1

INTRODUCTION AND CAUSAL CONCEPTS

OBJECTIVES

After reading this chapter, you should be able to:

1. Explain the history of causal thinking about disease and scientific inference from an epidemiologic perspective.

2. Explain the basis of component-cause models and how this concept helps to explain measures of disease association and the proportion of disease explained by a causal factor.

3. Explain the basis of causal-web models.

4. Describe the counterfactual concept and its utility in understanding disease causation and the estimation of causal effects.

5. Explain how observational studies and field experiments seek to estimate causal effects and how these relate to counterfactual and component-cause models.

6. Construct a logical causal diagram based on your area of research interest as a guide for your study design and analyses.

7. Apply a set of causal criteria to your own research and as an aid to interpreting published literature and planning future research.

1.1 INTRODUCTION

Epidemiology is largely concerned with disease prevention and therefore, with the "succession of events which result in the exposure of specific types of individual to specific types of environment" (*ie* exposures) (MacMahon & Pugh, 1970). Thus, epidemiologists strive to identify these exposures and evaluate their associations with various outcomes of interest (*eg* health, welfare, productivity) so as to improve the lives of animals and their keepers. Hence, this book is about associations: associations which are likely to be causal in nature and which, once identified, we can take advantage of to improve the health, welfare and productivity of animals and the quality and safety of foods derived from them. Associations between exposures and outcomes exist as part of a complex web of relationships involving animals and all aspects of their environment. Thus, in striving to meet our objectives, we (epidemiologists) are constantly struggling to improve our study designs and data analyses so that they best describe this complex web. It is only by studying these associations under field conditions (*ie* in the 'real world') that we can begin to understand this web of relationships.

As a starting place, we believe it is useful to review the history of the concept(s) of multiple interrelated causes (exposures) (see also Rothman *et al*, 2008). This will provide a sense of how we have arrived at our current concepts of disease causation and where we might need to go in the future. Because we want to identify associations which are likely to be causal (or at the very least useful for disease control (Olsen, 2003), it is appropriate to review the relevant areas of the philosophy of science that relate to causal inference. Following this brief review, we will proceed with overviews of the key components of veterinary epidemiologic studies and discuss some current concepts of disease causation. Our objective is to provide a foundation on which a deeper understanding of epidemiologic principles and methods can be built.

1.2 A BRIEF HISTORY OF MULTIPLE CAUSATION CONCEPTS

As noted, epidemiology is based on the idea that 'causes' (exposures) and 'outcomes' (health events) are part of a complex web of relationships. Consequently, epidemiologists base their research on the idea that there are multiple causes for almost every outcome and that a single cause can have multiple effects. This perspective is not universally shared by all animal-health researchers. In this current era, when great advances are being made in understanding the genetic components of some illnesses, a significant proportion of medical and veterinary research is focused on the characteristics of only direct causal agents and how they interact with the genetic makeup of the host of interest. As Diez-Roux (1998b) points out, while it is true that genetic abnormalities are important precursors of many diseases, in terms of maintaining health, the real questions relate to the extent that our current environmental exposures and lifestyles (animal management) lead to genetic defects as well as the extent to which these exposures and lifestyles allow specific genetic patterns to complete a sufficient cause of disease. (The concept of 'components of sufficient cause' is discussed in Section 1.6.1.)

From a historical perspective, it is evident that the acceptance of the concept(s) of multiple interacting causes has ebbed and flowed, depending on the dominant causal paradigm of the era. However, the roots of this concept can be traced back to at least 400 BC when the Greek physician, Hippocrates, wrote *Air, Water and Places*. He stated the environmental features that should be noted in order to understand the health of populations. Based on this aspect of his writing, it is clear that Hippocrates had a strong multicausal concept about exposure factors in

the environment being important 'causes' of disease occurrence. He carried on to discuss the importance of the inhabitant's lifestyle as a key determinant of health status, further expanding the 'web of causation.' Nonetheless, his concepts linking the state of the environment and lifestyle to the occurrence of disease seem to have been short-lived as, between 5 and 1750 AD, humoral imbalances (events within the individual) became the major paradigm of disease causation (Schwabe, 1982).

Between 1750 and 1885, the multifactorial nature of disease causation returned when man-created environmental filth became accepted as a central cause of disease, and the prevalent causal paradigm was that disease was due to the effects of miasmas (*ie* bad air). It was during the mid 1800s that John Snow conducted his studies on contaminated water as the cause of cholera (Frerichs, 2001). Using a combination of astute observations about the lack of spread of the disease among health workers, the geographical distribution of cholera, his findings in a series of observational studies, and his use of natural as well as contrived (removal of the Broad Street pump handle) experiments, Snow reached the correct conclusion about the transmission of cholera; namely, that it was spread by water contaminated by sewage effluent. It is noteworthy that he arrived at this conclusion almost 30 years before the organism (*Vibrio cholera*) was discovered, thus demonstrating an important principle: disease can be prevented without knowing the proximal causal agent.

A few years later (*ie* in the 1880s–1890s), Daniel Salmon and Frederick Kilborne determined that a tick (*Boophilus annulatus*) was associated with a cattle disease called 'Texas Fever' even though the direct causal agent of the disease (a parasite: *Babesia bigemina*) was not discovered until many years later (Schwabe, 1984). Their initial associations were based on the similar geographical distributions between the disease and the extent of the tick's natural range; theirs was the first demonstration of a parasite requiring development within a vector before transmission. Their work also provided the basis for disease control before knowing the actual agent of the disease. Thus, in this period (mid-to-late 1800s), the study of the causes of specific disease problems focused on multiple factors in the environment, albeit somewhat more specifically than Hippocrates had discussed earlier.

The multifactorial causal concept became submerged during the late 1800s to the mid 1900s, when the search for specific etiological agents (usually microbiological) dominated medical research. This 'golden era' of microbiology lead to a number of successes including mass-testing, immunisation, specific treatment, as well as vector control (*eg* the mosquito vector of malaria was now known) as methods of disease control. Indeed, control of many specific infectious diseases meant that by the mid 1900s, chronic, non-infectious diseases were becoming relatively more important as causes of morbidity and mortality in humans in developed countries. It was recognised early on that single agents were not likely responsible for these chronic diseases and large-scale, population-based studies examining the potential multiple causes of these diseases were initiated. For example, the Framingham Heart Study pioneered long-term surveillance and study of causes of human health beginning in 1949. Shortly after this time the observational studies on smoking and lung cancer began to appear and this spurred much discussion about causal inference (Berlivet, 2005). Large-scale, population-based studies of animal health were also undertaken. In 1957, the British initiated a national survey of disease and wastage in the dairy industry—the survey methods were later critiqued by their author (Leech, 1971). Thus, by the early 1960s, in human and animal-health research, there was once again a growing awareness of the complex web of causation.

By the 1970s, multiple interacting causes of diseases returned as a major paradigm of disease

causation. Building on the knowledge from the microbiological revolution, the concept of the agent-host-environment causal triad appeared in an early epidemiology text (MacMahon & Pugh, 1970). In this conceptual model, a number of component causes were required to come together (either sequentially or simultaneously) in order to produce disease; later, the complex of factors that would produce disease was known as a sufficient cause and it was assumed that most diseases had a number of sufficient causes. In addition to multiple causes, the component cause model was not constrained to have all causal factors at the same level of organisation. A traditional veterinary example used to portray some of these concepts is yellow shanks in poultry (Martin *et al*, 1987). When poultry with the specific genetic defect (an individual-level factor) are fed corn (ration is usually a herd/flock level factor) they develop a discolouration of the skin and legs. If all poultry are fed corn, then the cause of the disease would be a genetic defect; however, if all birds had the genetic defect, then the cause of the disease would be deemed to be the feed. In reality, both factors are required and the disease can be prevented by removing either the genetic defect, or changing the feed, or both, depending on the specific context.

The 1970s appeared to be a period of peak interest in causation (Kaufman & Poole, 2000). Susser's text on causal thinking appeared in 1973 (unfortunately, it has never been reprinted) and, 3 years later, the concepts of necessary and sufficient causes were published by Rothman (1976), followed by a set of criteria to help assess causation by Susser (1977). Large-scale monitoring of animal diseases also began in this period (Ingram *et al*, 1975). As an example, linking databases of veterinary schools across North America in the Veterinary Medical Data Program was initiated based on the concept of using animals as sentinels for the environment. Indeed, large-scale active surveillance was to become the cornerstone of efforts to prevent and control disease (Schwabe, 1993).

The 1980s seemed to be a quiet time as no major new causal concepts were brought forward. Hence (perhaps by omission), the aforementioned web of causation might have become restricted to studying individual-level, directly causal factors focusing on biological malfunctioning (Krieger, 1994). In 1990, epigenesis was proposed as a formal model of multivariable causation that attempted to link, explicitly, causal structures to observed risks of disease (Koopman & Weed, 1990). While this proved to be an interesting and exciting proposal, the limitations of this approach were later realised (Thompson, 1991) and the approach remained only a concept.

Since the mid nineties, there has been a lot of introspective writing by epidemiologists working on human diseases with much concern over an excess focus on individuals as the units of study and analysis. We shall not review these debates in detail because excellent discussions on these topics are available elsewhere (Diez-Roux, 1998a; Diez-Roux, 1998b; McMichael, 1999). What is apparent is that, whenever possible, elements of the social, physical and biological features of the defined ecosystem should be included in each study. The unit of concern can range from the individual, to groups (litters, pens, barns), farms/families, villages or communities, watersheds or larger ecosystems. Thus, epidemiologic research remains deeply rooted in the concept of multiple interrelated causal factors for disease occurrence and hence, for disease prevention. This conceptual basis has been supported by substantial progress in the development of epidemiologic research methodologies and these are the subject of this book.

In the first decade of the 21st century, perhaps the most visible shift in the focus of veterinary medicine and epidemiology has been to reassert the 'One Medicine' approach to world health. The earlier history of veterinary public health was reviewed by Schwabe, 1991. Historically, a

number of people, for example Dr William Osler, a Canadian physician, and the German pathologist Rudolf Virchow had stressed and contributed to the One Medicine approach. More recently the list of major contributors would also include Dr Jim Steele (Steele, 2008). However, in our opinion, Dr Calvin Schwabe was the most forceful veterinary leader in this regard and his classic text *Veterinary Medicine and Human Health* (Schwabe, 1984) is a unique and valuable resource in this regard. Since then, the movement has continued to expand (Cardiff *et al*, 2008; Franco *et al*, 2004; King *et al*, 2008; Pappaioanou, 2004; van Knapen, 2000). The One Medicine movement appeared to gain momentum following the occurrence of a number of serious disease outbreaks around the world including the bovine spongiform encephalopathy (BSE) epidemic, severe acute respiratory syndrome (SARS), and H5N1 avian influenza. In November, 2005, *The Veterinary Record* and the *British Medical Journal* published simultaneous issues exploring how the veterinary and medical professions could collaborate for mutual benefit. In 2006, The American Medical Association and the American Veterinary Medical Association approved resolutions supporting One Medicine or 'One Health' approaches that bridge the 2 professions. The importance of epidemiology in supporting this movement seems obvious. As of the date of writing this text (2009), the importance of sound epidemiological research to help us understand zoonotic diseases such as influenza has been reiterated.

1.3 A BRIEF HISTORY OF SCIENTIFIC INFERENCE

Epidemiology relies primarily on observational studies to identify associations between exposures and outcomes. The reasons are entirely pragmatic. First, many health-related problems cannot be studied under controlled laboratory conditions. This could be due to limitations in our ability to create 'disease' problems in experimental animals, ethical concerns about causing disease and suffering in experimental animals and the cost of studying diseases in their natural hosts under laboratory conditions. Most importantly though, if we want to understand the complex web of relationships that affects animals in their natural state, then we must study them in that state. This requires the use of observational studies, and inferences from these studies are based primarily on inductive reasoning.

Philosophical discussion of causal inferences appears to be limited mainly to fields where observation (in which we attempt to discern the cause) rather than experimentation (in which we try to discern or demonstrate the effect) is the chief approach to research. While the latter approach is very powerful, one cannot assume that the results of even the best-designed experiments are infallible. Recent discussions have however, included approaches to identifying and understanding causal factors in complex systems (De Vreese, 2009; Rickles, 2009; Ward, 2009). Nonetheless, because epidemiologists rely heavily on observational studies and field experiments for the majority of our research investigations, a brief review of the basis for scientific inference is in order. We pursue this review in the context that epidemiology is a pragmatic discipline, that our activities are tied to health promotion and disease prevention and, that as Schwabe, 2004, indicated, the key for disease prevention is to identify causal factors that we can manipulate, regardless of the level of organisation at which they act. We will briefly present the concepts of inductive and deductive reasoning. More complete reviews on the philosophy of causal inference are available elsewhere (Aiello & Larson, 2002; Weed, 2002; White, 2001). Based on our readings we present the following brief history:

Inductive reasoning is the process of making generalised inferences about (in our context) 'causation' based on repeated observations. Simply put, it is the process of drawing conclusions

about the state of nature from carefully recorded and analysed observations. Francis Bacon (1620), first presented inductive reasoning as a method of making generalisations from observations to general laws of nature. As 2 examples, John Snow's observations during the cholera outbreaks of the mid 1800s led to a correct inference about the mechanism of the spread of the disease, while Edward Jenner's observations that milkmaids who developed cowpox didn't get smallpox, led to his conclusion that cowpox might prevent smallpox. This, in turn, led to the development of a crude vaccine which was found to be effective when tested in humans in 1796. These were both dramatic examples of the application of inductive reasoning to important health problems. In 1843, John Stuart Mill proposed a set of canons (rules) for inductive inference. Indeed, Mill's canons might have been the origin of our concepts about the set of component causes that are necessary or sufficient to cause disease (White, 2000).

While it is easy to identify important advances in human and animal health that have been based on inductive reasoning, proponents of deductive reasoning have been critical of the philosophical basis (or lack thereof) of inductive logic. David Hume (1740) stated that "there is no logical force to inductive reasoning". He stated further that "we cannot perceive a causal connection, only a series of events". The fact that the sun comes up every day after the rooster crows, should not result in a conclusion that the rooster crowing causes the sun to rise. He noted further that many repetitions of the 2 events might be consistent with a hypothesis about causation but do not prove it true. Bertrand Russell (1872-1970) continued the discussion of the limitations of inductive reasoning and referred to it as "the fallacy of affirming the consequent." (In this process, we might imply that if A is present, then B occurs; so if B occurs, A must have been present.)

Deductive reasoning is the process of inferring that a general 'law of nature' exists and has application in a specific, or local, instance. The process starts with a hypothesis about a 'law of nature' and observations are then made in an attempt to either prove or refute that assumption. The greatest change in our thinking about causal inferences in the past century has been attributed to Karl Popper who stated that scientific hypotheses can never be proven or evaluated as true, but evidence might suggest they are false. This philosophy is referred to as refutationism. Based on Popper's philosophy, a scientist should not collect data to try and prove a hypothesis (which Popper states is impossible, anyway), but that scientists should try to disprove their theory; this can be accomplished with only one observation. Once a hypothesis has been disproven, the information gained can be used to develop a revised hypothesis, which should once again be subjected to rigorous attempts to disprove it. Popper argues that, only by disproving hypotheses do we make any scientific progress. It is partially for this reason that, when conducting statistical analyses, we usually form our hypothesis in the null (*ie* that a factor is not associated with an outcome) and, if our data are inconsistent with that hypothesis, we can accept the alternative hypothesis, that the factor is associated with the outcome. Thus, the current paradigm in deductive reasoning is to conjecture and then attempt to refute that conjecture. A major benefit of using Popper's approach is that it helps narrow the scope of epidemiologic studies instead of using a data-mining 'risk-factor' identification approach. It suggests that we carefully review what is already known and then formulate a very specific hypothesis that is testable with a reasonable amount of data. In the former approach, we often generate long, multipage questionnaires, whereas, in the latter, the required information is much more constrained and highly focused on refuting the hypothesis. Epidemiologic investigations which start with a clear hypothesis are inevitably more focused and more likely to result in valid conclusions than those based on unfocused recording and analysis of observations.

Two other important concepts that relate to scientific inference are worth noting. Thomas

Bayes, a Presbyterian minister and mathematician, stated that "all forms of inference are based on the validity of their premises" and that "no inference can be known with certainty" (1764). He noted that scientific observations do not exist in a vacuum, and that the information we have prior to making a series of observations will influence our interpretation of those observations. For example, numerous studies have shown that routine teat-end disinfection (after milking) can reduce the incidence of new intra-mammary infections in dairy cows. However, if a new study was conducted in which a higher rate of infections was found in cows that received teat-end disinfection, we would not automatically abandon our previous ideas about teat-end disinfection. His work has given rise to a branch of statistics known as **Bayesian analysis**, some of which will appear later in this book (Chapter 24).

More recently, Thomas Kuhn (cited in Rothman *et al* (2008)) reminds us that, although one observation can disprove a hypothesis, the particular observation might have been anomalous and that the hypothesis could remain true in many situations. Thus, often the scientific community will come to a decision about the usefulness, if not the truth, of a particular theory. This is the role of **consensus** in scientific thinking. While hard to justify on a philosophical basis, it plays a large role in shaping our current thinking about causes of disease.

Although philosophical debates on causal inference will undoubtedly continue (Robins, 2001; White, 2001), as a summary of this section we note that "... all of the fruits of scientific work, in epidemiology or other disciplines, are at best only tentative formulations of a description of nature ... the tentativeness of our knowledge does not prevent practical applications, but it should keep us sceptical and critical" (Rothman & Greenland, 2005). While keeping these historical and philosophical bases in mind, we will now proceed to an outline of the key

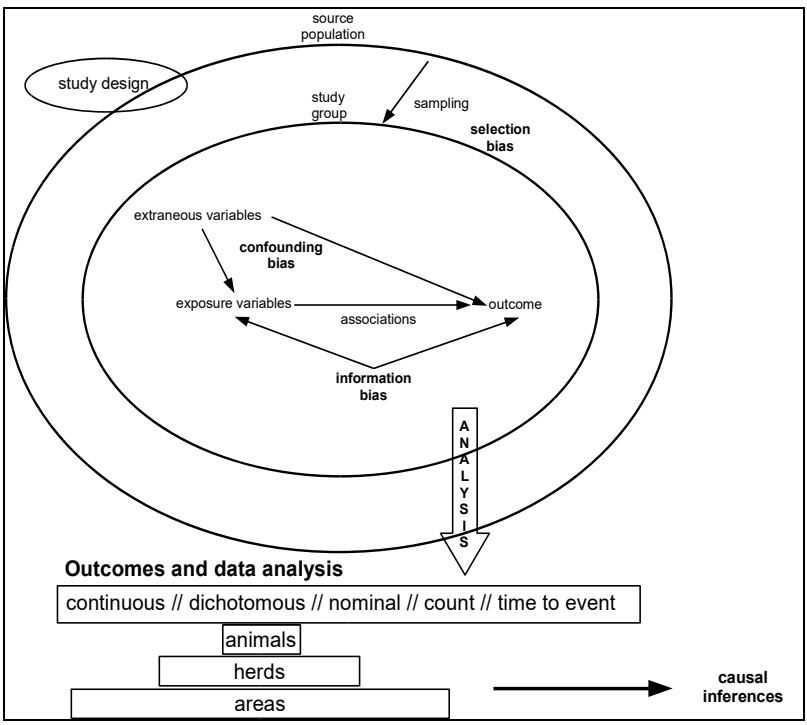


Fig. 1.1 Key components of epidemiologic research

components of epidemiologic research.

1.4 KEY COMPONENTS OF EPIDEMIOLOGIC RESEARCH

Fig. 1.1 (previous page) summarises key components of epidemiologic research. It is somewhat risky to attempt to simplify such a complex discipline and present it in a single diagram, but we believe it is beneficial for the reader to have an overview of the process of evaluating associations between exposure and outcome as a guide to the rest of the book.

Our rationale for doing research is to identify potential causal associations between exposures and outcomes (the centre of the diagram). In many cases, the exposures are risk factors and the outcome is a disease of interest. However, this is not the only scenario; for example, our outcome of interest might be a measure of productivity or food safety and the exposures might include certain diseases. Ultimately, we aim to make **causal inferences** (bottom right of diagram) about relationships between exposure and disease in the source population as a preliminary step toward developing policy and programs to maintain health and prevent disease.

An overview of the contents of this text is shown below:

- Chapter 1 gives a brief history of epidemiology and the scientific process and discusses some important **concepts of causation** as they relate to epidemiologic research.
- Field research starts with an overall **study design** and the main observational study types are discussed in Chapters 7-10, with **controlled trial** designs being presented in Chapter 11. In all studies, it is important to identify the **target population** and obtain our **study group** from the **source population** in a manner that does not lead to **selection bias**. **Sampling** is discussed in Chapter 2 and selection bias in Chapter 12.
- Once we have identified our study subjects, it is necessary to obtain data on exposure variables, extraneous variables and the outcome in a manner that does not lead to **information bias** (Chapter 12). Two important tools that are used in that process are **questionnaires** (Chapter 3) and **diagnostic and screening tests** (Chapter 5).
- In order to start the process of establishing an association between exposure and outcome, we need to settle on a **measure of disease frequency** (Chapter 4) and select a **measure of association** (Chapter 6) that fits the context. In many cases, the study design will determine the measures that are appropriate.
- **Confounding bias** is a major concern in observational studies, and the identification of factors that should be controlled as confounders is featured in Chapter 13, along with a variety of techniques to prevent this bias.
- With our data in hand, we are now able to begin to model relationships with the intent of estimating causal effects of exposure (Chapter 13). Individual chapters are dedicated to the analyses appropriate for outcomes that are **continuous** (Chapter 14), **dichotomous** (Chapter 16), **nominal/ordinal** (Chapter 17), **count** (Chapter 18) and **time-to-event data** (Chapter 19). Chapter 15 presents some general guidelines on model-building techniques that are applicable to all types of model.
- In veterinary epidemiologic research, we often encounter **clustered** or **correlated data** and these present major challenges in their analyses. Chapter 20 introduces these while Chapters 21 and 22 focus on mixed (random effects) models for continuous and discrete outcomes. Chapter 23 focuses on the specific issue of analysing repeated measures data.
- In Chapter 24 we introduce **Bayesian analysis.** The Bayesian approach formally

incorporates the degree of certainty we hold about a hypothesis before we see additional data (prior probability) and modifies this based on the information gained from new data to update the prior and obtain new (posterior) estimates about the certainty of that hypothesis.

- Chapters 25 and 26 present the basics of **geographical information systems** and **spatial statistics** that we use in epidemiology. These fields have developed a number of unique approaches that are useful in the study of diseases in populations. Recall the pioneering work using these methods by Salmon and Kilborne mentioned earlier.
- Chapter 27 describes **infectious disease epidemiology.** The ability of the living agent(s) to spread from subject to subject creates 'dependencies' (correlations) and other phenomenon such as herd immunity that must be accounted for in our research efforts.
- **Systematic reviews** and assessments of the literature in the form of **meta-analyses** are becoming increasingly important and are introduced in Chapter 28.
- Not all studies allow us to collect data on exposures and outcomes at the individual level and yet there is much that we can learn by studying disease in groups (eg herds). Thus, **ecologic studies** are introduced in Chapter 29.
- Finally, we complete the text with Chapter 30 which provides a 'road map' for investigators starting into the analysis of a complex epidemiologic dataset.

With this background, it is time to delve deeper into this discipline called epidemiology. And, at the outset it is important to stress that epidemiology is first and foremost a biological discipline, but one which relies heavily on quantitative (statistical) methods. It is the integration of these 2 facets, with a clear understanding of epidemiologic principles which makes for successful epidemiologic research. As Rothman and Greenland (1998), point out:

> Being either a physician (veterinarian) or a statistician, or even both is neither a necessary nor sufficient qualification for being an epidemiologist. What is necessary is an understanding of the principles of epidemiologic research and the experience to apply them. To help meet this goal, this book is divided roughly equally into chapters dealing with epidemiologic principles and those dealing with quantitative methods.

1.5 SEEKING CAUSES

As already noted, a major goal for epidemiologic research is to identify factors that can be manipulated to maximise health or prevent disease. "The true subject matter of epidemiologic practice and of textbooks of epidemiology is research design and methods for disentangling causes and effects" (De Vreese, 2009). In other words, we need to identify causes of health and disease in populations. That might seem like a simple enough task, but it is, in fact, complex. Here we want to focus on what a cause is and how we might best make decisions about whether a factor is a cause. For our purposes, **a cause is any factor that produces a change in the severity or frequency of the outcome**. Some prefer to separate biological causes (those operating within individual animals) from population causes (those operating at or beyond the level of the individual). For example, infection with a specific microorganism could be viewed as a biological cause of disease within individuals, whereas management, housing or other factors that act at the herd (or group) level—or beyond (*eg* weather)—and affect whether or not an individual is exposed to the microorganism, or affect the animal's susceptibility to the effects of exposure, would be deemed as population causes. We recognise, that whereas disease

occurs in individuals, "epidemiology deals with groups of individuals because the methods for determining causality require it" (De Vreese, 2009). Vineis and Kriebel (2006), review concepts of causality "from Koch to Rothman" (the component-cause model).

In searching for causes, we stress a holistic approach to health. The term holistic might suggest that we try to identify and measure every suspected causal factor for the outcome of interest. Yet, quite clearly, we cannot consider every possible factor in a single study. Rather, we place limits on the portion of the 'real world' we study and, within this, we constrain the list of factors we identify for investigation. Being pragmatists, often we attempt to identify causal factors that we can manipulate in order to help prevent disease, while recognising that some non-manipulatable factors also may be crucial to our understanding of disease patterns in populations. Usually, extant knowledge and current belief are the bases for selecting factors for study. Because of this, having a concept of causation and a causal model in mind can help clarify the data needed, the key measures of disease frequency and the interpretation of associations between exposure and disease. We also need to differentiate between a conceptual, or metaphysical view of causation which we develop at the individual level (*eg* counterfactual states) and the techniques we use to achieve our objectives at the population level. We begin with an overview of 2 important models of causation.

1.6 MODELS OF CAUSATION

Given our belief in multiple causes of an effect and multiple effects of a specific cause, epidemiologists have sought to develop conceptual models of causation. Usually, however, the actual causal model is unknown and the statistical measures of association we use reflect, but do not explain, the number of ways in which the exposure might cause disease. Furthermore, although our main interest in a particular study might focus on one exposure factor, we need to take into account the effects of other causes of the outcome that are related to the exposure (this process is usually referred to as control of confounding) if we are to learn the 'truth' about the potential causal effect of our exposure of interest.

Because our inferences about causation are based, at least in the main, on the observed difference in outcome frequency or severity between exposed and unexposed subjects, we will continue our discussion by examining the relationship between a postulated causal model and the resultant, observed, outcome frequencies. We begin with a description of component-cause and the causal-web models of causation.

1.6.1 Component-cause model

The component-cause model is based on the concepts of necessary and sufficient causes developed by Rothman in 1976. A **necessary cause** is one without which the disease cannot occur (*ie* the factor will always be present if the disease occurs). In contrast, a **sufficient cause** always produces the disease (*ie* if the factor is present, the disease invariably follows). However, both experience and formal research have indicated that very few exposures (factors) are sufficient in and of themselves, rather different groupings of factors can combine and become sufficient causes. Thus, a **component-cause** is one of a number of factors that, in combination, constitute a sufficient cause. The factors might be present concomitantly or they might follow one another in a temporal chain of events. In turn, when there are a number of chains with one or more factors in common, we can conceptualise the web of causal chains (*ie* a

causal-web). This concept will be explained further under the causal-web model (Section 1.6.2).

As an example of component causes, in Table 1.1 we portray the causal relationships of 4 risk factors for bovine respiratory disease (BRD). These include:

- a bacterium, namely *Mannheimia hemolytica* (Mh)
- a virus, namely the bovine respiratory syncytial virus (BRSV)
- a set of Stressors such as weaning, transport, or inclement weather, and
- other bacteria such as *Histophilus somni* (Hs).

Table 1.1 Four hypothetical sufficient causes of bovine respiratory disease

	Sufficient causes			
Component causes	**I**	**II**	**III**	**IV**
Mh	+	+		
BRSV	+		+	
Stressors		+	+	+
Other organism (eg Hs)				+

In this deterministic portrayal, there are 4 sufficient causes, each one containing 2 specific components; we assume that the 4 different 2-factor combinations each form a sufficient cause. Hence, whenever these combinations occur in the same animal, clinical respiratory disease will occur (as mentioned, one can conceive that these factors might not need to be present concomitantly, they could be sequential exposures in a given animal). Some animals could have more than 2 causal factors (*eg* Mh, BRSV, Stressors) but the exposure to the first of the 2-factor combinations would be sufficient to produce BRD. Note that we have indicated that only some specific 2-factor combinations act as sufficient causes; Mh is a component of 2 of the sufficient causes, as is BRSV. Because no factor is included in all sufficient causes, there is no necessary cause in our model of BRD. Obviously, if you have not guessed by now, you should be aware that the number of causal factors and their arrangement into sufficient causes, as presented here, are purely for the pedagogical purposes of this example.

Now, against this backdrop of causal factors, we will assume that we plan to measure only the Mh and BRSV components (*ie* obtain nasal swabs for culture and/or blood samples for antibody titres). Nonetheless, we are aware that, although unmeasured, the other components (Stressors and/or Hs) might be operating as components of one or more of the sufficient causes. In terms of the 2 measured factors, we observe that some cattle with BRD will have both factors, some will have only Mh and some only the BRSV components. Because of the causal effects of the other unmeasured factors (*eg* Stressors and Hs forming sufficient cause IV), there will be some animals with BRD that have neither of these 2 measured factors.

The effect of risk factor prevalence on disease risk

One of the benefits of thinking about causation in this manner is that it helps us understand how the prevalence of a co-factor can impact on the strength of association between the exposure factor and the outcome of interest. For example, assume that we are interested principally in the strength of association between infection with Mh and the occurrence of BRD (the various measures of association are explained in Chapter 6). According to our example in Table 1.1, Mh produces disease when present with BRSV, but also without BRSV when combined with Stressors. What might not be apparent however, is that changes in the prevalence of the virus,

or of the Stressors (since they are components of the same sufficient cause) can change the strength of association between Mh and BRD. To demonstrate this point, note the 2 populations in Examples 1.1 and 1.2.

This example is based on the component-cause model shown in Table 1.1 using 3 causal factors: Mh, BRSV and Stressors. The frequency of each factor indicated above the body of the tables in Examples 1.1 and 1.2 is the same {p(Stressors)=0.4 and p(Mh)=0.6} except that the frequency of BRSV is increased from 30% in Example 1.1 to 70% in Example 1.2. In our examples, all 3 factors are distributed independently of each other; this is not likely true in the field, but it allows us to examine the effect of single factors without concerning ourselves with the biasing (*ie* confounding) effects of the other factors.

If infection with Mh is our exposure factor of interest, it would be apparent that some but not all cattle with Mh develop BRD and that some cattle without Mh also develop BRD. Thus, Mh infection by itself is neither a necessary nor sufficient cause of BRD. Similarly for BRSV, some infected cattle develop BRD, some non-infected cattle also develop BRD. In order to ascertain if the occurrence of BRD is associated with Mh exposure, we need to measure and contrast the risk of BRD among the exposed (Mh+) versus the non-exposed (Mh-). In Example 1.1, these frequencies are 58% and 12%, and we can express the proportions relative to one another using

Example 1.1 Causal complement prevalence and disease risk—Part I

The number and risk of BRD cases produced by 2 measured and one unknown exposure factors assuming joint exposure to any 2 factors is sufficient to cause the disease are shown below. *Mannheimia hemolytica* (Mh) is the exposure of interest (total population size is 10,000; p(Stressors)=0.4; p(Mh)=0.6; p(BRSV)=0.3).

	Measured factors			
Unmeasured Stressors	BRSV	Mh	Population number	Number diseased
1	1	1	720	720
1	1	0	480	480
1	0	1	1680	1680
1	0	0	1120	0
0	1	1	1080	1080
0	1	0	720	0
0	0	1	2520	0
0	0	0	1680	0

Risk of disease among the Mh+	3480/6000 = 0.58
Risk of disease among the Mh-	480/4000 = 0.12
Risk difference in Mh+	0.58 - 0.12 = 0.46
Risk ratio if Mh+	0.58/0.12 = 4.83

Example 1.2 Causal complement prevalence and disease risk—Part II

The number and risk of BRD cases produced by 2 measured and one unknown exposure factors assuming joint exposure to any 2 factors is sufficient to cause the disease are shown below. *Mannheimia hemolytica* (Mh) is the exposure of interest (total population size is 10,000; p(Stressors)=0.4; p(Mh)=0.6; p(BRSV)=0.7).

	Measured factors			
Unmeasured Stressors	BRSV	Mh	Population number	Number diseased
1	0	1	720	720
1	0	0	480	0
1	1	1	1680	1680
1	1	0	1120	1120
0	0	1	1080	0
0	0	0	720	0
0	1	1	2520	2520
0	1	0	1680	0

Risk of disease among the Mh+	4920/6000 = 0.82
Risk of disease among the Mh-	1120/4000 = 0.28
Risk difference in Mh+	0.82 - 0.28 = 0.54
Risk ratio if Mh+	0.82/0.28 = 2.93

a statistic called the risk ratio which is 58/12=4.83. This means that the frequency of BRD is 4.83 times higher in Mh+ cattle than in Mh- cattle. We could also measure the association between Mh and BRD using a risk difference; in this instance, the RD is 0.46 or 46%. These measures are consistent with Mh being a cause of BRD, but do not prove the causal association.

In Example 1.2, the frequency of BRSV is increased, and the risk ratio for Mh+ cattle becomes smaller (2.93) and the RD larger (0.54 or 54%). Thus, we might be tempted to think that exposure to Mh+ in some sense acts differently from a causal perspective in one example to another, yet the underlying causal relationship of Mh exposure to the occurrence of BRD has not changed. The difference in the measure of association is due to a change in the frequency of the other components of the sufficient causes, namely BRSV in this example. The other components that can form sufficient causes are called the **causal complement** to the exposure factor. Here with sets of 2 factors being sufficient causes, the causal complements of Mh are BRSV or Stressors but not both (the latter cattle would have developed BRD from being stressed and having BRSV).

In general, we note that when the prevalence of causal complements is high, measures of association between the factor of interest and the outcome that are based on risk differences will be increased (especially when the prevalence of exposure is low) (Pearce, 1989). Some, but not

all, ratio or relative measures of association could have the opposite relationship with the prevalence of causal complements. In any event, although the causal mechanism remains constant, the strength of association will vary depending on the distribution of the co-factors, many of which we do not know about or remain unmeasured for practical reasons. As will be discussed, strength of association is one criterion of causation but it is not a fixed measure and we need to bear the phenomenon just discussed in mind when making causal inferences.

In addition to the above observations, you might verify that the impact of BRSV on BRD as measured by the risk ratio would be the same (*RR*=3.2) in both Examples 1.1 and 1.2 even though its (*ie* BRSV) prevalence has changed. Although this is only one example, we could state the general rule that the strength of association for a given factor depends on the frequency of the causal complements but, providing the distribution of the other causal factors is fixed, changes in the prevalence of the factor of interest do not alter its strength of association with the outcome. If we could measure all the co-factors including Stressors and the other causal component factors, the picture would change considerably. For example, if the Stressors were the only other causes of BRD, it would be obvious that, in the non-stressed animals, BRD occurred only when both Mh and BRSV were present together. This would be clear evidence of biological synergism, a feature that is detected numerically as statistical interaction (*ie* the joint effect of the 2 factors would be different than the sum of their individual effects—in this instance, they would have no 'individual' effect, only a joint effect) (for more advanced reading see VanderWeele and Robins, 2007b). In stressed cattle, all animals exposed to Mh or BRSV would get BRD but there would be no evidence of interaction because 100% of singly, as well as jointly, exposed stressed cattle would develop BRD.

Because changes in the prevalence of the 'unknown' or 'unmeasured' factor(s) will alter the magnitude of effect for the measured exposure, we accept that we need to think of measures of association as 'population specific.' Only after several studies have found a similar magnitude of effect in different populations should we begin to think of the effect as in some sense a biological constant. Further, as shown in our examples, even if the cases have arisen from an assumed model that incorporates biological synergism, because of the distribution of the unknown causal factors, interaction (indicating synergism) might not be evident in the observed data. Flanders, 2006 discusses the component-cause model and its relationship to the counterfactual model in a more complex multifactorial setting than we describe here.

So far, we have pursued the component-cause model as deterministic. However, in reality, because we virtually never know all of the component causes of a disease, there will be circumstances where it appears that a factor is causal and other circumstances where it appears to have no, or even a sparing, effect. The statistical models we use to identify possible component-causes average these effects across individuals. Indeed, it is possible that a factor which appears to elevate the risk of disease in a population can have no effect, or a sparing effect, on some individuals within their population (Rothman & Greenland, 2005). Because of this we need to stress that epidemiological measures of association are for groups not for individuals (this was also stressed in early writings on epidemiological methods by McMahon and Pugh, in 1970). Koopman and Lynch, 1999 indicated the need to broaden the scope of the sufficient cause model in individuals to include the effects of interactions between individuals and a population based approach, particularly when studying infectious diseases. Diez-Roux (2007) extends this approach to integrate social and biological risk factors in a systems approach to disease prevention in populations. Traditionally, social risk factors are deemed to be very indirect causes of disease through their impact on more proximate biological causes. In her view, a systems approach would not investigate individual risk factors (or individuals) one

at a time, but would investigate the behaviour and relationships of multiple elements in a particular population system while it is functioning.

Although the component-cause model is somewhat simplistic, we believe it has great merit in determining which factors to include in the study of a specific disease. As noted, clues about the potential influence of a factor from studies in basic biological sciences, or from other epidemiologic studies to identifying potential causal factors are more useful than an unfocused data-mining approach in which factors are studied merely because we already have data on them, or because the data are easily available. Nonetheless, by "studying disease causation in large groups makes us ... able to answer the question of what causes diseases without knowing much about the precise biological and chemical mechanisms involved" (De Vreese, 2009).

Proportion of disease explained by risk factors

Using the concepts of necessary and sufficient causes, we also gain a better understanding of how much disease in the population is attributable to that exposure (or alternatively the proportion of disease that we could prevent by completely removing the exposure factor).

As explained in Chapter 6, this is called the population attributable fraction (AF_p). For example, if we assume that the prevalence of each of the 4 sufficient causes from Table 1.1 is as shown in Table 1.2, then, if we examine the amount of disease that can be attributed to each of the component causes, it appears that we can explain more than 100% of the disease. Of course, we really can't; it is simply because the components are involved in more than one sufficient cause and we are double-counting the role that each component cause plays as a cause of the disease.

Table 1.2 Hypothetical sufficient causes of bovine respiratory disease and relationship to population attributable fraction

	Sufficient causes				
Component causes	**I**	**II**	**III**	**IV**	**AF_p (%)**
Mh	+	+			75
BRSV	+		+		60
Stressors		+	+	+	55
Other organism (*eg* Hs)				+	10
Prevalence of sufficient cause (%)	45	30	15	10	

Another important observation is that, when 2 or more factors are both essential for disease occurrence, it is difficult to attribute a specific proportion of the disease occurrence to any single causal factor. For example, in cattle that had all 3 factors, Mh, BRSV and Stressors—it would be impossible to decide the unique importance of each factor. Our model indicates that once any 2 of the 3 were present, then BRD would occur and the presence of the third factor is of no importance causally; thus, as the saying goes 'timing is everything'. Certainly, because the frequency of co-factors can vary from subgroup to subgroup, as with relative risk measures, one should not think of AF_p as being a 'universal' measure of importance.

Whereas the AF_p is an extremely useful measure of importance, we also need to be aware of the '**prevention paradox**'(De Vreese, 2009). As an example, suppose that the AF_p for a factor (*eg* a vaccine) is 50%. This would suggest that if the prevalence of the disease in unvaccinated subjects was 6%, then if we fully vaccinated the population only 3% of the subjects would

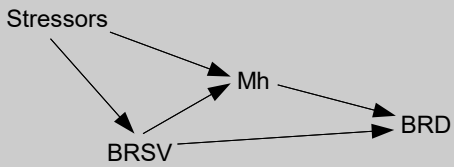
develop the disease. Indeed, this is an important reduction for the population. However, 94% of the subjects we vaccinated would not have developed the disease if left unvaccinated, and half of those who would have developed the disease in the absence of vaccination developed it anyway despite being vaccinated. Thus, when proposing to implement our findings, we need to be aware of the costs and the possible side-effects of the proposed policy or program.

1.6.2 Causal-web model

A second way of conceptualising how multiple factors can combine to cause disease is through a causal web (Example 1.3) consisting of multiple indirect and direct causes (Krieger, 1994). This concept is based on a series of interconnected causal chains or web structures; in a sense, it takes the factors portrayed in the sufficient-cause approach and links them temporally. In this model, a direct cause has no known intervening variable between that factor and the disease (diagrammatically, the exposure is adjacent to the outcome). **Direct causes** often are the **proximal causes** emphasised in therapy, such as specific microorganisms or toxins. In contrast, an **indirect cause** is one in which the effects of the exposure on the outcome are mediated through one or more intervening variables. It is important to recognise that, in terms of disease control, direct causes may be no more valuable than indirect causes. In fact, many large-scale control efforts are based on manipulating indirect rather than direct causes. Historically, this was also true: whether it was John Snow's work on cholera control through improved water supply, or Frederick Kilborne's efforts to prevent Texas Fever in American cattle by focusing on tick control. In both instances, disease control was possible before the actual direct causes (*Vibrio cholerae* and *Babesia bigemina*) were known, and the control programme was not focused directly on the proximal cause.

One possible web of causation of respiratory disease (BRD) based on the 3 factors in Examples 1.1 and 1.2 might have the structure shown in Example 1.3. The causal-web model complements the component-cause model but there is no direct equivalence between them. As we show in Chapter 13, formal causal-web diagrams are very useful to guide our analyses and interpretation of data. In our example, the model indicates that Stressors make the animal susceptible to both Mh and BRSV, that BRSV increases the susceptibility to Mh and that BRSV can 'cause' BRD directly (this might be known to be true, or it might reflect the lack of knowledge about the existence of an intervening factor such as Hs which is missing from the causal model). Finally, it indicates that Mh is a direct cause of BRD. If this causal model is true, it suggests that we could reduce BRD occurrence by removing an indirect cause such as stress, even though it has no direct effect on BRD. We could also control BRD by preventing the action of the direct causes Mh and BRSV (*eg* by vaccination, or prophylactic treatment with antimicrobials—we are not suggesting that you do this!). As mentioned, this model claims that Stressors do not cause BRD without Mh or BRSV infection and thus suggests a number of 2- or 3-factor groupings of component causes into sufficient causes. However, it does not explicitly indicate whether some of the proximal causes can produce disease in and of themselves (*ie* it is not apparent whether BRSV can cause BRD by itself or if it needs an additional unmeasured factor). From the previous examples, the outcome frequencies in BRSV-infected and non-infected cattle will depend on the distribution of the other component causes and whether, in reality, it can be a sufficient cause by itself. In Section 1.8, we will discuss the relationship of the causal structure to the design of our studies and as a guide to the correct approach in our analyses and interpretation of the study data.

Example 1.3 A causal-web model of BRD based on component causes from Example 1.1



1.7 COUNTERFACTUAL CONCEPTS OF CAUSATION FOR A SINGLE EXPOSURE

The most widely accepted conceptual basis for determining causation in epidemiology is called the counterfactual or potential outcomes model (Greenland, 2005). In a sense, it reflects the way many of us would make causal inferences and can be the basis for forming clearly defined questions for future research. Both Greenland (2005) and Hernan (2005) give examples (through hypothetical interventions) of the specificity required in counterfactual questions if we are to make progress in resolving complex health problems.

The following discussion closely follows that of Hernan (2004). Suppose we are interested in whether or not a vaccine would protect against a disease, while having concerns that the side-effects of the vaccine might be harmful. If we saw an exposed (*ie* in this instance vaccinated) subject who developed the disease we might begin to think that the exposure (or its side effects) caused the disease in that subject. If we imagined the same subject in the same time period except they were not exposed (not vaccinated), this would be referred to as the counterfactual state. Obviously, this individual does not exist, but it is what we would ideally like to observe in order to make valid causal inferences. If the disease did not occur in this hypothetical counterfactual individual, we would surely conclude that the exposure (vaccination) had caused the observed disease in that individual. Conversely, if the disease occurred in this non-exposed counterfactual individual, we likely would conclude that the exposure was not a cause of the disease in that subject (since the disease occurred regardless of exposure). We can make this thought process more formal by denoting the potential outcome in exposed subjects as D_{E+} and the potential outcome in the same subjects if they were unexposed as D_{E-}. Our thought process concludes that there is a causal effect in that subject if $D_{E+} \neq D_{E-}$. Note that a causal exposure need not be causal in all individuals principally because the other factors needed to complete a sufficient cause are absent. Further, in reality, we cannot determine a causal effect at the individual level because only one exposure level is observed and the data relating to what might have happened at the other exposure level is missing.

If we expand our thought process to the population level, we could compare the potential frequency of disease in a population if all of its members were exposed, $p(D_{E+}=1)$, to the potential frequency of disease in that same population if none of its members was exposed $p(D_{E-}=1)$ (recall again that because the subject might be missing a key component cause, not everyone would get the disease if exposed and because of other unknown sufficient cause complexes, not everyone would be disease-free if unexposed to a specific factor such as vaccination). Nonetheless, we would say there is a causal effect in the population if there is a difference in counterfactual means $p(D_{E+}=1)-p(D_{E-}=1)\neq 0$. An equivalent measure of causal effect based on relative frequencies is $p(D_{E+}=1)/p(D_{E-}=1)\neq 1$. Although these population measures are not directly observable, unlike at the individual level, we can estimate them under

specific conditions; namely, through the use of randomisation in the perfect experiment.

In Table 1.3, we summarise the observed exposure, actual disease outcome, and counterfactual outcomes in 20 subjects based on Hernan (2004). Here, 'i' is the subject counter, *C* a confounder, *E* the exposure and *D* the outcome. A 1 indicates the presence, and 0 the absence of the factor or the outcome. In the 2 columns on the right side of Table 1.3 are the counterfactual outcomes for the exposed and unexposed groups. We have set this example up such that the exposure (vaccination) causes (or would have caused) the disease in 3 individuals (subjects 7, 9 and 11) and prevents (or would have prevented) it in 3 others (subjects 1, 12 and 18). It had no effect in the remaining 14 individuals (their outcome did not change under the counterfactual state). Recall from our discussion of component causes that these effects (if real) could be due to the presence or absence of other component causes. However, since both ΣD_{E+} and ΣD_{E-} equal 10, there is no causal effect in the population. We should note that in the counterfactual (or potential outcome) setting, our inference about cause is made by comparing the potential outcomes in the exact same subjects under different exposure scenarios.

Now, our first practical approach to estimating the causal effect is to use a measure of association developed by contrasting 2 very similar but different groups of subjects, one of which is exposed and one of which is not. The observed probability (or risk) of the outcome in the exposed is defined as $p(D+|E+)$ and $p(D+|E-)$ in the non-exposed. Although this looks very similar to the comparisons in the counterfactual model, the risks now depend on observed data in the exposed and unexposed subsets of the actual population and reflect 'associations' not necessarily causation. In this instance, 7/13 (0.54) subjects who were actually exposed developed the disease, but only 3/7 (0.43) actually unexposed subjects developed the disease. Thus, the association measure does not equal the causal effect in this instance (and in general we will try and remind ourselves that association does not necessarily imply causation throughout this text).

So what accounts for the fact that the observed risks do not equal the counterfactual risks? And, given this, how do we design studies to obtain data suitable for causal inferences? The problem is that our comparison group (*E*-) is not a good counterfactual group in that it differs systematically from the *E*+ group in a manner that alters the risk of the outcome. In Table 1.3, in the *E*+ group 9/13=0.69 of the individuals were *C*+ but in the *E*- group, only 3/7=0.43 were *C*+. Consequently, the groups were not exchangeable. Exchangeability means the exposure status of the 2 groups could be switched without impacting the results, but because the groups were different, this was not possible.

A major problem for epidemiologists in their use of observational studies (as in our example) is that the exposed and unexposed groups of subjects are rarely exchangeable. The most likely reason for this difference is the presence of other factors that are related to the exposure and the disease (in our example, the *C*+ and *C*- subjects might have different exposure levels to infection and this impacts on disease occurrence). These factors are called confounders and the phenomenon of confounding will be explored in detail in Chapter 13. The presence or absence of this confounding factor is shown in the second column of Table 1.3. Given these data we note that among those possessing the confounding factor (*eg* being exposed to a high risk of infection), 75% were exposed (*ie* vaccinated) whereas among those not exposed to a high risk of infection, only 50% were exposed (vaccinated).

We will delay the discussion of techniques to control confounding until Chapter 13, and at this point only introduce the fact that there are a number of ways of trying to ensure that the

observed risks would equal the counterfactual risks. One way is to view the problem as trying to uncover the mechanism behind the allocation of exposure as stated by Rubin, 1991. For example the observed data could have resulted from a controlled experiment where the researchers decided to vaccinate a higher percentage of high risk than low risk study subjects.

Table 1.3 Observed and counterfactual results of an exposure (E) and disease (D)

Subject (i)	Confounder (C)	Actual Exposure (E)	Actual Outcome (D)	Counterfactual Results $D_{E=1}$	Counterfactual Results $D_{E=0}$
1	1	0	1	0	1
2	0	0	1	1	1
3	1	1	1	1	1
4	1	1	0	0	0
5	1	1	1	1	1
6	1	1	1	1	1
7	0	0	0	1	0
8	0	1	1	1	1
9	0	0	0	1	0
10	0	1	0	0	0
11	1	1	1	1	0
12	1	0	1	0	1
13	1	1	1	1	1
14	0	1	0	0	0
15	1	1	1	1	1
16	0	0	0	0	0
17	1	0	0	0	0
18	1	1	0	0	1
19	0	1	0	0	0
20	1	1	0	0	0
Totals	12	13	10	10	10
				$p(D_{E=1}=1)=0.5$	$p(D_{E=0}=1)=0.5$

Observed $p(D+|E+)=7/13=0.54$

Observed $p(D+|E-)=3/7=0.43$

	E=1	E=0
p(D+|C+)	6/9=0.67	2/3=0.67
p(D+|C-)	1/4=0.25	1/4=0.25

This approach leads to the development of propensity scores and proportional weighting of stratum specific outcome frequencies to obtain unbiased estimates of causal parameters (Hernan & Robins, 2006a). Related to this is the use of standardised risks/rates to adjust for the distribution of exposure in the different levels of the confounder(s) (Sato & Matsuyama, 2003). Other researchers have developed methods to prevent confounding based on 'instrument variables'. Historically, the traditional approach has been the use of physically stratifying the data based on the levels of the confounder(s) and using adjusted measures of association (relative risks and odds ratios) initially developed by Mantel and Haenszel in 1959 (see Chapter 13 for details). Here, we note that the risks of disease are the same in the exposed and unexposed subjects once the subjects are divided into those with a high risk of infection and those with a lower risk of infection. In order to make valid causal inferences, a major underlying assumption of all of these methods is that there is no residual confounding given the control of (adjustment for) measured confounders—this produces 'exchangeability' within the strata formed by the combinations of measured confounders.

1.8 Experimental versus observational evidence of causation

Experimental evidence

Traditionally, the gold standard approach to identifying causal factors is to perform an experiment. In most 2-arm experiments (see Chapter 11), we randomise some animals (or other units of concern) to receive the factor and some to receive nothing, a placebo, or a standard intervention (treatment). After a suitable time period, we then assess the outcome in the study subjects and proceed to assess if there are differences in the outcome between the 2 groups. As an alternative design, we might more nearly approach the counterfactual state by using a cross-over design in which subjects are randomly assigned to receive the treatment of interest, or serve as controls, in the first period of the experiment. After a suitable 'wash-out period, the subjects then receive the other level of the treatment (*ie* if they received the treatment in the first period they would receive the placebo in the second and vice-versa). This allows the subject to serve as their own control as in the counterfactual setting. In both of these experimental designs, the exposure (now denoted as X) explicitly precedes the outcome (denoted as Y) temporally and all other variables (known and unknown) that do not intervene between X and Y are made independent of X through the process of randomisation (this means that extraneous variables do not confound or bias the results we attribute to the exposure X). This independence of all factors from the treatment X produces exchangeability in the treatment groups; that is the same outcome would be observed (except for sampling error) if the assignments of treatment to study subjects had been reversed (*ie* if the treated group had been assigned to be untreated). In an experiment, the formal application of randomisation provides the probabilistic basis for the validity of this assumption. Factors that are positioned temporally or causally between X and Y are not measured and are of no concern with respect to answering the causal objective of the trial. In these experimental contexts, exposure X would be a proven cause of outcome Y if the value or state of Y changed following the manipulation of X.

The measure of causation in this ideal trial is called the causal-effect coefficient and indicates the difference in the outcome between the 'treated' and 'non-treated' groups (*ie* those with different levels of factor X). For example, if the risk of the outcome in the group receiving the treatment is denoted R_1 and the risk in the group not receiving the treatment is R_0, then we might choose to measure the effect of treatment using either an absolute measure (*ie* risk difference—*RD*) or a relative measure (*ie* risk ratio—*RR*) as shown in Chapter 6. If this

difference is greater than what could be attributed to chance, then we could say that we have proved that the factor is a cause of the outcome event. A key point is that all causal-effect statements are based on contrasts of outcomes in the different treatment groups; the outcome in the treated group cannot be interpreted without knowing the outcome in the untreated group.

Observational evidence

In observational studies, we estimate the difference in values of Y between units that happen to have different values of *X*. In contrast to the experimental setting, we do not control whether a subject is, or is not, exposed. As we have seen in Table 1.3 measures of association do not necessarily reflect causation. Variables related to both *X* and *Y* and which do not intervene between *X* and *Y* must be controlled to prevent confounding bias and support the estimation of causal effects. The major differences between observational studies and field experiments lie in the ability to prevent selection, misclassification and confounding bias, and dealing with the impact of unknown or unmeasured factors. Thus, by themselves, observational studies produce measures of association but cannot 'prove' causation. However, in the ideal observational study, with total control of bias, the measure of association will estimate the causal-effect coefficient. Nonetheless, in a given setting, experimental evidence is deemed to provide more solid evidence of causality than observational studies because, in reality, "To find out what happens to a system when you interfere with it, you have to interfere with it (not just passively observe it)." (Attributed to Box (1966) in Snedecor and Cochran (1989)).

Limits of experimental study evidence

Despite their advantages, performing 'ideal' experiments is not easy even at the best of times (see Chapter 11) and, furthermore, many potential causal factors of interest to epidemiologists would be difficult to study using a controlled-trial format. For example, it would be impossible to perform the perfect experiment to answer the question of whether or not badgers that are infected with *M. bovis* cause tuberculosis in cattle. Laboratory studies are useful to demonstrate what can happen when animals are exposed to a specific exposure (*eg* that factor A can cause outcome B), but, if the circumstances are too contrived (very large dose, challenge by an unnatural route, limited range of co-factors), laboratory results might not be much help in deciding the issue of causation under normal, everyday conditions. For example, we could conduct a laboratory experiment in which cattle and infected badgers are maintained within a confined enclosure and assess whether or not the cattle became infected. If they did, this would demonstrate that infected badgers can cause infection in cattle, but not the extent, or route of infection in the field.

In field trials that are subject to non-compliance, we often have to decide how to manage the non-compliance in assessing the role of the treatment on the outcome and, although any given field trial might provide more valid evidence for or against causation than any given observational study, it is not uncommon for differences in results to exist among apparently similar field trials. Hence, the ability to make perfect inferences based on field trials is illusionary. In addition, in many instances, it is impossible to carry out experiments under conditions that even remotely resemble 'real-world' conditions. Rickles, 2008, has discussed the particular limitations of interpreting causal effects when using experimental designs to intervene in complex systems.

1.9 CONSTRUCTING A CAUSAL DIAGRAM

Causal diagrams are helpful for displaying relationships among a number of possible causal

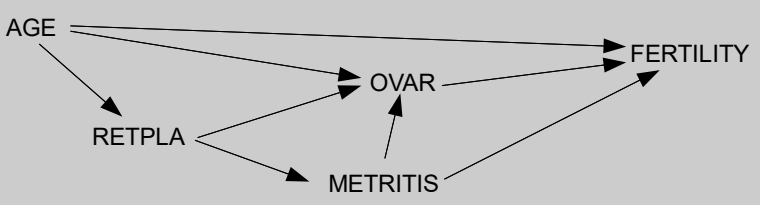
variables (variables are names for factors that we wish to study), as well as for deducing statistical associations that might arise from a given set of underlying causal relationships (Glymour & Greenland, 2008). The cause-and-effect relationships, and correlations, are best shown in a causal diagram (also called directed acyclic graphs, or modified path models). To construct a causal diagram, we begin by imposing a plausible biological causal structure on the set of variables we plan to investigate and translate this structure into graphical form that explains our hypothesised and known relationships among the variables. The causal-ordering assumption is usually based on known time sequence and/or plausibility considerations. For example, it might be known that one variable precedes another temporally, or current knowledge and/or common sense might suggest that it is possible for one factor to cause another but not vice-versa. We will explain the process using an example (Example 1.4) in which we hypothesise that reproductive diseases will impact on reproductive efficiency in dairy cattle. Causal diagrams are discussed further in Section 13.5.1.

The easiest way to construct the causal diagram is to begin at the left with variables that are pre-determined and progress to the right, listing the variables in their causal order. The variation of these variables (those to the extreme left such as AGE in Example 1.4) is considered to be due to factors outside of the model. The remaining variables are placed in the diagram in their presumed causal order; variables to the left could 'cause' the state of variables to their right to change. If it is known or strongly believed that a variable does not cause a change in one or more variables to its right, then no causal arrow should be drawn between them. Once completed, if the proposed model is correct, the analyses will not only be more informative about which variables we need to include in our study, but it will also provide more powerful analyses than approaches that ignore the underlying structure. The only causal models to be described here are called recursive; that is, there are no causal feedback loops (if these are believed to exist, they can be formulated as a series of causal structures).

Suppose the model is postulated to assess if reproductive diseases impact on the outcome, specifically fertility. In our model, AGE is assumed to be a direct cause of retained placenta (RETPLA), cystic ovarian disease (OVAR) and FERTILITY but not METRITIS. (This means that the risk of RETPLA and METRITIS change with the age of the cow, as does the measure of FERTILITY.) Note that METRITIS and OVAR are intervening variables between RETPLA and the outcome of interest FERTILITY. We will assume that our objective is to estimate the causal effect of RETPLA on FERTILITY based on the association between these 2 variables.

The model indicates that AGE can cause changes in FERTILITY directly and also by a series of pathways involving one or more of the 3 reproductive diseases. It also indicates that AGE is not

Example 1.4 A causal diagram of factors affecting fertility in cows



RETPLA = retained placenta
OVAR = cystic ovarian disease

a direct cause of METRITIS. In terms of understanding relationships implied by the causal diagram, the easiest way to explain them is to think of getting (perhaps walking) from an exposure variable (*eg* RETPLA) to a subsequent variable (*eg* FERTILITY). As we pass through variables in the direction of the arrows, we trace out a **causal path**. The rule for tracing the causal pathways is that you can start backwards from any variable but once you start forward on the arrows you cannot back up. Paths which start backwards from a variable are **spurious causal paths** and reflect the impact of confounders. In displaying the relationships, if there are variables that we believe are correlated because of an unknown or unmeasured common cause, we use a line to indicate this, and you can travel in either direction between these variables. If 2 variables are adjacent (connected by a single direct arrow), their causal relationship is deemed to be **directly causal**. Paths which start forward from one variable and pass through intervening variables to reach the outcome are deemed to be **indirect causal paths** (*eg* RETPLA can cause fertility changes through its effect on OVAR, but not directly). The combined effects through indirect and direct paths represent the **total causal effect** of the variable.

Okay, so, how does this help us? Well, in order to estimate the causal effect, we must prevent any spurious (confounded) effects, so the variables preceding an exposure factor of interest (RETPLA) that have arrows pointing toward it (*ie* from AGE) and through which FERTILITY (the outcome) can be reached on a path must be controlled. In this instance, that variable is AGE. The model also asserts that we do not control intervening variables so METRITIS and OVAR are not placed in the statistical model when estimating the causal effect. If we assume that there are no other confounders that are missing from the model, our analyses will estimate the causal effect of RETPLA on FERTILITY. (This also assumes the statistical model is correct, but that is another story.)

We should note that if we did control for METRITIS and OVAR in this model, we would not obtain the correct estimate of causal effect. Rather, we would only obtain the direct effect of RETPLA on FERTILITY if that direct effect existed (and in our example no direct effect exists). This feature will be discussed again when regression models (*eg* Chapter 14) are described as this is a major reason why we can inadvertently break down a causal web. In the causal diagram used here, we explicitly assume there is no direct causal relationship between RETPLA and FERTILITY (so this would be an inappropriate analysis for this reason also). However, RETPLA can impact on FERTILITY indirectly through the diseases METRITIS and/or OVAR, and controlling these variables would block these indirect pathways. Thus, only by excluding METRITIS and OVAR, and controlling for AGE, can we obtain the correct causal-effect estimate.

Greenland and Brumback (2002), discuss relations among causal diagrams, counterfactual models, component-cause models and structural equation (*ie* path) models. Howards *et al*, (2007) provide a good discussion on the use of causal diagrams with linkages to appropriate regression models for estimating the associations and examples of causal diagrams based on potential causes of perinatal disease. For more advanced reading see VanderWeele and Robins, 2007a.

1.10 CAUSAL CRITERIA

Given that researchers seek to make advances in identifying potential causes of disease using observational study techniques, a number of workers have proposed a set of causal guidelines (these seek to bring uniformity to decisions about causation (Evans, 1995; Susser, 1995)).

Because these depend on value judgements, we should accept that different individuals might view the same facts differently (Poole, 2001). The recent origin of these guidelines is attributed to Hill (1965) who proposed a list of criteria for making valid causal inferences (not all of which had to be fully met in every instance). These guidelines include: time sequence, strength of association, dose-response, plausibility, consistency, specificity, analogy and experimental evidence. Today, we might add evidence from meta-analysis to this list. Over the years, the first 4 of these have dominated our inference-making efforts (Weed, 2000) and recently, researchers have investigated how we use these and other criteria for making inferences (Waldmann & Hagmayer, 2001). In one study, a group of 135 epidemiologists were given a variety of realistic but contrived examples and varying amounts of information about each scenario. At the end of the exercise, they had agreed on causal inferences in only 66% of the examples. This stresses the individuality of interpreting the same evidence. Nonetheless, since we think that reference to a set of criteria for causal inferences is a useful aid to decision-making (they provide "a road map through complicated territory" (Rothman *et al*, 2008)), we will briefly comment on Hill's list of items and give our view of their role in causal inference.

Doll (2002) describes the application of Hill's guidelines of causation when deducing causation from epidemiological observations. Franco *et al* (2004), provide a good discussion of causal criteria in cancer epidemiology and examples of the collaborative impact between epidemiologists and laboratory scientists. Rothman and Greenland (2005) comment that we should "avoid the temptation to use causal criteria simply to buttress pet theories at hand, and instead ....focus on evaluating competing causal theories using crucial observations". Phillips and Goodman (2006) debate the value of causal criteria, but appear to accept their utility provided they do not degenerate into black-box algorithms which might replace "scientific common sense". Hofler (2005b) chooses to interpret Hill's criteria in a counterfactual setting; a setting he had elaborated upon in an earlier paper (Hofler, 2005a). In an interesting article, Lipton and Odegaard (2005), suggest that causal expressions are not required for the development of policy to prevent disease and are not as defendable as just stating clearly the methods used to arrive at the statistical association(s) between an exposure and disease. Lash (2007) accepts the utility of causal criteria but warns that in many instances researchers underestimate the magnitude of systematic errors and uncertainties in their data and fail to fully recognise "countervailing external information". Shapiro (2008a; 2008b; 2008c) provide a recent summary of the utility of guidelines for inferring causation. Ward (2009) published an extensive review of the use of causal criteria. He claims that their application does not fully satisfy either deductive or inductive reasoning, but that their application does provide a consistent basis for arriving at the best explanation for the statistical association.

At the outset, we must be clear about the context for inferring causation. As Rose (2001) stated, it is important to ask whether we are trying to identify causes of disease in individuals or causes of disease in populations. Indeed, with the expansion of molecular studies, the appropriate level at which to make causal inferences, and whether such inferences are valid across different levels of organisation remains open to debate. However, clear decisions about the appropriate level to use (think back to the objectives when choosing this) will guide the study design as well as inferences about causation. The following set of criteria for causation can be applied at any level of organisation, and the criteria are based on individual judgement, not a set of defined rules.

1.10.1 Study design and statistical issues

As will be evident after delving into study design (Chapters 7-10), some designs are less open to bias than others. For example, case-control studies are often assumed to be subject to more bias than cohort studies. However, much of this criticism is based on case-control studies using hospital or registry databases. We think it important that every study be assessed on its own merits and we need to be aware of selection, misclassification and confounding bias in all study designs.

Most often we do not make inferences about causation unless there is a statistically significant association between the exposure and the outcome (and one that is not likely to be explained by one or more of the previous biases). Certainly, if the differences observed in a well-designed study have P-values above 0.4, this would not provide any support for a causal relationship. However, outside of extremely large P-values, statistical significance should not play a pivotal role in assessing causal relationships. Like other researchers, we suggest an effect-estimation approach based on confidence limits as opposed to a hypothesis-testing approach. Despite this, recent research indicates that P-values continue to be used frequently to guide causal inferences: P-values of 0.04 are assumed to be consistent with causal associations and P-values of 0.06 inconsistent. At the very least, we believe this is an overemphasis of the role of assessing sampling variability vis-a-vis a causal association and is not a recommended practice.

1.10.2 Time sequence

While a cause must precede its effect, demonstrating this fact provides only weak support for causation. Further, the same factor could occur after disease in some individuals and this would not disprove causation except in these specific instances. Many times it is not clear which came first; for example, did the viral infection precede or follow respiratory disease? This becomes a greater problem when we must use surrogate measures of exposure (*eg* antibody titre to indicate recent exposure). Nonetheless, for inferring causation we would like to be able to demonstrate that an exposure preceded the effect, or at least develop a rational argument for believing that it did—sometimes these arguments are based largely on plausibility (*ie* which time sequence is more plausible) rather than on demonstrable facts.

1.10.3 Strength of association

This is usually measured by ratio measures such as risk ratio or odds ratio but could also be measured by risk or rate differences. The belief in larger (stronger) associations being causal appears to relate to how likely it is that unknown or residual confounding might have produced this effect. However, because the strength of the association also depends on the distribution of other components of a sufficient cause, an association should not be discounted merely because it is weak. Also, when studying diseases with very high frequency, risk ratio measures of association will tend to be weaker than with less common diseases. White (2004), studied the influence of relative prevalence of the agents when making causal inferences about the roles of 2 potential causal factors. It appeared that the agent with the higher prevalence (and in his studies the larger the etiologic fraction) was deemed to be more important causally. Hence, some could posit that we should base our judgement more on etiologic fractions than on risk ratios. In further work (White, 2005), it was shown that whereas people do put a lot of weight on what we would call etiologic fractions, they often modify their judgements based on the

impact of the second cause when the first is not present, and the judgements appeared to differ when the apparent effect was sparing instead of harmful.

1.10.4 Dose-response relationship

If we had a continuous, or ordinal, exposure variable and the risk of disease increased directly with the level of exposure, then this evidence supports causation as it tends to reduce the likelihood of confounding and is consistent with biological expectations. However, in some instances, there might be a cutpoint of exposure such that nothing happens until a threshold exposure is reached and there is no further increase in frequency at higher levels of exposure. These circumstances require considerable knowledge about the causal structures for valid inferences. Because certain physiological factors can function to stimulate production of hormones or enzymes at low doses and yet act to reduce production of these at higher levels, one should not be too dogmatic in demanding monotonic relationships.

1.10.5 Coherence or plausibility

The essence of this criterion is that if an association is biologically sensible, it is more likely causal than one that isn't. However, be careful with this line of reasoning. A number of fundamentally important causal inferences have proved to be valid although initially they were dismissed because they did not fit with the current paradigm of disease causation. As an example, when we found out that feedlot owners who vaccinated their calves on arrival subsequently had more respiratory disease in their calves than those who didn't, we didn't believe it—it didn't make sense. However, after more research and a thorough literature search in which we found the same relationship, we were convinced it was true. The problem likely related to stressing already stressed calves which made them more susceptible to a battery of infectious organisms.

Coherence requires that the observed association is explicable in terms of what we know about disease mechanisms. However, our knowledge is a dynamic state and ranges all the way from the observed association being assessed as 'reasonable' (without any biological supporting evidence) to requiring that 'all the facts be known' (a virtually nonexistent state currently). Postulating a biological mechanism to explain an association after the fact is deemed to be insufficient for causal inferences unless there is some additional evidence supporting the existence of that mechanism.

1.10.6 Consistency

If the same association is found in different studies by different workers, this gives support to causality. This was a major factor in leading us to believe that the detrimental effects of respiratory vaccines on arrival at feedlots were indeed causal. Not only were our studies consistent but there were numerous examples in the literature indicating (or suggesting) potential negative effects of the practice. Our beliefs were further strengthened by publications from experimental work that indicated a plausible explanation for the detrimental effects.

Lack of consistency doesn't mean that we should ignore the results of the first study on a topic, but we should temper our interpretation of the results until they are repeated. This would prevent a lot of false positive scares in both human and veterinary medicine. The same

approach might be applied to the results of field trials and, because there is less concern over confounding, we might not need to be as strict. Recent research has indicated that, in human medicine, once 12 studies have reached the same essential conclusion, further studies reaching the same conclusion are given little additional weight in making causal inferences (Holman *et al*, 2001).

Meta-analysis is used to combine results from a number of studies on a specific exposure factor in a rigorous, well-defined manner (Weed, 2000) and consequently helps with the evaluation of consistency. Evidence for or against a hypothesis can be obtained as opposed to dichotomising study results into those that support a hypothesis and those that do not. In addition, explanation of the methods used in meta-analysis tends to provide a clearer picture of the reviewer's criteria for causation than many qualitative reviews (see Chapter 28).

1.10.7 Specificity of association

Based on rigid criteria for causation such as Henle-Koch's postulates, it used to be thought that, if a factor was associated with only one disease, it was more likely causal than a factor that was associated with numerous disease outcomes. We no longer believe this and specificity, or the lack thereof, has no valid role in assessing causation—the numerous effects of smoking (heart, lungs, infant birth weight, infant intelligence) and the numerous causes for each of these outcomes should be proof enough on this point.

1.10.8 Analogy

This is not a very important criterion for assessing causation, although there are examples of its being used to good purpose. This approach tends to be used to infer relationships in cases of human diseases based on experimental results in other animal species. Today, many of us have inventive minds and explanations can be developed for almost any observation, so this criterion is not particularly useful to help differentiate between causal and non-causal associations.

1.10.9 Experimental evidence

This criterion perhaps relates partly to biological plausibility and partly to the additional control that is exerted in well-designed experiments. We tend to place more importance on experimental evidence if the same target species is used and the routes of challenge, or nature of the treatment are in line with what one might expect under field conditions. Experimental evidence from other species in more contrived settings is given less weight in our assessment of causation. Indeed, the experimental approach is just another way to test the hypothesis, so this is not really a distinct criterion for causation in its own right.

Swaen and van Amelsvoort (2009) developed a process for formalising the application of these causal criteria, for assessing the extent to which each criterion was true, and the application of a formal weighting of the criteria, using discriminant analysis, to estimate the probability that the observed associations between an exposure and an outcome were causal. However, details of this procedure are beyond the scope of this text.

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