rabies in cats.

Logistic modelling using the modified data-set with red-fox variant rabies cases excluded resulted in the identical suite of covariates being retained (Tables 2 and 3); however, the effect of raccoon epizootic stage on the risk of rabies in cats increased. The risk for rabies among cats associated with epizootic stages was approximately ten-fold higher than the reference level of the pre-epizootic era (Table 3). The risk during inter-epizootic stages was almost seven-fold higher than that of the pre-epizootic stage. The ORs for the other covariates in the model were very similar to those observed in Table 2 (see Table 3).

In the second model (Table 4) the first epizootic stage was separated from later epizootics and was associated with higher (OR = 12·2) risk for rabid cats (Table 4). The first inter-epizootic stage was distinguished by significantly lower association (OR = 5·8) with rabid cats than either the first raccoon epizootic or all subsequent temporal stages (OR = 7·5) (Table 4). The higher risk for rabid cats (ORs = 5–7·5) persisted in the later temporal stages compared to the pre-epizootic interval. In contrast to the earlier models, the number of raccoons testing positive was not significantly associated with rabies in cats. The other covariates associated with risk of rabies in cats were the same as those identified by other models with comparable ORs.

DISCUSSION

These analyses demonstrated a strong association between risk of rabies spillover to an important secondary species and the temporal dynamics of rabies in a wildlife reservoir. The greatest risk for rabid cats was associated with the first epizootic of raccoon rabies and the risk for rabies among cats was greatest when epizootics among raccoons were occurring.

The association between the first epizootic of rabies in a host species and a highly elevated risk for spillover infection in a second species was anticipated on the bases of results from previous studies [9, 10]. Several studies summarizing state surveillance

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activities have described an association between numbers of rabid raccoons and increased spillover to multiple species [24, 25]. Among the 169 townships in Connecticut, significant positive correlations were found between the total number of raccoons tested for rabies and the total number of other animals tested for rabies [15]. This association is anticipated by population dynamics models of rabies, although most models do not consider spillover into a secondary species [30, 31].

In our analysis, the monthly counts of raccoons testing positive were associated with the risk of a cat testing positive. In larger epizootics affecting more raccoons, there was an increased risk of rabies in cats. However, when the first raccoon epizootic and first inter-epizootic were separated from subsequent cycles, monthly counts of raccoons were no longer a significant variable, as this grouping of epizootic stages accounted for the disparity in epizootic size.

All models illustrated a persistent increase in risk for rabid cats after the first raccoon epizootic: 5- to 7·5-fold higher than existed before raccoon rabies entered a county. These findings were consistent with a review of 9 years of state surveillance data in Maryland [24]. The authors found that the number of rabid cats did not decline as rabid raccoon counts dwindled, and rabies remained at relatively stable levels far higher than existed before the raccoon variant entered the state [24].

Annual surveillance summaries of animal rabies also suggest a persistent elevation in rabid cats following in the wake of the spreading raccoon epizootic. The annual number of rabid cats reported in the United States between 1992 and 2001 varied between 266 and 300 cases. Most of these rabid cats originated from the enzootic area of the raccoon variant [14]. At the same time, the numbers of rabid raccoons declined from a peak of 5912 in 1993 to 2778 in 2001 [38]. However, caution is warranted in drawing such strict comparisons since denominators for animals tested were not considered.

Although the long-term impact of raccoon rabies on spillover rabies in New England is speculative, consideration of the situation in southeastern states may be informative. In the Southeast, elevated risk of spillover rabies to cats persists [6, 18]. In 2000, after five decades of enzootic rabies, Florida and Georgia combined reported 19 cats and 325 raccoons rabid; a ratio of 1:22. This ratio was similar to the 1:16 value for Connecticut and New York in the same year (36 cats, 568 raccoons), just a decade into their history with the raccoon variant [21]. In 1990, prior to the onset of the epizootic, Connecticut and New York had a ratio of 1:84 (1 cat, 84 raccoons).

The mechanism(s) by which persistent elevation of spillover rabies is affected remains unclear. One active area of investigation is the role of other wildlife species in the transmission of the raccoon variant to domestic species [23]. In our analysis, the number of rabid skunks was shown to be an independent risk factor for rabid cats in all models. The persistent, elevated risk of rabies in cats could be achieved if the raccoon variant was effectively transmitted by skunks and was maintained in a multi-host cycle or became established through host switching.

The association between less dense human populations in a county with an increase in the risk for rabies in cats suggests an urban–rural gradient trend. This association may reflect that rural cat owners may be more prone to permitting their cats to roam freely and become wild: unvaccinated cats from rural locations have disproportionately contributed to annual counts of rabid cats [19, 26, 39]. A national study of rabies among cats and dogs in 1988 found 57% of 187 rabid cats were considered stray or 'barnyard' cats and that 78% of the rabid cats originated from rural locations, while 17 and 3% were from suburban and urban settings respectively (with 2% unclassified) [19]. In Pennsylvania, the risk ratio for human exposures to a rabid animal was more than 2-fold higher in counties in the lowest quartile of human population density (<90 persons/sq. mile) compared with counties in the highest quartile (>400 persons/sq. mile) [26]. Two previous studies found a positive correlation between increasing human population density and counts of rabid raccoons [10, 15], presumably reflecting the greater potential for human–raccoon interaction. The methods and variables used in these studies make direct comparisons difficult.

The development of two distinct epidemiological models provides insight into the impact of a rabies epizootic spreading into a region with or without a pre-existing enzootic. The first models indicated the risk for rabies in domestic cats was seven-fold higher during epizootics associated with the raccoon variant. In this model, rabies among cats caused by the red-fox variant were occurring before the arrival of the raccoon variant. In the second model, the independent effect of the raccoon epizootic modelled by removing rabies cases suspected to be caused by the red-fox variant resulted in ORs for rabid cats 10- to 12-fold higher during epizootic stage(s).

Although, the last case of human rabies in the United States linked to a cat occurred in 1975 [40], cats are involved in many of the ~45 000 annual human 'exposures' to rabies virus that result in administration of post-exposure rabies prophylaxis (PEP) [41]. In rural Pennsylvania, cat encounters accounted for 44% of human PEPs, more than any other species [26]. In urban emergency rooms, cats accounted for >15% of patients receiving PEP [42]. The average rabid cat generates between 1 and 6 human PEPs [19, 24]. Rabid cats have been the cause of several mass exposures involving >25 PEPs [43] and, in one instance, >650 PEPs [27]. In the latter case, the cost of rabies vaccine and immunoglobulin alone exceeded $1 000 000. PEP represents only a fraction of the total public-health costs associated with rabid cats. Specimen submissions and diagnostic testing, contact tracing of exposed persons, and professional evaluation of the exposure prior to PEP are all resource-intensive activities [12, 44].

These outcomes indicate that mathematical models of host–pathogen dynamics may be valuable. In addition, these models have practical applications beyond linking a disease process in a reservoir host to spillover. Assessing the benefits of rabies control programmes using oral rabies vaccination [12, 44, 45] requires matching cost–benefit estimates for an area to the stage of the raccoon epizootic in that region. Domestic cats are a major source of potential human exposures to rabies. Understanding how spillover to domestic cats varies with the unfolding stages of the raccoon epizootic can provide useful information to health officials and residents in affected areas. These persons are increasingly faced with decisions concerning the advantages and costs associated with different rabies control options [46]. Finally, elevated risk for rabies in cats does not return to pre-epizootic levels and is likely to be a long-term consequence of the raccoon variant epizootic. Local and state health officials anticipating an 'epizootic end-dividend' may instead have to contend with continuing elevated costs arising from diagnostic testing, contact tracing, and PEPs associated with rabid cats.

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