Epidemiological information in sheep health management

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Abstract

We use epidemiology whenever we consider the management of sheep health. To measure a disease, we need a precise and unique case definition and we often use diagnostic tests to assist in defining a disease. Diagnostic tests are not always accurate and it is necessary to consider the decisions that will be taken based on the result of testing to decide the most useful approach to interpret a test based on its test sensitivity and specificity and the prevalence of the disease in a flock. This is particularly important when decisions on culling or selection of sheep to attain e.g. freedom from disease are made on the basis of test results. Infectious diseases spread within and between flocks in a variety of ways; brought-in sheep are the most likely source for introduction of a new pathogen or strain of pathogen. When a pathogen enters a naïve flock, it spreads through susceptible sheep and persists in the flock whilst there are susceptible sheep that can be infected. Pathogens use a variety of techniques to persist, including a change in the pathogen itself, an alteration in infected hosts that enable them to remain infectious for prolonged periods or to be re-infected or persist in another host species or the environment. We need to consider these strategies to decide whether elimination or control of a particular pathogen is more likely to be effective. Whatever the flock control strategy treatment of diseased individuals is essential for their welfare and can also protect the rest of the flock if treatment reduces the infectious period. Decisions on management of disease are based on our knowledge of the flock and its management and the evidence-base for various control strategies. There are now formal techniques for evaluating the evidence base that can assist in evaluating evidence. One area where we need to evaluate evidence is on cause. It is not possible to prove anything, but we can use the weight of evidence to evaluate likely cause. There are nine aspects of association with which we can evaluate a piece of evidence; these are: strength, consistency, specificity, temporality, dose response, plausibility, coherence, experiment and analogy.

Keywords: epidemiology, sheep, diagnosis, diagnostic tests, control of disease, causality, evidence-based medicine

1. Introduction

There are two key areas of sheep health where an understanding of epidemiological principles can assist in decision making. This first is in diagnosing disease and the second is in controlling

disease. Whether we realise it or not, we use epidemiology -the distribution, determinants and control of diseases in populations (Thrusfield, 1995)-whenever we consider the management of sheep health.

In this article, I discuss diagnosing individuals and consider case definition and the interpretation of diagnostic tests. I give some theoretical background on infectious disease processes to help explain some of the challenges that we face when we consider control of sheep diseases. Some aspects of control require us to establish cause and thus, I cover an approach that we can use to move from establishing a statistically significant link between an exposure and a disease and inferring cause.

Throughout I have given examples from my own research. This is not because these are the best examples, but because I am most familiar with them. Inevitably, this article is not exhaustive and, also inevitably, it is opinionated.

2. Case-definition

When we manage sheep diseases, we can consider two broad categories of disease, infectious and non-infectious. For both types of disease, we need case-definitions for each disease. Case-definitions need to be precise and unique; if we wish to compare across flocks, we need to ensure that the case-definition is consistent between flocks. For some diseases, case-definitions are relatively straightforward for diagnostic purposes, although not always well-recorded in sheep health management, but sometimes it is difficult to define a disease, and particularly to be consistent across a population of flocks.

3. Diagnosing disease

Imagine that we have a scenario where some sheep have aborted. There are several causes of abortion in sheep and we need to determine the cause(s) for this particular flock. We can take a history of the affected sheep: gestation stage at the time of abortion, clinical signs in ewes which aborted, macroscopic appearance of lambs and placentae, past history of abortions in the flock, introduction of new sheep into the flock (see below under introduction of pathogens). We can take the products of abortion and blood samples for further diagnostic tests. Our clinical observations and case history provide evidence to assist in making a diagnosis, but laboratory tests are needed to confirm the diagnosis.

4. How many sheep should we investigate?

We need to consider how many sheep we should investigate, which sheep and how will we be certain of our final diagnosis. Typically, we would sample six affected sheep. Six turns out to be a good number statistically (Green, 1999), in that it is the minimum number required if all six are

different from normal (Wilcoxon rank test; Petrie and Watson, 2008). This approach relies on all six sheep having the same abnormality and being certain that this is different from normal without taking samples from 'normal' sheep and of course that there are six sheep that have aborted. If this is not the case, we have less certainty (see below under sensitivity and specificity). We can improve our precision of diagnosis by taking blood samples from sheep that have not aborted and using them as controls, as well as by taking blood samples from sheep that aborted and those that did not after two weeks (having recorded their permanent identity, in order to be able to find them again!), which supports an investigation as to whether there has been a change in antibody levels to likely infectious diseases only in sheep that aborted.

5. Minimising costs

I would not consider making a diagnosis on clinical signs and history alone: although the clinical presentation of an abortion might have 'characteristic signs' or have been seen on the farm previously; there might be more than one cause of abortion and clinical signs are notoriously variable. This holds true for all diagnoses where micro-organisms are involved; e.g. a bloody milk sample in a sheep with mastitis might indicate infection by *Staphylococcus aureus*, but it may also indicate infection by *Mannheimia haemolytica* or anyone of many other pathogens.

However, there is a need to minimise the costs for the farmer. One way to do this is to take all the relevant samples that we need at each visit, but to only process them as necessary in order to reach a diagnosis. However, it is important to make a precise diagnosis, because the approach to control will vary depending on the cause of disease, not just the presenting signs. Ultimately, we might cost a farmer much more money by not honing the diagnosis; for example, if a disease is suspected and a vaccine then used without confirmation of the disease, and this were a live attenuated vaccine then the micro-organism (even be it in mutated form) is being introduced into the flock. This would be totally inappropriate if the pathogen was not already on the farm, and could lead to increased disease.

6. Test sensitivity and specificity

It is easy to act on the results of diagnostic tests (clinical signs, laboratory tests or a combination of both) without reflecting on their accuracy. A perfect test that correctly identifies all diseased sheep as diseased and all non-diseased sheep as non-diseased is the 'gold standard'. For many diseases there is no 'gold standard' (at least not in live sheep) and we use tests that do not always produce correct results.

There are several other measures that we need to be aware of, in order to assess usefulness and appropriateness of a diagnostic test. Two of these are its sensitivity and specificity. The sensitivity indicates the proportion of truly affected sheep that are detected by the test. The specificity indicates

the proportion of truly negative sheep that the test defines as negative. For most practical purposes, the sensitivity and specificity of a test are independent of prevalence of disease and consistent across populations. Manufacturers of a diagnostic test should provide its sensitivity (tested on known infected individuals) and specificity (tested on known uninfected individuals) and a reference to how these were estimated. So, if we have a (fictitious) test for toxoplasmosis with a sensitivity of 85% and a specificity of 95%, and if 100 sheep in a flock of 1000 *truly* have toxoplasmosis, then we can expect the test to identify 85 out of the 100 *truly* infected sheep and 855 out of the 900 *truly* uninfected sheep: a further 15 infected sheep would be defined as uninfected (i.e. 15/1000 false negatives) and 45 uninfected sheep would be defined as infected (i.e. 45 / 1000 will be false positives), hence our test would tell us that 130 sheep have toxoplasmosis and 870 do not.

If we forget to consider the test sensitivity and specificity, we might make an incorrect decision about the management of an individual or a flock. For example, if we suspect that there is *Toxoplasma* abortion in a flock and we test one sheep that truly has toxoplasmosis with our fictitious test above, then there is a 15% chance that the test result would be negative. By testing two sheep, this error reduces to <3% ($0.15^{\wedge 2}$); by testing six sheep, there is <0.01% ($0.15^{\wedge 6}$) risk of incorrectly defining the flock as negative. So, by testing six sheep and getting at least one positive individual, we can be fairly certain that the flock has *Toxoplasma* abortion.

For an individual ewe, by retesting the same sheep with the same test (assuming that the test error is chance- rather than a host specific-characteristic), we again increase our precision to <3% error. Suppose a ewe is *truly* negative, at the first test 5% of truly negative sheep will have a test positive result. The probability that a sheep tests negative twice, when she is positive is $0.05^{\wedge 2}$, thus we have a 2.5% error that we say a truly positive sheep is negative for *Toxoplasma* infection. What do we do when a sheep tests positive to one test and negative to another? We have to decide whether we want to raise the sensitivity (any test positive) or specificity (any test negative) to define diseased and non-diseased sheep. We can also use a different second test with a different sensitivity and specificity. For example, we might choose a sensitive test initially to ensure that all truly positive sheep are identified, accepting that some sheep that are false positives will be included, then use a more specific test to identify the truly positive sheep.

7. Test sensitivity and specificity are linked

For most tests with a cut-off value that determines a positive or negative result, as sensitivity increases specificity decreases (Fig. 1). If we know this information, then we can use it to our advantage. We can alter a diagnostic test's sensitivity and specificity by altering the cut-off value used to define a positive and negative test result. This is not to suggest anything untoward!

This might be useful if we wish to use a test for a certain procedure. For example, if we want to select only disease-free individuals, we can choose a cut-off that makes a test highly sensitive, so

that all truly affected individuals are indeed test-positive (i.e. 100% sensitivity). Inevitably, the test specificity will be low and there will be individuals that are false-positive. However, we can select our disease-negative sheep from the group that are test-negative with a high degree of confidence that they are truly negative. Conversely, there are occasions when we would want a highly specific test. If we decide to cull pedigree sheep with a disease, we might not wish to cull sheep that are true negatives for this disease, because of the financial cost with no benefit, so we might choose a specific test. This does of course raise the concern that we might fail to eliminate the disease!

8. Predictive value of a test

Repeating a test or using a second test on a subset of sheep 'works', because by taking a group of sheep already positive to a test we are increasing the proportion of the sample that are test-positive, i.e. we 'increase' the prevalence of the disease. The result of this is that we increase the positive predictive value of the test. The positive predictive value of the test is the probability that a sheep has a disease given that it has a positive test result. The positive predictive value of a diagnostic test increases as prevalence increases for a set sensitivity. The negative predictive value of a test increases as the prevalence of a disease decreases (Fig. 2a). If disease prevalence is very low, then the positive predictive value of a test is low (Fig. 2b) and vice-versa. This is intuitive, if you take a moment to think about it, because if we have a test that *can* give false positive results, we *will* have positive test results even in a population free from disease. In this circumstance, 100% of test positive results are false positives; e.g. using our test for toxoplasmosis above with a sensitivity of 85% and specificity of 95%, if the prevalence of disease is 5%, then <50% of the 90 test-positive individuals will be true positives. This has implications if our decision is to remove these individuals from the flock. We can try to reduce the proportion of false positive sheep culled unnecessarily, if we use further tests. It is also unwise to use an imprecise test in such a situation, because it is not possible to know which of the test positives are truly negative; for example, the current test for caseous lymphadenitis has relatively low sensitivity and specificity in sheep and thus, the proportion of the flock removed that are uninfected, particularly towards the end of an elimination programme is too high to make this a feasible approach (O'Reilly et al., in press).

9. Estimating absence of disease - is a disease present in a flock?

One question of interest for flock health schemes is whether a disease is present in a flock. If we wish to be confident that a disease is absent from a flock, we could test every individual in the flock. This is usually prohibitively expensive and unnecessary if we are prepared to compromise slightly. We can use a statistical formula to estimate how many sheep we need to sample to be sure that if a disease is present, it is present at below a certain prevalence with a certain confidence around

this prevalence, for example <1% of animals infected ±0.5% precision. This is more or less the calculation used by countries to estimate freedom from disease (Thrusfield, 1995).

10. Populations and individuals

Good management of sheep flocks will use information from the whole flock on health (e.g. disease status, vaccinations used, diagnoses and treatments, on-farm deaths, abnormalities observed at the abattoir (Green et al., 1994; Green et al., 1997)) and productivity (e.g. lambing percentages, lambs born alive, lambs born dead, body condition of ewes, cull rates, carcass quality (). However, flocks vary in the amount and quality of information available and its accessibility. Pedigree flocks might have more information on planned breeding and flocks in health schemes will have information on diseases that are under surveillance.

This whole flock information is of use to assess likely productivity of the flock and profitability, if it can be tied in with fixed and variable costs. It can also be used to monitor flock health and target improvements in, for example, lambing percentage or growth rate. Monitoring the flock also assists us in identifying and targeting individuals for special care, for example supplementing feed of thin ewes to prevent pregnancy toxaemia or treating individual diseased sheep. No flock can ever be free from all disease and so it is crucial that whole flock management does not become an alternative to care of individuals in the flock. For infectious diseases, management of individuals (from quarantine to rapid treatment and isolation) can also protect the flock and so can be an efficient way of controlling disease, particularly those where there is no effective vaccine. An appreciation of how infectious diseases transmit aids understanding of the role of individuals in allowing pathogens to persist in a flock. This is described in the sections below.

11. Introduction of a new pathogen

A new pathogen can be introduced into a naïve flock via infectious sheep, infectious other-host species or infectious host products, such as skin, milk or wool. It can also enter through vectors, such as insects, or via fomites, such as vehicles or boots. Infectious conspecifics (sheep in this case) are the most likely source of infection and this is why quarantine is a very useful procedure. Note that quarantine facilities therefore, need to be sufficiently far from the flock with separate care for quarantined sheep to prevent infection transmitting to the main flock. To ensure that quarantine is successful it needs to be for a sufficiently long duration to prevent introduction of the pathogen. In this time, the pathogen will either die out or the disease will manifest and the sheep can be managed accordingly (treatment, culling, delayed entry to the flock). There are some pathogens for which quarantine is unlikely to be successful (e.g. scrapie), because of a long incubation period. All of the above also holds true for *re-introduction* of an existing pathogen, although we might not notice re-

introduction if a pathogen is already present it is an important route for persistence of pathogens within a flock. In this case, pathogens are moving in a meta-population (flocks of sheep linked by some degree of contact). A topical example would be re-introduction of roundworms, particularly with the concern of anthelminthic resistance.

12. Spread of a new pathogen within a flock

Once in a flock, the pathogen spreads through the susceptible sheep by one or more routes (e.g. respiratory, oral-faecal, vector borne). We can use R_0 (the reproduction number), which is the average number of secondary cases from an infectious individual in a naïve population (Anderson and May, 1991), as a guide to the spread of the pathogen. R_0 might tell us whether on average a pathogen infects 5 or 50 sheep from one infectious host. It does not tell us the speed with which this occurs; we need the average infectious period for this. It is also worth remembering that R_0 varies in time and space (that is the value of R_0 might vary for different flocks infected with the same pathogen); for example, O'Reilly and others (2008) described four flocks infected with *Corynebacterium pseudotuberculosis*, which all had different estimates of R_0.

Hosts can be in a variety of states in relation to a pathogen (Fig. 3). Hosts can be susceptible or infectious, and depending on the nature of the pathogen and host, the host might die, become resistant, partially resistant (i.e., they can be infected again), a carrier or susceptible again (Table 1). The SIR (susceptible, infective or recovered) model is a simplification of this process (Fig. 4). These schematics can help us understand infectious processes. When we develop models from them we aim to realise what we do not understand / know (Green and Medley, 2002). They are generally specific to a particular pathogen and the underlying host structure is an important determinant in how the pathogen will transmit.

13. Persistence of a pathogen within a flock

Once a susceptible population has been exposed to a new pathogen, the proportion of the population susceptible usually declines and so disease is present at a lower prevalence. It is typically less severe than when a new pathogen enters a naïve population, this is usually thought to be an adaptation for persistence: it is in the pathogen's interest for the host to survive for sufficiently longs to increase its chances of contacting as many susceptible hosts as possible. Persistence of a pathogen arises when it remains sufficiently long in a population to encounter new susceptible hosts. Pathogens can persist in the host, for example herpes viruses or retroviruses, in another host species, for examples *Dichelobacter nodosus* persists in sheep, goats and cattle, or in the environment, for example *Salmonella*, in order to facilitate persistence (Green, 2007).

14. The spread of infectious diseases between flocks

Sheep are typically kept in fairly small populations (flocks). Generally, infectious diseases cluster within flocks, i.e. occur at a higher or lower incidence than chance when compared with the population average. The risk of introduction of a new pathogen or re-introduction of an existing pathogen into a flock is dependent on how the pathogen spreads (as described above) and on how the populations are connected. This connection of flocks is described as a meta-population structure and the contact between flocks determines the pattern of transmission of a pathogen between flocks. It is possible that some pathogens persist by moving between flocks through these contacts and are repeatedly re-introduced. We have seen this with Porcine Respiratory-Reproductive Syndrome Virus in pigs (Evans et al., 2008; 2009); in fairly isolated herds with <250 sows, the virus is likely to fade out of the herd, unless it is re-introduced via an infective pig.

15. Control of infectious diseases

Once we understand how a pathogen spreads and persists, we can consider control strategies. Infectious diseases can be controlled by preventing introduction or re-introduction or by elimination or by minimising their impact on host health. We can eliminate disease by culling the whole flock if the pathogen persists in the sheep, rather than in the environment or in other hosts and if the replacement flock can be sourced from known disease-free stock. We can also eliminate by removing infected individuals through test and cull strategies. These are most effective when the inter-test interval is shorter than the latent period and all individuals that are infected are removed before they become infectious Test and cull is less effective when the infectious period is shortened, but not prevented and on average one infectious individual must infect less than one other individual to eliminate disease. They are not successful if the inter-test interval permits normal transmission of pathogen. When successful, restocking or test and cull strategies lead to a totally susceptible population and so the flock is very vulnerable to re-introduction of disease. Elimination can also be achieved by ensuring that there are no susceptible hosts until the pathogen has died out. This is usually done by vaccination. A vaccine which prevents transmission of the pathogen removes susceptible individuals and raises herd immunity. This might be sufficient to eliminate the pathogen and ultimately lead to cessation of use of vaccine. Other vaccines control disease, but are not designed to prevent transmission of the pathogen and so elimination is not possible. This usually means that disease is minimised rather than absent. Even quite poor vaccines can be effective if used strategically. The aim is to ensure that a sufficient proportion of a flock is protected against disease at all times, in order to protect the flock to the level that provides flock immunity.

Control can also be established without vaccination for some diseases, through managing the environment to ensure hosts are healthy and well-fed and kept in good conditions (fields or buildings)

and that their exposure to the pathogen is minimised or timed to lead to good immunity without disease,. Whatever the approach to control the nature of the pathogen, host range, transmission routes, diagnostic tests, vaccines available and flock attributes need to be considered to decide the best strategy to optimise control of the disease.

16. Treatment of individuals

There is no situation where it is acceptable to neglect individual diseased sheep, because there is no known prevention or flock control measure.

17. Relevance to sheep health

If we understand the process of spread of a pathogen, the infection states of individuals and the mechanisms for persistence or fade out of pathogens, we can evaluate how best to manage a pathogen in a flock with the current available evidence. This will be both scientific and experiential and is often incomplete for diseases of sheep. We aim to optimise health and appreciate what is likely to be successful in our management of a disease. This will vary by flock and pathogen and by owner / carer. One example would be management of footrot; we (Kaler and Green, 2008) reported that farmers vary in their willingness to treat individual sheep with footrot: 20% of farmers in that study did not do so. For flocks under the care of such farmers, an alternative strategy that minimises lameness is required that needs to be based on our understanding of the behaviour of the pathogen. Another example would be control of caseous lymphadenitis. Given our current understanding of transmission, infectiousness, detection of disease and diagnostic tests, I would suggest that eradication is. unfeasible (O'Reilly et al, in press).

18. Evidence-based medicine

Evidence-based medicine is a combination of a clinician's expertise and all external relevant research (Sackett et al., 2006). It is widely used in human medicine, where its main output is review articles (http://www.cochrane.org), which are produced using a transparent, objective and repeatable method and which summarise and evaluate the current evidence for treatment of a disease using individual research papers sourced from throughout the world. Over 5000 conditions from the management of back pain to eczema to cancer have been reviewed. The aim of the reviews is to use a systematic and transparent process to evaluate the evidence and thus assist practitioners to remain informed of best current evidence. This, combined with a practitioner's skill and knowledge of an individual patient, should provide the patient with the best treatment. In veterinary medicine, we discuss the use of 'evidence-based medicine', but there are currently no formal collaborations and

standards as there are for human medicine. As the number of research publications in veterinary science increases, it becomes increasingly difficult to keep abreast of individual pieces of evidence as they are produced. Hopefully, in the future there will be a similar system for review for veterinary topics. Until then, we have to do our best to read and evaluate literature germane to our areas of interest.

19. On cause

We need to know how to assess whether an exposure is a likely cause if we are to use evidence-based medicine. That is, we make our decisions on management and treatment based on the current evidence available together with our knowledge of the flock. In veterinary medicine, there are many areas where there is little evidence, but we should use what there is! It is easy over time to believe that we are managing diseases optimally, because of our own experience and it is important to challenge what we do as new evidence arises.

In all biological studies we use the results of statistical tests to tell us whether there is an association between two factors. These associations come from a variety of types of study (Table 2), from closely controlled experimental studies through to cross sectional observational studies. Each study design has a particular set of purposes and all will provide statistical associations, however, no statistical tests for significance (in *any* discipline from immunology and molecular biology to epidemiology) provide an answer for the question of proof. We use them to estimate the likelihood that an association is chance or unlikely to be chance with varying degrees of confidence and if a measure of association (e.g. relative risk or odds ratio) is estimated we can consider its magnitude. Beyond that statistics contribute nothing to interpretation of cause - I repeat again, for *any* scientific discipline.

Bradford Hill (1965) suggested nine questions that we can ask of results that help with inferring causality, assuming that we have a 'significant' association. These are listed below. I have used the evidence that we have to date to evaluate whether routine and treatment trimming sheep feet is beneficial to prevention or recovery from footrot - a contentious issue, at least a few years ago (Abbott and Lewis, 2005).

19.1. Strength

We measure strength of associations with relative risks or odds ratios. It is important to appreciate how these are calculated (especially odds ratios, which can be misleadingly large), but generally, the larger these values (further from the baseline positively or negatively) the more strongly associated an exposure is with a disease. For example, in our research on routine foot trimming, for every one sheep affected, farmers who routinely trimmed the feet of their sheep twice or more than

371 twice per year had 1.65 and 2.11 sheep affected respectively (Wassink et al., 2003): this is a moderate
372 association compared with e.g. the 20-fold risk reported between smoking and lung cancer (Bradford
373 Hill, 1965).
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375 *19.2. Consistency*
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377 'Has it been repeatedly observed by different persons, in different places, circumstances and
378 times?' We have repeatedly seen a link between routine foot trimming and increased prevalence of
379 lameness, footrot and interdigital dermatitis (Wassink et al., 2003, 2004; Green et al., 2007; Kaler and
380 Green, 2009). There is evidence that trimming the feet of sheep lame with footrot, there was a delay in
381 healing of lesions in the UK and Australia (Kaler et al, 2009; Jordan et al., 1996). Routine trimming of
382 cattle feet has also been reported as a risk factor by Barker and others (2007) and Espejo and Andres
383 (2007) in observational studies, but as protective factor in a controlled trial by Manske and others
384 (2002).
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386 *19.3. Specificity*
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388 Is the exposure specific to one disease? To my knowledge, there is no association between
389 foot trimming and other diseases than footrot - but this is hardly surprising, maybe once CODD has
390 been more widely studied we might see a link between these diseases.
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392 *19.4. Temporality*
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394 Does the association occur before the disease? This is where study design becomes important
395 and cross sectional studies (Table 3) are less useful, unless the exposure is not time dependent. For
396 example, if a certain breed or sex is more likely to get a disease, then time is less important. For
397 footrot, the studies of those by Jordan and others (1996) and Green and others (2007) are temporally
398 robust.
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400 *19.5. Biological gradient*
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402 That is, is there a dose-response, i.e. more exposure gives a stronger measure of association.
403 For the foot trimming and footrot studies, this association is present in observational studies, where
404 the more frequently a flock was trimmed, the higher the peak prevalence of footrot (Wassink et al.,
405 2003), but has not been done in clinical trials.
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407

19.6. Plausibility

Is the causation biologically plausible? This is interesting, but I think a challenging question, because it is possible to make most things 'plausible' or 'implausible'! So, we can hypothesise that trimming feet either makes the sheep trimmed more susceptible to invasion with *D. nodosus* (the micro-organism causing footrot) or more infectious to other sheep in the group or that trimming is not causal, but is a correlate for not treating footrot in individuals (for which there is strong evidence for efficacy of antibacterial treatment (Jordan et al., 1996; Grogono Thomas et al., 2003; Kaler and Green, 2008; Kaler et al., 2009)).

19.7. Coherence

Cause-and-effect should not seriously conflict with the 'generally known facts of the natural history and biology of the disease'. The tradition for foot trimming sheep feet probably comes from the pre-antibiotic era, when exposing *D. nodosus* to air killed this facultative anaerobe (Mohler and Washburn, 1904). Its logic, now that parenteral administration of antibacterial agents is available, is less robust. Indeed, anecdotally expert practitioners are now promoting foot trimming to maintain foot shape (Winter, 2008) rather than the traditional recommendation that it controls footrot (Morgan, 1987; Winter, 2003;).

19.8. Experiment

A well designed experiment that demonstrates statistical association gives a strong inference for causality. If it is of sufficient power, well designed and well run (Thrusfield, 1995), then a comparison between treatment and control is most useful. This has been done by Jordan and others (1996).

19.9. Analogy

We can sometimes use judgement by analogy. That is, if we have seen an association in one situation that was causal, then we can accept slighter but similar evidence in another. I cannot think of an example for footrot, but if, for example, the evidence continues to grow and we do move towards accepting that foot trimming feet is detrimental to cure and control of footrot in sheep, we might be ready to accept evidence that it is also detrimental to treatment and control of contagious ovine digital

dermatitis, another infectious disease of the hoof in sheep, if some preliminary evidence became available.

It is remarkable that there are so few sheep diseases where causes can be assessed on all of the above. This does mean that we need an open mind when we think about disease and maybe a good starting point is that the point of science is to disprove rather than prove. If we are prepared for our current assumptions to be disproved, our minds can be opened up to a wide range of possibilities. One example from my career that uses some of the considerations on causality occurred during my PhD. I studied lambs reared in straw-bedded barns from birth to slaughter. These lambs never went out to pasture. At 3 to 4 weeks of age, many lambs had a non-regenerative anaemia typical of iron deficiency, when compared with outdoor reared lambs of the same age (Green et al., 1994). Iron deficiency seemed likely, because we know that piglets and calves reared without contaminant iron from soil develop iron deficiency anaemia, because the demands for iron are high with the physiological change from foetal to adult haemoglobin (Coherence, Plausibility, Analogy). The lambs haematological values were within the normal range quoted in the reference manual (Schalm, 1981), but in the original article used for these values lambs were housed in straw-bedded barns and some were removed from the study because they were anaemic (!) (Consistency). A within farm clinical trial run in 1994, where 50% of lambs were given with iron dextran soon after birth, prevented this anaemia and lambs grew faster to weaning (Green et al., 1997b) (Experiment, Temporality, Specificity). The paper by Green and others (1997b) was rejected initially, because the reviewers rejected the recommendation that lambs born and housed indoors (even for a few weeks after birth when foetal haemoglobin changes to adult haemoglobin) should receive external iron. This paper was finally published when a smaller study that reported similar results was published (Bassett et al., 1995) and the editor revised his opinion. The reviewers that rejected the paper by Green and others (1997b) initially did so from their opinion on the management of lambs and not from the scientific evidence or iron deficiency. This takes us nicely back to evidence-based medicine, where there are two aspects to consider, one is the evidence base and one is a clinician's knowledge of a flock and its carers. I strongly believe that new scientific evidence should be published and I think that there is strong evidence that lambs reared in the absence of soil for their first week of life can become deficient in iron. How one manages this in a flock, whether by supplementation or altering exposure to soil, is a decision for the clinician and carers.

20. Conclusions

We use epidemiology in many ways, as we manage sheep diseases from diagnosing disease and treating individuals to managing flocks and controlling disease. Understanding disease processes, pathogen behaviour in populations and knowledge to evaluate evidence and test results together with a

good knowledge of our patients can all contribute to good evidence-based management of sheep health.

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Legends of figures

Fig. 1. Relationship between true disease and apparent disease from diagnostic test.

Fig. 2a. Predictive value of a test.

Fig. 2b. Impact of prevalence on PVP and PVN, sensitivity and specificity 99%.

Fig. 3. Impact of infectious disease on an individual.

Fig. 4. The link between individuals and the impact of the pathogen (epidemiological parameters).

Table 1

Possible states of a host as a pathogen cycles through a population

Possible patterns of host state dependent on the infecting pathogen					Likely example pathogens
Susceptible	Infected	Infectious		Dead	Scrapie agent, *Mycoplasma bovis*
Susceptible	Infected			Dead	Scrapie agent
Susceptible	Infected	Infective	Recovered	Immune	*Rinderpest Virus*
Susceptible	Infected	Infective	Recovered	Carrier	*Corynebacterium pseudotuberculosis*
Susceptible	Infected	Infective	Recovered	Susceptible	*Dichelobacter nodosus*
Susceptible	Infected	Infective		Susceptible	Pathogens causing mastitis (e.g., *Staphylococcus aureus*)
Susceptible	Infected	Infective	Susceptible	Partially immune	Nematode helminth infections

Table 2. Epidemiological definitions used in sheep health management

Epidemiology	The occurrence, distribution and determinants of disease in a population
Host	The animal infected with a pathogen
Case definition	A unique measurable set of criteria for an aspect of production and disease that enables us to monitor flock health with precision
Gold Standard	The perfect test to define a disease
Sensitivity	The proportion of individuals that are truly diseased that are positive by the test
Specificity	The proportion of individuals that are truly negative to the disease that are negative by the test
Prevalence	The amount of disease at one point in time or over a time period
Incidence	The new case rate in a given time
Predictive value of a positive test	The proportion of test positive individuals that are truly positive
Predictive value of a negative test	The proportion of test negative individuals that are truly negative
Measure of effect	The magnitude of association between an exposure and a disease
Exposure	Factor possibly associated with a disease
Eliminate	Remove a disease from a selected population (flock, region, country)
Eradicate	Remove a disease from the world

Table 3. Types of study design used in epidemiology

Study type	Observational or experimental	Association with time	Main uses	Useful for elucidating cause
Case study	Observational	None	Describes a novel presentation of disease in an individual or population	Useful for defining case definition for a novel disease
Cross sectional	Observational	One point in time	Estimate prevalence, generate hypotheses	Only for non-time varying exposures
Case control	Observational	Retrospective	Identify risks for rare diseases	Reasonable, but risk of recall bias
Cohort	Observational	Prospective or occasionally retrospective	Estimate incidence, identify risks for more common diseases	Good, because subject disease and exposure status monitored in real time
Intervention study	Experimental, unit of study might be a group	Prospective	Investigate impact of putative control measure	Very good, because comparing a controlled situation
Clinical trial	Experimental, unit more often an individual		Investigate impact of putative control measure	Very good, because comparing a controlled situation

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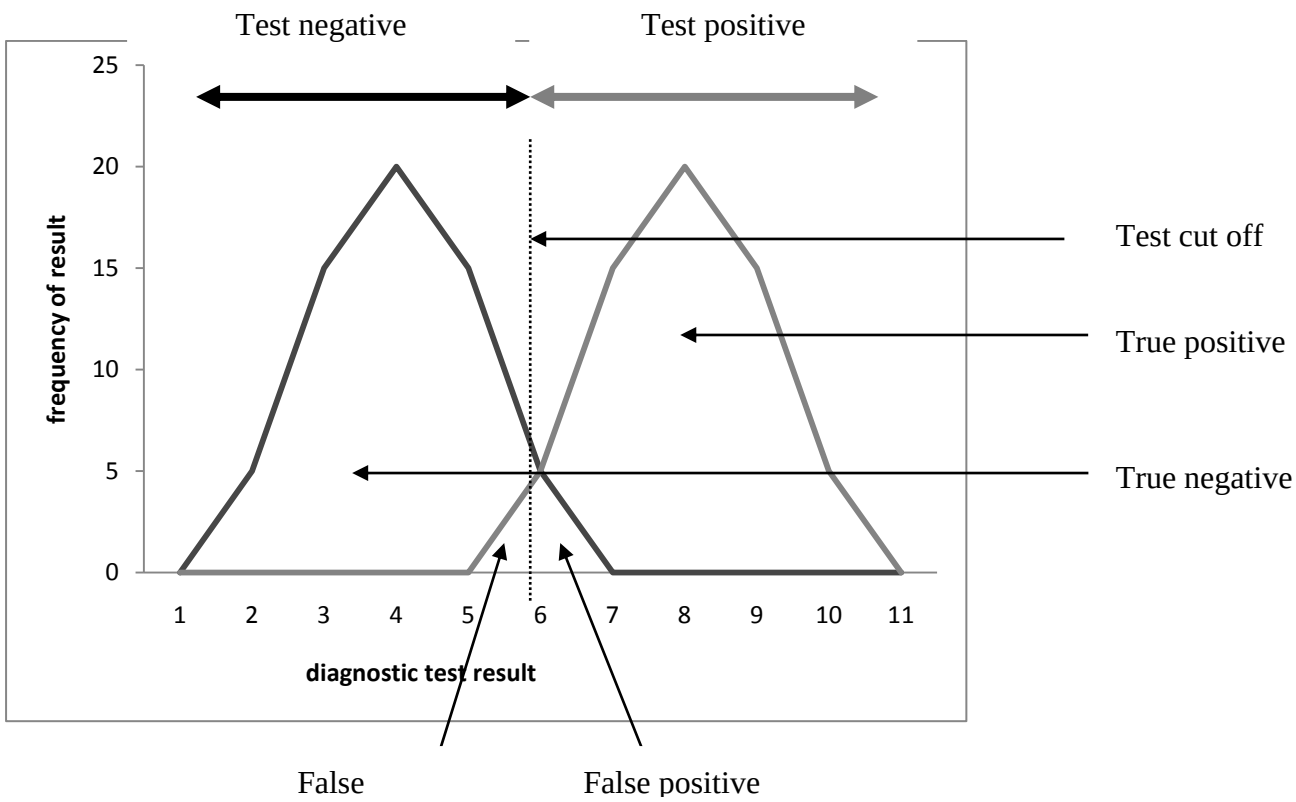
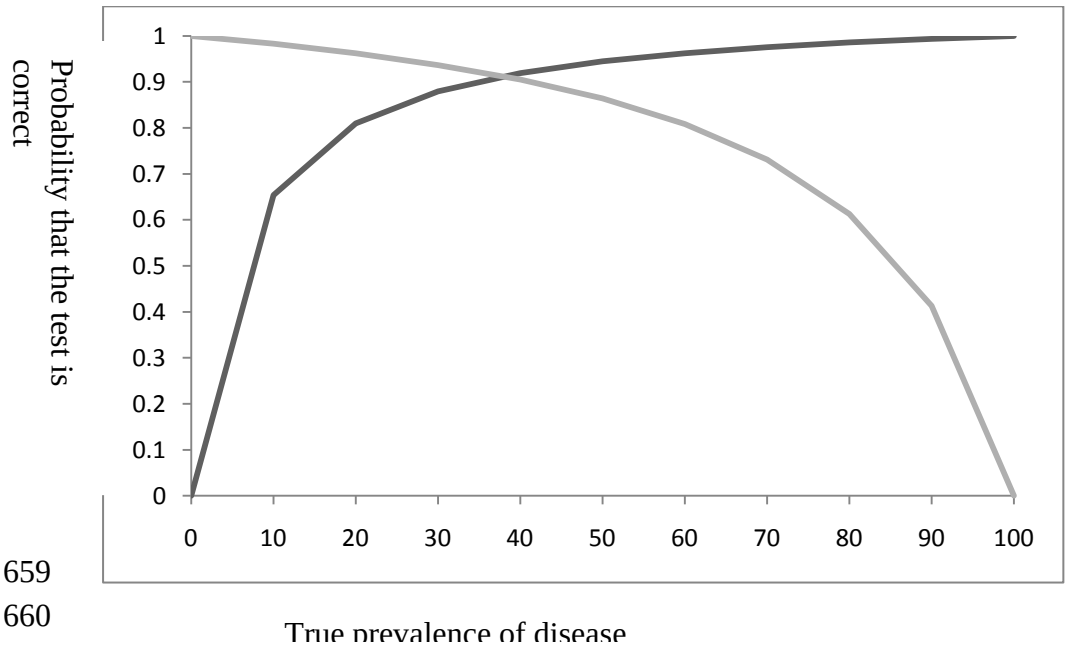
Figure 1. Relationship between true disease and apparent disease from diagnostic test.



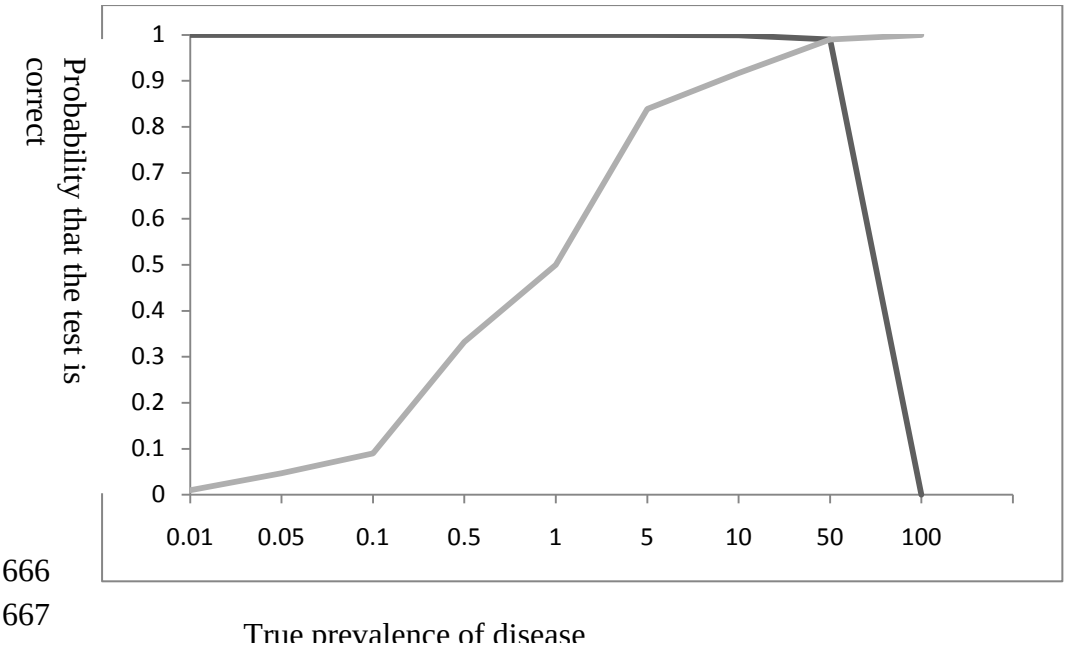
Black curve = distribution of truly disease free individuals, grey curve = distribution of truly diseased individuals. Whilst the mean value for the diagnostic test results is different between diseased and non-diseased, there is an overlap in test results, some individuals with test values 5 – 7 are truly positive (area under the grey curve), others are truly negative (area under the black curve). If we set the cut off at 6 we have both false positive and false negative individuals. If we set the cut off at 7 (increasing the test specificity) we have no false positive individuals but many false negatives. If we set the cut off at 5 (increasing the test sensitivity) we have no false negative individuals but many false positives.

Figure 2. Predictive value of a test



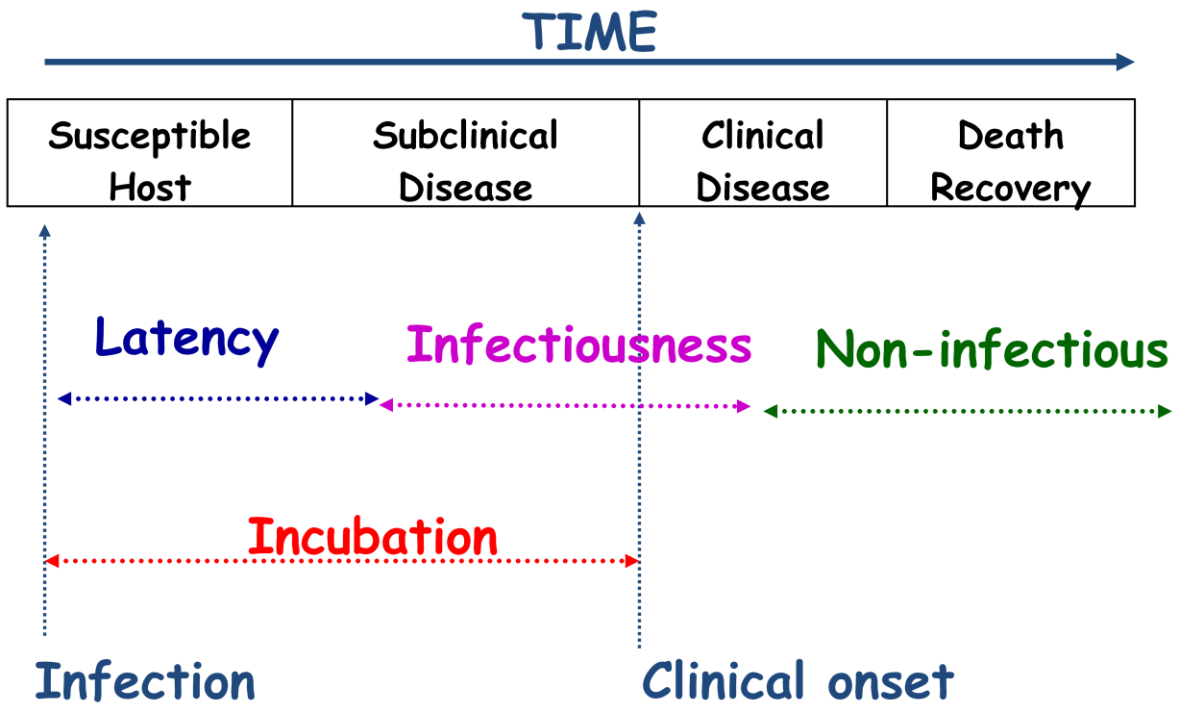
black = predictive value of a positive test, grey = predictive value of a negative test.

Figure 2b. Impact of prevalence on PVP and PVN, sensitivity and specificity 99%



black = predictive value of a positive test, grey = predictive value of a negative test.

Figure 3. Impact of infectious disease on an individual



677 Figure 4. The link between individuals and the impact of the pathogen (epidemiological parameters)
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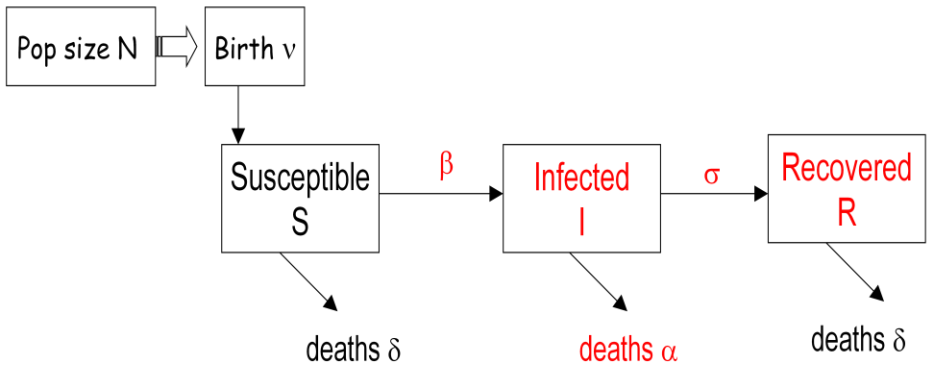

Hosts
N = population size
S = number susceptible
I = number infected
R = number recovered
ν = birth rate
δ = death rate from other causes

Pathogen impact on hosts
β = successful contact rate between infectious and susceptible hosts
α = additional death due to the disease
σ = rate of recovery (=1/infectious period)

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