Making better medical decisions

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Abstract

Cattle veterinarians should know how to describe the occurrence of a health condition in a population, compare the risk for the condition between subjects with different characteristics, be able to evaluate the impact that those characteristics or exposures may have on the occurrence of the health condition in that population, and use those metrics to make appropriate medically and economically sound client recommendations. Incidence is analogous to the probability, or rate, for a subject to become a case in a given time-period. Measures of incidence are the basis for comparing disease risk for differing exposures, determining the impact of the exposure on the exposed, as well as the impact of that exposure on the disease burden of a population. Medical interventions are intended to reduce the burden of disease, and statistics such as number needed to treat help the veterinarian determine how effective, and costly, those interventions might be. Recognizing certain statistical traps, such as regression to the mean, can help the veterinarian avoid mistakes in interpreting data. By using certain population-based statistics correctly, veterinarians can better recognize what is happening in a herd, make more informed recommendations to their clients, and evaluate the outcomes resulting from their advice.

Key Words: Epidemiology, incidence, prevalence, relative risk, attributable fraction, number needed to treat, regression to the mean

Introduction

Veterinarians often feel obliged to do something once a client presents a problem, either by directly deciding to act medically or surgically or by making a recommendation for an action to be taken by the client. As clinicians, we often rely on experience and intuition to guide our thinking, but the process of moving from problem to action may sometimes require critical thought. Experienced practitioners commonly employ System 1 thinking, which relies on rules of thumb and intuition to guide their medical decisions and recommendations. System 1 is efficient, and those actions are commonly correct. But spending some time in critical thought (System 2 thinking) can improve medical outcomes.[3] Using evidence to guide the thought process may lead to better clinical outcomes.

Like other health professionals, veterinarians learn a common language to describe their findings from a physical examination or necropsy of individual animals so that they can communicate their findings with others that are others similarly trained. However, veterinarians in cattle practice typically work with populations of cattle and therefore may need to evaluate the health and performance of a population rather than of an individual in the course of medical decision-making. Just as the examination of the individual animal seeks to differentiate normal from abnormal, there may be reasons to know if population-level occurrence of health conditions is normal or abnormal. In addition, the population-based practitioner may want to weigh the importance of the occurrence of health conditions within the population on the overall health, wellbeing, and productivity of the herd. This means the cattle veterinarian should know how to describe the occurrence of a health condition in a population, compare the measures of disease occurrence between groups with different characteristics, be able to evaluate the impact that those characteristics or exposures may have on the occurrence of the health condition in that population, and use those metrics to make appropriate medically and economically sound recommendations.

Measures of disease occurrence

Prevalence describes the proportion of subjects in a population that have a disease or infection at a single point in time. This is analogous to the probability of a given subject being a case at that point in time. Prevalence is a function of the incidence and duration of the disease and therefore, is not a primary measure of disease occurrence in a population.

For example, 30 cows are observed to be nursing calves in a herd of 270 cows. The prevalence of cows with calves in the herd is 30/270 = 11%.

Incidence is a measure of the number of new cases of disease or infection among the population at risk for a given period of time. Incidence is analogous to the probability, or rate, for a given subject to become a case in that time period. The numerator for incidence is always the number of new cases in the given time period. However, the denominator for incidence is estimated in several ways, depending on the data available. The denominator for cumulative incidence, a measure of risk, may be the population at risk at the start of a time period in stable populations, or the average population at risk over a time period in a less stable population. The denominator for incidence density, a rate, is the sum of time that each subject was at risk for the condition; for example, the time until the subject had the event, died, left the population, or until data collection was ended. Incidence is a measure of the driving force of a condition or disease and is the primary measure of health condition occurrence in a population. Note that throughout the rest of this paper the term disease may represent any health condition. The reader is advised that the health condition could include infection or other health states, such as pregnancy.

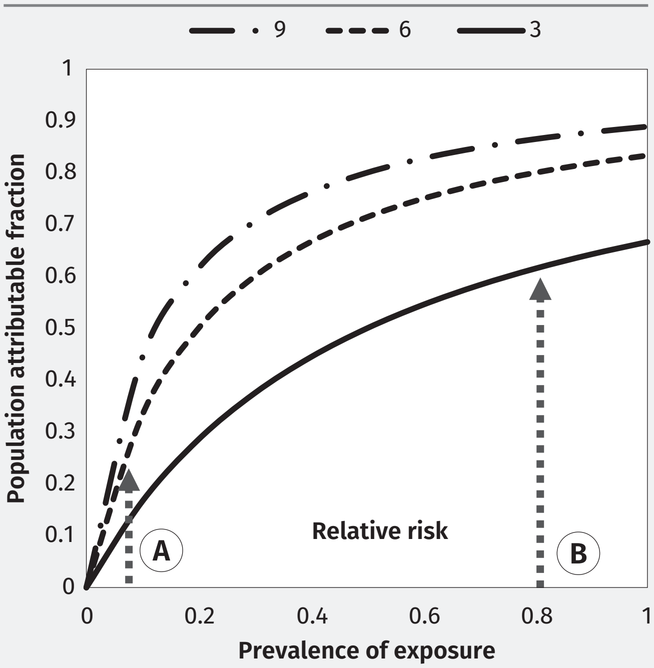
There are other measures used to describe the health status of a population. For example, the mortality rate is the incidence of deaths (in general, or due to a specific cause) in a particular population when the time-period is specified. Statistics that provide prognostic information include the case fatality rate – the proportion of those individuals with the disease that die, and the case recovery rate – the proportion of those with the disease that survive. As we will see, it is important to be wary of health statistics such as morbidity, mortality, and pregnancy percentage that do not define a time interval.

For example, in the herd of 270 cows described above, 40 cows calved in the following week. The cumulative incidence of calving in that week was 40/240 = 17%. Note that the denominator is 240, not 270, because 30 cows had already calved and were therefore not at risk for calving in the next week. If pregnancies were staged by pregnancy examination or if calving dates were recorded, then one could estimate the rate of conceptions (calves) per 21-day estrus period. In the herd of 270 cows, 253 cows conceived (and had calves) during a total of 587 estrus opportunities over a 105-day breeding season. The incidence density of conception (calves) per 21-day estrus period was 257/587 = 0.44 conceptions (calves) per 21-day estrus cycle. This is equivalent to saying that the probability of a cow in this herd conceiving on a given estrus was 44%. The incidence density of conception is commonly reported as a pregnancy rate.[4] Note that many veterinarians and cattle producers report a pregnancy (or calving) percentage, defined as the number of pregnancies (or calves) per cow exposed to breeding.[1] In this example, the pregnancy percentage is 257/270 = 95%. Pregnancy percentage, analogous to an attack rate, is a misleading statistic in this situation because it does not account for the length of time of the breeding season. A 95% pregnancy percentage in a 105-day breeding season has a lower incidence of conception than 95% pregnancy percentage in a 60-day breeding season.

Strength of association

We may wish to know if a certain characteristic (e.g., age, gender or breed) or exposure, (e.g., to a vaccine, transportation or a dietary ingredient) is associated with a greater or lesser risk or rate of disease. The most common method to evaluate the strength of association is to compare the incidence of the disease among those with the characteristic or exposure to those without in the form of a ratio. This ratio is called relative risk (RR) or rate ratio (RR) depending on the measure of incidence used. If RR is close to one, then there is little or no difference in the occurrence of disease between the 2 levels of exposure. If RR is greater than 1, then the exposure is associated with increased risk of disease. If RR is less than 1, then the exposure is protective against the disease – a sparing effect. The difference between the incidence with exposure to incidence without exposure is called the risk difference (RD). The RD is a measure of how much the incidence of disease increases (or decreases) with the exposure. In some study designs, such as case-control studies, it is not possible to measure incidence, but it is possible to estimate the odds of having the exposure among the cases and comparing this to the odds of having the exposure among the controls. The ratio of these two odds is called the odds ratio (OR). The interpretation of the OR is the same as with RR. Also, regardless of the study design, the OR is the output of some methods of statistical analysis, such as logistic regression.

Figure 1: Population attributable fraction at various measures of association between disease and exposure and various prevalence of exposure. A common exposure with a lower strength of exposure (B) may have more impact on a population than a rare exposure with a stronger strength of association (A).



Referring again to the hypothetical herd of calving cows, the records indicated that the 32 3-year-old cows in the herd had 30 conceptions (calves) out of 92 21-day cow-cycles, a pregnancy rate of 0.33 calves per 21-day cow-cycle. The remaining 238 cows, 4 years of age and up had 227 conceptions (calves) out of 495 21-day cow-cycles, a pregnancy rate of 0.46 calves per 21-day cow-cycle. The rate ratio for conception (calving) of older cows to 3-year-old cows was 0.46/0.33 = 1.4. Older cows were conceiving at a rate 1.4 times greater than 3-year-old cows. The RD was 0.21, meaning that older cows had 0.21 greater conceptions per 21-day cow-cycles. Both statistics of association suggest that the low rate of conception (calving) among the 3-year-old cows compared to older cows should be investigated.

It happened that the body condition of the 3-year-old cows had been recorded at calving. Of the 32 cows, 18 (56%) were too thin, having a body condition score of 4 or less on a 9-point scale. These data do not help us understand the difference in pregnancy rate between these cows and the older cows, but they do let us evaluate whether being thin at calving affected the pregnancy rate among 3-year-olds. Thin cows had a pregnancy rate of 0.26 conceptions (calves) per 21-day cycle, whereas the cows in good condition at calving had a pregnancy rate of 0.47 conceptions (calves) per 21-day cycle. Therefore, the pregnancy rate among 3-year-old cows in good condition was 1.8 times greater than that among thin cows.

Measures of impact

We may want to understand how much impact an exposure (or characteristic) has on the health and productivity of those exposed or how important the exposure might be to the health and productivity of the entire population. Understanding the impact of the exposure on disease might help us rank its importance to disease control and prevention.

Attributable fraction (AFE) is a measure of the relative impact an exposure had on the occurrence of disease among those diseased individuals with the exposure. An exposure might be known to increase the risk or rate of disease, but that exposure may not be necessary or sufficient to cause the disease. That is, there may be other exposures that are also causally associated with the disease. Therefore, not every case of disease can be attributed to 1 causal exposure. The AF describes how likely it is that a subject's disease was due to the exposure. For example, smoking tobacco products has been causally associated with lung cancer in people. However, some non-smokers also get lung cancer. Therefore, if a smoker gets lung cancer the cause cannot be solely attributed to their smoking because other non-smoking factors also contribute to the risk. The strength of association (RR or OR) is the only statistic needed to calculate AFE.

AFE = (RR-1)/RR

In the example of the 3-year-old calving cows, the attributable fraction of good body condition cows conceiving during an estrus was (1.8-1)/1.8 = 0.8/1.8 = 0.45. In other words, 45% of the reason for a cow in normal body condition conceiving at a given estrus could be explained by the fact that she was in good condition. Other factors played a role in the risk for conceiving on an estrus, but among cows having good body condition that factor was a big player.

Vaccine efficacy (VE) is a special case of attributable fraction. In this case, it is a measure of the decreased risk in disease for disease that is due to a vaccine or other preventive intervention.

VE = 1-RR when RR is expressed as the ratio of the incidence of disease among vaccinated subjects to the incidence of disease among non-vaccinated subjects.

For example, if the incidence of disease was 20% among non-vaccinated animals and 5% among vaccinated the RR of disease for vaccinated animals compared to non-vaccinated animals would be 0.05/0.20 = 0.25 and VE would be 1-0.25 = 0.75. So, the risk for the disease among vaccinated animals was reduced by 75%.

Population attributable fraction (PAF) is the proportion of disease in a population that can be attributed to a certain exposure. The statistic is used to estimate the proportion of disease that could be prevented if the exposure factor was removed from the population, assuming the exposure relationship is causal. The PAF is a useful statistic for deciding if an intervention might be worthwhile to implement in a given population. Common exposures with a lower RR might have a greater impact on disease in a population than rare exposures with stronger measures of association.

PAF= PE x (RR-1) / (1+(PE x (RR-1)))

PE is the prevalence of the exposure in the population

In this example, the impact of being in good condition on the pregnancy rate in the population of 3-year-old cows can be estimated by calculating the PAF. In this case, it is 0.44 x (1.8-1)/1+(0.44 x (1.8-1))) = 0.26. So, in this population of 3-year old cows, 26% of the risk to conceive on an estrus was explained by cows in good body condition.

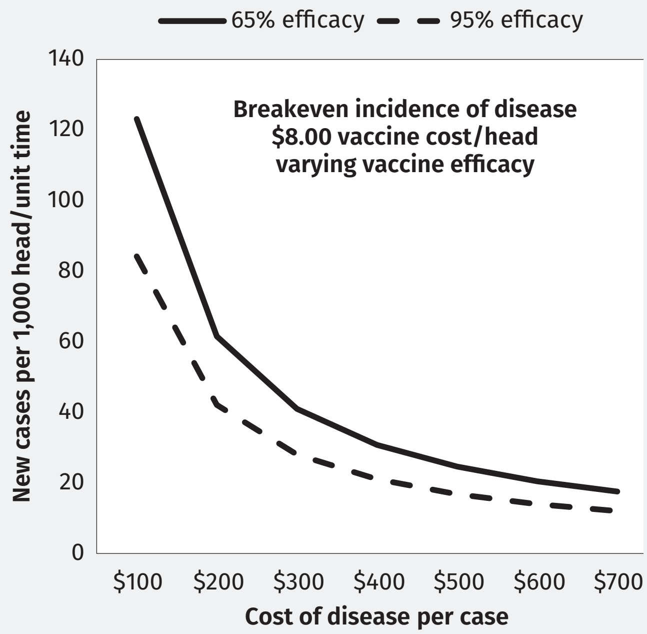
Number needed to treat (NNT) describes the number of subjects that need to receive the preventive or curative intervention (e.g., a vaccine or antimicrobial therapy) to prevent or cure 1 case of the disease. This captures the concept that disease is not prevented in every subject that receives a vaccine or curative medication and gives an idea of the effectiveness of the intervention. A perfect medication would have an NNT equal to 1.

NNT =1 / RD

For example, using a vaccine that is 75% effective at reducing disease in a population with an expected annual cumulative incidence of disease of 10% would results in an incidence of 2.5%. The RD is 0.1-0.025 = 0.075. The NNT is 1/0.075 = 13.3. For every 13 individuals receiving the vaccine, one case of disease would be prevented.

Number needed to harm (NNH) is a corollary to NNT. The NNH describes the average number of subjects that receiving the preventive intervention that results in one adverse event.

Figure 2: The disease incidence at which the cost of prevention is equal to the cost of the disease by preventive efficacy. The analysis considers the cost of the preventive (including cost to administer it), the preventive's efficacy, and the cost of the disease (including cost of treatment, death loss, lost productivity).



Clinicians may compare NNT to NNH before deciding to recommend an intervention.

NNH = -(1/RD of the adverse event)

For example, in a population where no subjects are expected to die from anaphylaxis, but one of 10,000 vaccinated subjects die from anaphylaxis, the NNH = -1/-0.0001 = 10,000. This means that one cow is expected to die from anaphylaxis for every 10,000 cows vaccinated. If greater than 5 kg less milk production in the week following treatment of dairy cows with a placebo vaccine was 10%, but 45% among vaccinated cows, then the NNH was –(1/(0.1-0.45)) = 2.9. This means that for approximately every 3 cattle that receive the vaccine, one will experience milk loss greater than 5 kg. The costs associated with the adverse event should be considered against the benefits of providing immunity. The NNH reminds us that vaccines and other preventive practices are not always innocuous.

If you know the cost to administer a vaccine, the NNT can be used to estimate the cost to prevent a case. If the total cost for the vaccine protocol described above was $10 per head, it would cost $133 to prevent one case of the disease in that population. However, using the same vaccine in a population with an expected annual cumulative incidence of 1% would result in an NNT of 133.3, and the cost to prevent one case would be $1,333.

This example provides an important lesson about the economics of prevention programs. The cost-effectiveness of a health prevention program depends on the cost of a case of the disease, how common the disease is, the cost of the prevention (e.g., a vaccine), and the effectiveness of the prevention (Figure 2). The cost-effectiveness of a vaccination program for a given vaccine is greater as the expected incidence of disease in the herd without vaccination increases. The incidence of disease at which it becomes cost-effective to vaccinate (IDBREAKEVEN) can be determined by knowing the cost of the disease (DC), the cost of the vaccination program (VC; e.g. the cost of the vaccine product, labor, and facilities), and vaccine efficacy (VE).[5]

IDBREAKEVEN = VC / (DC x VE)

Regression to the mean

Regression to the mean is a statistical phenomenon that can lead to improper conclusions and inappropriate medical decisions or recommendations.[2,3] Expected variation in biological data means that on occasion extreme values are observed by chance. When repeatedly measuring data, extremes of high or low values may prompt us to act when, in actuality, we are simply observing normal variation. The problem is that rare extreme values are likely to be followed by values closer to the norm in the subsequent measurement. If we take some action to intervene at the occurrence of a rare observance and the value subsequently returns to closer to the norm, then we may erroneously believe it was our intervention that was responsible for the correction.

For example, it is common to record and monitor the percent of cows found pregnant during routine reproductive health visits on the dairy. Let's say that on a particular farm the expected percentage of pregnant cows among those presented for pregnancy exam is 50%, and typically 40 to 60 cows are examined for pregnancy each visit. During one visit, 24 of 54 cows (44%) were pregnant. This low percentage of pregnancies is below the expected 50%, so you recommend some management changes that are actually ineffective. Because of regression to the mean, the percentage of cows pregnant was greater at the following visit, reinforcing the false belief that the management changes were responsible for the improvement. Similarly, it may be disheartening to see the percentage of pregnant cows plummet just after congratulating the dairyman for a high pregnancy percentage when, in reality, the 2 observations were expected variation around a mean (Figure 3).

When outcomes are monitored over time, statistical process control rules may aid in determining when the process is in fact out of control, but the problem of regression to the mean finds its way into unexpected places. For example, another way veterinarians can be misled by regression to the mean is through research publications or product adds with testimonials of the results of using their product in herds that have experienced some worst-case scenario and then had a meaningful improvement following the intervention.

Conclusion

Veterinarians rely on heuristics and rules of thumb for clinical expediency but applying quantitative skills and critical thought enhances clinical judgement and may improve medical outcomes. By understanding how to use certain population-based statistics, veterinarians can better recognize what is happening in a herd, make more informed recommendations to their clients, and evaluate the outcomes resulting from their advice.

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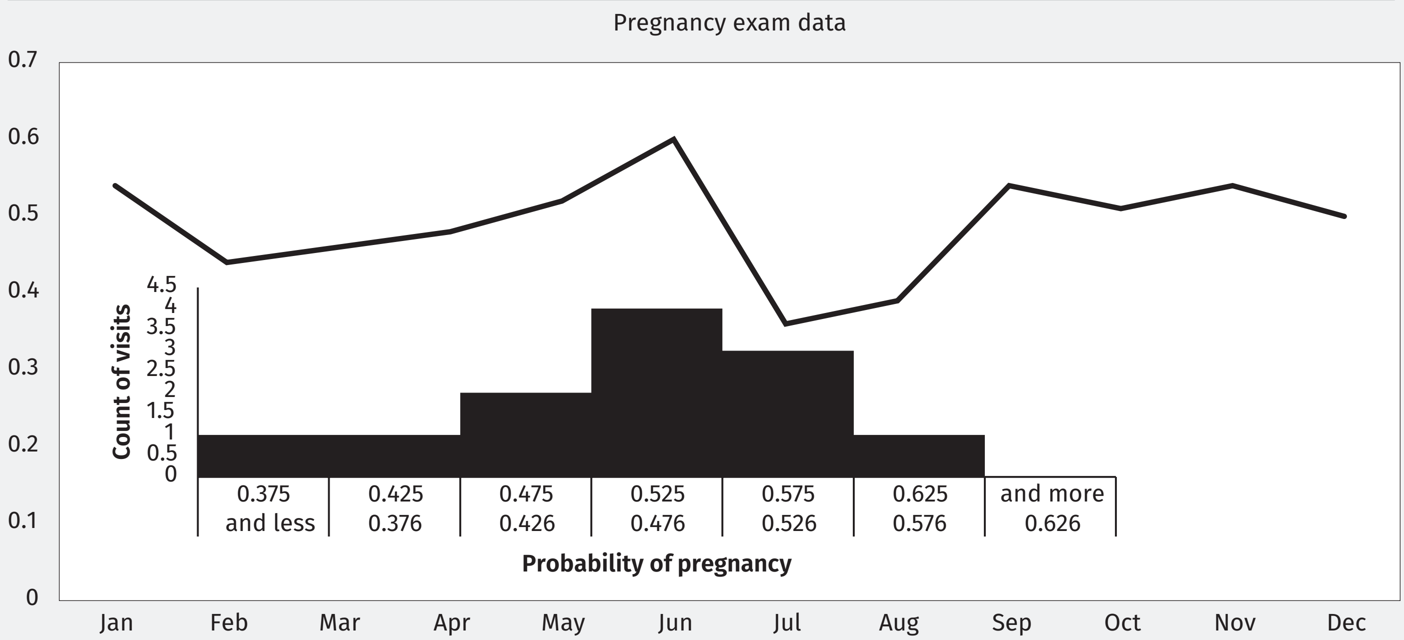
Figure 3: An example of regression to the mean using pregnancy examination data recorded over one year of monthly visits. The percentage of cows determined pregnant at each visit. During each visit 40 to 60 cows are examined and the expected percent pregnant is 50%. Extreme values such as those observed in February, June and July are usually followed by values that are closer to the expected value. The frequency histogram inset show the distribution of pregnancy percentages for the 12 monthly visits.



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