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ECOGEOGRAPHIC PATTERNS OF RABIES IN SOUTHERN ONTARIO BASED ON TIME SERIES ANALYSIS

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ABSTRACT: We describe a method based on time series analysis that divided the rabies enzootic area of southern Ontario into 13 regions using data collected at the township level, the smallest available geographical unit for Ontario (Canada). The intent was to discover ecogeographic patterns if such existed. For the period 1957–89, the quarterly time series of fox rabies cases for each of the 423 townships in the study area was correlated with the time series of its adjacent neighbors. Townships were then linked to adjacent townships provided the pair-wise correlations had significant correlation coefficients. This procedure produced 13 clusters that remained stable when additional lead/lag relationships between townships were examined. Furthermore, those clusters, which we then termed “rabies units,” had different behaviors in terms of species distribution, persistence, and periodicity. Time series in adjacent units were not synchronous. We discuss how our findings influenced the rabies control program in Ontario, how they relate to recent findings about the distribution of fox rabies virus subtypes, and how they lend support for the role of metapopulation structure in persistence of disease.

Key words: Arctic fox variant, clustering, metapopulation structure, persistence, rabies, regionalization, spread of rabies, time series analysis.

INTRODUCTION

The arctic fox variant of rabies virus invaded most of Canada south of 60°N and east of the Rocky Mountains in the early 1950s. It died out in most of that range, but persisted for over 40 years in southern Ontario with sporadic incursions into narrow adjacent strips in western Quebec and northern New York, USA (Tabel et al., 1974; MacInnes, 1988; Lagacé, 1998). The principal vectors were red foxes (*Vulpes vulpes*) and, to a lesser extent, striped skunks (*Mephitis mephitis*; Johnston and Beauregard, 1969; Tabel et al., 1974; MacInnes, 1987; Charlton et al., 1991). During the period 1957–89, Ontario experienced more animal rabies cases than any other North American jurisdiction almost every year, and over 95% of those cases were limited to the southernmost 10% of the province's land area.

The patterns defined by the initial invasion of Ontario (Figs. 1 and 2) have persisted in those vectors until almost eliminated by oral vaccination, which began in 1989 (MacInnes et al., 2001; Nunan et al., 2002). Understanding the patterns and

persistence of enzootic rabies in southern Ontario has been a priority of the Ontario Ministry of Natural Resources (OMNR) starting with Johnston's work in the late 1960s. Rabies is also a major concern to public health authorities and, like other jurisdictions in the world, analysis was typically linked to political boundaries, which in Ontario were the public health units based on county boundaries. During our initial attempts to understand the patterns of occurrence and develop a forecast system for outbreaks, it became clear that different regions, defined as clusters of counties, were subject to important differences in the length and magnitude of “cycles” (MacInnes et al., 1988). We began to call those clusters “rabies units.” It also became obvious that the large size and variable shape of the county boundaries obscured our efforts to understand how local ecogeography and other physical or human factors influenced the differences in cycle characteristics, and hence our forecasts. Our first step, reported here, was to develop a methodology to redefine those geographic clusters using the smallest re-

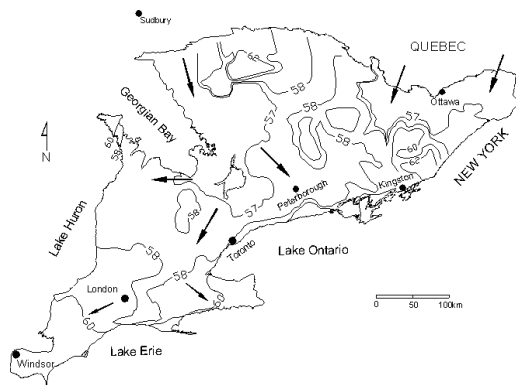


FIGURE 1. Spread of fox rabies into southern Ontario. The arrows show the general directions of spread and the contours show the limits of spread at the end of a given year.

porting unit for which we could assemble data, the township. As well, we report on the characteristics of the resulting rabies units and discuss how the spatial pattern of units had several practical applications in Ontario's rabies control program. We suggest some possibilities for further understanding the spatial evolution of virus subtypes and the persistence of rabies within a region.

METHODS AND MATERIALS

We used fox rabies data in our analysis because foxes were the principal vectors and cases in other species tended to lag behind fox rabies by 1–6 mo. The period of study was from 1957 to 1989, the year the control program began in the fall. Our data are ultimately derived from the Canadian Food Inspection Agency (CFIA, and its legal predecessors), the federal agency responsible for the collection protocols and the laboratory diagnosis of submitted specimens that were suspected of being rabid. District veterinary officers in distributed throughout Canada are responsible for specimen collection and the decision to send specimens to federally operated laboratories for testing. Although the formats of data capture/dissemination changed over time, as did the diagnostic procedures, we have worked with these data for many years and found no correlation between those changes and the temporal patterns of reporting fox cases. One of us, as part of a previous study on changing CFIA's method of geocoding submissions (Tinline and Gregory, 1988), conducted interviews with district veterinarians on how

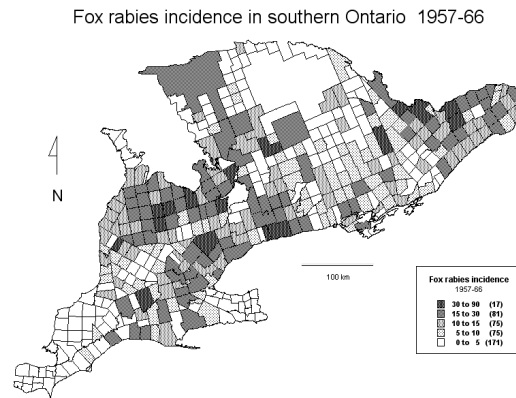


FIGURE 2. Fox rabies cases in southern Ontario for period 1957–66. The darker areas define the major areas of occurrence, areas which also dominated the pattern of outbreaks for the following two decades.

they submitted specimens. Although there were variations between districts in interpreting the circumstances that warrant a submission, the submission practices of each district appeared to be internally consistent over time.

We chose township data for our study because the township was the smallest reported unit for which we could consistently obtain the location of rabies cases from the CFIA records (Fig. 2). Over the study period many small townships were merged as a result of provincial restructuring initiatives. Almost all of those changes, however, involved mergers using existing boundaries so we were able to agglomerate township data to 1988 boundaries. The resulting 423 townships in this study had a median size of 256 km² with the 25th and 75th percentiles at 188 km² and 310 km², respectively. The frequency distribution of township sizes was right skewed with nine large outliers (>3 standard deviations) at the northern edge of the study area responsible for the skew. With the exception of the latter, adjacent townships in the rest of the study area were approximately the same size. Therefore, in terms of the methodology described below, variations in the size of townships had little impact on our results.

Our method focused on building up units by aggregating adjacent townships on the basis of similar quarterly time series behavior for numbers of rabid foxes. The quarter (3 mo) was the smallest temporal unit we could use without having too many zero observations. Although rabid foxes also occurred in the western portion of Quebec, we did not use that information because there was no municipal unit in Quebec similar in size and compact shape to the town-

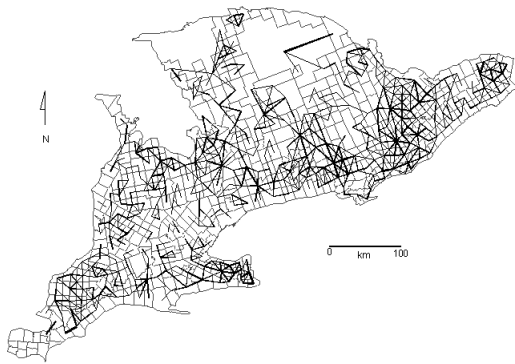


FIGURE 3. Significant times series correlations between adjacent townships. The 423 townships on which the analysis was based are shown in the background. The lines between the centers of townships link those townships that had significant ($\alpha=0.05$) time series correlations at lag zero. Similar patterns were obtained for lags 1, 2, and 3.

ship in Ontario. We correlated the time series of a given township with the time series of each of its adjacent townships (adjacency means sharing any common boundary including corners) using Pearson product moment correlation coefficients. Standard practice in time series analysis is to break the series in question into its trend, cycle, and random noise before analysis as the presence of a trend can influence the value of cross-correlations between series (Warner, 1998). For the period 1957–88, we examined the time series for all fox cases in southern Ontario and for the units we subsequently defined. We found a weak ($R^2=0.107$) but significant ($\alpha=0.05$) upward linear trend in the time series for all fox cases. That trend was produced by similar upward trends in the groupings of townships that we subsequently defined as units 2, 3, 7, and 9. None of the other areas, however, had significant linear trends over time. Further, those weak upward trends were diminished when the time series were re-examined for the time period that we considered rabies was established in an area (i.e., after the first peak of cases [quarters 19–47 depending on the area] to the end of the series [quarter 132]). Given these results and because cycles dominated the time series, we did not remove trend from the time series in our analysis. Our method is based on determining the cyclical influence of one township on its adjacent townships. We also made no attempt to determine the relative magnitude of submission levels between districts. Correlation analysis is not affected by the relative magnitude of the times series being examined pro-

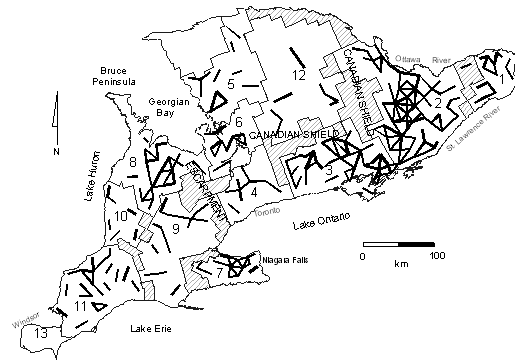


Figure 4. The boundaries of the rabies units in southern Ontario. The numbers are the unit identifiers. The shaded areas represent “transition” areas that were not assigned to a unit. The lines within each unit define pair-wise correlation coefficients between townships that were greater than 0.4. Those linked townships defined the “core” of a rabies unit. The wider the line between a pair of townships, the larger the correlation.

vided the difference in magnitude is constant. Since trends were weak or not significant in the data and since we had some evidence that reporting practices were consistent over time, we felt comfortable with our approach. Once the cross-correlations were calculated, we plotted vectors on a map of townships to show the significant ($\alpha=0.05$) cross-correlations between adjacent townships (Fig. 3).

Examination of this pattern of correlations showed several core areas where adjacent townships had high ($r>0.4$) pair-wise correlations (Fig. 4). Once those cores were defined, our algorithm linked adjacent townships to the core provided those townships had significant correlations with one of more of their neighbors in the core. We continued adding townships to the expanding core until we reached a township that did not have a significant link ($\alpha=0.05$) with a neighbor in the core or had a higher correlation with a township in another core. When the process was finished, some townships had no significant relationship with any neighbor. If such a township was entirely surrounded by townships linked to a core unit, it was assigned to that core unit. If the township was on the periphery of a unit and was also on the periphery of an adjacent unit, we classified it as a “transition” township. This process is our version of “linkage” analysis (McQuitty, 1966) that we modified to include an adjacency constraint. The resulting agglomerations of townships defined 13 rabies units (Fig. 4) and several transition areas (for convenience

denoted as unit 14). Note that unit 13 was not defined by the above “rules.” There were too few cases for time series analysis between townships. It was not a transition area since the townships were isolated at the southwestern tip of southern Ontario. We classified it as a unit because of the general absence of rabies over time (the first case was in quarter 62), its isolation, and its short but well-defined epizootic starting in quarter 125. The procedures for determining adjacency, plotting vectors, and linking townships were developed by the authors using spatial analysis query functions in AutoCad Map 2000i (Autodesk, 2000) in combination with the query capabilities of Microsoft Access 2000 (Microsoft, 1999). Correlations were calculated with the cross-correlation function (CCF) in SPSS Version 11.0.1 (SPSS, 2001).

We also examined lead and lag relationships between adjacent townships by repeating the time series analysis at lead (or lag) of 1, 2, and 3 quarters. For example, we correlated the time series for township A at a time t with the series of its adjacent townships (B, C, D, ...) at $t+1$, $t+2$, and $t+3$ quarters. In theory, if there is a spread over time between townships A and B, then one or more of the correlation coefficients at lead 1, 2, or 3 quarters should be higher than the correlation coefficient when the time series are synchronous (lead/lag 0). As well, noting the lead value at which the highest correlation occurs should help indicate the length of time (in quarters) for spread between townships A and B. Conversely, since a leading relationship between townships A and B is a lagging relationship between B and A, we can also trace the source of infection for any given township. The patterns revealed by this analysis strongly reinforced the previous selection of the core townships in the units but did nothing to refine our estimates of the outer boundaries of the units or the transition areas. Hence, the results of the lead/lag analyses are not shown here.

Once the rabies units were defined, we aggregated the rabies data by unit by species to investigate the characteristics of each unit. We examined species distribution by calculating their relative proportions within each unit. To measure the persistence of rabies within a unit, we calculated the percent of quarters in which rabies data occurred in foxes in each unit and then repeated the calculations using all species. We used the autocorrelation function (ACF) in SPSS version 11.0.1 (SPSS, 2001) to determine the periodicity of fox cases within each unit. Finally, we examined the lead/lag relationships between units using the CCF in SPSS. Warner (1998) provided a useful description of the use

of ACF and CCF in determining the periodicity of time series.

RESULTS

Five units, units 2, 3, and 4 in eastern and central Ontario and units 8 and 9 in western Ontario, accounted for more than 68% of total rabies cases for all species (Table 1). Those same units also accounted for 65% of all fox data during the study period. As well as dominating in absolute numbers, those units had the highest density of cases expressed in rabid foxes per 100 km². The transition areas between units accounted for 12% of total cases and 11% of fox rabies cases. The peripheral units to the north (units 5 and 12) and the peninsular units (units 7 and 13) accounted for only 5.3% of the total cases. Units 5, 12, and 13 also had the lowest density of fox rabies per 100 km². Unit 1 is relatively small and not well defined, but it is probably part of a larger structure extending into western Quebec, which as previously indicated was not part of our analysis.

The units clearly differed in the ratio of rabid foxes and skunks within each unit. Units in the east and north of the study area (units 1, 2, 5, 12) had fox/skunk ratios of >3 (Table 1). Units from unit 4 westward had fox/skunk ratios <3 . This east to west pattern reversed for livestock. Western Ontario typically had higher proportions of cases in livestock (over 30%) than most areas in eastern and northern Ontario (units 1, 2, 3, 5, and 12; mean of combined units = 22%). There were no distinct patterns for companion animals (cats and dogs) and “others” with the exception of high values for unit 13, which, as noted previously, were anomalous because of very small numbers of cases.

Measures of persistence and periodicity in each unit are shown in Table 2. The five dominant units (units 2, 3, 4, 8, 9) also had high persistence; rabies was present in over 90% of the quarters during the study period whether measured in terms of foxes alone or all species. Persistence was much

TABLE 1. Rabies occurrence by species in rabies units in southern Ontario from 1957 to 1988.

Rabies unit ^a	Total cases	Total cases in fox (%)	Total cases in skunk (%)	Total cases in cat and dog (%)	Total cases in livestock (%)	Total cases in other species (%)	Overall prevalence (%)	Area (km ²)	Rabid foxes/100 km ²
1	1,344	56.9	8.9	8.2	23.9	2.1	3.0	3,808	6.1
2	7,904	53.7	15.4	7.8	20.1	3.0	17.7	17,003	25.0
3	4,889	42.6	14.3	11.7	28.0	3.4	10.6	10,845	19.2
4	4,086	32.8	30.3	9.7	23.7	3.6	9.0	5,633	23.8
5	627	71.4	5.5	9.4	10.7	3.1	1.4	13,545	3.3
6	1,750	41.0	25.0	9.4	21.5	3.1	3.8	3,683	19.5
7	1,223	44.2	20.4	13.4	20.0	2.0	2.6	3,453	15.7
8	6,779	39.1	15.2	6.7	36.7	2.3	14.8	9,655	27.5
9	7,574	36.2	21.6	9.4	30.1	2.6	16.2	10,762	25.4
10	2,073	35.1	22.1	8.0	32.6	2.2	4.5	3,958	18.4
11	3,094	36.2	15.1	12.6	32.3	3.7	6.2	9,866	11.4
12	609	67.9	6.9	12.0	10.7	2.4	1.3	16,957	2.4
13	97	23.5	17.6	35.3	11.8	11.8	0.0	1,950	0.0
14 ^b	5,521	41.8	19.3	10.5	25.9	2.5	12.0	19,063	12.1

^a See text for description of the rabies units.^b This row is the sum of all transition townships that were not assigned to a unit.

lower in the peripheral units, especially areas in the north (units 5 and 13) and the peninsular areas (units 1, 7, and 13). Unit 13 had very low persistence, with fox rabies appearing in only 26% of the quarters during the study period.

The cycle of occurrence by unit ranged from 8 to 24 quarters (2–6 yr). Periods for

units 1, 5, 6, and 12 were not significant because of low numbers of cases. The period for the transition areas was not calculated because those areas were not contiguous. The periods for the other units were typically clearly defined with the exception of units 9 and 11. A clearly defined cycle in unit 2 with a period of 3–4 yr is

TABLE 2. Persistence and periodicity of rabies within rabies units in southern Ontario from 1957 to 1988.²

Unit	Quarters with no rabies (all species)	Quarters with rabies (all species) (%)	Quarters with no rabid foxes	Quarters with rabid foxes (%)	Estimated cycle period (quarters) ^b	Other cycle peaks
1	20	84.8	42	68.8	NS	
2	3	97.7	5	96.2	12	13, 14, 15, 16
3	5	96.2	11	91.7	12	12, 15, 16
4	6	95.5	16	87.9	12	
5	38	71.2	53	59.8	NS	
6	19	86.5	35	73.5	NS	
7	22	83.3	51	61.4	15	16, 17
8	5	96.2	11	91.7	12	
9	5	96.2	10	92.4	4	8, 12, 16, 20, 24
10	8	93.9	31	76.5	12	
11	15	88.6	27	79.5	8	12, 16, 24
12	33	75.0	50	62.1	15	
13	111	15.9	123	6.8	NS	
14	3	97.7	6	95.5	NA	

^a NS = not significant; NA = not applicable.^b The predominant peak in the autocorrelation function of the series.

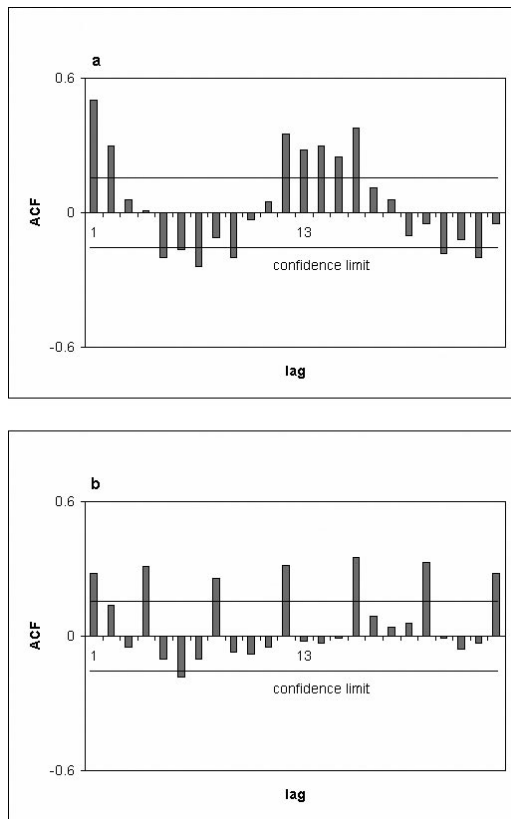


FIGURE 5. (a) The autocorrelation function for the time series analysis of unit 2. The y axis shows the correlation coefficient of the series correlated against itself at lags of 1, 2, 3, . . . 24 quarters. Significant correlations occur above (or below) the 95% confidence limits on the figure. Unit 2 shows the classic pattern where a series repeats itself at periodic intervals. In this case the period is 12–16 quarters (3–4 yr). (b) The autocorrelation function for the time series analysis of unit 9. Since the series repeats every four quarters, the time series in unit 9 has an annual cycle.

shown in Figure 5. Unit 9, on the other hand, had harmonics at 4, 8, 12, 16, and 24 quarters, indicating a yearly cycle and, as noted previously, high persistence. Unit 9 had no clear core as shown in Figure 4. Together, these results suggest that unit 9 is internally complex and may not be a single unit. Results of the cross-correlation analyses between adjacent units to lead or lag of occurrence between units are shown in Figure 6. Time series within the units in southeastern Ontario are clearly sepa-

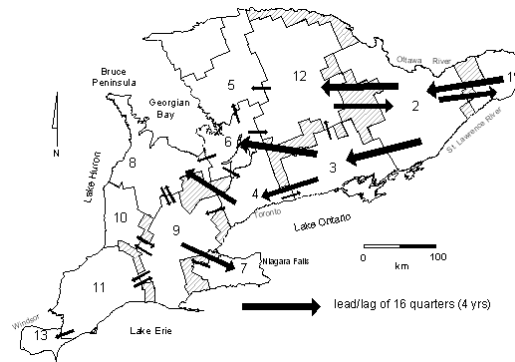


FIGURE 6. Lead/lag relationships between units. The longer the arrows, the greater the lead or lag between the quarterly time series between adjacent units. An arrow between units shows that the time series in the originating unit leads the other unit. In the cases shown with two arrows of the same length, there was no clear lead/lag relationship between units.

rated in time from adjacent units in the order 12–16 quarters (3–4 yr). The situation is not as clear in the western portion of the study area where the lead/lag relationship between adjacent units is in the order of 1 yr. Only unit 9 had a strong (3-yr lead) relationship with adjoining unit 7 (the Niagara Peninsula).

DISCUSSION

We demonstrated that, on the basis of time series behavior alone, townships in southern Ontario could be aggregated into 12 rabies units. Another unit (unit 13) was defined by geographic isolation and the long-term absence of rabies. Several townships acted as transitions between units. The 12 units had different behaviors in terms of species composition, persistence, and periodicity. There were clear differences between southwestern and southeastern Ontario. The ratio of rabid skunks to rabid foxes was greater in the southwest, and the lead/lag differences between units were higher in the southeast. We suspect that the higher numbers of rabid skunks in the southwest reflect milder winter temperatures and more urban development. We believe that the differences in lead/lag relations reflect the sharp differences in

physiography between units. The Canadian Shield, for instance, acts as the boundary between units 2, 3, and 12. The built-up area of greater Toronto helped to separate units 3 and 4. The only major barrier in southwestern Ontario appeared to be the Niagara escarpment that runs from Niagara Falls around the western tip of Lake Ontario and then north to Georgian Bay where it parallels the shoreline of Georgian Bay to the tip of the Bruce Peninsula. The escarpment appeared to be a transition zone separating units 4 and 6 from units 8 and 9 (Fig. 4). We hypothesize that the lead/lag differences also demonstrate that, in the absence of strong physiographic barriers, the relative location of unit boundaries will vary over time and may also reflect the changing distribution of species, and possibly the virus. Unit 9 is a case in point. Although it dominated other units in terms of cases it had no clear cycle, it had ambiguous lead/lag relationships with its neighbors and no clear core area. We suspect that unit 9 is an area with two or more quasi-independent rabies outbreaks that moved around in such a way that the same townships were affected at different times. Thus, a potential extension of our analysis will be to break our time series into shorter series and examine the stability of units over time. Where there are strong physiographic barriers, we expect that the units will be stable. The remarkable feature of the initial invasion from 1957 to 1966 is that the initial paths of spread (Fig. 1) and the resulting foci of infection (Fig. 2) appear to define the spatial pattern of occurrence until 1989, and this is strongly reflected in the pattern of units we have delineated.

We found only weak upward linear trends in the time series data and only in some areas despite the doubling of the population of Ontario during the study period. Past studies have demonstrated that human population density can influence the number of animals submitted for testing (Wilson et al., 1997) and the magnitude of epizootics as measured by counts

of rabid animals (Childs et al., 2001). We were encouraged by the lack of corresponding increase in the number of rabid foxes over time because it supported our working assumption that the reporting of rabies cases was not unduly influenced by human population density.

Our methodology worked because our time series were long (132 observations) and data were available in reasonably small and uniform units (townships) and were collected by one agency (CFIA) in a relatively uniform manner throughout the study period. These advantages also highlight the potential weaknesses in our methodology if those conditions cannot be met. For example, our methodology did not work in the area we subsequently called unit 13 because sparse data meant that reliable correlations between townships could not be calculated. Our methodology would also be problematic if we could not assign that data collection procedures had been consistent over the study period.

The major use of rabies units to date has been to help the Ontario Ministry of Natural Resources plan the fox rabies control program and to make annual rabies forecasts published in the ministry's *Rabies Reporter*. Based on an earlier analysis of units at the county level, the control program began in 1989 and focused on what we now define as unit 2 in eastern Ontario (MacInnes et al., 1988). That unit was a practical starting location for several reasons. First, the red fox was clearly the principal vector within the unit and the vaccine bait was effective in foxes but not in skunks. Second, the unit was well defined, with the Ottawa River to the northeast, the St. Lawrence River to the south, and the Canadian Shield to the west. Third, in 1989 there were not enough baits available to cover the unit completely so that the oral vaccine baits were dropped on its eastern and western borders to "wall it in" for subsequent control efforts. Since unit 1 was the eastern border of unit 2 and the "doorway" to Quebec, it was baited

completely in 1989. Fourth, unit 2 had a well-defined cycle in its time series, and we had predicted that occurrence in the core area would bottom out in 1990. Finally, previous rabies simulation modeling efforts (Voigt et al., 1985) had demonstrated that, given a strong cycle, oral vaccination efforts were more likely to be successful when the susceptible population was low (i.e., when the epizootic was waning). Thus we had a coincidence of logistics and theory. With our limited resources we could start baiting on the periphery of unit 2 in 1989 and then bait the core area in accordance with our theory the following year. From 1990 to 1994 the entire area of units 1 and 2 were baited. By 1995, fox rabies had disappeared from those units (MacInnes et al., 2001).

In 1993, our wall strategy was extended to the western edges of units 4 and 6 (a line from Georgian Bay across Lake Simcoe and south to Lake Ontario) to isolate unit 3 for baiting in 1994, a period of waning cases. After baiting, there were no fox rabies cases by the third quarter of 1995. By 1996 occurrence was low throughout southwestern Ontario so that the baiting area was extended to cover all the units in southwestern Ontario except unit 13, which, we believed, could not sustain rabies. The northern units (units 5 and 12) were never baited, since our analysis indicated that rabies never originated in those units. Our thinking was that controlling rabies in adjacent units would prevent rabies from entering units 5 and 12, and that if it did, it would soon die out.

The delineation of rabies units has suggested two areas for future research. There appears to be a broad relationship between spatial distribution of rabies units and the four major subtype variations in fox rabies virus identified in southern Ontario (Nadin-Davis et al., 1999). The subtypes mirrored the initial invasion routes into southern Ontario, reflected the difference between the fox/skunk ratios in the eastern and western portions of southern Ontario, and appeared to be bounded by

the same broad physiographic features that defined the boundaries of the rabies units. We suggested that, in units such as unit 9 with no clear physiographic barriers, the distribution of virus subtypes might follow the advance and retreat of rabies across the unit. These results suggest that our rabies units may either be the result of, or part of the explanation for, the subtype variations in the fox rabies virus. Presumably that indicates that there have been local adaptations by the arctic fox rabies variant. Those can be identified by their unique cyclic behaviors, as indicated by this analysis. Hopefully, more genetic data will be collected to further explore those relationships.

The second area of research concerns the spread of rabies within and between units and the comparative analysis of species distribution between units. We suspect that detailed tracking of spread will shed more light on the influence of physiography on spread and may help understand the local variations in subtype noted in the research of Nadin-Davis et al. (1999). Furthermore, Tinline (1988) hypothesized that the ability of rabies to persist in southern Ontario was related to movement between units. The enzootic may persist because an outbreak in one unit spreads to adjacent units that had a peak some time ago, so that the pool of susceptible animals has been rebuilt and is large enough to sustain another epizootic. If there were not separate units, the probability of extinction of rabies virus after a sharp peak in a single area would be high since the rabies virus violates two of the more important rules for successful pathogens: it kills most infected hosts, and it has no known resting stage outside the living host. Based on our observation that different subvariants of the virus coincided with groupings of two or more units, it may well be that the persistence of rabies depends primarily on linkages between those smaller groupings rather than linkages across the whole of southern Ontario as Tinline (1988) suggested previously.

Unfortunately we do not have tissue samples from earlier decades to assess possible changes in the subvariants of the virus over the entire study period.

We believe that our set of units and the linkages between them constitutes a metapopulation structure, as described by Harrison (1994), which within the limits set by May (1994) is key to understanding persistence of rabies in wild systems. The thorough review by Hassel (2000) covers insects and parasitoids, but his overall description of a metapopulation structure consisting of partially autonomous local population "patches" loosely connected to other such patches so that population dynamics of the local patches are asynchronous makes an excellent mental model to extend our study of the behavior of rabies.

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