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## Veterinary Epidemiology: Principles and Methods

# Part 2: Studying Disease in Animal Populations

## Chapter 4: Descriptive Epidemiology

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# Descriptive Epidemiology

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Health represents the dynamic balance between the host and its environment. That this balance is frequently tipped against the host resulting in disease is obvious to all; a major role for the epidemiologist is the identification and description of the circumstances and factors leading to the imbalance. Like an ecologist, the epidemiologist is interested in the relationship between the factors (the host and the environment including the agent) and how the relationship changes. The occurrence of virtually every disease is influenced by factors representing each of the host, environment, and time categories. In addition to humane considerations, the effects of disease on productivity should be a feature when describing the epidemiology of a disease.

During the past century, the study of disease has primarily concentrated on the pathogenesis of disease, and many important epidemiologic features have been ignored. In many instances, the identification of the sources, transmission, survival, and effects of agents of disease was considered as describing the epidemiology of disease. However, epidemiologic investigations go beyond the agent and concentrate on the factors of host, environment, and time that alter the occurrence and/or severity of disease for groups of individuals. In these pursuits, epidemiology is essentially a holistic discipline, whereas most other medical disciplines are reductionistic. (This statement is not meant as a criticism of other disciplines, it merely points out two divergent views of health and disease. Society will be served best by cooperation and understanding between the proponents of each viewpoint.)

This chapter outlines and discusses those factors of the host, environment, and time that should be included when describing the epidemiology of disease; these factors are sometimes referred to as its natural history. Since epidemiology is a pragmatic discipline, it is hoped that subsequent to their identification a means of manipulating causal factors will exist so that

the knowledge may be of practical value. At the very least, a thorough description of the natural history of disease should enhance the understanding of that disease. Although there are separate sections in this chapter for host, environment, and time factors, it is important to note that these categories are closely interrelated in terms of their effects on health.

Often, host factors are of secondary interest in epidemiologic studies. Despite this, it is important to describe the relationship of host factors to disease occurrence and, if necessary, to control the effects of host factors (e.g., by analytic methods such as standardization of rates—see 4.2). Otherwise, host factors may distort the observed association between environmental factors and disease. Only when it is known that host factors do not exert a significant effect on the occurrence of disease can they be ignored.

#### 4.1 Host Factors

The major intrinsic host factors are age, sex, and breed. Depending upon the circumstances, other host factors such as species or physiologic state (e.g., pregnancy) should be considered. The occurrence of disease at different levels of these factors is best described by using incidence rates or prevalence proportions, rather than proportional morbidity rates or counts of cases. As mentioned previously, incidence rates and prevalence proportions provide estimates of the risk (probability) of disease occurrence at different levels of the host factor (e.g., in males versus females, intact versus castrated, old versus young, Holsteins versus Jerseys). On the other hand, case counts are influenced by the risk of disease and the number of animals in that host-factor category. Thus, the distribution of cases with respect to host factor(s) probably does not reflect the underlying risk of disease. Some veterinary medical texts describe the pattern of disease and make inferences about the risk of disease based solely on the number of occurrences, rather than adjusting for the population at risk. The reader should be alert to note and hesitant to accept inferences about risk of disease made in this manner. For example, although 60% of all cases of mastitis may occur in 4- to 7-year-old cows, one should not conclude that cows of this age are necessarily at increased risk of mastitis in comparison to other age groups. One must relate the age distribution of cases to that of the source population in order to make inferences about the risk of mastitis.

Sometimes the underlying population rates are unknown and cannot be estimated easily. In these instances the effects of host factors on the occurrence of disease can be described by comparing the relative frequency of the host factor in cases to its frequency in noncases. A formal statistic for this purpose is the odds ratio (see 5.3.1).

#### 4.1.1 Age

Age is probably the most important host variable, because the risk of disease usually is more closely related to age than to other host factors. Thus, age should always be included when describing the distribution of disease. There are many factors, however, that can affect the pattern of disease occurrence with age. It is important to consider whether the distribution is due to age itself, the current effects of recent environmental exposures on animals of different current ages, or the different past environmental exposures of animals of different current ages. Techniques for separating these effects will be described later in this chapter (see 4.10). Whether age per se actually changes the risk of disease independent of the environmental factors is unknown. However, epidemiologists attempt to identify environmental factors that accompany but are separable from age that may alter the risk of disease. For example, the cumulative insults of machine milking may provide a more reasonable explanation for the progressive increase in risk of mammary gland infection as cows become older than age per se. Such a hypothesis is quite easily tested and if support for it is found, better milking machine design and/or more careful milking techniques should provide methods of preventing at least some of the increased risk related to age. Some unavoidable and unalterable changes in the mammary gland due to aging may persist however.

If age-specific rates are plotted (e.g., as a histogram), the shape of the resultant plot will depend on whether morbidity rates (incidence or prevalence), mortality rates, or the rates of other intermediate events such as culling are used. If age exerts a major influence on the risk of the disease in question, one would expect either a uniform increase or decrease—not necessarily linear—or a unimodal pattern of disease occurrence with age. For example, data on the occurrence of a number of syndromes in dairy cattle indicate that the incidence rate (risk) of most diseases increases with age. For many of the diseases the increase is consistent with a linear trend, whereas for others the pattern is curvilinear. Some diseases (e.g., various pneumonias in cattle) have a U-shaped age pattern (Dohoo et al. 1984b). That is, the disease occurs relatively frequently in young and old animals—probably either because of recrudescence or increased susceptibility—but with low frequency during the middle years. This pattern would probably be more pronounced if cohorts of cattle were followed from birth rather than from first calving.

Often, only prevalence data from periodic surveys are available, and this makes it difficult to determine the risk of acquiring infection or disease by age. Formulas are available to estimate age incidence from prevalence, but most are based on the assumption that the substance being measured (usually antibodies) is present for the life of the animal and that immigration and emigration in the population are minimal. Based on these assump-

tions, a constant probability (risk) of acquiring infection with age will produce a curvilinear age-specific prevalence pattern that increases with age. Similarly, it is difficult to make inferences about the risk of infection based on age-specific disease rates, or to make inferences about the risk of disease based on age-specific mortality rates. Nonetheless, knowing the age pattern of disease and mortality can help generate useful hypotheses about factors that might influence infection and disease respectively.

If the pattern of disease occurrence with age appears to be bimodal (i.e., two peaks are present), this may indicate that there are in fact two distinct syndromes present—although they may have clinical or pathological similarities—or that factors influencing disease occurrence in the different age groups differ. Apparently, bimodal patterns exist for feline leukemia (Essex 1982) and canine progressive retinal atrophy (Priester 1974). Infectious bovine rhinotracheitis (IBR) virus is associated with a number of syndromes, the frequency of which produces a bimodal or trimodal pattern with age. In calves less than 1 month of age, the virus produces an enteric syndrome. In older calves, 6–18 months of age, an upper respiratory tract syndrome is seen. In adult females, the virus is associated with both infertility and abortions. Since the same virus is common to these different conditions, the different syndromes probably reflect changes in the physiologic condition of animals as they age and differences in environmental conditions, rather than differences in the virus itself.

In humans, the young have a higher risk of most infectious diseases than do teenagers or adults, because the latter have an acquired immunity due to past exposure to the agents of these diseases, and because of physiologic and behavioral changes with age. Despite the higher rate of occurrence in the young, the severity of disease (chiefly under host control) often is less in the young than in the old. This is particularly true if the initial exposure of the young occurs while they have passive protection. The level and duration of passive protection in the young depend chiefly on the extent and timing of exposure of their mothers to the agent. When infections such as measles or poliomyelitis enter populations that have not been exposed for a number of generations, the differential rate of occurrence with age is absent and the increased severity of the disease in mature people becomes apparent.

The above age-related phenomenon probably occurs in animals also, but the pattern may be obscured for a number of reasons. First, a large percentage of domestic animals are slaughtered prior to reaching an age equivalent to adulthood in humans. Second, the hygienic standards on most farms facilitate the early exposure of animals to the more common pathogens, and vaccination programs may have altered the pattern of resistance in both adult and young populations. For example, if one observed cohorts of feral cats, the pattern of diseases such as panleukopenia would

probably be quite different than the pattern in domesticated felines. These differences would reflect the divergent environmental exposures of these groups of cats, as well as possible inherent host differences such as genotype. Severe outbreaks of disease (such as infectious bovine rhinotracheitis or bovine virus diarrhea) in closed herds probably represent an analogy to the "island" outbreaks of human measles. Maintaining closed herds may free the owner from the everyday problems of endemic diseases; however, additional vigilance is required to prevent serious outbreaks following the introduction of infection to this highly susceptible population.

Most measures of productivity also are age related; examples range from racing ability in horses to milk production in dairy cows. Young animals appear to be more efficient than adults at converting feed energy into usable products, be it eggs or muscle protein. Despite this, there may be economic value in prolonging the life of certain animals. For example, the average survival time of dairy cows in Canada is about 4 years after their first calving. Since a cow's production potential does not decrease markedly between 7 and 10 years of age, the dairy industry might benefit if diseases leading to premature involuntary removal from the herd could be prevented. This is particularly true because of the large investment in rearing replacements for swine, beef, and dairy herds. Of course, this potential benefit must be balanced against the increased opportunity for genetic improvement afforded by replacement of culled stock. The economics of culling and purchasing or raising replacements should also be considered. As previously mentioned (see 3.6.1), because of the marked and consistent effect of age on the absolute level of production, some parameters (e.g., milk production in dairy cows) are standardized to facilitate direct comparisons of production in animals of different ages.

#### 4.1.2 Sex

A number of diseases are associated with the sex of animals; for example, infectious diseases may occur more frequently, or with greater severity, in young male humans than in young females. On the other hand, female dogs have a much greater risk of diabetes mellitus than males (Marmor et al. 1982). This is also true of humans, and is an indication that dogs may be a good model for studying the pathogenesis of diabetes.

Many of the sex-associated diseases are directly or indirectly related to anatomic and/or physiologic differences between the sexes. Such diseases include parturient paresis (milk fever), mastitis, metritis, and cancer of the mammary glands in females, as well as sex-related behavioral problems such as abscessation as a result of fighting and urine spraying in male cats.

Neutering also may be associated with disease occurrence. These associations range from a sparing effect on the risk of mammary gland cancer in spayed bitches to an increased risk of laminitis in castrated ponies, the

latter also being related to behavioral and husbandry changes. The risk of the feline urologic syndrome is increased in castrated males; however, not all of this increase is likely due to anatomic changes because spayed females also have a higher risk than intact females (Willeberg and Priester 1976). When investigating the effects of neutering, the age at neutering should be considered.

Sex of the animal also needs to be taken into account when productivity is being evaluated, since racing ability, weight gains, deposition of body fat, and feed efficiency may differ between sexes.

#### 4.1.3 Breed

Breed differences in risk of disease and level of productivity are common, and breed effects should be considered and controlled (adjusted for) when studying the effects of other factors on disease occurrence or productivity. In general, breed differences may be separated into two components: differences due to genetic factors and differences due to phenotypic factors.

Population genetics, like epidemiology, is highly dependent on the collection and analysis of data from observational studies. Both disciplines are interested in determinants of disease, and as it is often unclear at the outset whether a disease has genetic determinants, there is much overlap between the two disciplines. Animal geneticists have developed a set of specialized analytic methods for identifying the heritability of continuous production traits. Recently these techniques have been modified to study the heritability of discrete traits such as the presence or absence of disease. The equivalence between these techniques and epidemiologic statistics such as the population attributable fraction (see 5.3.3) remain to be clarified. Although still in its infancy, one thing is clear: few diseases are determined solely by genotype or environmental factors. In fact, our current genetic make up is a result of the selection pressures exerted by the environment on our ancestors.

The close relationship between genetic and environmental determinants may be demonstrated by two avian diseases, yellow shanks and pendulous crops. Yellow shanks occurred when poultry with a specific genetic defect were fed yellow corn. If a farmer had only genetically defective birds and fed both yellow and white corn, the ration would appear to be the determinant, since only those fed yellow corn would develop yellow shanks. If a farmer had normal and genetically defective birds and fed only yellow corn, genotype would appear to be the determinant, since only genetically defective birds would develop the condition. In this syndrome both factors are required to produce the disease, and in the syntax of sufficient causes (see Chapter 5), the genetic defect and the specific environmental factor (yellow corn) would be considered necessary components of the sufficient cause (i.e., both must be present for the disease to occur). Pendulous crop

in turkeys is slightly more complex in that three factors—genotype (bronze turkeys), environment (very hot weather), and excess water intake—combine to produce the syndrome. Assuming no restriction on water intake and only bronze turkeys being present, the disease appears to be environmentally determined. If two or more breeds are raised under hot conditions, the disease appears to be genetically determined. Again, genotype and environmental factors are components of a sufficient cause. Phenylketonuria represents an analogous disease in children in that both environmental and genetic factors are involved. In these examples, because both factors (genotype and environmental) are required for the disease to occur, the interaction between genotype and environmental factors is said to be complete.

The relationship between genotype and environment as determinants of many diseases is often not as obvious as in the previous examples. If the disease has determinants other than a particular genotype–environmental factor combination, the statistical interaction between genotype and environment is less than complete. Although feasible, it is more difficult to identify putative causes in these instances. In general, the sensible approach would be identifying the role that each factor plays as a determinant of the disease, and using this knowledge to prevent the disease in so far as the factors can be manipulated.

In some cases, diseases initially considered to be genetic in origin were later shown to be essentially determined by environmental factors. For example, detailed experiments were conducted to prove that a particular cyclopic malformation in sheep was caused by a genetic defect. The experiments failed, and later observational and experimental studies identified a poisonous plant, *Veratrum californicum*, as the major cause (Binns et al. 1962). In retrospect, careful analysis of the available observational data might have convinced the investigators of this without the need of expensive experimental studies. In this case, as well as in early Texas fever investigations, the observations of ranchers were eventually validated, although veterinary investigators initially ignored and sometimes ridiculed the initial observations.

Diseases due to genetic defects such as baldy calves, dwarfism, and spastic paresis in bulls (most following a Mendelian inheritance pattern) have been identified. The heritability of diseases following more complex patterns (e.g., Galtonian characteristics) has not been studied as well as the simpler Mendelian type characteristics. Certainly, resistance to infectious disease has a genetic component as demonstrated by experiments with laboratory animals (e.g., the selection and breeding of leukosis-resistant strains of poultry and Aleutian disease resistance in mink). However, identification of the heritability of most diseases of domestic animals must await the development of large, accurate data bases, similar to those currently available for recording production. Preliminary work suggests that diseases such

as mastitis, atrophic rhinitis, and cystic ovarian disease have a genetic component, and that their heritability is sufficiently large so that sire and dam selection could reduce their incidence rate. Also, data from some swine herds indicate that the variability in the mortality rate in litters due to sire is quite large, varying from two to six times. This suggests that sire selection could reduce piglet mortality significantly (Straw et al. 1984).

In companion animals, the risk of many diseases including cancers, arthritis, and heart defects varies greatly among breeds. However, the proportion of this difference in risk that is genetically based is unknown. For example, phenotypic factors probably alter the risk of diseases such as hip dysplasia, with large breeds having an excess risk. Yet, there is a significant variation in the risk of hip dysplasia among dogs of the same general phenotype, and more than 25% of certain low-risk phenotype breeds develop dysplasia. Both of these facts suggest an important role of genotype. It has been shown that for some breeds, dogs owned by one person have significantly higher or lower rates of hip dysplasia than the breed average (Martin et al. 1980). This again supports the potential role of genotype and/or shared environment as determinants of this disease. To further complicate the issue, the effects of genotype and phenotype on the risk of hip dysplasia appear to be partially confounded with environmental factors, such as the amount of exercise the dog receives when young.

Phenotypic factors are believed to be important determinants in a number of diseases, ranging from bone cancer in dogs to displaced abomasum in dairy cows. A lack of pigmentation increases the risk of cancer-eye in Hereford cattle whereas gray coloration increases the risk of melanoma in horses. The underlying reasons for these associations are unknown in most cases. Data bases will be available in the near future that should allow an assessment of these types of multifactor problems. For example, one should be able to assess the impact of sire, phenotypic factors (e.g., size of cow, depth of chest, shape of abdomen), and other variables such as calving ease (which may be related to size of pelvic inlet and size of fetus) on the risk of abomasal displacement and other diseases.

Dogs have been and will continue to be studied intensively to aid understanding of the role of genotypic and phenotypic factors on disease occurrence and to identify models of human diseases. No other domesticated species has such a wide range of genotype and phenotype, and dogs share man's environment intimately and the occurrence of their diseases (such as bladder cancer) may be indicative of toxic substances in the environment of potential danger to man (Hayes et al. 1981).

As previously mentioned, host factors can distort the association between disease and factors of more immediate interest. For example, female canine diabetics were 16 times more likely to have a diagnosis of benign

mammary tumor than female dogs with other endocrine diseases. When a summary statistic (odds ratio) adjusted for age was calculated (using the Mantel-Haenszel technique, see 5.4.1) the odds ratio was reduced to 5.6 (Marmor et al. 1982). This technique is used frequently in analytic studies to control for the effects of extraneous factors.

## 4.2 Standardization of Rates

Because host factors are often determinants of disease, host-attribute specific rates (e.g., age, sex, and/or breed specific rates) should be used to describe patterns of disease. Each level of the attribute is used to form a stratum; the stratum-specific rates should be studied carefully before any attempts are made to summarize them, since summary rates ignore and often oversimplify and/or distort the true pattern of disease in the study population. However, despite these drawbacks, it may be desirable to have a single, unbiased, summary statistic (free from the influence of host factors) to describe the frequency of disease. One method that can be used to produce such summary rates is standardization (or adjustment) of rates (Fleiss 1973, pp 155–64). Standardization can also be used to prevent distortion from factors other than host characteristics. (In this respect it is very similar to the Mantel-Haenszel technique discussed in 5.4.1; however, it is not as powerful and is used chiefly for descriptive purposes rather than for hypothesis testing.) The two methods of standardization are direct and indirect.

### 4.2.1 Direct Standardization

With direct standardization the observed stratum-specific rates (OBS  $R_i$ ) must be known, and a standard population distribution (STD  $P_i$ ), with respect to the factors being adjusted for, is used as the basis for adjustment. The STD  $P_i$  is the proportion of the standard population in each of the strata, the stratum indicator  $i$  ranging from 1 to the number of strata being considered. Each stratum represents each level of age, breed, sex, or combination thereof.

The choice of the standard population for direct standardization is not crucial; however, when possible it is desirable to select a standard that is demographically sensible. For example, if the disease rates in various areas of the country are to be compared and adjusted for age, the population-age distribution for the entire country would be an appropriate standard. If no obvious standard exists, construct a standard by taking the average distribution over all groups to be compared.

The general approach to direct adjustment of rates in each of the groups to be compared is:

direct adjusted rate = proportion of standard population in stratum  $i$ , multiplied by observed rate in stratum  $i$ , with the product summed over all strata  
 = sum of  $P_i$  (standard)  $\times$   $R_i$  (observed) over all strata  
 =  $\Sigma$  (STD  $P_i \times$  OBS  $R_i$ )

This calculation is repeated for each group to be compared as shown in Table 4.1. The adjusted rate gives the rate expected if the observed stratum-specific rates applied in the standard population. Any differences between

**Table 4.1. An example of direct standardization of rates**

Suppose you are studying the association between source of cattle (ranch versus salesyard) and the occurrence of pneumonia in the 3-week period subsequent to arrival at the feedlot. Your initial study, based on random samples of 500 calves coming directly from ranches and 500 calves purchased at salesyards, gives the following results.

Source	Pneumonia	No pneumonia	Total	Incidence rate (%)
Salesyard	120	380	500	24
Ranch	25	475	500	5

Superficially, these results incriminate salesyards as a determinant of pneumonia. You are concerned, however, that these results might be distorted because of the age of cattle, since both calves and yearlings are purchased. The following method may be used to adjust the rates for the effect of age.

Source	Number of cattle	Observed distribution OBS( $P_i$ )	Number developing pneumonia	Incidence rate OBS( $R_i$ ) (%)	Standard population distribution STD( $P_i$ )
Salesyard					
Calves	400	.8	112	28	.45
Yearlings	100	.2	8	8	.55
Ranch					
Calves	50	.1	7	14	.45
Yearlings	450	.9	18	4	.55

It is obvious that age has a marked effect on the rate of pneumonia, but source also appears to have an effect. The standard population distribution was obtained by averaging the two observed distributions [i.e.,  $0.45 = (0.8 + 0.1)/2$ ].

The directly adjusted rates are found by multiplying the observed disease rate in each stratum by the standard population distribution in that stratum and adding the products over all the strata.

For the salesyard group:  $(0.28 \times 0.45) + (0.08 \times 0.55) = 0.17$  or 17%

For the ranch group:  $(0.14 \times 0.45) + (0.04 \times 0.55) = 0.085$  or 8.5%

The difference, 17% versus 8.5%, still suggests that source is a determinant of pneumonia. At the very least, the latter difference is not due to the effects of age; these effects having been removed by the process of standardization.

the adjusted rates must be due to factors other than those included in the adjustment procedure. Directly adjusted rates can only be compared to other directly adjusted rates when the same standard population distribution is used as the basis for standardization. Statistical tests are available to assess the likelihood that sampling variation can explain any differences among the group summary rates which remain after adjustment (Armitage 1971).

#### 4.2.2 Indirect Standardization

Indirect standardization may be used if the strata-specific rates are unknown, provided the distribution (OBS  $P_i$ ) of the factor(s) of interest (e.g., age) in the groups to be compared is known. It is also useful when the number of animals in the strata are small, and hence the stratum-specific rates are imprecise.

The adjustment is realized by using a set of stratum-specific rates from a standard population (STD  $R_i$ ). The choice of the standard rates should be guided by the same general considerations as used in direct adjustment. However, it is very important that the standard population rates reflect what likely occurred in the groups being compared. The first step in indirect adjustment is to calculate the anticipated rate (overall expected rate), given that the standard population rates apply in each of the groups to be compared, as shown in Table 4.2. The general approach is:

$$\begin{aligned} \text{Overall expected rate} &= \text{the proportion of the observed group in stratum } i \text{ is multiplied by the rate in stratum } i \text{ of the standard population, with the product summed over all strata} \\ &= \text{sum of } P_i \text{ (observed)} \times R_i \text{ (standard) over all strata} \\ &= \Sigma (\text{OBS } P_i \times \text{STD } R_i) \end{aligned}$$

Then, the observed crude rate is divided by the overall expected rate; the quotient is called a standardized morbidity/mortality ratio (SMR) depending on the endpoint (it may be another event such as culling). To complete the calculations, the indirect adjusted rate is found using the following formula:

$$\text{Overall average rate in standard population} \times \text{SMR}$$

Differences in indirect adjusted rates (or in the SMRs) are interpreted in a manner similar to direct adjusted rates; that is, any remaining differences are not due to the factors considered in the adjustment process. It should be noted, however, that indirect adjustment removes most but not

**Table 4.2. An example of indirect standardization of rates**

Suppose that two random samples of dairy cattle, each obtained from a different area of the country, were obtained. A blood sample was taken from each animal and its age was also recorded. The blood samples were sent to a laboratory and tested for the presence of antibodies to bovine virus diarrhoea virus. Three hundred of 575 animals from area A and 325 of 625 from area B had positive titers. Unfortunately, only the area was marked on the vials and hence it was not possible to calculate age-specific reactor rates. Nonetheless, you wish to remove any distortion in the overall rates due to age differences between the samples. The indirect method of adjustment may be used for this purpose.

Age (years)	Number in sample				Standard population rates (STD $R_i$ )
	Area A		Area B		
	No.	(OBS $P_i$ )	No.	(OBS $P_i$ )	
2-3.9	100	.17	25	.04	.3
4-5.9	200	.35	100	.16	.4
6-7.9	150	.26	250	.40	.5
8-9.9	75	.13	150	.24	.6
10+	50	.09	100	.16	.7
Total	575		625		
Reactors	300		325		Average reactor rate for standard population is
Crude rate	0.52		0.52	0.42	

Assume that a set of standard age-specific population reactor rates (STD  $R_i$ ) is available and these will be used to obtain the expected rate of reactors. The rate expected if the standard rates applied in area A is:

$$0.17 \times 0.3 + 0.35 \times 0.4 + 0.26 \times 0.5 + 0.13 \times 0.6 + 0.09 \times 0.7 = 0.46$$

The rate expected if the standard rates applied in area B is:

$$0.04 \times 0.3 + 0.16 \times 0.4 + 0.40 \times 0.5 + 0.24 \times 0.6 + 0.16 \times 0.7 = 0.53.$$

These lead to standardized reactor ratios of  $(0.52/0.46) \times 100 = 113\%$ , and  $(0.52/0.53) \times 100 = 97.7\%$  for areas A and B respectively.

The indirect adjusted rates are found by multiplying the standardized ratio for each area (expressed as a proportion) by the average rate for the standard population. This leads to indirect adjusted rates of  $1.13 \times 42\% = 47.5\%$  for area A and  $0.98 \times 42\% = 41.2\%$  for area B. This difference suggests that, after adjusting for differences in age, the prevalence of antibodies to bovine virus diarrhoea virus is higher in area A than area B. At least the remaining difference is not due to differences in age structure of the animals in the two areas.

all of the effects of different distributions of the factors in each group. This is why the selection of the standard population rates to reflect the (unknown) rates in the groups being compared is important. The advantage of indirect standardization is that the stratum-specific rates in each group are not required, only the distribution of the host factors in the groups being compared. As mentioned, indirect standardization is preferred over direct methods if the number of individuals in the various strata is small.

Standardized morbidity or mortality ratios are often used in pictorial displays of disease occurrence in different geographic areas. This allows one to visually compare the level of disease in many areas without concern

about the effect of differences in the underlying population structure.

As an example of the use of standardization, rate adjustment is used in the Danish pig health scheme. In this program, the observed rate of enzootic pneumonia in swine at abattoirs in different areas of the country is adjusted for herd size before making comparisons of the prevalence of pneumonia in these areas. (The adjustment is required because herd size has an important influence on the level of enzootic pneumonia, and the distribution of herd sizes differs from one area of Denmark to another. Therefore, in order to get a fair comparison of the rate of disease among abattoirs, without the comparison being distorted by herd size effects, it is necessary to adjust the rates for herd size [Willeberg et al. 1984].)

### 4.3 Immunity in Populations

Whether a disease spreads or persists depends not only on the nature of the causal agent, but also on the immunity of individuals and the structure and dynamics of the population (Fox et al. 1971; Yorke et al. 1979).

The ability of individual animals to resist infection, or to resist becoming diseased if infected, is referred to as immunity and may be either innate or acquired. Innate immunity is most often genetic in origin and is not dependent on previous contact with an agent by the individual or its parents. Examples include the resistance of horses to foot-and-mouth disease virus and current resistance of European rabbits in Australia to myxomatosis virus. Acquired immunity is resistance resulting from previous contact with an agent by the individual (active immunity), or resistance passed on from its mother (passive immunity) as a result of her contact with the agent. Contact with the agent may be natural or artificial (i.e., following vaccination). In simple terms, acquired immunity is humoral (antibody mediated) and/or cellular (cell mediated) in nature.

Immunity in individuals is relative rather than absolute, depending on the nature of the agent, the challenge dose, and the individual's environment. For purposes of discussion here, it will be classified as high, moderate, or low. From the viewpoint of the infecting organism, a host with high immunity presents a major stumbling block to survival since it is difficult to infect and hence the organism may die. A host with moderate immunity is more favorable to survival since it allows infection, some multiplication, and often shows little evidence of disease. Hosts with low or no immunity (i.e., highly susceptible individuals) are easily infected, and the organism may multiply freely, often resulting in disease in the infected host. This latter state may pose a great danger to other animals because of the increased challenge to their immunity. The best plan for survival for the organism might appear to be to invade highly susceptible individuals and multiply freely. However, if as a result of disease the host is killed and the

host population is decimated, contacting a new susceptible host could become difficult, and the organism may die. Thus, a strategy appropriate for short-term survival of the organism in an individual is not necessarily appropriate for long-term survival in the population.

The ability of groups of animals to resist becoming infected or to minimize the extent of infection (i.e., the number and/or the severity of cases) is termed herd immunity. Like individual immunity, herd immunity may be innate or acquired and should be considered a relative rather than absolute state. In most groups of animals the distribution of individual immunity varies from very susceptible to very resistant. Frequency of contact between individuals within the herd plays a key role in determining the level of herd immunity. (In current models of herd immunity, such as the Reed-Frost model, frequency of contact is referred to as probability of adequate contact. The latter is the probability that an individual in the population will have contact with another individual; the nature of the contact varying with the disease but being sufficient to transmit the infection from an infected to a susceptible individual. (See 8.3.2 for details.) This factor together with the number of susceptible individuals in the herd plays the predominant role in determining the level of herd immunity. Just as individual immunity determines whether an organism can persist in the individual, herd immunity determines whether an organism can survive in the herd (Yorke et al. 1979).

The number of susceptible animals is chiefly influenced by population dynamics such as the number of births, deaths, additions, and removals from the population, as well as by past exposure of the population to the agent. To a large extent, the rate of contact is influenced by the husbandry, housing, and behavior of the animals. If the rate of contact between individuals in a population is low, or there are only a few susceptible animals in the population, most infectious agents will not spread; they may even die out. In contrast, if the rate of contact is high, or if there are many susceptible animals, the infectious agent can easily become widespread. Whether disease develops subsequent to infection is mainly influenced by immunity at the individual level, although population factors can serve to alter the amount of exposure and thereby change the likelihood of disease occurrence (see Fig. 11.3).

The initial experimental studies of herd-immunity phenomena (Topley and Wilson 1923) are both interesting and enlightening. One must recall that in the early years of the twentieth century it was generally believed the rise and fall of epidemics was due to a combination of increasing and then decreasing virulence of the organism, as well as the active immunization of individuals by chance exposure to small doses of the organism. During the 1920s and 1930s, experiments in laboratory-animal colonies were con-

ducted to formally investigate some of the factors influencing the spread of agents in populations.

In general, the format of these experiments was to infect a number of laboratory animals (usually mice) and place them in a colony with other susceptible mice. The organisms used (generally *Salmonella typhimurium* or, more recently, *Ectromelia* virus) produce disease and/or death in a high proportion of infected animals, and thus the spread of infection through the colony was easily monitored (Yorke et al. 1979). The total number of mice in the colony, the number of susceptible mice in the colony, and the rate (frequency) of contact were varied. The rate of contact was altered by changing the type of housing or by forced mixing of the animals in one large pen for varying periods of time. The major results of these experiments may be summarized as follows: (1) For any given rate of contact the number of diseased animals or deaths was directly related to the number of susceptible animals; (2) If the number of susceptible animals was reduced below a critical level, the infection either failed to become established or died out; (3) Often, not all susceptible animals became infected during an outbreak nor did outbreaks always occur, although there were many susceptible animals in the population; (4) For any given number of susceptible animals, outbreaks of disease could be terminated or prevented by dispersing the mouse colony into a large number of groups, each containing only a small number of animals. (This effectively reduced the frequency of contact between members of the mouse population.)

These experiments demonstrated the key role played by the number of susceptible animals and the frequency of contact. The results also indicated that there was a genetic basis to disease resistance, and later experiments demonstrated that in heterogeneous groups of mice there was an interaction between nutrition and genetic factors and resistance to disease. More specifically, the resistance to infection was greater in certain genetic lines of mice on specified diets than was predicted, based on the general effect of that genetic line of mouse or diet. Recently it has been postulated that some of the increased susceptibility to disease following the mixing of mice in large colonies or the introduction of new, susceptible mice to the colony was the result of decreased immunity due to an adrenal-cortical stress reaction. For example, behavioral characteristics of the animals and disruptions in the social pecking order within the population are thought to be important features of individual and herd immunity.

The results of these early experiments have also been validated by numerous case studies and observational studies on human populations (e.g., the occurrence of measles and poliomyelitis). They have also proved invaluable in understanding the so-called island epidemics and the cyclical pattern of human diseases such as measles.

Undoubtedly, herd immunity is an important phenomenon in diseases of wild, companion, or domestic animals. For example, fox density (number of foxes per hectare) is a major determinant of rabies transmission in Switzerland (Steck and Wandeler 1980) and also in Canada. In Switzerland, rabies is rarely diagnosed in areas where the fox population is below 0.3 foxes per km<sup>2</sup>. At the same time, fox vaccination campaigns that reach only about 60% of the fox population appear to be effective in halting the spread of rabies. If this is true, it may be that protecting about one-half of the foxes in an area decreases the number of susceptible foxes to below the critical density, thus preventing continued spread and perpetuation of the virus. As another example, the density of dogs appeared to influence the spread of parvovirus enteritis. In Stockholm, Sweden, where the dog density was high, parvovirus outbreaks were seen; whereas in other areas of the country with lower dog densities, the disease occurred only sporadically if at all (Wierup 1983).

Outbreaks of feline panleukopenia are probably influenced by the lack of herd immunity. In this case, large numbers of kittens are born in the spring and early summer. These kittens become susceptible through the loss of maternal antibodies at 3 to 4 months of age. This is also the time kittens become dispersed, in both feral- and pet-feline populations, and may explain the late summer-early fall outbreaks of feline distemper (Reif 1976).

Although not well documented, the lack of herd immunity may help explain the dual findings of increased disease occurrence (chiefly respiratory disease) in herds or pens containing large numbers of animals, and the negative impact of mixing animals from different sources. Exposure of these animals to new environments and/or adverse weather probably reduces the immunity of individuals also. Thus, under these conditions, organisms that are normally present without producing disease can become pathogens.

#### **4.4 Environmental Factors**

The environment includes all the biotic and abiotic components of a place, be it a pen within a barn or a large geographic area. Knowledge of the rate or risk of disease according to place is a first and essential step in understanding disease. In initial investigations the number of potential differences between areas where disease is frequent and where it is infrequent is so large that only general theories can be developed to explain its distribution. Subsequently, more detailed investigations of specific components of the environment may be pursued. General categories of environmental factors include features of the landscape or place, abiotic elements (i.e., air, soil, water, and climate), and biotic features including the flora and fauna. Immediate causes of disease, whether living organisms or toxicants, should

also be sought and their importance as causes of the disease quantified. Whether one should concentrate initially on general features, such as air quality or the plant life of an area, or on the identification of specific agents depends on the setting and the nature of the problem. As a general suggestion one should not concentrate interest on specific agents to the exclusion of studying more general features of disease occurrence. Often, knowledge of the general features provides useful guidelines in generating a logical series of hypotheses about the involvement and nature of specific agents (Stallones 1972).

As an example of this approach, consider multiple sclerosis in humans, the ultimate cause of which still eludes researchers. The frequency of multiple sclerosis is directly correlated with latitude and increases dramatically with distance from the equator. Thus, one major thrust to current epidemiologic studies is to concentrate on cohorts of people who either enter or leave high- or low-risk areas. Since the change of risk of disease in these individuals appears to be related to their age at migration, the presence of a specific agent in high-risk areas is suggested (Nathanson and Miller 1978).

When disease occurs more frequently in certain areas than in others, the disease is said to be clustered. Disease may be limited geographically for a variety of reasons, many of which relate to forces that act upon the host, vector, or agent of disease. Geographic features such as rivers, lakes, and mountains can also serve to restrict the spread of disease. Sometimes disease is limited to traditional migration or market routes; this was true of Texas fever (bovine piroplasmiasis). Although usually large, the geographic area of interest can vary in size from pens within a barn, to barns within a farm, to areas within a country. A recent serial provides data on the distribution of a variety of diseases and disease outbreaks in countries throughout the world (Commonwealth Agricultural Bureaux 1983).

Historically, knowledge that certain geographic markers (e.g., bogs or marshes) were predictive of increased risk of disease was used to prevent disease simply by avoidance of these areas. Some diseases like swamp fever (equine infectious anemia) are named after their association with these geographic features. During the 1800s, the observation that the distribution of Texas fever was analogous to that of the tick suspected of spreading the disease was instrumental in gaining support for further study of the role of the tick. The tick was subsequently shown to be the reservoir of the agent and capable of passing the infection by vertical transmission to succeeding generations of ticks. More recently, the study of the association between agents of disease and certain ecosystems or geographic markers has expanded and has been termed landscape epidemiology (Levine 1966).

There are a number of ways of determining spatial clustering, many of which are based on fairly rigorous mathematical procedures. For most practical purposes, simple graphic methods of detecting clustering are suit-

able. These include cartographic techniques such as spot maps, transparent overlays, isodemic maps, and grid maps.

#### 4.4.1 Cartographic Methods

Spot maps are a basic tool for studying the geographic pattern of disease. Each occurrence of disease is plotted on a standard map, the scale of which depends on the investigation. Spot maps can be modified to show the change in distribution of disease over time. For example, different colors can be used to plot the occurrence of disease during different time periods, or each spot may be numbered to indicate the relative time of disease occurrence (see Fig 11.3).

Sometimes, instead of plotting each case individually, the average level of disease on a farm or in an area may be represented by different types of markings on black and white maps, or different colors on colored maps. Adjusted rates or, more frequently, standardized morbidity or mortality ratios may be plotted rather than unadjusted rates (host factors that may affect the level of disease are usually included in this adjustment). Although too elaborate for routine use, three-dimensional, computer-drawn maps (with the height proportional to the level of disease) provide tremendous insight into the geographic distribution of disease. The fox population of Switzerland has been displayed using this technique (Steck and Wandeler 1980).

Transparent overlays are also useful in mapping disease. One could describe the spread of a disease (such as rabies across a country) by plotting the extent of rabies in different time periods on separate transparencies; then the spread of disease can be displayed by sequentially overlaying the transparencies.

Grid mapping is not particularly useful for the practitioner, but it is useful when maps may be drawn using data in computer files. In this instance, each particular location is referenced by a specific  $x - y$  coordinate (a longitude and latitude marker). Using this technique, large volumes of data about the location of specific cases can be stored easily in computer files, and the same files can be utilized to create the map. The files may be updated regularly and maps easily redrawn as required.

One's ingenuity is the only real limitation to the usefulness of cartographic techniques. However, since the population at risk is frequently not uniformly or randomly distributed, one must be careful in interpreting clustering if only the distribution of cases is plotted. Steck and Wandeler (1980) provide many good examples of the use of cartographic techniques.

Isodemic mapping is a cartographic technique used to correct for non-random distribution of the population at risk. In ordinary maps, the area of different portions of the map reflects the actual physical area of the administrative unit. Thus, two counties of equal geographic size will be

represented by equal-size areas on a map. In isodemic mapping each administrative area (e.g., a county) retains its original shape, but the size of each area when mapped corresponds to the relative magnitude of the population at risk, not the actual physical size of the area.

#### 4.4.2 Analytic Methods

Often, a plot of infected premises may indicate clustering, suggesting farm-to-farm spread. However, in the absence of data on the distribution of all farms in the area such clusters are difficult to interpret. One way of assessing this apparent clustering is to compare the average distance between any two infected farms to the average distance between two randomly-selected noninfected farms, or to the distance between randomly-selected noninfected farms and the closest infected farm. The distance may be “by road” or “as the crow flies” depending on the situation. If automobiles or trucks are suspected of spreading the infection, road distance would be used. (This would not preclude the tracing of known vehicle movement and relating this to the distribution of affected farms.) If airborne spread were suspected, a straight-line distance would be more suitable. The latter can be obtained using calipers to measure the distance on an accurately plotted map of appropriate scale. If farm-to-farm spread is an important means of transmission, one would expect the average distance between pairs of infected farms to be less than the average distance between a noninfected farm and the closest infected premises. A similar method was used in a case-control study of brucellosis in two counties in Ontario, Canada. The case farms were infected farms identified from the district regulatory veterinarian’s records. The controls were obtained by taking a random sample of herds with negative tests, provided the tests were conducted during the time period selected for the study. The average distance between the two closest infected farms was less than the distance between a noninfected and the nearest infected farm, supporting the hypothesis of farm-to-farm spread (Kellar et al. 1976; data not presented). This technique will not discriminate between “fence-line” and airborne spread, but it does provide an indication of whether the clustering is an artifact due to the distribution of farms or a real phenomenon.

#### 4.4.3 Interpretation of Clustering

Once a relationship between a disease and geographical areas has been documented, it should be studied to see if characteristics of animals in the area can explain the association. If an explanation in terms of host factors can not be found, the following observations provide additional evidence that factors localized to a geographic area may be responsible for the association: animals leaving the high-risk area subsequently develop a lower risk of disease, and healthy animals entering the area experience an in-

creased risk of disease; most animals of the herd or species of concern have a high rate of disease in the suspect area, and animals of the same breed or species do not have high rates of disease outside the suspect area; and animals of different breeds or species all have an increased rate of disease in the high-risk area. The latter observation is supportive but not essential, because only one breed of animal may be at risk of the disease. This could be due to inherent behavioral traits of the breed or to the system of husbandry imposed on it.

#### 4.5 Abiotic Elements of Environment

Abiotic elements include the air, soil (rock), and water, plus the climate of the area. In developed countries, chemical air pollution also is a major concern from the standpoint of its effects on health and the environment. Outbreaks of fluorosis and lead poisoning have been recorded in animals pastured around fertilizer manufacturing and lead smelting plants. Historically, deaths of cattle at the Smithfield Fat Stock Show in England were early indications of the adverse effects of air pollutants; the chief pollutant being sulphur oxides resulting from the burning of coal (Schwabe 1984, p 563). These deaths preceded the first documented large-scale increases in mortality in humans by a number of years. The death of cats from mercury poisoning (Minamata disease) may similarly have predicted the adverse effects of pollution—in this case, water pollution—on humans (Goldwater 1971). Another example of the effect of unspecified air pollutants on health is the finding of more pulmonary disease in dogs living in polluted areas than in dogs living in relatively pollution-free areas (Reif and Cohen 1970; see Table 2.7). In fact, domestic and companion animals may serve as excellent sentinels of environments dangerous to man (Schwabe et al. 1971; Priester 1971; Hayes et al. 1976).

With regard to airborne transmission, droplet nuclei (1–2 microns in diameter) may contain living organisms or chemical pollutants. These nuclei do not “settle out” very rapidly, and they readily reach the lung when inspired. Noninfectious protein material may be transported to the lung in a similar manner and lead to hypersensitivity-type pneumonias. Despite the potential importance of airborne transmission of disease producing agents, two facts should be kept in mind. The nasal turbinates function to warm and filter in-coming air but apparently are not essential for the animal to have a normal lung. Pigs possessing moderately- to severely-distorted nares as a result of atrophic rhinitis appear to have only a slight increase in pneumonia over their penmates with normal turbinates (Takov 1983). Second, airborne transmission of some respiratory tract infections (e.g., human rhinoviruses) may be a less important route of transmission than direct contact and fomite transmission (Gwaltney and Hendley 1982). This may

also be true of strangles in horses and pasteurellosis of cattle, as mentioned previously. When cattle lower their heads to drink, large volumes of infected nasal mucus and discharge may drain into the water. Although little evidence exists to support the hypothesis, it may be an important source of infection for other animals in the group.

Soil type can influence the survival of living agents as well as the availability of minerals (e.g., selenium) to plants and hence to animals. Zoonotic fungi such as *Histoplasma* and *Cryptococci* survive better in soils with high organic content. Anthrax bacilli appear to survive better in soils along river valleys. Soils containing limestone and dolomite are indicative of the likely presence of leptospiral organisms. A nationwide survey of soil in the United States for clostridial organisms has been conducted; 4 east-west transects were sampled at 50-mile intervals to ensure a representative country-wide sample. *Clostridium tetani* was present in approximately 30% of the samples regardless of soil type, whereas *Clostridium botulinum* appeared more frequently in some soil types than in others (Smith 1978). This points out the potential hazard of soil organisms including the potential for contaminating feed stuffs (such as honey) especially in areas where significant airborne soil erosion occurs. Recent large-scale outbreaks of botulism in human infants were concentrated in, but not restricted to, dry areas of the southwestern United States (Arnon et al. 1981). (The authors note, however, that the presence of large referral hospitals for children may have influenced this distribution.)

Water may carry toxic chemicals as well as infectious organisms. The temperature and flow pattern of water can also influence the concentration of intermediate hosts or vectors of infectious agents (Harris and Charleston 1977). Under certain environmental conditions, waterborne organisms may proliferate; in the case of blue-green algae, potent toxins leak into the water when the algae die and decompose. In other circumstances, humans and animals may defecate and urinate in irrigation ditches; infectious microorganisms and other parasites may thus contaminate food items, which then serve as sources of infection for other humans or animals.

Precipitation (rain or snow) "scrubs" the air, bringing infectious agents, radioactive particles, and pollutants to ground level. Contamination of pasture fields and crops can occur by this mechanism. The long-term damage from acid rain, one type of pollutant distributed by this mechanism, may be much more severe than any short-term problems.

Climate is an important determinant of many diseases. Adverse weather may affect the management and care of animals, stress the animal directly, or provide conditions suitable for survival of microorganisms and parasites or their vectors. Unfortunately, unraveling the effects of weather is not easy. Reasons for this include: its components are often very indirect determinants of disease; it may have multiple effects because there are a

large number of weather components (e.g., minimum, maximum, and mean temperature; diurnal temperature fluctuations; day-to-day fluctuations; rainfall; humidity; windspeed); and it is difficult to separate the effects of various weather components. Further, the general macroclimate (for which data are available) may be quite different than the microclimate (i.e., weather within a barn or at ground level). Data on microclimate within various types of shelters are not readily available, and few studies on the effects of microclimate on disease and productivity have been reported. One study of microclimatic effects conducted in California dairies confirmed previous macroclimatic studies of the association between weather and the health status of calves (Thurmond and Acres 1975).

Despite the difficulties, even a cursory examination of data on respiratory disease in humans or animals indicates the potential impact of weather on disease occurrence. In California, where most calves are raised outdoors, adverse weather was shown to significantly increase calf mortality during mid-summer and mid-winter. Although management factors apparently accounted for most of the large variation in mortality rates among farms, the effect of weather was still apparent, even when the average level of mortality on a farm was low (Martin et al. 1975). Many feedlot owners and veterinarians believe weather exerts a significant effect on the health and productivity of their animals. Formal analyses tend to support this theory, although the percentage of disease explained by weather is small. Certainly, intensively reared animals (poultry, swine, or cattle) require careful control and manipulation of their microclimate to remain healthy and productive. Knowledge of the exact microclimatic requirements and the benefits of different types of housing and ventilation systems are lacking, however, partly because of the paucity of formal studies on this subject.

Another example of the effect of climatic factors is the demonstration of windborne spread of foot-and-mouth disease virus in England. Veterinarians in many European countries also believe that introduction of this and other infections into their countries may be due to windborne transmission. It is thought that wind is an important factor in spreading and prolonging outbreaks of Newcastle disease virus and infectious bronchitis virus of poultry; however, these theories remain to be adequately tested.

The importance of accurate and complete documentation of the geographic pattern of infected premises is demonstrated by the 1967 outbreak of foot-and-mouth disease in England. It might generally be thought that windborne spread would transmit the agent from infected premises to nearby farms. Although this pattern was present, it was also found, subsequent to the outbreak, that a meteorological phenomenon known as lee waves may have accounted for the 18- to 20-km downwind distances between clusters of infected farms (Tinline 1972). Had the outbreak not been

well documented, in terms of time and location, the appropriate data to identify the lee wave spread would not have been available.

#### 4.5.1 Bioclimatograms

A useful graphic method for investigating the relationship between two climatic factors and survival of parasites is the bioclimatogram (Schwabe 1969, p 621). For example, temperature may be plotted on the *Y* or vertical axis and precipitation on the *X* or horizontal axis. For each month of the year the average temperature and precipitation are plotted as one point. Each of these points is joined by a line beginning at January, connecting with February's point, and continuing to completion at December's point. If the temperature and moisture requirements for the survival and/or development of an agent or its vector are known, the bioclimatogram can provide a visual display of the months when the temperature and precipitation requirements are sufficient to allow survival and/or development of the particular agent. As an example, the rate of disease each month could be displayed directly on the bioclimatogram (or with the use of transparent overlays) to visually assess if the occurrence of the disease might be associated with temperature and precipitation. This knowledge could be applied, for example, to design housing for calves in a manner to lower the incidence of enzootic pneumonia. By plotting the average temperature and humidity requirements for the survival of an agent (such as mycoplasma) one could plan housing so that the temperature and humidity within the barn were consistent with conditions necessary to maintain calf health, but inconsistent with the environmental survival of mycoplasma agents.

## 4.6 Biotic Elements: Flora and Fauna

Because veterinarians focus their attention on only a few species of animals, it may be easy to forget that a large number of diseases in humans and animals are a result of a complex interplay between animal and plant species. Under natural conditions, the evolution of plant species directly influences the number and types of animals present in a defined ecosystem. This is less true today in our highly manipulated agricultural ecosystems, where the majority of foodstuffs may be grown some distance from the animal industry and transported to farms by truck and train.

### 4.6.1 Flora

Plants may be important as causes of disease because they form the basis of the ration or diet of most animals. The selection and processing of plants and their products to form a nutritious diet at minimal cost is now a highly specialized and competitive industry. Also, the availability and cost

of major ration components (such as corn) may dictate the expansion or contraction of animal industries.

Not all plants are edible however. Plant toxicities (e.g., alkaloid toxicities from lupin species, Japanese yew, and *Crotalaria* or *Senecio* genera) occur commonly. Deficiency diseases (e.g., hypomagnesemia resulting from prolonged feeding of oats and/or barley; acute vitamin A deficiency in beef cattle resulting from grazing on inadequate pastures, and poor reproductive efficiency in cattle being fed inadequate amounts of energy, protein, and phosphorous) are well recognized. Dry hay may be a better roughage than corn silage for starting stressed calves because of the much higher levels of potassium in hay, and it is believed that the requirement for potassium is increased during periods of stress.

Plants may also be indirectly causally associated with a number of diseases. Facial eczema in sheep results from eating pasture heavily contaminated with fungi (*Pithomyces chartarum*). Sheep also become infected with metacercaria of liver flukes encysted on plants, as well as the larval forms of *Echinococcus granulosus*. Similarly, cattle may ingest the larval forms of *Dictyocaulus* from contaminated herbage. *Thermophilus* fungi contaminating hay may lead to interstitial pneumonia in humans and cattle (called farmer's lung); whereas other fungi produce toxins (often hepatotoxic) such as aflatoxin or ochratoxin as well as estrogenic substances such as zearalenone. Dicoumarol production by moldy sweet clover was at one time a major source of poisonings in North America. Today, low coumarin cultivars may allow renewed production of this very high-yielding legume. As mentioned previously, pollutants may settle onto fodder crops and be ingested in large doses.

Decaying plants may produce disease through the formation of toxic gases. Examples include silo-filler's disease (caused by the production and release of nitrous oxides in fermenting silage), and the effects of toxic gases such as methane, hydrogen sulphide, and ammonia released from decaying manure. The chronic effects of these gases on the health of livestock and the role they may play in predisposing the respiratory tract to infectious agents are of interest and concern for intensively reared livestock such as poultry, swine, and beef cattle.

Finally, feedstuffs of plant origin may serve as vehicles for a variety of microorganisms and parasites. Examples include *Listeria monocytogenes* in corn silage (perhaps because the organism grows well in silage, or because of the rodent concentration in silage), and the spread of toxoplasma cysts in grain, due to the habit of cats defecating in granaries while purportedly keeping the rodent population in check.

#### 4.6.2 Fauna

With respect to animal species, and for most infectious diseases, any particular group of animals may be at risk of infection from other members

of its own species or from members of other species of animals or invertebrates. The zoonoses (infectious diseases common to humans and animals) provide a good illustration of the complex way different species may combine to ensure the survival and transmission of infectious agents. For purposes of presentation, the zoonoses have been classified on the basis of their cycle of perpetuation as direct, cyclo-, meta-, and saprozooses (Schwabe 1984, pp 196–208).

**4.6.2.1 DIRECT ZOOSES.** Direct zoonoses may perpetuate in a single host species. Examples include bovine brucellosis and tuberculosis; rabies in wild, domestic, and companion animals; and pseudorabies in swine. Although these diseases can survive in one species, there may be local exceptions.

Before pursuing this, a brief discussion of the distinction between reservoirs and carriers is in order. A reservoir is the species without which the agent is unlikely to perpetuate. A carrier, on the other hand, may silently (since it is subclinically infected) transmit the organism, but it is not necessary for the perpetuation of the agent. Thus, many species are carriers. For example, many species (including dogs, cats, and sheep) are susceptible to *B. abortus* infection but they are carriers only, not reservoirs, and do not sustain the infection for prolonged periods. Bovine tuberculosis essentially depends on the family *Bovidae* for survival, although local potential reservoirs (such as the badgers in England and opossums in New Zealand) are recognized. Cattle may be infected with the virus of pseudorabies, but again, they appear to be short-term carriers and usually develop clinical disease (“mad-itch”) and are dead-end hosts. The major reservoir for rabies appears to vary with locale; for example, foxes are the reservoir in continental Europe, foxes and skunks in central Canada, and the raccoon in the southern United States. Bats (both insectivorous and bloodsucking) appear to be the primary reservoir of rabies in areas such as Mexico.

**4.6.2.2 CYCLOZOOSES.** Cyclozoonoses require more than one vertebrate species for survival. Examples include the taeniad and echinococcal parasites. Hydatid disease, discovered fortuitously less than 20 years ago in California, depends on the dog-sheep cycle for survival. However, in California and probably other western states, the disease now has established itself in wildlife, particularly the coyote-deer cycle.

**4.6.2.3 METAZOOSES.** Metazoonoses require a vertebrate and an invertebrate host for perpetuation. There is a long list of these diseases; chiefly parasitic, viral, rickettsial, and, less frequently, bacterial agents are involved. Examples of parasitic diseases include African trypanosomiasis with its devastating effects on animals and humans, and canine heartworm in North America. Heartworm has been recognized as endemic in the

southeastern United States for many years, but only recently it has also been found to be hypoendemic in southern Ontario, Canada (Slocombe and McMillan 1979). In Ontario, mosquitoes are the presumed vectors and will sustain development of the parasites, although no locally trapped mosquitoes have been found to be infected.

Viral metazooses include eastern and western equine encephalitis and bluetongue. Avian species are the reservoir of the equine encephalitic viruses and bird-to-bird transmission is achieved by mosquitoes. It is fortunate for both humans and animals that these mosquitoes prefer to feed on birds. Had agricultural systems not encroached on the natural marshland ecosystem of the reservoir avian species, these viruses would likely have remained as only silent infections of birds. Bluetongue is currently a perplexing problem in North America because cattle are probably functional reservoirs. However, cattle are not unduly affected, and the virus is spread by biting insects, such as *Culicoides*. On the other hand, sheep develop severe clinical disease.

Plague is perhaps the most interesting of the bacterial metazooses. This infection is endemic in many ground squirrel colonies in the southwestern United States. It is spread primarily by fleas who prefer the ground squirrel to other species. Sporadically, however, dogs, cats, and humans may be infested and bitten by fleas, and hence become infected with bubonic plague. Outbreaks of plague may be observed subsequent to massive die offs in the squirrel colonies.

**4.6.2.4 SAPROZOOSES.** Saprozoonoses require a nonanimal site, usually soil or water, to develop and/or survive. Many of the mycotic saprozooses do not require a vertebrate for their perpetuation, whereas most parasitic saprozootic agents require a vertebrate for at least part of their cycle of perpetuation. Examples of mycotic saprozooses include histoplasmosis, coccidiomycosis, blastomycosis, cryptococcosis, and aspergillosis. Parasitic saprozooses include coccidiosis, visceral larva migrans, ancylostomiasis, and ascariasis.

Although presented here to complete the classification of zoonoses, the survival and multiplication of the agents of saprozooses often is highly dependent on the structure and composition of the soil as mentioned in 4.5.

#### 4.6.3 Within-Species Infections

Despite the importance of the zoonoses, the greatest problem facing the private veterinary practitioner is the threat and spread of infection among members of a species of animal. These diseases (some of which are zoonoses) greatly reduce the productive efficiency of domestic animals and threaten the health of companion animals. Examples include rinderpest,

foot-and-mouth disease, brucellosis, and mastitis in cattle; strangles, corynebacterium pneumonia, and infertility in horses; distemper, parvovirus enteritis, kennel cough, and pneumonitis in companion animals; *Haemophilus* and *Mycoplasma* pneumonia in swine; and infectious laryngotracheitis and Newcastle disease in poultry.

Although all the above diseases have an agent as the proximate cause, feeding, housing, and management (including the use of quarantine) are probably important components of the causes of these diseases. Subsequent chapters contain methods and concepts that should prove useful in identifying causal factors that can be manipulated to prevent and/or control many of these diseases.

#### 4.7 Agents of Disease

Most diseases have specific agents identified as one of their causes; in fact, many diseases are named on the basis of the agent (e.g., salmonellosis, brucellosis, lead poisoning, mercury poisoning). In other instances, organisms are named based on the signs of the syndrome with which they are associated (e.g., African swine fever virus, bluetongue virus, and equine infectious anemia virus). This linking of agents and disease has had much utility in terms of disease prevention and control; however, it also demonstrates some of the biases that have crept into nomenclature and conceptualization of the role of specific agents in disease processes. For example, meningococci normally reside in the pharynx and upper respiratory tract together with organisms called pneumococci; neither producing disease in this location. The names of these organisms reflect the anatomic location of the disease syndrome they cause when reaching the meninges or lungs respectively. The conditions under which the meningococci infect the nervous system are not totally understood; perhaps the genesis of this human syndrome is similar to the disease of the nervous system produced by *H. somnus* in cattle, an apparently normal resident of the respiratory tract and other mucosal surfaces. Pneumococci regularly enter and are removed from the lungs, but clinical disease may result in humans with lowered resistance.

The properties of living agents (including size, structure, and metabolism) and the properties of nonliving agents (such as size and chemical make up) are important to understanding specific diseases; however, these are the subject matter of other disciplines, particularly microbiology, parasitology, and toxicology. What the epidemiologist requires most frequently is an indication of whether a specific type of agent is present, where it is present (the host, vector, or vehicle), and the concentration of the organism (ie. organisms per gram of tissue, gram of feces, or ml of water). Obviously the sensitivity and specificity of the diagnostic procedures used are of in-

terest, as well as the sampling procedure, including items such as how were samples collected or what animals were selected for obtaining swabs. Often, what is designated as "intermittent shedding" might more properly be termed "continuous shedding" because the nature of the sampling procedure is such that only infrequently would one expect to find the agent. Another example of this occurs with the dissection of vectors (e.g., mosquitoes) for the presence of parasites (e.g., heartworm larvae), or the culture of vectors for the presence of disease. The probability of finding the agent in one insect is extremely low; hence, pools of insects are examined. Mathematical procedures have been developed that provide assistance in deciding on the optimal number of insects per pool, as well as interpretation and extrapolation of results (Walter et al. 1980).

As yet, satisfactory sampling regimes to identify the presence of and concentration of agents in populations have rarely been applied. Hence, little is known of the distribution of most agents. Recently, a screening program was employed to identify the presence of selected bacteria (*Salmonella*, enteropathogenic *Escherichia coli*, and *Campylobacter*) on dairy farms (Waltner-Toews 1985). The program was based on fecal sampling of up to two calves less than 2 weeks of age at the time of visit. The sensitivity of this procedure for identifying infected premises is unknown (probably low); however, on the basis of this screening procedure, about 22%, 41%, and 13% of farms are known to be infected with *Salmonella*, *E. coli*, and *Campylobacter* respectively. The association between the presence of these infectious agents and disease occurrence is unknown at this time; however, the majority of culture-positive calves were normal at the time of sampling. This type of work together with multiphasic sero (cellular) epidemiologic screening needs to be greatly expanded to adequately establish the natural history of these agents and their associated diseases. Unfortunately, the latter activities are out of fashion for most microbiologists and immunologists; the leading technologies in these disciplines having shifted to more reductionistic activities directed at the basic biologic building blocks, including recombinant DNA technology.

The common sources of the agent should be identified when possible; again, it is useful to rank the sources in order of frequency (importance) rather than listing all possible sources and/or means of transmission. It is also important for the epidemiologist to investigate different methods of transmission. The possibility of water-bowl and feed-trough contamination as sources of infection for respiratory disease (such as strangles in horses and pasteurellosis in cattle) requires further study. Recently, it was demonstrated that rhinoviruses in humans are more likely to be spread by contact and/or vehicles than by aerosols (Gwaltney and Hendley 1982).

It is important to understand agents' requirements for survival or persistence. For nonliving agents this might include items such as whether it is

bioconcentrated in the food chain, what form the chemical is most stable in, and whether it is affected by drying or by sunlight (Goldwater 1971). For infectious agents, it is important to know their optimal conditions for survival (including whether they survive outside living tissue), what vehicles provide protection for the organism, and its resistance to drying, sunlight, and antimicrobial agents, including disinfectants. As an example, the conditions for survival in aerosols of a number of viruses of cattle was investigated by Elazhary and Derbyshire (1979).

Finally, because of the dynamic nature of infectious agents and the lack of knowledge about their distribution, it is important to examine healthy animals as vigorously as diseased animals using the same test procedures. Because the overwhelming majority of organisms are ubiquitous, little importance can be attributed to the detection of a specific organism in diseased animals or tissues. With respect to investigations of the relationship between an agent and a disease, the question is usually not whether an organism can cause a specific disease (since this has often been demonstrated in laboratory studies), but rather, what evidence exists that the particular organism is an important cause of the disease under natural conditions. In addition, identifying the circumstances under which an agent can produce disease may be more useful in terms of preventing and controlling disease than relying primarily on directed action against the organism.

## 4.8 Temporal Factors

Just as the occurrence of disease is related to host and environmental factors, there are changes in the frequency of many diseases with time. These temporal patterns of disease occurrence should be elucidated clearly and detailed explanations for them sought using formal studies. In this section various graphic methods used to identify the pattern of the temporal changes in disease frequency are presented. Knowledge of temporal patterns may provide insight into factors affecting the balance between the host and agent. For example, in outbreaks of disease, the pattern of change (particularly its abruptness) may suggest an optimal method of investigation of the outbreak.

### 4.8.1 General Temporal Patterns

When plotting the number of cases or the rate of disease against time, the shortest practical time scale should be used. If the disease occurs infrequently and without discernable pattern, it is classified as sporadic. If the disease occurrence has a predictable pattern, it is classified as endemic. Seasonal or cyclical fluctuations in disease occurrence do not preclude the correct use of the term endemic, so long as the changes are predictable (i.e.,

occurring with regularity). The average frequency of endemic diseases may be low (hypoendemic), moderate (mesoendemic), or high (hyperendemic). If the level of disease occurrence is significantly greater than usual (more than two standard deviations above average) and the increase is not predictable, the disease pattern is classified as epidemic. If the epidemic occurs throughout a number of countries, it may be termed pandemic.

The three patterns of disease occurrence (sporadic, endemic, and epidemic) provide useful information about the host-agent balance. Sporadic patterns suggest that the agent either infrequently infects the host, or the agent is usually present and clinical disease results from the effects of other factors. Clinical mastitis in dairy cows and infectious thromboembolic meningoencephalitis in feedlot cattle are diseases which occur sporadically. The infectious agents of these diseases usually are present, but clinical disease occurs infrequently and is not readily predictable. Some evidence indicates that meningoencephalitis tends to be associated with outbreaks of respiratory disease, and the stress and physiologic changes resulting from the respiratory disease may allow the *Haemophilus* organisms to enter the circulatory system, subsequently producing lesions in the central nervous system. It could be argued that a large percentage of infectious diseases seen by veterinarians are sporadic in nature and probably result from unknown factors tipping the agent-host balance in favor of the agent, rather than from intrinsic properties of the agent per se.

Endemic diseases are a result of a predictable, probably long-term balance between the agent and host. The lower the level of disease (degree of endemicity), the better the balance between the host and agent. The balance is quite dynamic, however, and both the level and the stability of the balance can be influenced by environmental as well as host factors. Subclinical mastitis is mesoendemic in North American dairy cows and dairy calf mortality is mesoendemic in California dairy farms. The increase in disease (chiefly respiratory disease) that occurs after feedlot cattle are assembled should also be termed endemic because of its predictability. The level of endemicity is less certain, but it appears that management is a major determinant of it. Although it is almost always fatal for individual foxes, rabies is endemic in the Canadian fox population and increases in occurrence, quite predictably, in the fall of each year when the fox kits leave their home and search for new territory.

Epidemic patterns suggest a gross imbalance with the agent having the upper hand. This imbalance is common when a new strain of organism is produced (e.g., by mutation), or during the initial exposure of the host to an organism. Currently, no adequate explanation of the pandemic of canine parvovirus enteritis exists.

All the above patterns of disease with time relate to explicit geographic limits. Diseases (such as foot-and-mouth disease) that may be endemic in

some areas of the world, may produce epidemics in other areas, even though the number of cases in the epidemic area might be far less than in the area designated as endemic.

It is a general epidemiologic tenet that over time the relationship between a host and agent changes from the parasitic (favoring the agent) to a commensal state (favoring neither host nor agent). Thus, given time and a stable environment, the pattern of disease changes from epidemic to endemic and finally to sporadic. In the natural state the more resistant hosts have an increased probability of survival. From an ecologic viewpoint, the production of disease or death rarely favors the perpetuation of the agent; thus natural selection favors less pathogenic organisms. Rabies and plague are notable exceptions to this rule. Thus, although in the short-term there usually is a positive correlation between the level of infection, disease, and death, this will not likely be true over a long period. Rather, the number of cases or deaths relative to the number of infected animals declines with the passage of time. Under laboratory conditions it is possible to select for increased virulence by repeated passages of the agent, usually in the same species. This does not contradict the previous principle, and is primarily due to the unnatural selection—if the previous process is called natural selection—of the sickest individuals for culture and repeated passage of the isolated agent. Under these restricted artificial conditions, the more virulent strains of organisms have a marked selection and survival advantage.

The history of the biological control efforts aimed at the European rabbit, *Oryctolagus cuniculi*, in Australia provides an excellent opportunity to examine the evolution of a host-parasite relationship. The rabbit was introduced into the southern part of Australia by Thomas Austin in 1859. In the ensuing years, because of the lack of natural predators, it advanced at a rate of approximately 70 miles per year over large parts of the country. By 1887 the rabbit population had multiplied so proficently that the government offered a reward for a method that would exterminate it (Fenner 1954).

Although it had been previously observed that myxomatosis was very lethal for *Oryctolagus*, the first to suggest the use of myxoma virus as a method of biological control was a Brazilian investigator named Aragao. Experiments were subsequently carried out to determine whether the virus would be harmful to other Australian animals. It was not, and myxoma virus was deliberately introduced into the rabbit population in 1950. Within 10 months, infected rabbits were found over an area of approximately 500,000 square miles. By the third year following virus release it was estimated that the original rabbit population of approximately 500 million had been reduced by 80–90%. However, within several years of its initial release, the virus being isolated in the field was less virulent (the case fatality rate decreased from 99% to approximately 90%), and the time between

infection and death had increased (Burnet and White 1972). Change in the resistance of the rabbit was slower to develop but was also evidenced by 1957. By this time, the rabbit population in some locations had been exposed to five successive epidemics each having at least a 90% case fatality rate. Using virus that killed approximately 90% of rabbits selected from previously unexposed areas, the case fatality rate in the latter repeatedly exposed population was less than 50%. This degree of protection was not due to any acquired immunity due to previous exposure, as the vast majority of these rabbits and their parents had never encountered the virus although their ancestors had. The changed resistance was innate and inheritable—an example of natural selection in a very intensive form acting to favor gene mutations (Burnet and White 1972). By 1965 it was estimated that the rabbit population and the virus had evolved to a state with the rabbit population at around 20% of their numbers before the advent of myxomatosis (Fenner and Ratcliffe 1965).

#### 4.8.2 Graphic Techniques

The temporal patterns of morbidity and/or mortality may be investigated and displayed by appropriate graphic techniques. Initially, one can plot the number of events of interest or, more preferably, the rate (incidence, prevalence, or mortality) against time. Patterns may be obvious at that point. By general agreement, secular trends describe changes over many years or decades; cyclical changes are those with a periodicity of 2–5 years; and seasonal changes have a periodicity of 1 year or less.

Often the random variation in disease occurrence can obscure temporal patterns. A technique known as a moving average is useful to remove the unwanted fluctuations and allow visual identification of any underlying patterns. Moving averages of 3 to 5 months are useful for investigating seasonal patterns; 15- to 25-month moving averages for cyclical patterns; and 37-month moving averages for long-term (secular) trends. To plot a 3-month moving average, the rates for January, February, and March are averaged and plotted against February, the temporal midpoint for the average. Then, the rates for February, March, and April are averaged and plotted on March. This continues until all the data have been included. Obviously, many years of data are required to adequately identify cyclical or secular patterns.

When interpreting secular changes, one should look for marked trends or abrupt changes, since useful explanations (hypotheses) often may be found. When attempting to explain the changes, it is important to assess whether other factors (e.g., differences in diagnostic accuracy, completeness of reporting, changes in duration of disease, differences in host characteristics) can explain the disease pattern. Indications that the trend is real may be found by identifying different trends in different breeds, or different

trends in different diseases of equal diagnostic difficulty. In addition, if a disease is not fatal, its prevalence among necropsied animals and/or abattoir specimens over a period of time can be used to assess long-term changes. Gradual changes in disease occurrence are difficult to interpret and rarely suggest useful explanations for the change because a large number of differences (particularly in environment) may have occurred during that time.

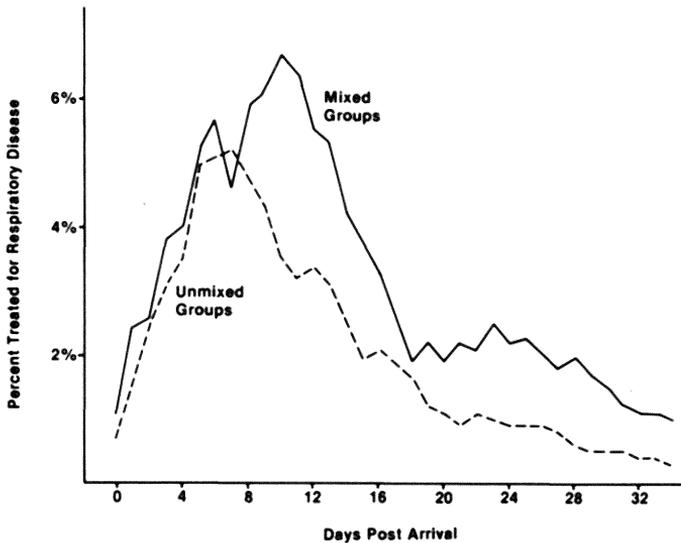
When cyclical changes are noted, a likely explanation is that herd immunity underlies the pattern. This might involve alterations in the immune percentage (due to lack of exposure or the birth of susceptible animals) or changes in the probability of contact, possibly because of variations in population size.

Seasonal variations in disease occurrence may have a number of different causes, ranging from direct effects of weather on the agent or host, to indirect effects of weather due to changes in flora and fauna, or to management and housing changes of animals in relation to weather. Diseases in which wildlife with seasonal habits serve as reservoirs or carriers and those transmitted by insect vectors tend to have seasonal patterns. It is also possible for dramatic yearly increases in the susceptible population to lead to seasonal patterns of disease. This may explain the seasonal occurrence of feline panleukopenia. However, usually more than one birth cohort is required to increase the number susceptible to the point where a disease outbreak is likely to occur. This would explain the 2–5 year periodicity for cyclical changes.

#### 4.9 Disease Occurrence in Absolute Time

In this approach for describing the temporal pattern of disease occurrence, the time of disease occurrence is displayed relative to one or more events of interest; (MacMahon and Pugh 1970, pp 169–73) the calendar date of occurrence is ignored, since it is not important in this context. Figure 4.1 is an example of this approach, in which the rate of treatments in groups of calves is graphed with respect to the time after arrival in a feedlot. The day of arrival becomes day 0, the next day, day 1, and so forth. The shape of the epidemic curve and the time after arrival when the treatment rate is highest can be noted. The day on which the cumulative proportion of treatments reaches 50% is called the median day and may be used to demarcate the midpoint of the outbreak.

As another example, parturition in a number of species appears to directly or indirectly lead to a number of diseases; that is, the diseases cluster temporally around parturition. Obvious examples include milk fever and retained fetal membranes; less obvious clustering exists for clinical mastitis and abomasal displacements. Recently, the average time to post-



4.1. Prevalence proportion of animals treated in Bruce County feedlots by days post arrival.

partum occurrence of a number of diseases was determined (Dohoo et al. 1984a, 1984b) and provided indirect evidence of clustering for some of them (Table 4.3). Use of the more formal approach as follows to validate these observations and identify if the occurrence of other diseases (such as foot diseases) are temporally associated with parturition also is suggested. If they are temporally associated, new avenues of study to elucidate the pathogenesis of the syndromes may be opened.

The simplest approach to a formal evaluation of time clustering occurs when there is only one suspect causal factor (e.g., parturition) that seems worth investigating. Initially, the variability among the dates of onset of the disease (the standard deviation of the period between the day of onset and the median day of the outbreak) is calculated. This is then compared to the variability (standard deviation) of the period between exposure to the suspect factor and disease occurrence. If the variability of the latter is less than the variability of the date of onset, this would support the hypothesis that the factor may have been the cause of the disease.

A recent report stated that 70% of all cases of parvovirus enteritis in vaccinated dogs occurred within 2 weeks of vaccination (Sabine et al. 1982). This time clustering of cases is certainly suggestive of a temporal clustering between the vaccination regime and clinical disease. A formal investigation of this hypothesis could be made by calculating the variance

**Table 4.3. Counts and incidence rates of first diagnosis of selected dairy cattle diseases by 7-day intervals, up to 56 days postpartum (2711 lactations)<sup>a</sup>**

Days postpartum	Abomasal displacement	Ketosis	Severe mastitis
0-7	15 <sup>b</sup> (0.6) <sup>c</sup>	77 (2.8)	30 (1.1)
8-14	8 (0.3)	44 (1.7)	3 (0.1)
15-21	2 (0.1)	39 (1.5)	1 (0.0)
22-28	1 (0.1)	13 (0.5)	3 (0.1)
29-35	2 (0.1)	10 (0.4)	1 (0.0)
36-42	0 (0.0)	5 (0.2)	1 (0.0)
43-49	0 (0.0)	3 (0.1)	1 (0.0)
50-56	0 (0.0)	3 (0.1)	2 (0.1)

Source: Dohoo et al. 1984a.

<sup>a</sup>37% of all foot problems were diagnosed within 60 days of parturition.

<sup>b</sup>Number of incident cases of the disease diagnosed in the time period.

<sup>c</sup>Incidence rate (%).

of dates of onset of parvovirus enteritis relative to the date of vaccination, and comparing this to the variance of the time between the date of vaccination and the date of onset of enteritis in other dogs in the same areas. If the latter was greater than the former, it would support the hypothesis. Two possible explanations for this clustering are that animals were incubating the infection at the time of vaccination, or that they contracted the infection while at the veterinary clinic for vaccination. (The reader might consider how to retrospectively assess each of these factors as explanations of this temporal clustering.) It should also be noted that vaccination may trigger clinical disease occurrence in some vaccinated individuals, while at the same time be effective in preventing disease. Hence, the above approach does not shed light on the overall potential value of a vaccine.

This approach may be extended to identify the most likely cause of an outbreak when all animals are exposed to the putative causal factor(s). (This latter situation precludes the comparison of exposed and unexposed groups to identify the most likely reason for the outbreak.) The variability of the period between exposure to the true cause of the disease and subsequent disease occurrence should be less than the variability of the period between disease occurrence and exposure to noncausal factors. As an initial step, the time between exposure to each putative factor(s) and the occurrence of disease in that individual is calculated. (If groups of animals constitute the sampling units, the median time of the outbreak is noted and the time between the median day and exposure to the putative factor(s) is calculated.) Then, the average time period and the standard deviation of the period between disease occurrence and exposure to each suspect factor is determined. If the average periods are approximately the same duration, the factor having the smallest standard deviation (or variance) is the most likely cause or source of the problem. If the averages differ greatly in

magnitude, the coefficient of variation (standard deviation divided by the average) should be used for making this inference.

## 10 Age and Time Interrelationships

As mentioned earlier, the patterns of disease with age can assist in generating hypotheses to explain disease occurrence. However, care is required when interpreting these patterns.

The existence or occurrence of an event (i.e., disease, death, or culling) may be affected by age per se, and/or by factors acting temporally close to the occurrence of the event (the current environment), and/or by factors that existed at some time prior to the occurrence of the event (the past environment). For example, the current milk production of dairy cows is related to the probability of being culled and may be influenced by current age, current environmental factors (such as the presence or absence of mastitis in the herd) and past environmental factors (such as whether or not the cows had pneumonia as calves). The problem is to identify which of these factors plays an important role in the level of production and hence of culling.

The usual method of examining age patterns (such as those of culling) implicitly relates the occurrence of the event to a current time period; that is, the rates portray the age pattern of occurrence currently existing. This method of calculating rates has been called periodic, cross-sectional, or current; the latter being preferred here. Current rates for a specified calendar time period have the following general form which is similar to that used for most rates:

$$\frac{\text{no. animals of age } X \text{ with event in current time period}}{\text{average no. animals of age } X \text{ at risk in current time period}}$$

The formula may be modified depending on what is being studied (i.e., prevalence or incidence, mortality, culling). When interpreting current rates, assume the event of interest is influenced by the current environment; however, the effects of age cannot be separated from the effects of the current environment, and the effects of past environment must be ignored.

If the age pattern of disease occurrence could be influenced by past environmental experience (including the animal's history with regard to previous disease occurrence) another approach known as cohort analysis is useful. Cohort analysis describes the rate of the event of interest in a defined cohort over a series of time intervals. Cohort analysis uses rates calculated as for risk rates and have the following general format for each time period:





**Table 4.6. Prevalence of antibodies to BLV in a purebred Holstein herd, by age and calendar year**

Age (months)	1977		1978		1979		1980	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
<24	9/53*	17.0	2/47	4.3	2/85	2.4	0/29	0.0
24-35	24/94	25.5	16/65	16.9	3/92	3.3	6/128	4.7
36-47	9/31	29.0	19/79	24.1	9/57	15.8	5/76	6.6
48-59	13/55	23.6	5/20	25.0	18/72	25.0	6/34	17.6
>60	6/32	18.8	13/56	23.2	14/59	23.7	23/73	31.5
	61/265	23.0	50/267	18.7	46/365	12.6	40/340	11.8

Source: Huber et al. 1981, with permission from Am. J. Vet. Res.

\*Numerator = number positive; denominator = number tested.

ing.) The reactor rates also appear to increase with age, except for the lack of an obvious pattern in 1977. Assuming these changes reflected the effect of current environment and age, the changes are consistent with horizontal spread of an endemic infection. That is, the older animals get, the more likely they are to have contacted the endemic infectious agent and have antibodies to BLV. An explanation for the decrease in prevalence with time is not obvious.

Table 4.7 portrays the same data using a cohort format. Note that there is only a slight increase in prevalence, according to age, within each cohort. (The cohorts are birth cohorts, but due to the method of testing there are missing data; some cohorts were 4-years-old before they were tested.) Note also that the prevalence proportion decreases in the more recent cohorts. Taken together, the results of the current and the cohort analyses imply a large cohort effect, a small increase in prevalence with age, and no effect of current environment. (Recall the conditions described earlier for age, cohort, and current effects.) There appears to be minimal spread of infection among cohorts in this herd. Why each succeeding cohort should have a lower prevalence of reactors than its predecessor (in the

**Table 4.7. Prevalence of antibodies to BLV, by age and birth cohort of Holstein cows**

Birth cohort	Initial test	Age at testing (months)									
		<24		24-35		36-47		48-59		>60	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
1977	1979	2/85*	2.4	6/128	4.7	...	...	...	...	...	...
1976	1978	2/47	4.3	3/92	3.3	5/76	6.6	...	...	...	...
1975	1977	9/53	17.0	11/65	16.9	9/57	15.8	6/34	17.6	...	...
1974	1977	...	...	24/94	25.5	19/79	24.1	18/72	25.0	23/73	31.5
1973	1977	...	...	...	...	9/31	29.0	5/20	25.0	14/59	23.7
1972	1977	...	...	...	...	...	...	13/55	23.6	13/56	23.2

Source: Huber et al. 1981, with permission from Am. J. Vet. Res.

\*Numerator = number positive; denominator = number tested.

absence of a control program) is an interesting question to ponder; although there is no obvious explanation for it, the cohort effect is nonetheless real.

These data are not intended as the final word on BLV in dairy herds. Many people believe (primarily based on current rates) that the prevalence rate increases with age as a result of horizontal transmission of the virus. A recent prospective cohort analytic study investigated the time(s) at which horizontal spread of BLV appeared greatest (Thurmond et al. 1983); the data from this study indicated an increasing prevalence of BLV antibodies with age (i.e., a true age effect).

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