# Disease Outbreak! What Can You Do?

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## The situation

You get an urgent telephone call to visit a property in your practice area because 25 of a group of 200 animals are affected with a disease which the owner has never seen before in his animals. He describes the clinical signs, and they do not fit anything you are used to seeing in the practice either. You grab your favourite textbooks for comfort and jump into the car. What should you be thinking as you drive 15 km to the farm?

## Is this likely?

Much more likely than you think. If we think in terms of a broad definition of new syndromes you may see in the course of your work, our research into how veterinarians in practice deal with what we called "new situations" - problems or decisions which they had not previously dealt with - showed that they faced such an issue between once a month and once every three months, and that new disease syndromes were prominent on the list of items which created a new situation. In my clinical work I have dealt with at least four new syndromes over the last two years - most or all of which practitioners must have seen and not recognized as clinical entities new to the area. In my experience practitioners have difficulty discriminating between genuinely new problems and those which are just variations on well known ones. They tend to miss significant new developments because time pressures dictate that their endpoint is no further complaint from the owner, rather than proven resolution of the problem.

New syndromes may cover a wide range. At one end of the spectrum are important evolutionary changes in disease patterns, such as the emergence of anthelmintic-resistant nematodes in ruminants over, recent years, or the arrival of a new immunogenically distinct strain of a common pathogen. Unusual problems may also be seen when a disease varies over time in its geographical distribution, and appears in an area only occasionally. Sporadic bovine encephalomyelitis and various arthropod-borne agents such as Akabane virus fit this category. Unusual combinations of disease agents may also produce what appears to be either a new syndrome, or a familiar syndrome which suddenly fails to respond to the traditional treatment.

The syndrome may also be a previously undescribed one - for the locality, the country or the world. Exotic disease scares and true emergencies are common enough that a substantial proportion of veterinarians will face this diagnostic possibility during their careers, and all of us would like to handle the situation adroitly if it happens to us. Even if the disease is not one for which emergency action would be appropriate, someone has to be the first person ~to recognize canine parvovirus infection, feline infectious peritonitis or porcine pleuropneumonia in the country. In almost every such case, subsequent investigation reveals that others had seen the condition previously and failed to recognize it.

At the worldwide level, on average at least one important new disease and a number of less significant new syndromes have been identified in man and animals per year over the last 20 years as a result of investigation of disease incidents. Whether it be as momentous as the identification of AIDS or bovine spongiform encephalopathy, or a minor discovery such as a new plant poisoning, someone has to be first to identify and characterise the condition and produce some initial hypotheses about its cause and transmission. And twenty or two hundred people have to admit secretly to themselves that they could have made the discovery, but missed it or dismissed it.

So in one way or another, most veterinarians will have need for an approach to investigating disease syndromes which they do not adequately understand.

The epidemiological approach to such investigations grew out of the clinical approach, but includes important improvements which provide a more reliable strategy for investigating disease outbreaks and for improving understanding of disease syndromes under practical field conditions.

### The clinical approach

The focus is strongly on the diseased animals, by identifying the features which distinguish the animals affected by the disease from normal animals. Normality is defined in relation to the overall experience of the clinician, rather than any particular comparison group.

In principle this should lead to a correct diagnosis. In fact it does so provided two conditions are met. These are that the "true" diagnosis is included in the differential diagnostic possibilities considered by the clinician (which implies, *inter alia,* that it is a disease known to occur in the area); and that a single identifiable disease is present. However a substantial proportion of difficult diagnoses present a challenge precisely because multiple factors interact to produce the syndrome. Thus the investigator is dealing with a causal web rather than a causal chain, and the condition can only be understood through a multifactorial view of disease, in which "cause" and "diagnosis" are replaced by concepts of multiple disease "determinants" and their combined "outcome".

Research on the process of clinical diagnosis in human medicine has shown that the final diagnosis made by a clinician in a particular case is almost always drawn from among the list of possible diagnoses formulated at the outset of the investigation. Thus the clinician works in reality according to a different series of logical steps from those taught as clinical examination procedure. Rather than dispassionately collecting data and then formulating a diagnosis when all the information is available, the rear-life clinician immediately formulates a list of differential diagnoses and then proceeds to rule various of them in or out as the examination proceeds, until (ideally) only one tenable diagnosis is left. Of course, if the true diagnosis was not included in the original list and has not been added as a result of later consideration, then the final diagnosis must be wrong. This is much more common than we like to believe.

The accuracy of the diagnosis will also be influenced by the areas of special expertise of the individual, both positively and negatively. If the true diagnosis lies within the person's areas of expertise, then a wider range of differential diagnoses will be included, and the correct answer is more likely to be found. However if the true diagnosis is outside these areas of expertise, the clinician may be influenced to force the syndrome to fit one with which he or she is familiar, rather than to fully consider conditions with which the person lacks experience.

### The epidemiological approach

The fundamental advance in the epidemiological approach is that it removes the assumption that there is any absolute standard of normality against which an animal or herd can be judged, and focuses on comparison of sub-groups of animals. The investigation is structured more tightly than a purely clinical one, and aims to keep the process as objective and free from bias as possible. The hallmark of the epidemiological approach is its systematic approach and the use of precisely defined comparisons between sub-groups and the establishment from such comparisons of putative disease patterns.

If the condition is simple and clearcut then epidemiological thinking plays a relatively minor part in reaching a conclusion, and the epidemiological approach becomes difficult to distinguish from the clinical. However if the condition is new or complex, then the epidemiological approach comes into its own.

## Steps in the epidemiological approach

*Establish a case definition*

The first action is to collect enough history and clinical data after arrival on the property to establish the principal features which affected animals share in common, and the extent to which the owner's views on this agree with your personal findings. These features may include such animal characteristics as age group, breed, sex and reproductive states of affected animals.

Evidence about the nature of the condition is then collected by direct examination of a sample of animals to establish the main features of its manifestation - whether this be clinical disease or perhaps a sharp and unexplained drop in milk production.

In making this examination it is essential to remember that owners are surprisingly biased in selecting animals for examination under such circumstances. I have been misled far too many times in such investigations by allowing the owner to select animals for examination and finding inexplicable inconsistencies between the findings and the other evidence about the outbreak, only to discover after delving more deeply that the owner had chosen quite atypical cases for my examination - presumably because they stood out from the crowd!

At this stage of the investigation it should be possible to produce a short written list of the salient features of the condition, which can be considered as the case definition. These will be primary points which are shared by almost all affected animals but not by the population as a whole, and which appear to be *both necessary and sufficient conditions* to define the syndrome you are facing. There will always be additional features which are of potential importance but do not appear to be central to the nature of the condition. These secondary features should not be allowed to clutter the case definition, but will become important in the later work-up of the problem.

Having established a case definition, it becomes possible to begin to work systematically through the initial investigational steps to provide an epidemiological appraisal of the problem, and particularly of the comparison between cases and unaffected animals, which we usually call controls.

The objective of this paper is to give you a flavour of each of the investigational techniques which will be described in detail later in the course, so I will mention various specific tools in the epidemiological armoury without explaining them in detail, since that would steal the thunder of later speakers. Terms which will be covered in later papers are printed in italics.

*Describing the Syndrome*

Having decided on a case definition, the next step is to collect history, clinical and productivity data on an adequate sample of cases and unaffected animals in the herd. Most herd investigations which draw wrong conclusions do so because they concentrated too much on the diseased animals, without making comparisons with at least an equal number of controls. They miss the more subtle features which differ in distribution between the two groups, or (even more importantly) are shared to a greater extent by both groups than would appear at first sight.

In order to do this, the same items of data must be collected on both groups, and counts must be made of the frequency of each feature in cases and their controls. Missing observations will reduce the value of the information, and may seriously bias it in some cases.

The greatest challenge for avoiding bias is the method of selection of cases and controls. There are no universal rules for doing this - the criterion should be that animals selected will give an unbiased estimate of how common a particular finding is in affected animals and in a comparable population of unaffected animals. The samples must also be chosen so that data collected is not subject to *confounding*. Confounding occurs when information is gathered in such a way that two potentially important influences cannot be separated. For example, a sample of horses may be selected in such a way that it contains thoroughbreds more than five years old and standardbreds less than three years old, when both age and breed are potentially important factors. This is an extreme example to illustrate the point, and confounding in field investigations is frequently subtle and not recognized until the investigation is complete.

As a general guideline, if possible all cases of the disease should be included in the investigation. If that is not practical, cases should be chosen in a truly random fashion from the total population of case animals. In some special circumstances, it may be necessary to identify an important factor which is already known to influence the disease, and to *stratify* the population on that factor before choosing randomly. For example, if there are affected animals in two mobs of sheep at similar *prevalence*, but one mob is much larger than the other and the farmer is convinced that the problem is related to how he managed the large mob, it may be necessary to randomly select cases *within* each mob, to ensure that between-mob comparisons may be made. Otherwise a truly random sample may come entirely from the larger mob, since true random samples always obey Murphy's Law in such cases. Most people are surprised that true random samples tend to be patchy rather than evenly spread across a group, because they wrongly equate random with their concept of "representative" sampling, which always involves selection rather than sampling, and is prone to serious bias.

With regard to the selection of control animals for comparison purposes, there are two options. In principle, controls should be selected randomly from the unaffected animals, because then straightforward comparisons can be made with cases. However if it is already known that some factor is very influential on the disease and it is necessary to eliminate its influence in comparisons, then each control can be selected randomly from animals which match a particular case animal on that feature, or perhaps even two features. For example, the lesions seen in lameness in first lactation dairy cows differ from those seen in mature cows. In investigating an outbreak of lameness in a herd by comparing frequency of various lesions between cases and controls, the comparison should be between animals within lactation number, or the findings will be confounded by the known age-variation in lesion categories. However if a factor is used for matching in the investigation, then it cannot be considered also in the analyses of the data - it is automatically excluded. Matching should be based on as few factors as possible.

As well as making direct comparisons with control animals, it is often useful to compare affected animals with the "rest of the herd", which means all non-affected animals. This will show the ways in which the affected animals have characteristics which are not typical of those of the herd as a whole.

*Examining time distribution*

In a true outbreak, one of the most useful aspects to study is the pattern of cases over time, both in the group as a whole and in sub-groups within it. This gives valuable insights into the likely method of transmission or initiation. An infectious disease will commonly show a time pattern with an initial steep rise to a peak and then a more gradual decline, possibly with multiple peaks due to successive waves of transmission. Point outbreaks due to a common source of the agent becoming available to all animals at the one time will show a much more peaked curve with a very clear start which should link to the initiating factor. Other diseases show typical kinds of curves according to the factors which initiate the outbreak, and it is at least often possible to use the curve to rule out some potential diagnoses. The curve is drawn by identifying the first or *index case*, then graphing subsequent cases by the number per day or week from the index case through to the end of the outbreak.

*Examining place considerations*

In medical epidemiology, "place" is an important preliminary risk factor to look at, since place of residence and workplace are major explanatory variables in understanding human disease. Location can be an important factor in animal disease, although because of herd management it is frequently confounded with managerial factors. Nevertheless, as a preliminary step it can be very valuable in an outbreak investigation by identifying where the outbreak is occurring within and among farms, so that subsequent work to identify risk factors can be set up so that it will separate management from pure location factors. Unless this preliminary work is done, the final conclusions may still have location and management confounded and incapable of separation.

*Examining risk factors*

In considering a disease syndrome, the investigator looks both at the relevant outcome variables (such as major clinical signs, milk yield, wool quality, probability of death, etc.), and at *risk factors* - those variables in the animals and their environment which may be linked in some way with the outcome variables of interest. Some of these will be putative *determinants* of the disease or productivity indicator, which are either true causal factors in the multifactorial causal web, or may be factors which are simply correlated with a true causal factor. Some such factors are merely a nuisance, complicating analysis of a problem with spurious associations which must be investigated only to be found not to be true determinants. However in certain other cases the association may be put to use if the true causal variable is difficult or laborious to measure, but can be represented by a highly correlated *surrogate variable,* which is easy to work with. For example, it is very difficult to quantify the management skills of a farmer, but an indication of these skills can be obtained by measuring certain personality characteristics or by assessing whether or not the person adopts certain technical innovations widely used by better managers.

*H,ow many variables to measure?*

When carrying out an epidemiological investigation, it is important io measure more variables than the ones you think are important - a common error is to select for study only those considered in advance to be influential. If almost all of the variables you thought would be important turn out to be statistically associated with the disease and few if any of the others are associated, then you can have greater confidence in your hypothesis since it has both positive and negative support. On the other hand, if variables you identified show only patchy association and others turn out to be unexpectedly important, you need to rethink the hypothesis. This is much more valuable than merely confirming or refuting your specific hypothesis without obtaining any corroborating evidence.

This does not mean that you should measure everything you can think of, but it does mean that there should be a spread of variables across the factors of possible importance. It is common practice to start with a modest but well thought out list of variables in an initial outbreak investigation, then if the problem proves difficult to crack, to expand the list in later more structured investigations of the problem, as outlined later. Even if it proves necessary to go to the more comprehensive approach, the data gathered in the first stage will be helpful in deciding the details of the next stage.

## Interpreting the data

When you have gathered the necessary data - whether it takes 30 minutes or 3 weeks - you need to appraise what you have gathered and determine its importance and meaning.

The first issue to decide is whether or not the outbreak is genuinely an unusual event worthy of special attention. To qualify as an outbreak, the number of cases per unit time should be substantially above the long-run average in the entire herd or population, or in a sub-group within the population (for example, a disease occurring frequently in adults, when it is normally limited to young animals. Quantitative estimates of disease occurrence during an outbreak can be calculated as *attack rates.*

It is quite common for an animal owner to see a problem as an outbreak, but for a veterinarian to conclude that it is not atypical, or that multiple conditions occurring simultaneously have mistakenly been lumped together to create an impression of an outbreak, whereas in fact all the diseases are occurring at normal incidence and the concentration in time is a chance phenomenon.

It should also be remembered that rumours and epidemics behave in exactly the same way, and a rumour can mimic an epidemic. These phantom or hysterical epidemics are surprisingly common in human medicine and appear almost indistinguishable from the real thing. While true hysterical epidemics cannot occur in animals, comparable phantom disease outbreaks can be reported. These usually result from conflicts between staff, where individuals report unusually high levels of disease either to undermine another person, or to create the impression that they are more vigilant than others. Sometimes they result from inexperienced staff over-diagnosing a condition.

If it appears that the outbreak is genuine, then it is necessary to look for risk factors which are more closely associated with cases than controls (or vice-versa if some factor is protective). The epidemiologist identifies risk factors by comparing groups - for example to see if a factor is present at a significantly higher level among case animals than among randomly chosen controls, or than among the rest of the herd. The skill lies in choosing the comparisons to make, so that the process is efficient but yet quickly identifies risk factors which appear to be disease determinants. Comparisons will be between animals exposed versus not exposed to a risk factor, or between levels of a risk factor - perhaps age or daily milk production.

In the first step, *odds ratios* are commonly used to assess the importance of each factor. Those which appear important can be investigated further. This approach al)ows only single factors to be assessed, and does not fully solve the problem of clarifying'complex causal webs. It is however often adequate since each of the major factors will show up in the odds ratio analysis, and can be interpreted jointly.

This will be quite adequate in most cases, and will produce an adequate explanation of the nature of the outbreak. The investigational approach which has so far been described is a case study of the affected herd, with case-control comparisons within the herd.

At this stage it should be possible to draw up a provisional epidemiological *path diagram* (Lessard and Perry, 1988) which lays out the factors thought to be involved in the outbreak, using arrows to link factors into a set of causal pathways comprising the causal web. The web may be simple and the causal chain may have become quite clear in the course of the investigation. If the causal process hypothesized from epidemiological principles agrees comfortably with the data gathered in the field investigation and no major questions remain open, all that may remain is to take corrective action.

However the conclusion at this stage may be that the findings do not mesh neatly with current knowledge concerning diseases occurring in the area. If the problem is sufficiently unusual or important that it deserves additional investigational effort beyond the initial herd, then other epidemiological methods such as a *case-control study* or *cohort study* become the best method for the next stage. Whereas in the ad-hoc investigation of a problem in a single herd the analytical approach must be kept simple, if the problem requires assessment within a more structured epidemiological investigation, it becomes possible to use more advanced analytical approaches such as *multivariate techniques* to look at interactions between factors in determining disease occurrence. This has for example been used in a veterinary practice to investigate management and environmental factors involved in the epidemiology of lameness in dairy cattle (Chesterton et al, 1989), combining straightforward but comprehensive field data collection with powerful path analysis procedures to identify key variables in this disease complex.

Such epidemiological techniques can be used effectively in veterinary practice to solve difficult disease problems at the farm or regional level.

## References

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