

Techniques for analysis of disease clustering in space and in time in veterinary epidemiology

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Abstract

Techniques to describe and investigate clustering of disease in space — the nearest-neighbour test, autocorrelation, Cuzick-and-Edwards' test and the spatial scan statistic — and in time — the Ederer–Myers–Mantel test and the temporal scan statistic — are reviewed. The application of these techniques in veterinary epidemiology is demonstrated by the analysis of a data set describing the occurrence of blowfly strike — both body strike and breech strike — between August 1998 and May 1999 in 33 commercial sheep flocks located within two local government areas of southeastern Queensland, Australia. By applying a combination of these methods, the occurrence of blowfly strike in the study area is well-characterised in both space and time. Guidelines for investigating disease clusters in veterinary epidemiology are discussed. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Investigation of possible clustering of disease occurrence is a foundation of epidemiology, providing valuable information on possible causes of the disease of interest and methods that may be used for disease control and prevention. Indeed, drawing epidemic curves and constructing maps are two of the basic skills used by an

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epidemiologist when confronted by a disease outbreak. Investigations of disease clustering may be used either to generate or test hypotheses concerning disease causation. As with statistical methods generally, the approach is based on comparing observed patterns of disease occurrence with that expected — given certain assumptions. The universal null-hypothesis in cluster investigations is that of randomness. The alternative hypothesis may take a number of forms. One-tailed examples would be that cases of disease are grouped more closely than expected or that some units contain more cases than expected (clustered) under an assumption of randomness. On the other hand, the alternative hypothesis may be that cases are either clustered or uniformly dispersed, with a two-sided test being applied. The type of pattern observed may be used to generate hypotheses regarding factors associated with disease occurrence.

Clustering of disease in space may be investigated simply by mapping points or areas and visually examining such maps for patterns, and similarly the clustering of disease over time can be described by plotting an epidemic curve (time-series). Whilst these simply graphical techniques can provide powerful tools for understanding the epidemiology of the disease process, quantitatively describing, comparing and interpreting maps and plots can be a difficult task and results may be invalid. Clustering of disease can be subtle and quite complex — e.g., when populations change substantially over time and are not uniformly distributed in space. As with all epidemiologic investigations, statistical techniques are helpful — and sometimes essential — in understanding the disease process. Spatial and temporal statistics have three special attributes in these circumstances: (1) they add precision to qualitative description; (2) they facilitate the comparison of distributions by offering objective, quantitative criteria; (3) they might draw attention to characteristics unlikely to be noticed by visual inspection (Hammond and McCullagh, 1978).

A variety of statistical methods to detect and describe spatial and temporal clustering have been developed in a range of disciplines (such as geography, ecology, econometrics, biostatistics and medicine). The diversity of methods evolved — particularly for spatial analyses — partly because of the range of data types used from epidemiologic studies and partly because no one method is clearly superior in all applications. Increased data quality and availability through the development of modern animal-disease and -production monitoring and surveillance systems, new techniques such as remote sensing, the ability to sort and recombine data using geographical information systems (GISs), and the increasing availability of software packages over the past three decades have created an ideal environment for epidemiologists to apply spatial and temporal analytical techniques to disease problems. However, relatively few such examples have been published in the veterinary literature. The aim of this paper is to present techniques that can be readily used by veterinary epidemiologists for detecting and describing spatial and temporal clustering of disease.

2. Investigating disease clusters

Guidelines have been drafted for investigating clusters of health events (Centers for Disease Control, 1990). A four-stage approach has been recommended: (1) initial

contact and response; (2) assessment; (3) major feasibility study; (4) aetiologic investigation.

The use of cluster statistics is particularly helpful in stage two of cluster investigations, in which a mechanism for evaluating whether an excess of disease has occurred is initiated. Major feasibility studies and aetiologic investigations are unlikely to proceed if the occurrence of a disease cluster cannot be verified in stage two of the investigation.

Several problems exist in studying clusters. Disease events are often rare and an increased case occurrence may be small and may occur over a long period. Information on the population-at-risk may be unavailable, and the rates of disease expected in the absence of clustering may be unknown. Also, clusters occur in a space-and-time continuum — but the choice of spatial and temporal units may obscure the presence of clusters. Statistical tests for clustering in time or space are useful when disease rates are low, or when characteristics of the population-at-risk are poorly defined. No omnibus test exists for assessing spatial and temporal clusters of disease. Thus, investigators have been advised to “perform several related tests and to report the results that are most consistent with validated assumptions” (Centers for Disease Control, 1990). As part of an overall approach of investigating clusters, the information provided by these tests is useful for developing a better understanding of disease causation.

3. GISs and spatial tests

Use of statistical tests to investigate spatial clustering of disease in veterinary medicine is uncommon. For example, a search of CAB abstracts (1987–1997) (WinSPIRS Version 2.1, SilverPlatter, NV) identified only 13 papers published in the peer-reviewed veterinary literature in which statistical tests had specifically been used to detect spatial clustering. Use of tests to investigate temporal clustering appears to be even less common — a similar search identified only two published papers (both using the temporal scan statistic). In contrast, the application of GIS technology has increased rapidly in the past decade. Central to GIS technology is a database-management system that allows spatial data sets from diverse sources to be managed and analysed (Sanson et al., 1991). However, analysis of data in such systems does not routinely use statistical tests of spatial clustering. Rather, GISs generally have been used to analyse (through visual interpretation) the relationships between potential risk factors and the occurrence of disease (incidence or prevalence) on a geographical basis.

Several types of analyses routinely used in GISs have been described by Sanson et al. (1991). They include neighbourhood analysis (all features which meet certain criteria and are adjacent to a particular feature are found and listed), buffer generation (generation of buffer zones around or along certain features), overlay analysis (merging of two or more layers or maps to identify areas of intersection), network analysis (modelling of networks and calculation of parameters such as the shortest distance between two locations), surface area and distance calculations and three-dimensional surface modelling. These analytical methods are used to generate hypotheses. Because methodology is now available to test hypotheses regarding disease clustering, it is

somewhat surprising that the use of statistical tests has not become integral to GISs, although a few examples exist in medical epidemiology (Kitron, 1998). The statistical analysis of spatial distributions remains a weak point in the application of GIS technology. If GIS technology is to fulfil its potential as a general-purpose tool for handling spatial data, it needs stronger analytical capabilities (Paterson, 1995). Development of statistical software to investigate disease clustering and integration into GISs will improve the ability of epidemiologists to identify and describe determinants of disease.

4. Descriptive spatial statistics

4.1. Mean and weighted mean

The central tendency of a unimodal set of points may be described by the arithmetic mean or by a weighted mean. The arithmetic mean (mean centre) of a set of N points is calculated as the mean of the x and y coordinates of the data, $\sum x_i/N$ and $\sum y_i/N$. When points possess a weight, w (e.g., reflecting population size or disease occurrence such as prevalence or incidence), a weighted mean may be calculated as $(\sum x_i w_i)/N$ and $(\sum y_i w_i)/N$ to reflect the weight and the geographical location of the points. The degree of dispersion of a set of points for each of the measures of central tendency described above is the standard distance deviation. It is calculated as $\sqrt{\sum_{i=1}^N d_{ic}^2/N}$, where $d_{ic} = (x_i - \bar{x})^2 + (y_i - \bar{y})^2$. Standard distance deviation and weighted standard distance deviation can be calculated more efficiently as

$$\sqrt{\left(\frac{\sum_{i=1}^N x_i^2}{N} - \bar{x}^2\right) + \left(\frac{\sum_{i=1}^N y_i^2}{N} - \bar{y}^2\right)} \quad \text{and} \quad \sqrt{\left(\frac{\sum_{i=1}^N w_i x_i^2}{N} - \bar{x}_w^2\right) + \left(\frac{\sum_{i=1}^N w_i y_i^2}{N} - \bar{y}_w^2\right)},$$

respectively, where \bar{x}_w and \bar{y}_w are mean weighted coordinates (Hammond and McCullagh, 1978).

4.2. Nearest-neighbour index

The distribution of locations selected for inclusion in a spatial-analysis study can be described using the nearest-neighbour technique. The nearest-neighbour index (R) — developed by Clark and Evans (1954) — may be used to define individual distributions or to compare two or more spatial distributions. The index ranges from 0 (clustered) to 2.15 (uniform). An index of 1 indicates a random distribution of points. The index is the ratio of mean Euclidean distance between nearest-neighbour points in a given area ($\bar{D}_{\text{observed}}$) to mean distance expected from a randomly distributed series of points in that area (\bar{D}_{random}), where $\bar{D}_{\text{random}} = 0.5\sqrt{A/N}$ and $\bar{D}_{\text{observed}} = \sum d_{ij}/N$, N is the number of points, A the study area size, and d_{ij} is the distance between nearest-neighbour points i and j . The statistical significance of R may be determined by calculating a z -statistic:

$|(\bar{D}_{\text{observed}} - \bar{D}_{\text{random}}) / \sigma_{\bar{D}_{\text{random}}}|$, where $\sigma_{\bar{D}_{\text{random}}} = 0.26136 / \sqrt{N(N/A)}$ (derived using calculus from the expected mean distance between nearest neighbours). In addition, the distance between nearest neighbours expected under spatial randomness can be calculated based on the probability density function, $p(\omega) = 2\hat{p}\pi\omega \exp(-\hat{p}\pi\omega^2)$, where ω is the nearest-neighbour distance and p is the Poisson parameter, estimated as the number of cases of disease divided by the study area (Jacquez, 1994a).

5. Tests for spatial clustering

5.1. Types of distributions

Three types of distributions may be observed when studying populations, diseases or other events: uniform (evenly distributed), clustered (aggregated) or random. If points are uniformly distributed, they are located at approximately equal distances from their nearest neighbours and maximally dispersed in the study area. In the clustered distribution, there is a definite, discernible aggregation of points. A random distribution of points is a combination of uniform and aggregated distributions.

5.2. Types of tests

Tests used in spatial analysis can be broadly categorised into global-cluster tests, focused-cluster tests and cluster-detection tests. Most tests for spatial clustering of disease are tests for global clustering. These methods test for clustering throughout the study region without the ability to locate the sites of specific clusters.

Examples of global clustering tests used in veterinary epidemiology include autocorrelation (Moran, 1950) and Cuzick-and-Edwards' test (Cuzick and Edwards, 1990). Hungerford (1991) and Hungerford and Smith (1996) investigated clustering of bovine anaplasmosis in Illinois, and Ward and Carpenter (1995) investigated bluetongue virus infection in Queensland cattle herds using autocorrelation. Cuzick-and-Edwards' test has also been used by Ward and Carpenter (1995) and Ward et al. (1996) to assess clustering of bluetongue virus in Queensland cattle herds, by Rodríguez-Lainz et al. (1996) to examine the clustering of papillomatous digital dermatitis in southern California dairy farms, and by Singer et al. (1998) to assess spatial clustering of resistant strains of *Pasteurella multocida* and *P. haemolytica* isolated from Californian cattle herds. The latter two studies also used the nearest-neighbour index.

Focused-cluster tests are used when there is a pre-specified point source for a presumed epidemic, and the question of interest is whether there is an elevated risk of the disease around that specific source. These tests should not be used if the point source has been defined using the data itself, otherwise pre-selection bias exists and resulting *P*-values are invalid. These tests do not appear to have been used extensively in veterinary epidemiology and are not the subject of the present discussion.

The spatial scan statistic is a cluster-detection test, able to locate both the site and test the significance of specific clusters (Turnbull et al., 1990). When using cluster-detection tests, the cluster size must be specified before examining the data (otherwise, the

procedure is invalid). If a point source is defined without examining the data beforehand, then a focused test should be used rather than the spatial scan statistic because it will have greater power by focusing on a specific site of interest. Studies using cluster-detection tests do not appear to have been published in the veterinary literature. Global cluster tests and cluster-detection tests complement each other well — both having application for spatial analysis of disease clustering within any particular epidemiologic study.

5.3. Autocorrelation

The spatial autocorrelation coefficient for point data (I) is similar to the traditional Pearson correlation coefficient, except that the correlation examined is between different values within the same variable and a weight matrix is included to define the spatial relationships between points. The coefficient is calculated as the ratio of the mean deviation product and the sums of squares of x (e.g., longitude) and y (e.g., latitude) coordinates:

$$I = \frac{N \sum_i \sum_j w_{ij} (x_i - \bar{x})(x_j - \bar{x})}{J \sum_i \sum_j w_{ij} \sum_i (x_i - \bar{x})^2},$$

where N is the number of points in the study, J the number of pairs of points examined, x_i the value (e.g., disease incidence) of point i and x_j is the value of point j (x_i and x_j are two nearest neighbour points) and w_{ij} is the weight matrix (e.g., 1 for nearest neighbours and 0 otherwise, or some measure of inverse distance between nearest neighbours). A positive value of I implies clustering and a negative value implies dispersion. The expected value of I is $-1/(N-1)$ — which approaches 0 as N increases — and a z -statistic can be calculated in the usual manner, using the standard deviation of I , σ_I .

5.4. Spatial scan statistic

The scan statistic was first proposed as a test of temporal clustering (Turnbull et al., 1990). Recently, the scan statistic has been adapted to investigate spatial clustering (Kulldorff and Nagarwalla, 1995). The procedure uses a theoretical circular window placed on a map of all locations included in a study. This scanning window is sequentially centred around one of many possible centroids in the study area. For each centroid, the window radius may vary continuously from zero to some upper limit selected by the investigator. An upper limit of 50% of the study area is recommended (Kulldorff et al., 1998). The procedure is considered invalid if the choice of radius is made after examining the data and estimating the size of potential clusters, or if the procedure is used to identify the window that best fits the data (Kulldorff et al., 1998). Thus, the procedure creates — in theory — an infinite number of distinct geographical circles, containing within them different sets of neighbouring locations. Each set of locations is a possible candidate for a cluster. However, since discrete locations (longitude, latitude) or the centroid of areas within a study are used in spatial analysis, the number of candidate circles that must be assessed is finite.

The scan procedure is flexible in that data can be analysed using two different probabilistic models — based on the Bernoulli or Poisson distributions. For the Bernoulli model, the data have the form of cases and non-cases coded as ‘0’ or ‘1’. Cases and non-cases may be selected from the study population, or may represent the entire study population. For the Poisson model, the number of cases at each location or within each area is assumed to be Poisson distributed. Under the null-hypothesis, the expected number of cases at each location is proportional to the population size or population-time at-risk at that location. For spatial analysis, results from using both models are generally similar (Kulldorff et al., 1998). When there are few (<10%) cases compared to controls, the Poisson model is a very good approximation of the Bernoulli model — although it may produce slightly conservative *p*-values. Calculations using the Poisson model typically take less computer time to complete than if the Bernoulli model is used (Kulldorff et al., 1998).

The spatial distribution of grazing livestock is almost always heterogeneous — some areas may be intensively grazed and other areas may not. Similarly, the distribution of livestock enterprises (such as dairies, feedlots, or poultry houses) may either cluster around centres of human populations (e.g., cities) or may be dispersed away from these centres. This has implications for selecting a spatial cluster statistic. The question of interest is usually “Does spatial clustering occur above and beyond the spatial clustering of cases that arises due to spatial variation in population density?”. Adjustment for spatial variation in population density may be achieved using commonly available methods such as standardisation. Regardless of the model (Bernoulli or Poisson) used in the spatial scan procedure, adjustment for lack of population homogeneity is achieved by conditioning on the total number of cases observed to calculate the expected number of cases for each location — a form of indirect adjustment.

The spatial scan statistic is a cluster-detection test, able to both locate and test the significance of clusters (Turnbull et al., 1990). The scan procedure may be used to detect clusters with high, low or high and low rates of disease. The latter is equivalent to a two-sided test. The most-common analysis is to scan for areas with high rates, i.e., for clusters. For each location and size of scanning window used, the alternative hypothesis is that there is an elevated — or decreased or either elevated or decreased — rate within the window as compared to outside. The likelihood function is maximised over all windows, identifying the window that constitutes the most-likely cluster — the cluster that is least likely to have occurred by chance. The likelihood ratio for this window is the maximum likelihood–ratio test statistic. Its distribution under the null-hypothesis and its corresponding *P*-value is obtained by repeating the same analytic exercise on a large number of randomly selected replications of the data set generated under the null-hypothesis (in a Monte Carlo simulation).

5.5. *Cuzick-and-Edwards test*

Adjustment for spatial variation in population density may be achieved using commonly available methods such as standardisation. However, in veterinary medicine, the population information necessary to perform such adjustments and retain

interpretability may be unavailable. Cuzick and Edwards (1990) developed a test for spatial clustering that takes into account the heterogeneous distribution of populations. This test compares the spatial coordinates of case and control locations. Controls are assumed to be selected from the same source population as cases (thereby accounting for clustering that may occur in the population regardless of the clustering of cases). The test is therefore appropriate for assessing clustering in heterogeneous populations (i.e., populations in which the underlying distribution of members is non-random). The test statistic T_k is the number (summed over all cases and controls) of cases that are nearest neighbours to each individual case; $T_k = \sum_{i=1}^n \delta_i d_i^k$, where $\delta_i = 1$ if observation i is a case and 0 if it is a control, and $d_i^k = 1$ if the k th nearest neighbour to i is a case and 0 otherwise. When cases are clustered, the nearest neighbour to a case will tend to be another case and T_k will be large. Conversely, when all cases have controls as nearest neighbours, T_k will be zero. Cuzick-and-Edwards' test allows the nearest-neighbour order to be selected by the researcher. For example, if $k=2$, $d_i^k = 1$ if the second closest neighbour to i is a case and 0 otherwise. Using higher-order nearest-neighbour values may reveal more-subtle and -complex clustering than if $k=1$ is used. The expected value of T_k ($E[T_k]$) is calculated as pkn , where n is the sample population size and k is the number of nearest neighbours being considered and $p = (c/n)[(c-1)/(n-1)]$ (c denoting the number of cases and n denoting the total sample size). A z -statistic can be calculated to test the significance of T_k using an estimate of the variance of T_k ($\text{Var}[T_k]$) as $(T_k - E[T_k]) / \sqrt{\text{Var}[T_k]}$. The P -value associated with each k can be combined to produce an overall test of significance — e.g., by using the standard Bonferroni method or using Simes' method (Simes, 1986) in which the overall P -value is estimated by ranking the array (i to n) of P -values and finding the minimum of $(n+1-i)P_i$.

6. Descriptive temporal statistics

A number of techniques are available for describing time-series data. Time-series analysis — which includes descriptive procedures as well as autoregressive integrated moving average (ARIMA) models — can be used if the time-series is of sufficient length (a minimum of 50–60 time-unit observations is usually required). Models can be used to investigate either patterns within the series or the association between dependent and independent variables over time. Recent examples of the use of time-series analysis in the veterinary literature include the association between bluetongue virus infection and the southern oscillation index (Ward and Johnson, 1996), the relationship between climatic factors and equine *Corynebacterium pseudotuberculosis* infections (Doherr et al., 1998) and the temporal patterns of domestic and wildlife rabies in Namibia (Courtin et al., 2000). For shorter, single time-series — or those lacking a seasonal, cyclical or long-term trend — methods such as the sets and runs tests can be used to describe the temporal distribution of cases (Singer et al., 1998). A basic statistic to describe a time-series of disease occurrence is the median time of occurrence. To describe the amount of variability in median time of occurrence, percentiles may be found. Visualising a time-series requires a plot of the number of cases or incidence of disease over time. A moving average can be used to “smooth” the series and enable modes to be identified. Further

smoothing and summarising may be achieved by fitting one or more statistical distributions to the time-series.

Methods are also available to detect permanent changes in disease frequency over time. For example, Christensen and Rudemo (1996) have described procedures for identifying and describing both single and multiple change-points in disease incidence. These parametric procedures are based on the Poisson model of disease occurrence and are useful in situations where disease incidence or prevalence is the outcome of interest and where disease occurrence does not necessarily return to some pre-outbreak level (Christensen and Rudemo, 1998). The tests described by Christensen and Rudemo (1996) assume that the rate parameter of the Poisson model (m) is constant within time intervals but changes over time (at each change-point).

7. Tests for temporal clustering

7.1. Ederer–Myers–Mantel test

The test developed by Ederer et al. (1964) to detect clustering of events in time uses for the test statistic (m_i) the largest number of cases occurring in any time interval of time-series i . The sum of the test statistics for each series is used to construct a χ^2 statistic:

$$\chi^2 = \frac{[|\sum_{i=1} m_i - E(\sum m_i)| - 0.5]^2}{\sum \text{Var}(m_i)}.$$

The expected value and variance of m_i under the null-hypothesis that cases are allocated randomly among the t time intervals are taken from tables published by Ederer et al. (1964) and Mantel et al. (1976). Time-series in which the number of cases is ≤ 1 are not used in calculating the test statistic, because the concept of a maximum number of cases is meaningless for such time-series. The Ederer–Myers–Mantel test procedure can be used to identify in which time-series significance clustering exists, although correction needs to be made for multiple testing. This test is most powerful when there is a single large cluster within each time-series. It should not be used for series with sparse data. Although this test is not sensitive to differences in population size between areas from which the time-series originate, it is biased by changes in population size over time. The number of intervals within each time-series must be at least two. The maximum number of time intervals that may be analysed with available software is 12. For longer series, subsets can be analysed or data can be reorganised into fewer time intervals.

7.2. Temporal scan statistic

Naus (1966) proposed a test of temporal clustering known as the “scan test”. The temporal scan statistic is analogous to the previously described spatial scan statistic, but used in a temporal dimension. The test statistic is the maximum number of cases observed in a predefined subinterval of time, and is found by “scanning” all time-series

in the study using the predefined subinterval (window). As with the spatial scan procedure, the temporal scan procedure can be based on either a Poisson or Bernoulli model. In the Poisson model, population data at one or more time points may be specified and the population that is assumed to exist between such time points is estimated through linear interpolation. For the Bernoulli model, the time of occurrence of cases and non-cases must be known. The length of the window used must be at least as long as the unit of observation, but may be up to 90% of the study time period. The procedure can search for temporal clusters with high, low or high and low rates of disease. A likelihood–ratio test can be used to test the statistical significance of an identified temporal cluster in the same manner as for the spatial scan procedure.

The scan statistic is intuitively appealing, although it may become mathematically complicated as the study time period increases and the scanning window selected decreases. The scan statistic was developed to detect a sudden temporal clustering of disease in a defined population (Naus, 1965). The test is most sensitive to clustering when the scanning window is of the same width as natural clusters in the data. If this window is small and the data are continuous over the study time period, the scan test is more powerful than the Ederer–Myers–Mantel test (Naus, 1966). In the scan test proposed by Naus (1965), count data are used. If the population-at-risk (denominator) within a study changes over time, test results can be biased and significance may be found even though underlying clustering is absent. Generalisations of the scan statistic have been proposed that adjust for changes in the population-at-risk (Weinstock, 1981), or for increasing or decreasing temporal trends in the study population (Kulldorff et al., 1998).

The scan statistic has been used for temporal analysis of disease patterns in veterinary epidemiology. For example, Paré et al. (1996) used the scan statistic to detect temporal clustering of horses shedding *Salmonella krefeld* during hospitalisation, Singer et al. (1998) used the scan statistic to investigate the temporal clustering of antimicrobial-resistant strains of *Pasteurella* species isolated from Californian cattle and Doherr et al. (1999) used it to examine temporal clustering of cases of equine *C. pseudotuberculosis* infections. Problems identified by these authors when applying the scan statistic to their data sets included difficulty defining the scanning “window” to use in analyses, and lack of homogeneity in the study population-at-risk over time. Ideally, the scanning window should be defined on the basis of disease biology. Subjectivity in defining this window can affect the validity of test results.

8. Software

The lack of availability of user and familiarity with statistical software has restricted the spatial and temporal analyses of data sets for disease clustering. For example, to analyse the spatial clustering of anaplasmosis in Illinois cattle herds using binary autocorrelation, Hungerford and Smith (1996) wrote a specific module using Microsoft[®] FORTRAN. However, software written to perform a range of tests is becoming more available. Appropriate statistical tests can now be accessed in programs such as Stat! (BioMedware, Ann Arbor MI, <http://ic.net/~biomware/>), CLUSTER (US Department of Health & Human Resources, Atlanta, GA), CAST (Applied Biomathematics, Setanket, NY,

<http://www.ramas.com/ramas2.htm#cast>) and SaTScan (Kulldorff et al., 1998; <http://dcp.nci.nih.gov/BB/SaTScan.html>). Some problems that remain include the cost of purchasing such software and the ability to perform all appropriate tests using the same program.

9. Example data set

Information on blowfly strike was obtained from a questionnaire survey of sheep producers in southeastern Queensland, Australia. The study area consisted of the local government areas of Stanthorpe and Inglewood shires. These two areas are located adjacent to each other in southeastern Queensland, bordering New South Wales and approximately 200 km southwest of Brisbane and 250 km north of Armidale. The total land area covered is approximately 10 000 km², and the annual average rainfall is 650–750 mm. Within Stanthorpe and Inglewood shires, approximately 482 000 sheep are grazed in 204 flocks.

A questionnaire survey was mailed in June 1999 to all commercial sheep producers with Stanthorpe or Inglewood shire addresses. The sampling frame used is maintained by the Queensland Department of Primary Industries (DPI). Commercial producers listed in the frame are those grazing more than 500 sheep. Producers failing to respond to the initial questionnaire were posted the questionnaire a second time and requested to respond by July 1999. The questionnaire requested information on property and flock characteristics (property size, flock size and structure, time of last shearing and wool growth, rainfall), flock management and husbandry (shearing, crutching, mulesing and pesticide treatments for each class of sheep during the period August 1998–May 1999), occurrence of blowfly strike (number and type of strike for each class of sheep) and the use of fly traps to prevent flystrike. Flock-location information was available from farm name and wool district; flocks were located using longitude and latitude coordinates. The average flock size and total property size of questionnaire non-responders was estimated using recorded information maintained by the Queensland DPI, and was not significantly ($P>0.05$) different. The locations of the flocks included in the study and their flystrike status are shown in Appendix A. Number of cases of body strike and breech strike are shown in Appendices B and C. The age/class structure of flocks is shown in Appendix D.

10. Data analysis

The central location of flocks included in the study during the monitoring period was described using the mean centre statistic. To describe the possible influence of flystrike cases on the mean centre, both weighted and unweighted means were estimated. The incidence (risk) rate of blowfly strike at each location during the monitoring period was used as the weighting value. The standard distance deviation was calculated for each mean centre estimated. In addition, the mean centre for each month during the study period (August–May) was estimated, weighted by either the monthly incidence of body

strike or breech strike at each location. Calculations were performed using Excel 97 (Microsoft, 1997).

The spatial distribution of all flocks included in the study was described using the nearest-neighbour test. Spatial clustering of both body strike and breech strike was investigated using the autocorrelation statistic, Cuzick-and-Edwards' test and the scan statistic. For all procedures, flock location was described by longitude (x) and latitude (y). For the nearest-neighbour procedure, the number of locations (N) was 33. The relationship between locations (d_{ij}) was characterised using Euclidean distance, $((x_i - x_j)^2 + (y_i - y_j)^2)^{1/2}$. The size of the study area (A) was assumed to be that based on a rectangle enclosing the area formed by all flocks included in the study, approximately 7221 km² (0.66 square longitude–latitude units). The statistical significance of R was assessed by calculating a z -statistic. The distance between nearest neighbours expected under spatial randomness was calculated based on an estimation of the Poisson parameter: number of flocks divided by study area. For the autocorrelation statistic, the number of points (flocks) in the study (N) was 33, and the number of pairs of points examined (J) was $33(33-1)=1056$. The value (x_i) used at each location was the incidence of either body strike or breech strike during the monitoring period. The weight matrix (w_{ij}) used was the inverse of the Euclidean distance between flock locations. The statistical significance of I was assessed by a z -statistic, calculated using σ_I . For Cuzick-and-Edwards' test, flock locations were coded 1 at which either body strike or breech strike was observed (25 and 14, respectively), or 0 otherwise. Nearest-neighbour orders (k) from 1 to 10 were examined. Statistical significance was determined using calculated z -statistics and associated P -values for each nearest-neighbour order k examined. P -values were combined using Simes' method correction (Simes, 1986). For the spatial scan procedure, the Poisson model was used because <10% of the study population were cases. Case information consisted of the number of cases of either body strike or breech strike observed within each flock during the monitoring period. Population information consisted of the number of sheep present in each flock at the most-recent shearing prior to administration of the questionnaire. Only clusters with high — rather than low or low and high — rates of flystrike were identified. The likelihood–ratio test was used to test for statistical significance. Its distribution under the null-hypothesis — that the rate of disease within a scanning window based on a certain location is not different from the rate of disease outside the window — and its corresponding P -value was obtained by repeating the likelihood calculations on a large number (999) of random replications of the data set generated under the null-hypothesis using Monte Carlo simulation (Kulldorff et al., 1998). For all spatial clustering analyses, an overall Type-I error of 0.05 was used. Nearest-neighbour and autocorrelation calculations were performed using Excel 97 (Microsoft, 1997). The distribution of nearest-neighbour distances expected under spatial randomness and Cuzick-and-Edwards' test were performed using Stat! (Jacquez, 1994b). Cluster analysis using the spatial scan statistic was performed with SaTScan version 2.1.3. (Kulldorff et al., 1998).

The temporal clustering of flystrike in the 33 flocks included in the study was described by plotting the monthly incidence (risk) rates of either body strike or breech strike. Population information for each flock — as previously described — was used as the rate denominator. The median month of occurrence was estimated by coding for each

case its month of occurrence as 1–10, corresponding to August 1998–May 1999. Quartiles were also estimated.

Temporal clustering of both body strike and breech strike was investigated using the Ederer–Myers–Mantel test and the temporal scan statistic. For both procedures, time of flystrike occurrence was coded by month, August 1998=1, September 1998=2, . . . , May 1999=10. Thus, 33 time-series of cases for both body strike and breech strike were created. The statistical significance of the Ederer–Myers–Mantel test was assessed by a χ^2 statistic. For clustering within each time-series, Type-I error was corrected for multiple testing to achieve an overall Type-I error of 0.05, so that individual tests were performed at a Type-I error of 0.0015. For the temporal scan statistic, a Poisson model was used. Case information consisted of the number of cases of either body strike or breech strike observed within each flock during each month of the monitoring period. Population information consisted of the number of sheep present in each flock at the most-recent shearing. Only temporal clusters with high — rather than low or low and high — rates of flystrike were identified. The scanning window used was equal to a period of 1 month. The likelihood–ratio test was used to test for statistical significance. Its distribution under the null-hypothesis was obtained through Monte Carlo simulation. A Type-I error of 0.05 was used. The Ederer–Myers–Mantel test was performed using Excel 97 (Microsoft, 1997). Temporal scan statistic analyses were performed using SaTScan version 2.1.3. (Kulldorff et al., 1998).

11. Use of techniques to investigate spatial and temporal clustering

During the 10-month period of observation, body strike and breech strike was observed in 25 and 14 flocks, respectively. A total of 1259 and 548 cases of body strike and breech strike, respectively, were observed. Most cases of body strike (41%) and breech strike (44%) were observed in March 1999. The overall cumulative incidence of body strike and breech strike during the observation period was 1.1 and 0.5%, respectively. The median flock incidence for body strike and breech strike was 1.0% (95% CI, 0.4–1.9%) and 0.3% (95% CI, 0–0.6%), respectively. Wether sheep (neutered males) made up the largest (57%) proportion of the population.

The mean centre of all flock locations was 28.559°S, 151.536°E (S.D.=0.2829). The mean centre — weighted by the incidence of body strike — was approximately 8 km to the north-east (28.513°S, 151.600°E, S.D.=0.2788) of the unweighted mean centre. The mean centre — weighted by the incidence of breech strike — was approximately 11 km to the north-west (28.527°S, 151.422°E, S.D.=0.3250) of the unweighted mean centre. Mean centres (weighted by either the monthly incidence of body strike or the monthly incidence of breech strike) are shown in Fig. 1. The location of all flocks included in the study was similar to a random distribution: the observed distance between nearest-neighbouring flock locations was 7.4 km and the expected distance under random distribution was 8.5 km. The nearest-neighbour index was 1.16 ($z=1.74$, $P=0.08$). The observed and expected distribution of nearest-neighbour distances is shown in Fig. 2.

The autocorrelation statistic — weighted by the incidence of either body strike or breech strike at each flock location during the monitoring period — was 0.003

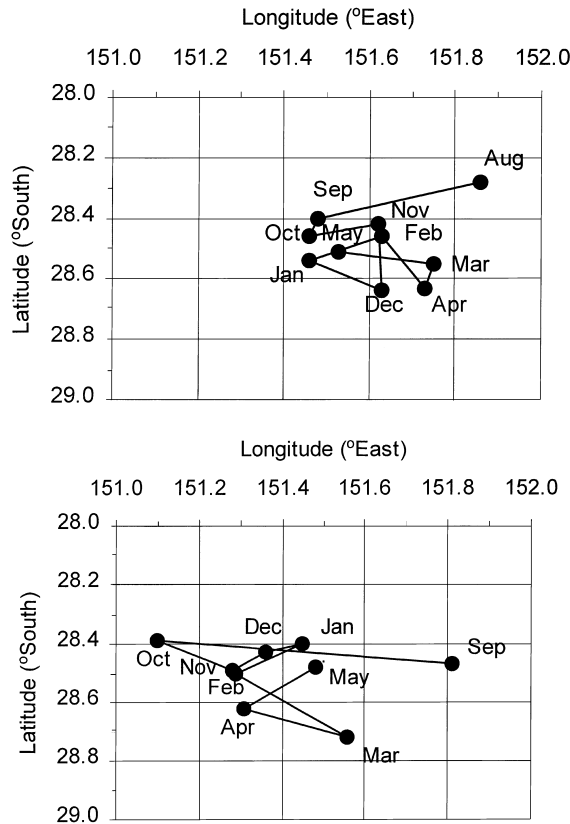


Fig. 1. Mean monthly centres (●) of the location of 33 flocks in southeastern Queensland, Australia (weighted by the incidence of body strike (upper) and breech strike (lower) observed during the period August 1998–May 1999).

(S.D.=0.935, $z=0.037$, $P=0.97$) and -0.041 (S.D.=0.719, $z=-0.013$, $P=0.99$), respectively. Results of Cuzick-and-Edwards' test applied to case and control flock locations are shown in Tables 1 and 2. Overall, no significant clustering of case flocks was detected for either body strike ($P=0.85$) or breech strike ($P=0.38$). Using the spatial scan statistic, the most-likely (log likelihood ratio=462, $P=0.001$) cluster of flocks with more cases of body strike (821) than expected (310) is shown in Fig. 3. It consisted of 10 flocks (9, 30, 34, 42, 44, 56, 62, 68, 74 and 77). The risk of body strike in this cluster was 2.7 times higher than expected. The most-likely (log likelihood ratio=247, $P=0.001$) cluster of flocks with more cases of breech strike (381) than expected (134) is also shown in Fig. 3. It consisted of five flocks (8, 19, 21, 73 and 79). The risk of body strike in this cluster was 2.8 times higher than expected.

The monthly incidence of body strike and breech strike is shown in Fig. 4. The incidence of body strike appeared to be bimodally distributed (October 1998 and March 1999), whereas breech strike incidence appeared to be unimodally distributed (March

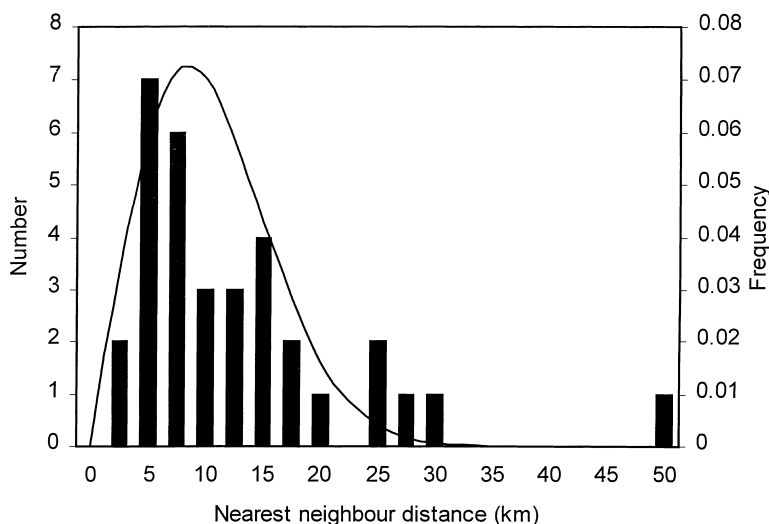


Fig. 2. Frequency distribution of observed and expected (—) nearest-neighbour distances of the locations of 33 flock in southeastern Queensland, Australia, included in a study of blowfly strike, August 1998–May 1999.

1999). The median month of occurrence of body strike and breech strike was January and March 1999, respectively. First and third quartiles were November 1998 and March 1999, and February and April 1999, respectively.

Two or more cases of body strike and breech strike were reported in 24 and 14 flocks, respectively. Significant overall temporal clustering of both body strike ($\chi^2=15808$, $P<0.0001$) and breech strike ($\chi^2=3693$, $P<0.0001$) was detected using the Ederer–Myers–Mantel test. Within flocks in which ≥ 2 cases of flystrike were reported, temporal clustering of body strike was significant ($P<0.05$) in all but two flocks — flocks 21 and 24, and clustering of breech strike was significant ($P<0.05$) in all but three flocks —

Table 1

Analysis of spatial clustering of body strike at 33 flock locations in southeastern Queensland, Australia between August 1998 and May 1999 using Cuzick-and-Edwards' test

k	T	$E[T]$	$\text{Var}[T]$	z	P
1	17	19	4.91	-0.79	0.79
2	33	38	11.82	-1.31	0.90
3	53	56	18.05	-0.76	0.78
4	76	75	22.95	0.21	0.42
5	88	94	29.26	-1.06	0.86
6	108	113	36.79	-0.74	0.77
7	130	131	42.75	-0.19	0.58
8	147	150	44.01	-0.45	0.67
9	164	169	50.52	-0.67	0.75
10	179	188	69.34	-1.02	0.85

Table 2

Analysis of spatial clustering of breech strike at 33 flock locations in southeastern Queensland, Australia between August 1998 and May 1999 using Cuzick-and-Edwards' test

k	T	$E[T]$	$\text{Var}[T]$	z	P
1	7	6	4.12	0.65	0.26
2	13	11	9.28	0.53	0.30
3	17	17	14.18	-0.02	0.51
4	24	23	18.27	0.29	0.39
5	30	28	22.99	0.33	0.37
6	33	34	27.99	-0.21	0.58
7	39	40	31.73	-0.14	0.56
8	45	46	33.72	-0.09	0.53
9	51	51	37.47	-0.03	0.51
10	59	57	45.45	0.32	0.38

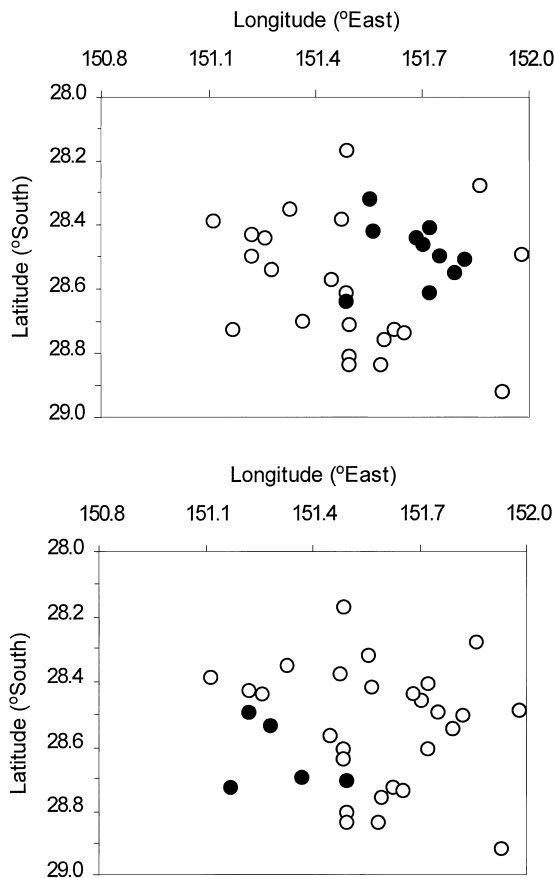


Fig. 3. Locations of 33 flocks in southeastern Queensland, Australia, in which clustering (●) of body strike (upper) and breech strike (lower) during the period August 1998–May 1999 was detected using the scan statistic.

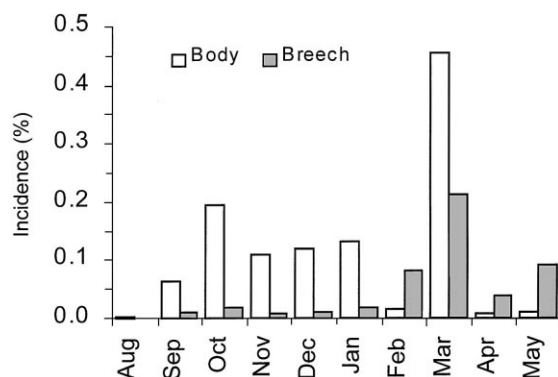


Fig. 4. Monthly cumulative incidence of body strike and breech strike reported between August 1998 and May 1999 from 33 flocks located in southeastern Queensland, Australia.

flocks 21, 24 and 26. Plots of the observed test statistic (m_i) for each flock against its expectation are shown in Fig. 5. Using the temporal scan statistic, clustering of body strike in flocks included in the study was identified during March 1999 — in which 517 cases (41%) were reported and 128 cases were expected, an overall relative risk of 4.0 (log likelihood ratio=408, $P=0.001$). Clustering of breech strike was also identified during March 1999 — 237 cases (44%) were reported and 55 cases were expected, an overall relative risk of 4.3 (log likelihood ratio=202, $P=0.001$).

12. Discussion

Autocorrelation appears to have been the method most-commonly used to detect spatial clustering in studies published in the peer-reviewed veterinary literature in the last decade. It is an easily understood technique that has many similarities with traditional correlation. For example, de la Rúa-Domènech et al. (1995) cited the fact that the spatial autocorrelation statistic is well-characterised in the statistical literature as a reason for using it in a study of the spatial clustering of equine motor-neuron disease in the United States. However, those authors also identified a major drawback in its use: the assumption of homogeneity of the population-at-risk. Whilst this assumption may be reasonable — e.g., where study sites have been selected to represent the spatial distribution of the study population and these sites are fixed for the duration of the study — it is unlikely to be appropriate in situations in which a secondary data set is used and selection of study sites was undertaken without regard to the spatial distribution of the study population. The nearest-neighbour technique has a similar restriction when used to test for spatial clustering. In these situations, the question of interest changes from whether or not clustering exists to whether or not the clustering that is present is greater at affected (“case”) versus unaffected (“control”) locations. An approach to answering this question has been provided by Cuzick and Edwards (1990). Their approach accounts for non-uniformity by assuming that both cases and controls are randomly selected from the

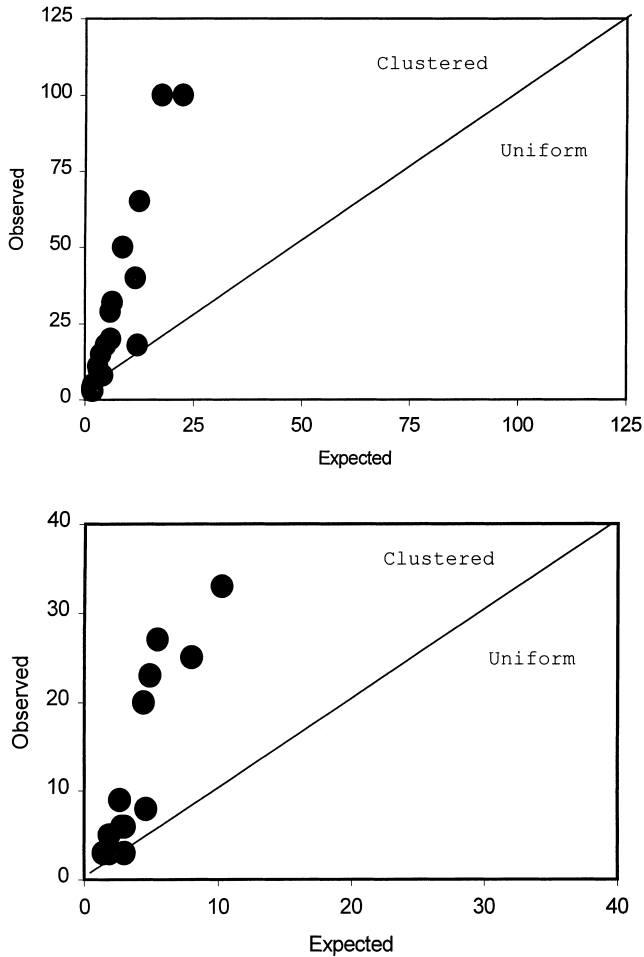


Fig. 5. Observed Ederer-Myers-Mantel test statistic (largest number of cases in any time interval of time-series i) and its expectation for reported body strike (upper) and breech strike (lower) in flocks located in southeastern Queensland, Australia, during the period August 1998 to May 1999. Two outliers — flocks 30 (332 cases of body strike observed, 42 cases expected) and 73 (182 cases of breech strike observed, 38 cases expected) — are not shown.

population-at-risk. Thus, both case and control series reflect the distribution of the population-at-risk and clustering in the case series in excess of that in the control series is used as evidence of disease clustering. This approach also has the advantage of being able to control confounders — both known and unknown — through the judicious selection of controls. Thus, Cuzick-and-Edwards' test approach seems well-suited to investigations of the spatial clustering of diseases in veterinary epidemiology. A disadvantage in using Cuzick-and-Edwards' test is that data recorded on an interval scale must be dichotomised as “case” and “control” locations. This might represent a substantial loss of information.

Whether this loss of information can be tolerated will depend on the disease of interest and the hypothesis being tested. Often the focus is on disease presence versus absence; in these situations, data dichotomisation of data into case and control locations poses no disadvantage. In addition, if the accuracy of an interval measurement is not high, dichotomisation can be tolerated and may even be appropriate. An alternative to using Cuzick-and-Edwards' test to account for heterogeneity among the population-at-risk is the spatial scan statistic (Kulldorff and Nagarwalla, 1995). In effect, incidences of disease at locations can be used. A disadvantage associated with the use of this statistic is that the population-at-risk must be enumerated in each area or at each location. This information might not be available — particularly if the data being analysed are from a secondary data source — so that the use of the spatial scan statistic may be prevented. Although a formal comparison of Cuzick-and-Edwards' test and the spatial scan statistic does not appear to have been undertaken, the scan statistic should be more powerful (in theory) because all available information (number of cases and population-at-risk) is used in the procedure. In addition, the spatial scan statistic is a cluster-detection test, whereas Cuzick-and-Edwards' test is a global test of clustering. The spatial scan statistic is able to locate the most-likely cluster within the study area and therefore provides more information than Cuzick-and-Edwards' tests. Although use of the spatial scan statistic on the example data set provided more information in this study than use of Cuzick-and-Edwards' test, we recommend that both procedures should be used — if the necessary information is available — to detect and characterise clustering of disease in epidemiologic studies.

Tests for temporal clustering of disease generally assume that the population-at-risk remains relatively stable over time, or that disease occurrence is rare. These assumptions were made when analysing the example data set used in this study. The Ederer–Myers–Mantel test implicitly assumes that the population-at-risk is constant over time by focusing only on cases of disease. In contrast, the temporal scan statistic is able to accommodate changes in the population-at-risk over time if that information is available. In the example data set used, we had an estimate of the population-at-risk at one point in time. If this information had been available at two or more points in time, we could have incorporated it into analyses. Another advantage of the temporal scan statistic is its ability to locate the time interval in which clustering is most likely to have occurred. The Ederer–Myers–Mantel test is most sensitive when there is a single large cluster in each time-series (Jacquez, 1994a). Thus, for detection of unimodal patterns (e.g., epidemic curves), the Ederer–Myers–Mantel test is useful. The Ederer–Myers–Mantel test and temporal scan statistic are flexible in that the length of the scanning window can be altered and thus more-complex patterns of clustering can be detected. Thus, the pattern of temporal clustering expected is an important criterion to consider when selecting an appropriate test to use. A disadvantage of using tests where the time interval in which clustering may occur can be altered is that subjectivity is introduced into the testing procedure. It is recommended that the scanning window should be based on biological characteristics of the disease being studied. For example, Paré et al. (1996) used a window of 2–14 days in length to investigate temporal clustering of *Salmonella krefeld* infection in horses admitted to an intensive-care unit of a veterinary hospital. This was based on the average duration of hospitalisation, the known lag period between infection

and shedding of *Salmonella* species, and the need to perform multiple cultures to detect *Salmonella* organisms. In contrast, Singer et al. (1998) and Doherr et al. (1999) used a range of window lengths in their studies — apparently to generate disease-causation hypotheses. Obviously, the more analyses performed using a wide range of scanning windows, the more likely it is that significant clustering will be detected. Thus, the investigator needs to consider the aim of analysis carefully and to review available literature and expert opinion on the disease of interest prior to selecting one or more scanning windows to use. We suggest that selection of a scanning window a priori will provide more-robust results. As with any hypothesis test, *P*-values produced by applying the scan statistic many times to the same data set are likely to be excessively liberal.

13. Conclusion

Investigations of disease clustering in either time or space in veterinary epidemiology can be greatly enhanced through the use of a variety of analytical techniques. In particular, statistical tests can allow both clustering of disease events to be detected and to identify when and where this clustering has occurred. These techniques add considerable information to disease investigations and provide the veterinary epidemiologist with a firm foundation on which to build causal hypotheses and implement control strategies. The challenge now is to implement these techniques as routine procedures within animal disease-control and -prevention programs. Some issues that must be addressed in the future include development of techniques that are more flexible with respect to assumptions of homogeneity of the population-at-risk, the routine collection of spatial and temporal information from animal health surveillance and monitoring programs, and the development of software that can be easily accessed, used and understood by veterinary epidemiologists. Publication of more examples of the application of techniques to investigate spatial and temporal clustering of disease in veterinary epidemiology will assist epidemiologists and statisticians addressing these issues.

Acknowledgements

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Appendix A.

Location of 33 sheep flocks (longitude, latitude) in southeastern Queensland, Australia and occurrence of flystrike between August 1998 and May 1999 (1=yes (case), 0=no (control)) are shown in the following table.

Flock	Latitude	Longitude	Body strike	Breech strike
2	28.17	151.48	1	0
8	28.54	151.27	1	0
9	28.61	151.72	1	0
17	28.43	151.21	0	1
19	28.73	151.16	1	0
21	28.50	151.21	1	1
24	28.57	151.44	1	1
26	28.38	151.47	1	1
27	28.28	151.86	1	1
30	28.51	151.82	1	0
34	28.41	151.72	0	0
35	28.81	151.49	1	0
40	28.44	151.25	1	0
41	28.49	151.98	1	0
42	28.64	151.48	1	0
44	28.46	151.70	1	0
48	28.84	151.58	0	1
50	28.76	151.59	0	0
53	28.39	151.10	1	1
56	28.44	151.68	1	0
61	28.84	151.49	1	0
62	28.55	151.79	1	1
68	28.42	151.56	1	0
71	28.61	151.48	0	1
73	28.71	151.49	1	1
74	28.50	151.75	1	0
76	28.73	151.62	0	0
77	28.32	151.55	1	0
78	28.64	151.48	0	1
79	28.70	151.36	0	1
82	28.92	151.93	1	1
83	28.35	151.32	1	0
99	28.74	151.65	1	1
Total	–	–	25	14

Appendix B.

Number of cases of body strike recorded in 33 sheep flocks in southeastern Queensland, Australia and occurrence of flystrike between August 1998 and May 1999 are shown in the following table.

Flock	Month										Total
	August	September	October	November	December	January	February	March	April	May	
2	0	5	0	0	0	0	0	0	0	0	5
8	0	20	0	10	0	0	0	0	0	0	30
9	0	0	0	20	100	0	0	0	0	0	120
17	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	50	0	0	50
21	0	0	0	0	0	0	0	0	1	3	4
24	0	0	0	0	0	2	3	0	0	0	5
26	0	0	10	0	0	0	0	2	0	0	12
27	4	0	0	0	0	0	0	0	0	0	4
30	0	0	0	0	0	0	0	332	0	0	332
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	15	0	0	0	0	15
40	0	0	100	0	0	60	0	0	0	0	160
41	0	0	0	0	0	11	0	0	0	0	11
42	0	0	40	0	0	20	0	12	0	0	72
44	0	0	0	0	0	0	4	18	0	0	22
48	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	5	5
56	0	14	65	0	0	0	0	0	0	0	79
61	0	0	0	0	20	10	0	0	0	0	30

62	0	0	0	0	0	0	0	6	8	4	18
68	0	12	7	10	9	9	11	18	0	0	76
71	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	29	0	0	29
74	0	0	0	32	0	0	0	0	0	0	32
76	0	0	0	0	0	0	0	0	0	0	0
77	0	20	0	50	0	0	0	0	0	0	70
78	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	50	0	0	50
83	0	0	0	0	5	22	0	0	0	0	27
99	0	0	0	0	0	1	0	0	0	0	1
Total	4	71	222	122	134	150	18	517	9	12	1259

62	0	9	0	0	0	0	0	0	0	0	0	9
68	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	6	2	2	0	10
73	0	0	0	0	0	0	0	76	182	0	38	296
74	0	0	0	0	0	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	27	27
79	0	0	0	0	0	0	0	0	0	23	0	23
82	0	0	0	0	0	0	0	0	20	0	0	20
83	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	6	4	1	0	0	0	0	0	11
Total	0	12	20	9	11	19	91	242	42	102	548	

Appendix D.

Structure of 33 sheep flocks in southeastern Queensland, Australia at the most-recent shearing prior to June 1999 are shown in the following table.

Flock	Class				Total
	Lambs	Wethers	Ewes	Rams	
2	0	2000	0	0	2000
8	800	500	100	20	1420
9	–	–	–	–	6000
17	92	0	81	2	175
19	0	2800	0	0	2800
21	350	1035	1100	15	2500
24	565	1779	1827	21	4192
26	640	2421	2400	39	5500
27	346	285	396	5	1032
30	2139	1700	1995	33	5867
34	0	700	0	0	700
35	630	1300	280	15	2225
40	0	3060	0	0	3060
41	190	380	900	13	1483
42	700	3600	700	14	5014
44	320	290	250	0	860
48	0	4800	500	0	5300
50	1000	3000	3000	50	7050
53	700	5039	450	11	6200
56	0	0	1658	472	2130
61	608	1455	993	20	3076
62	300	500	600	9	1409
68	0	4000	300	0	4300
71	0	2800	0	0	2800
73	3800	7580	7100	121	18601
74	0	711	0	0	711
76	0	1340	20	0	1360
77	0	900	0	0	900
78	0	4144	0	0	4144
79	181	890	1312	18	2401
82	265	580	575	11	1431
83	0	4900	0	0	4900
99	0	0	1909	0	1909
Total	13626	64489	28446	889	113450

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