

A Bayesian Approach to Causality Assessment

by

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University of Minnesota
Technical Report No. 472
June 1986

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¹ This research has been supported by grants from the University of Minnesota Graduate School, the Drug Information Association, the American Medical Association Education and Research Foundation and Ciba-Geigy Canada. Except for the principal author, the authors are listed alphabetically. The principal author wishes to acknowledge the helpful comments and criticisms of his colleagues Tom Rector and Bill Sudderth.

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A BAYESIAN APPROACH TO CAUSALITY ASSESSMENT FOR SUSPECTED
ADVERSE DRUG REACTIONS I: CONCEPTUAL FRAMEWORK

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This research has been supported by grants from the University of Minnesota Graduate School, the Drug Information Association, the American Medical Association Education and Research Foundation and Ciba-Geigy Canada.

Manuscript pages: 29
Tables : 0
Appendices : 5
Figures : 2

ABSTRACT

A new approach to the problem of assessing causality for adverse drug reactions is presented. The approach uses Bayes' Theorem to answer the causality assessment problem in a logically satisfying and nonarbitrary way. The posterior odds in favour of drug causation is obtained by multiplying the prior odds by likelihood ratio terms that describe the differential diagnostic content of five separate categories of information about the case: the history of the patient before the adverse event occurred; the timing of the adverse event; the characteristics of the adverse event; the effect of dechallenge; and the effect of rechallenge. Although much work remains to be done before the method can be easily implemented, the approach satisfies basic criteria for causality assessment methods, a claim that cannot be made for any other currently available technique.

Key words: adverse drug reactions, causality assessment, probability, coherence

INTRODUCTION

The answers to important clinical, research and policy questions can depend in part on the extent to which one is justified in believing that particular adverse clinical events were caused by specific drugs. For example, should a clinician discontinue the use of an effective anti-inflammatory drug in a patient to whom it may be causing anginal pain? How should a pharmaceutical manufacturer react to the fact that two patients in a clinical trial of a new antiulcer drug developed liver disease? Should a trial of a new heart failure drug be terminated because four of nine patients on the drug died suddenly within the first three months of treatment? How should an epidemiologist studying the incidence of in-hospital iatrogenic diseases decide whether a particular case of renal failure is drug-induced?

All these questions involve the causality assessment problem: given all the available information, what is the probability that a given adverse clinical event was caused by some particular drug to which the patient had been exposed? In a previous paper [1], two of us developed criteria that methods for solving the causality assessment problem should satisfy, and we argued that no current method satisfied these criteria. In this paper, we describe a new approach to the causality assessment problem, and we show that this approach satisfies the criteria discussed in [1]. Ideas related to the new approach can be found in [2] and [3]. The new approach is based on Bayesian probability theory. In Section A, we explain the essential ideas of this theory and present reasons why it should be applied in the causality assessment context. The new approach is described in Section B, and in Section C, it is discussed in relation to the criteria of [1].

A. BAYES' THEOREM AND CAUSALITY ASSESSMENT

Two features of the causality assessment problem contribute substantially to its difficulty. The first of these is uncertainty. The assessor is usually uncertain about many of the key elements he must integrate into his assessment. His uncertainty may be about some of the facts of the case (Did the patient actually take the drug before the adverse event began? Has the patient ever experienced a similar event before?); about background information that affects how these facts are to be interpreted (How long should it take before toxic quantities of the relevant metabolite of the drug have accumulated at the target organ? What is the incidence of events like this in patients similar to the present one, but who have not taken the suspected drug?); or about the assumptions that it is appropriate to make when determining the evidentiary significance of the clinical data (If the event is an adverse reaction to the suspected drug, is the mechanism dose-dependent or immunologic? Could the adverse event be a clinical sequela of the disease for which the patient is taking the drug as treatment?). Somehow, the assessor must take into account this uncertain information and the extent of his uncertainty when he evaluates the probability that the suspected drug caused the adverse event.

The second feature is the complexity of the information that affects causality assessment. Several different factors are relevant to any causality assessment and the evidence about each of them usually comes from several different sources. The factors include background incidence of similar events (in patients who had previously taken the drug, as well as in those who had not), aspects of the patient's history (including previous experience with similar drugs and similar adverse events, as well as demographic and clinical information), timing of the event in relation to drug administration, clinical

characteristics of the event (including drug levels in tissues or body fluids), and the patient's response to dechallenge (withdrawal of the drug) or rechallenge (readministration of the drug), when these occur. Information sources include the assessor's previous clinical experience and his clinical judgment, clinical observations and laboratory findings on the patient in question, data from epidemiologic studies, as well as facts and theories from pharmacology and other basic sciences. Frequently, information from one source or about one factor conflicts with information from another source or about another factor. Even when the information is not mutually contradictory, some way must be found to weight the significance of each piece of information and combine these "weights of evidence" in a reasonable way.

The difficulties described are not unique to the assessment of adverse drug reactions. They apply to the general problem of differential diagnosis in medicine. In assessing a possible adverse drug reaction, drug causation is simply one of the main "diagnoses" being considered. The added difficulty that this entails arises because the main way that physicians usually solve differential diagnostic problems -- the performance of tests that help to distinguish between the various possible diagnoses -- is usually not helpful for identifying adverse drug reactions. There are no good tests for drug causation. In the remainder of this section however, we will suggest that a generalization of the main strategy used for the interpretation of diagnostic tests -- Bayes' Theorem -- also provides a solution to the problem of causality assessment in adverse drug reactions.

1. Bayes' Theorem

As used for interpreting diagnostic tests [4] Bayes' Theorem uses information about the characteristics of the test (sensitivity, specificity etc.) and the prevalence of the disease in the population from which the patient came to interpret a particular test result. Thus for a positive test result:

$$P(D|T^+) = \frac{P(D) \times P(T^+|D)}{P(D) \times P(T^+|D) + P(D^c) \times P(T^+|D^c)}$$

D = Disease Present

D^c = Disease Absent

T⁺ = Positive test result

"|" = Conditional probability: the probability of the proposition on the left of the "|" given that you accept the proposition on the right of "|" as true.

The same formula can be used to determine P(D^c|T⁺), the probability that the patient does not have the disease:

$$P(D^c|T^+) = \frac{P(D^c) \times P(T^+|D^c)}{P(D^c) \times P(T^+|D^c) + P(D) \times P(T^+|D)}$$

These two results can be combined to calculate the odds that the patient has the disease (the ratio of the probabilities that the patient does and does not have the disease):

$$\frac{P(D|T^+)}{P(D^c|T^+)} = \frac{P(D)}{P(D^c)} \times \frac{P(T^+|D)}{P(T^+|D^c)}$$

Posterior odds = prior odds x likelihood ratio.

The odds form of Bayes' Theorem has a very attractive attribute: it describes the contribution of the diagnostic test result in a very simple way, the likelihood ratio. Examine the likelihood ratio formula. In words, it answers the question: How many times more likely would you be to see a positive test result if the disease was present compared with if it was absent? This can be rephrased in a more general way: how many times more likely would you be to see a particular finding if the disease was present compared with if it was absent? Also, we could change the phrase "if the disease was present..." to any other diagnostic proposition such as "if the drug was the cause of the adverse event compared with if something else caused it". Thus, in principle, the Bayesian formula can incorporate any data that helps discriminate between any diagnostic proposition and its alternative. The likelihood ratio formulation also makes it easy to see how the same method could incorporate information from many different sources. Each source of information would contribute a new likelihood ratio term that would transform a prior odds (prior to information about that factor) to a posterior odds (posterior to information about that factor). The posterior odds for the first factor would serve as a prior odds for the second factor and the process would continue until all of the relevant sources of information had been exhausted.

Thus it is clear, in principle, how this approach could provide a solution to any complex differential diagnostic problem. In the adverse drug

reaction context each important finding of the case (history, timing, dechallenge, etc.) would contribute a likelihood ratio term that would express how much more (or less) likely that finding would be with drug versus other causation. The individual likelihood terms would then be combined with the prior odds of drug causation as described above to arrive at the probability (odds) that the drug caused the adverse event.

However, application of the method appears to face an insurmountable problem: estimating the probabilities that make up the prior odds and likelihood ratio terms appears to require more data than we have or can ever hope to have. We believe that this view derives from a misunderstanding of what probability really means and why we measure it.

2. Probability

Consider why we measure probabilities in medicine. We measure probabilities because they help us decide how to act when faced with uncertainty. We wish to know how likely the patient is to have a particular disease because that probability will determine whether or not we will treat him for it. The more likely it is that he has the disease the more likely we are to treat him as if he had it. Considered in this light probabilities measure our propensity to act as if the proposition that we are evaluating is true.

The interpretation of probabilities as subjective measures of degree of belief that determine our propensity to act is not new. This is the central idea in the pioneering work of the Italian mathematician Bruno de Finetti [5,6]. De Finetti reduced the assessment of probability to an economic decision, where the act to be taken and the values of their consequences are clear. To understand how this works, evaluate the probability for you of a proposition A according to the following "thought experiment": decide upon a number p such that you are neutral between buying and selling for $\$p$ a ticket

that will be worth \$1 if A is true and otherwise it will be worth nothing. For any number greater than p, the price is too high, and you would be unwilling to buy the ticket, while you would not agree to sell the ticket for less than p. This number p is your probability that A is true (You must imagine that at some specified time in the future, you will find out for sure whether A is or is not true). Note that if you are sure that A is true, p must be 1, and if you are sure that A is false, p must be zero; otherwise, there is a unique number p between 0 and 1 satisfying the definition. It may be difficult to determine p exactly, just as it is difficult to decide exactly how much you would be willing to pay for a new house. In principle however, both quantities exist, and, at the least, bounds on both could be determined by how you act when you bet, or when you negotiate for the house.

3. Coherence

With the de Finetti definition of probability, it is possible to give a precise meaning to consistent (and inconsistent) reasoning in the face of uncertainty. Suppose, as in the assessment of a suspected drug reaction, you simultaneously assess the uncertainty you feel about many different propositions that are related in various ways. Using de Finetti's definition as your measure of uncertainty, you have simultaneously set the price for many tickets. Is it possible, in principle, that someone could transact with you for some of these, at your prices, in such a way that you must pay out more than you receive from him, no matter which of the propositions are true and which are false? If so, in your assessments you have in effect made economic decisions with unacceptable economic consequence, certain financial loss. The possibility of such loss is a concretization of the inconsistent reasoning that underlies it.

As a very simple example, suppose A represents the proposition that a patient will have a recurrence of an adverse drug reaction within 24 hours of re-exposure to a suspected drug and A^c that he will not. There is nothing inherently wrong with assessing $P(A) = 0.25$, nor with assessing $P(A^c) = 0.25$. On the other hand, it is clearly inconsistent to assess both quantities as 0.25: if you did so, and sold tickets at the assessed prices, someone could buy one of each ticket for a total outlay of 50¢ — and give them back to you today demanding \$1 in return, since one or the other proposition is bound to be true tomorrow, and hence one of the tickets must be worth \$1, while the other will be worth nothing. The 50¢ sure loss you (the assessor) face in this situation reveals the inconsistency in the simultaneous assessments of 0.25 for the two probabilities $P(A)$ and $P(A^c)$.

A set of bets that makes money no matter what happens is called a Dutch book in gambling circles. The rules of probability theory (Appendix I) guarantee that all your probability assessments fit together in such a way that a Dutch book cannot be made against you. In this sense, you either reason about uncertainty consistently with these rules — or you act like someone who is willing to give money away without any chance of getting it back. And, since your probabilities for the various propositions exist whether you determine them or not, this result remains true whether you explicitly and quantitatively assess your uncertainty or you just do it implicitly and qualitatively, as in most current approaches to causality assessment. A set of probability assessments that is consistent with the rules is called coherent, and any reasoning about uncertainty that is not consistent with them is called incoherent.

4. Bayes' Theorem and Causality Assessment

The de Finetti definition frees probability from its dependence on frequency information. All our uncertainties about interpretation of a case, informed by whatever facts, theories, or intuitions that we can bring to bear, can be legitimately treated as probabilities and combined by the rules of probability theory (from which Bayes' theorem is derived, see Appendix II) to decide on the probability of drug causation. More than that, the de Finetti definition of probability implies that we must do so if we wish to ensure that our overall assessment is coherent.

A necessary step in this process must be to assign a number to each of our component uncertainties about the case. Many people may be uncomfortable with this idea. When asked, for example, what is the chance that a patient with a certain clinical condition treated in a particular way will experience some particular untoward clinical event in some specified time period, they will respond that they just do not know. To attach a number to their uncertainty would be to introduce a meaningless quantification to something essentially vague and even unknowable. We believe that this position is incorrect, for the following three reasons:

1) Using de Finetti's measure the quantification of uncertainty is not meaningless. There is certainly some justice in applying the charge of meaningless quantification to some previous approaches to causality assessment that have used uncalibrated, analogue probability-like scales ranging from 0 to 1 (or 100) [7,8], for which the resulting numbers have no clear interpretation and hence no real meaning (as discussed in [8]). But this is not true for the ideas developed in this paper, since the de Finetti approach gives a precise meaning to the measurement of uncertainty. Furthermore,

Bayesian probability theory shows how optimal decision-making in the face of uncertainty depends, in fact, on probabilities defined in this way [9]. In addition, any optimal decision must be consistent with some coherent set of probability assessments for the relevant uncertain outcomes, whether these assessments are made explicitly or not. The chance that a set of assessments that are made implicitly are actually coherent must be exceedingly remote.

2) If the purpose of the causality assessment is to guide particular decisions, it is not usually necessary to evaluate each component probability precisely. As we shall show in Section B, a Bayesian causality assessment requires the evaluation of the probabilities of several different propositions. Suppose an assessor determines that his probability for one of these propositions lies somewhere between two numbers, say $1/3$ and $1/2$, but he finds it very difficult to evaluate it with greater precision. It is always possible to go through the entire causality assessment, using $1/3$ wherever the probability in question appears, and then repeat the analysis using $1/2$ instead. If the overall causality assessment is not very different, then there is no need to evaluate this particular probability more precisely. If it is, and some contemplated decision might hinge on the difference, then further work is unavoidable. The point is that such "sensitivity analyses" can always be carried out, with respect to the probabilities that prove to be the most difficult to assess; if it turns out to make no real difference which number in a certain range is used, then there is no need to introduce what seems like an arbitrary precision. If it matters, some creative tinkering using Bayes' Theorem or some other device based on probability theory is necessary to solve the problem.

3) What is the alternative to quantifying uncertainty? It is hard to see how the evidence about different factors and from different sources can be weighed and merged in a reasonable and nonarbitrary way without using quantitative methods that start with the explicit measurement of uncertainty. Certainly, as we argued in [1], no qualitative methods yet developed have come close to achieving this goal.

There is still one important issue to address: how can you know if a probability appraisal is "right"? If probability measures subjective degree of belief, then this question seems meaningless (unless it addresses the problem of how someone else could determine whether the assessor is honestly announcing his real opinions, a problem that we shall not address here). But this is not the end of the story. Probabilities of propositions about future observables can be converted into predictions about the values that these observables will assume, and the validity of the predictions can be subjected to empirical checks. For example, suppose two different coherent assessment methods are used to produce probabilities for a set of propositions about future observables, and one method consistently assigns higher probabilities to the propositions that turn out to be true, and lower probabilities to the ones that turn out false, than the other method. Then it seems reasonable to conclude that even though both methods are coherent, one of the methods is more in tune with the world than the other, and in the future (everything else remaining reasonably the same), one would want to modify his own opinions to concur with probabilities generated by that method rather than by its less effective alternative.

Now, the proposition that the suspected drug caused the adverse event is certainly not about any future observable. It is retrodictive rather than predictive in character, and typically whether the drug actually caused the

adverse event in that particular case or not will never be known with certainty. Thus, the validity of a causality assessment method is not subject to direct empirical check, in which the probabilities it produces are converted into predictions and the accuracy of these predictions is determined. Nonetheless, using Bayes' Theorem, it is possible to convert the causality assessment problem into a series of probability assessments, the propositions in each of which are about the values of future observables. Thus, in principle, the Bayesian approach to causality assessment allows the logical incorporation of a series of methods for evaluating components of the overall uncertainty about drug causation, and each of the methods can be subjected to empirical tests of its soundness.

B. AN OUTLINE OF THE BAYESIAN APPROACH

1. Collecting the Facts

The first step in the Bayesian approach is to collect the facts of the case. The assessor is required to identify the patient's clinical condition preceding the onset of the adverse event, the type of adverse event, the possible causes of the event, and the details of the evolution of the event:

1) Identify the clinical condition M and the type of the adverse event E_t

M is a "generic" specification of the disease for which the patient is undergoing treatment, along with known co-morbidity (for example, M might denote pneumococcal pneumonia or severe congestive heart failure). E_t is

the "generic" type of the adverse event (for example, gastritis or aplastic anemia), not a detailed description of the particular case at hand, which is denoted by E. These identifications can be made with different degrees of specificity. However, the important point is that they should be made explicitly at the beginning of the assessment, and thereafter whenever the assessment refers to "M" or "E_t", the meaning should remain the same.

2) List the possible causes for the adverse event E

The Bayesian approach requires that the alternative etiologies be listed in such a way that the elements of the list are mutually exclusive and exhaustive. The list should include possible drug causes (D₁ to D_n), the clinical condition M, nondrug treatment modalities, environmental exposures, and, of course, the possibility of some "unknown" cause.

It is necessary to clarify what it means to say that a drug "causes E". The proposition "D \rightarrow E" is true if E would not have happened as and when it did had D not been administered. This does not preclude the possibility that some attributes of the clinical condition M were also necessary for E to occur. Thus, if the listed possible causes are the drug D, the clinical condition M and "unknown", then the proposition "M \rightarrow E" means not only that E was a sequela to M, but also that E would have happened if D had not been administered. That is, D-causation includes the possibility of an "interaction" between D and M, while M-causation expressly rules out D involvement.

Suspected drug interactions must be specifically incorporated into the list of possible causes. More precisely, when there is more than one drug as a causal candidate, if an interaction between drugs D₁ and D₂ is considered a

priori as a possible cause, the list must include the hypotheses D_1 alone, D_2 alone, and D_1 and D_2 jointly.

The list of causes is important in the Bayesian approach, since the approach works by partitioning the total probability, 1, among the various causal hypotheses, given all the elicited evidence. Thus, if a new etiological candidate is introduced to the list of causes, the causality assessment can change.

3) Record the relevant details about the case at hand

It is most convenient to think about the case information that needs to be recorded in terms of the chronology or time-course of the event E, an example of which is illustrated in figure 1. The symbols H_i , T_i , Ch , De and Re , which refer to different chronological classes of case information, are defined as follows:

H_i (patient's history) contains information about the patient that antedates E. Typically, H_i might include data about previous experiences with the suspect (and related) drugs and special demographic, behavioral, clinical or genetic risk classes for events of type E_t to which the patient belongs.

T_i describes the time of onset of E in relation to the administration of the drugs the patient has received, including (when available) the time-course of prodromal events like subclinical findings and early clinical signs and symptoms.

Ch (characteristics of E) refers to the period between the time of onset and dechallenge (or until E clears, if no dechallenge occurs). Ch might include data about drug levels in tissues or body fluids, as well as other details in clinical presentation, laboratory results, pathological findings, or time-course that allow E to be more precisely described or classified.

De and Re refer to events in time periods initiated by dechallenge and rechallenge with the suspect drugs, when these occur. With respect to withdrawal of a particular drug D, De typically includes whether the symptoms associated with E abated when D was withdrawn (or its dosage reduced), and, if so, the time-course and clinical characteristics of this response. Similarly, Re typically records whether an event of type E reappeared following rechallenge (reintroduction of the drug or increase in dosage after previous dosage reduction), as well as the time it took for this to happen and any characteristics of the new event that provide differential etiological information. If a second dechallenge occurred following a positive response to rechallenge, a new class of information, De₂, must be introduced; similarly, Re₂, De₃, and so on may be necessary. In each case, all information about events in the relevant time period that can help distinguish between the various etiological candidates should be included in the appropriate chronological class.

2. Evaluating the Evidence

After the facts have been collected, their evidentiary significance must be assessed. In this section, we describe the goal of this assessment and the Bayesian strategy for achieving this goal.

The Goal

According to the Bayesian approach, the goal of causality assessment can be defined in the following way: for a drug D suspected as a cause of the adverse event E, calculate the posterior odds in favor of D-causation,

$$(1) \quad \frac{P(D \rightarrow E | B, C)}{P(D \not\rightarrow E | B, C)}$$

Here $D \not\rightarrow E$ represents the proposition that the drug D did not cause the event E; that is, that E would have occurred as and when it did even if D had not been administered. C is the case information (that is, Hi, Ti, Ch, De, and Re) described in the previous section. The additional conditioning term (B) that is not shown in the formula for Bayes' theorem in section 1 is background information. B contains the fact that an event of type E_t has occurred in a patient with clinical condition M at some time after the drugs on the list of possible causes have been administered in a specified way. Unlike the case-specific information in C, the information in B makes no further reference to the particular patient whose case is currently undergoing assessment. In addition, B contains all the background information that the assessor might bring to bear to analyze any such case, including information about the drugs, their pharmacology and kinetics, indications, and risk factors that alter the chance of adverse effects.

The Strategy

Using de Finetti's measure, one could evaluate directly the probabilities in the numerator and denominator of the posterior odds displayed in equation

(1), but, given the complexity of most causality assessment problems, such an act of "global introspection" could almost never be carried out consistently with all the opinions one holds about the meaning and relevance of the information in B and C. Thus, an alternative approach to the evaluation of the posterior odds is required. The strategy we adopt (figure 2) is to decompose the posterior odds into a series of component factors, each of which requires probability evaluations for propositions much more specific and accessible to the experience and knowledge of the evaluator than the proposition "D→E".

We do not mean to imply that the component probability evaluations are "automatic". They may require careful thought, and the assessor may be far from confident in his answers. Nonetheless, we believe that these evaluations are addressable problems, and future work should lead to better techniques for their solution.

FIGURE 2 GOES HERE

Strategy Step 1: Reduce to Single Suspect Drug

In many cases, the list of possible causes will include more than one drug or drug interaction. The first step in the Bayesian approach is to restrict to the case in which there is only one suspect drug, which we shall denote by D. This restriction involves no loss of generality, as we show in Appendix III (the reason is that Bayes' Theorem can be used to merge coherently the solutions of the causality assessment problems that arise when each suspect drug is treated in turn as though it were the only possible drug cause, into a solution to the overall assessment problem).

Strategy Step 2: Use Bayes' Theorem to Decompose the Posterior Odds

We now turn to the Bayesian decomposition of the posterior odds. The first part of this step is to apply Bayes' Theorem in odds form, as presented in section 1:

$$(2) \frac{P(D \rightarrow E | B, C)}{P(D \not\rightarrow E | B, C)} = \frac{P(D \rightarrow E | B)}{P(D \not\rightarrow E | B)} \times \frac{P(C | D \rightarrow E, B)}{P(C | D \not\rightarrow E, B)}$$

posterior odds prior odds likelihood ratio

The first term on the right-hand side of equation (2), the prior odds, gives the odds in favor of drug causation taking into account just background information and disregarding any details about this particular patient and his adverse event. The second term on the right-hand side, the likelihood ratio, compares how likely are the details observed in this particular case under two competing etiologic hypotheses: that the drug did and did not cause the adverse event E.

The advantage gained by the decomposition in equation (2) derives from the following consideration. As we have seen, the probabilities in the posterior odds refer to inherently unverifiable propositions: that the particular event E was or was not caused by D. On the other hand, the propositions whose probabilities appear in the prior odds and in the likelihood ratio are closely linked to predictive probabilities that can in principle be validated. We now turn to the connection between the prior odds and predictive probabilities.

Strategy Step 3: Reformulate Prior Odds in Terms of Predictive Probabilities

First, note that there is an important difference between the posterior and prior odds terms. Since both are evaluated conditionally on B (background information), they both refer to a patient with clinical condition M who has been administered drug D and experienced an event of type E_t . However, the identity of the patient to whom the statement refers is different in the two terms. In the posterior odds, it is the particular patient for whom the causality assessment is being carried out, while in the prior odds it is a "generic" patient (for example, the "next" patient with M who suffers an event of this type after receiving D, for example) with the three defining properties — clinical condition M, exposure to D and adverse event of type E_t . To reinforce this distinction, we shall substitute the expression " $D \rightarrow E_t$ " for " $D \rightarrow E$ " when the proposition refers to the "generic" patient who developed the "generic" event (E_t) rather than the particular patient and the particular adverse event.

To see the connection between prior odds and predictive probabilities most clearly, it is easiest to focus on a special case. Imagine that records are available for a large group of patients with clinical condition M, and that the subgroup consisting of those patients who have received D is similar to the subgroup who have not, with respect to the distribution of any variables that are prognostic for the occurrence of events of type E_t (except, of course, for exposure to D).

The incidence of events of type E_t among those patients who take D is the sum of two components: the incidence of the events caused by D and the incidence of events not caused by D. Since the patients taking and not taking D are otherwise prognostically equivalent, the incidence of events not caused by D in the patients taking D is the same as the incidence of all the events

of type E_t in the patients not taking D. Since the prior probability that an event is caused by D is just the ratio of the incidence of events caused by D to the overall incidence of events among patients who receive D, we can summarize this discussion by the following equation:

$$(3) \quad P(D \rightarrow E_t | B) = \frac{P(E_t | D) - P(E_t | D^c)}{P(E_t | D)}$$

And, similarly:

$$(4) \quad P(D \not\rightarrow E_t | B) = \frac{P(E_t | D^c)}{P(E_t | D)}$$

where $P(E_t | D)$ is the probability that a patient who received D will experience an event of type E_t , and $P(E_t | D^c)$ is the probability that a patient who did not receive D will experience an event of this type. Both these probabilities clearly generate predictions of the incidence of events of type E_t , among future patients with M who do and do not receive D.

Applying the results of the above equations to the numerator and denominator of the prior odds we get:

$$(5) \quad \frac{P(D \rightarrow E_t | B)}{P(D \not\rightarrow E_t | B)} = \frac{P(E_t | D) - P(E_t | D^c)}{P(E_t | D)} \div \frac{P(E_t | D^c)}{P(E_t | D)}$$

$$= \frac{P(E_t | D) - P(E_t | D^c)}{P(E_t | D^c)}$$

Strategy Step 4: Decompose the Likelihood Ratio

Trying to evaluate the probability of all the case details simultaneously is too hard, since there is far too much to think about at once. Therefore, we shall decompose the likelihood ratio into a series of factors each involving probabilities for propositions about only one of the five chronological classes H_i , T_i , Ch , De , and Re :

$$(6) \frac{P(C|D \rightarrow E, B)}{P(C|D \not\rightarrow E, B)} = LR(H_i) \times LR(T_i) \times LR(Ch) \times LR(De) \times LR(Re)$$

Where

$$(7) LR(H_i) = \frac{P(H_i|D \rightarrow E, B)}{P(H_i|D \not\rightarrow E, B)}$$

$$LR(T_i) = \frac{P(T_i|D \rightarrow E, B, H_i)}{P(T_i|D \not\rightarrow E, B, H_i)}$$

$$LR(Ch) = \frac{P(Ch|D \rightarrow E, B, H_i, T_i)}{P(Ch|D \not\rightarrow E, B, H_i, T_i)}$$

$$LR(De) = \frac{P(De|D \rightarrow E, B, H_i, T_i, Ch)}{P(De|D \not\rightarrow E, B, H_i, T_i, Ch)} \quad \text{and}$$

$$LR(Re) = \frac{P(Re|D \rightarrow E, B, H_i, T_i, Ch, De)}{P(Re|D \not\rightarrow E, B, H_i, T_i, Ch, De)}$$

In words, $LR(H_i)$ might be called the likelihood ratio factor evaluating historical information, $LR(De)$ the likelihood ratio factor evaluating dechallenge information, and so forth. The order in which these factors

appear in equation (6) (and which factors appear as conditioning sets) is determined by chronology. Note that the probabilities that comprise the numerator and denominator of each likelihood ratio are conditioned on B (background information) and on the information in the likelihood terms that have already entered into the equation.

Strategy Step 5: Recombine the Prior Odds and the Likelihood Ratio Terms to Obtain the Posterior Odds

Recombining the prior odds and the likelihood ratio terms gives the Bayesian decomposition of the posterior odds for causality assessment of a suspected adverse drug reaction:

$$\text{Posterior Odds} = \text{Prior Odds} \times \text{LR(Hi)} \times \text{LR(Ti)} \times \text{LR(Ch)} \times \text{LR(De)} \times \text{LR(Re)}$$

C. CAUSALITY ASSESSMENT CRITERIA AND THE BAYESIAN APPROACH

In a second paper we address the main tactical questions for the Bayesian approach: how can an assessor evaluate the prior odds and the likelihood ratio factors? In this section we examine whether the Bayesian strategy satisfies the six criteria for causality assessment introduced in [1]. We state each criterion (for justifications and discussion, see [1]) and then discuss how it relates to the Bayesian approach.

Criterion 1: Repeatability. When the same "state of information" is used more than once as input, a causality assessment method should produce the same "degree of belief" as output.

In its present form, the details of the Bayesian approach are insufficiently specified to achieve repeatability. The difficulty is not so much that there are too many probability assessments to make, each of which may vary from one evaluation to the next even when the "state of information" does not change. Rather, the main problem is to determine in a standardized way what probabilities need to be evaluated for each of the components of the posterior odds. We believe that it will be possible to develop algorithmic methods based upon the Bayesian approach, in the context of specific drug-induced diseases (like cholestatic jaundice or Stevens-Johnson syndrome) or specific drugs (like digoxin). In such specific problem areas, "canonical" questions for eliciting the relevant information, as well as standardized methods for operating with this information to determine the appropriate probabilities, can be constructed. The more algorithmic the methods become, the more they will be able to satisfy this criterion.

Criterion 2: Explicitness. A causality assessment method should require that its user make explicit his "state of information", including the uncertainty he feels about each of its elements.

The essence of the Bayesian approach is the explicit evaluation of uncertainty, so this requirement of the criterion is certainly satisfied. Since probabilities are most easily evaluated the more exhaustively the problems are decomposed, the approach encourages the user to make explicit all his relevant information and the relations between its elements.

Criterion 3: Transparency. A causality assessment method must make it clear to the user how it produced the output "degree of belief" from the information it elicited.

The Bayesian approach reaches its conclusions from the component probability evaluations of the user by following the rules of prescriptive probability theory. The effect of the information in each factor on the output posterior odds is clear, since the posterior odds is just the product of the prior odds and the five likelihood ratio factors. In particular, it is easy to see at a glance which factors are the important ones in any assessment.

Criterion 4: Completeness. Any fact, theory, or opinion that can affect an evaluator's belief that a drug D caused an adverse event E must be incorporable by a causality assessment method into the "state of information" on which the assessment is based.

In principle, any such fact, theory, or opinion can become the subject of a probability evaluation or the basis upon which such an evaluation is carried out. In particular, the Bayesian approach can deal with the three kinds of information singled out in [1] as essential, but not incorporable into other current assessment methods: uncertain information, quantitative information, and background information, especially epidemiological data about incidences and mechanistic theories from the basic sciences. Thus, the Bayesian approach already satisfies this criterion in principle; as better models are constructed to facilitate the incorporation of particular kinds of information, it will increasingly be able to satisfy it in practice.

Criterion 5: Etiological balancing. Methods cannot evaluate case data just in terms of their concordance or discordance with the hypothesis that the drug D caused the event E; rather, they must compare how much more (or less) compatible the findings are with drug versus other causation.

This criterion is embedded in the architecture of the Bayesian approach.

Criterion 6: No a priori constraints on the effects of factors. A causality assessment method should not limit a priori the effect that information about any particular factor can have on the final result.

Each of the five likelihood ratio factors and the prior odds can range anywhere between zero and infinity, so the Bayesian approach places no a priori limits on their possible effects. Rather, these effects are only limited by the amount of information available and the state of the user's uncertainty about that information.

DISCUSSION

The Bayesian approach to causality assessment of adverse drug reactions provides an internally consistent and logical framework for assessing the probability that an adverse event was caused by drug therapy. The approach also satisfies, in principle, five of six criteria that we previously proposed for the evaluation of causality assessment schemes. The qualification "in principle" is necessary, because as presented, the approach is difficult to implement and does not yet qualify as a standardized assessment method. Nonetheless, the Bayesian approach does substantially better with respect to these criteria, compared with other currently available causality assessment methods [1]. The approach does not, however, ensure the quality of the user's component assessments and does not solve the problem of how best to convert the assessments into probabilities. Clearly, an optimal result will require expert evaluation of the individual components. There is also much work to be done on how to elicit the relevant probabilities, although many useful ideas

and techniques already exist. The second paper in this series describes and illustrates some of these techniques for turning opinions about a clinical case into the probabilities that comprise the Bayesian assessment.

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APPENDICES

Appendix I: The Fundamental Rules of Probability Theory

A collection of conditional probability assessments is coherent if and only if the following three conditions are satisfied:

1) The Normalization Condition: For every pair of proposition A,B, $P(A|B)$ must be between 0 and 1, inclusive.

2) The Additivity Condition: If A and C are mutually contradictory propositions, and B is any proposition.

$$P(A \text{ or } C|B) = P(A|B) + P(C|B)$$

3) The Multiplicative Condition: For any propositions A,B and C,

$$\begin{aligned} P(A \text{ and } C|B) &= P(A|B) \times P(C|A \text{ and } B) \\ &= P(C|B) \times P(A|B \text{ and } C) \end{aligned}$$

Appendix II: Derivation of Bayes' Theorem

Bayes' Theorem is derived from the multiplicative condition (Appendix I), which establishes the following equality:

$$(1) \quad P(A|B) \times P(C|A \text{ and } B) = P(C|B) \times P(A|C \text{ and } B).$$

Dividing both sides of (1) by $P(C|B)$ and transposing sides gives

$$(2) \quad P(A|C \text{ and } B) = [P(C|A \text{ and } B) \times P(A|B)] / P(C|B)$$

which is Bayes' Theorem. To derive the odds form of Bayes' Theorem, apply the theorem with A^c in place of A to obtain

$$(3) \quad P(A^c|C \text{ and } B) = [P(C|A^c \text{ and } B) \times P(A^c|B)] / P(C|B).$$

Finally, divide equation (2) by equation (3), yielding

$$(4) \quad \frac{P(A|C \text{ and } B)}{P(A^c|C \text{ and } B)} = \frac{P(C|A \text{ and } B)}{P(C|A^c \text{ and } B)} \times \frac{P(A|B)}{P(A^c|B)}$$

$$= \frac{P(A|B)}{P(A^c|B)} \times \frac{P(C|A \text{ and } B)}{P(C|A^c \text{ and } B)}$$

Posterior Odds = Prior Odds x Likelihood Ratio

Appendix III: The One-Drug-at-a-Time Strategy

Let D_1, \dots, D_n represent all the (mutually contradictory) drug hypotheses on the list of causes, and group all the other hypotheses (for example: M , "other", etc.) as N (for nondrug).

Write $PO(D_i)$ for the posterior odds in favor of cause D_i . Now let A_i represent the hypothesis " D_i or N " (that is, the cause of E is either D_i , or a nondrug cause), and write $PO(D_i | A_i)$ for the posterior odds in favor of cause D_i , given A_i :

$$(1) \quad PO(D_i | A_i) = P(D_i \rightarrow E | B, C, A_i) / P(D_i \not\rightarrow E | B, C, A_i).$$

Notice that $PO(D_i | A_i)$ solves the causality assessment problem for a case in which there is only one drug causal candidate, D_i .

Claim: The following formula gives the posterior odds in favor of cause D_i :

$$(2) \quad PO(D_i) = PO(D_i | A_i) / [1 + \sum_{j \neq i} PO(D_j | A_j)].$$

That is, if the assessor calculates the conditional posterior odds in favor of cause D_j , $PO(D_j | A_j)$, for each possible drug cause D_j , (other than D_i) then he can merge these condition odds to obtain the unconditional posterior odds in favor of cause D_i .

Proof of Claim: For succinctness, we omit B and C from the right of " $|$ " in all the probabilities that appear in this proof. By the multiplicative condition (Appendix 1):

$$P(D_i \text{ and } A_i) = P(A_i) \times P(D_i | A_i)$$

Dividing by $P(A_i)$ and transposing sides

$$P(D_i | A_i) = P(D_i \text{ and } A_i) / P(A_i)$$

Since $P(D_i \text{ and } A_i) = P(D_i)$

And $P(A_i) = P(D_i \text{ or } N) = P(D_i) + P(N)$

(3) Then $P(D_i | A_i) = P(D_i) / [P(D_i) + P(N)]$

Similarly, since $P(D_i^c \text{ and } A_i) = P(N)$

(4) Then $P(D_i^c | A_i) = P(N) / [P(D_i) + P(N)]$

Thus,

(5) $P(D_i | A_i) / P(D_i^c | A_i) = P(D_i | A_i) / P(D_i^c | A_i) = P(D_i) / P(N)$

Applying equation (5) for each drug cause D_i , the right-hand side of equation (2) is equal to

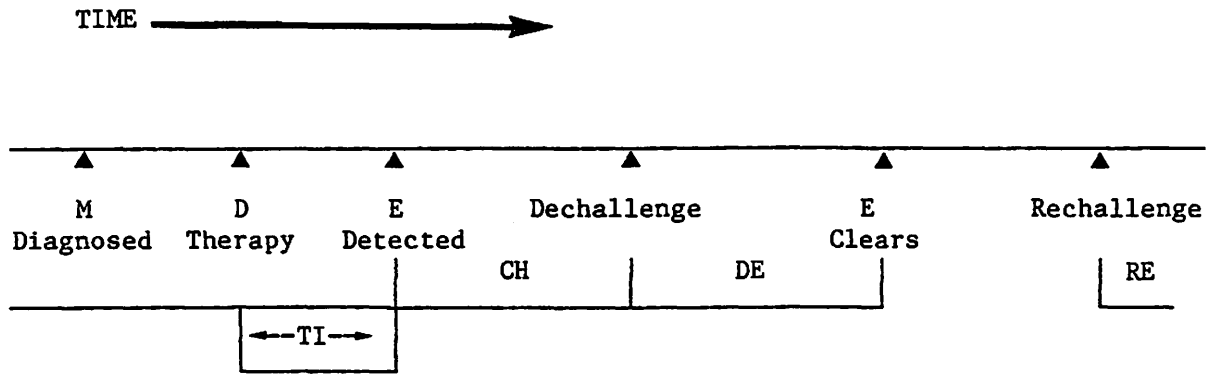
(6) $[P(D_i)/P(N)] / [1 + \sum_{j \neq i} P(D_j)/P(N)] = P(D_i) / [P(N) + \sum_{j \neq i} P(D_j)]$

Since $[P(N) + \sum_{j \neq i} P(D_j)]$ includes all possible causative hypotheses other than D_i this term = $1 - P(D_i)$.

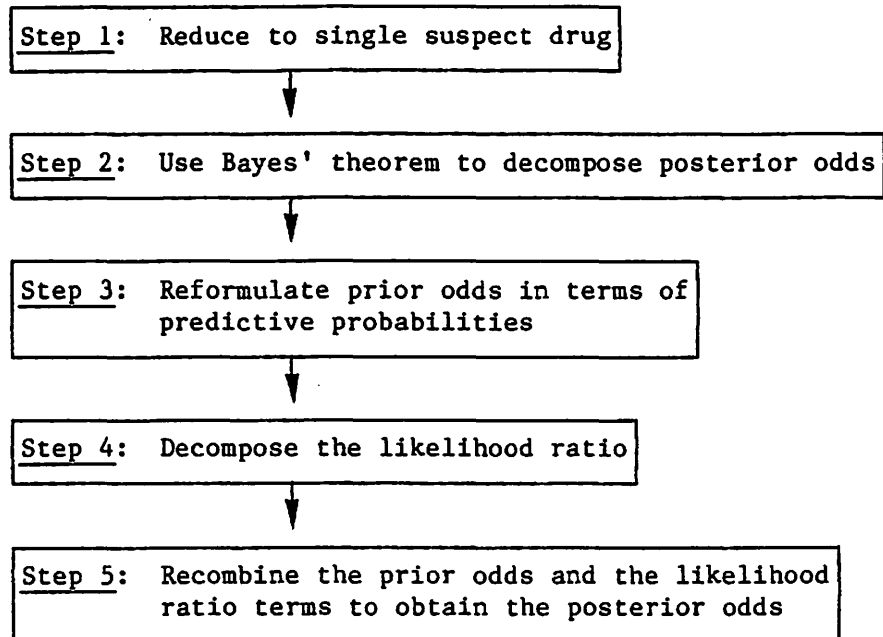
Therefore, the right hand side of the equation becomes

$$\begin{aligned} & P(D_1) / [1-P(D_1)] \\ & = PO(D_1) \end{aligned}$$

which completes the proof of claim.

FIGURE 1Categories of Case Information Defined by Chronologic Sequence

- M = Disease for which patient is undergoing treatment
- D = Suspected Drug
- E = Adverse Event
- Hi = Patient's History
- Ti = Timing of onset of adverse event
- Ch = Characteristics of Adverse Event
- De = Dechallenge
- Re = Rechallenge

FIGURE 2Strategy for Arriving at the Posterior Odds of Drug Causation

A BAYESIAN APPROACH TO CAUSALITY ASSESSMENT FOR SUSPECTED
ADVERSE DRUG REACTIONS II: TECHNIQUES FOR IMPLEMENTATION

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This research has been supported by grants from the University of Minnesota Graduate School, the Drug Information Association, the American Medical Association Education and Research Foundation and Ciba-Geigy Canada.

Manuscript pages: 30
Tables : 3
Appendices : 6
Figures : 0

ABSTRACT

Techniques are presented for implementing a Bayesian approach to causality assessment for adverse drug reactions. Four general techniques for probability evaluation are described: conditioning; analogy; the use of frequencies; and models. The use of these techniques in evaluating the prior odds and the likelihood ratio terms of the Bayesian approach is discussed and their application illustrated by a case in which amoxicillin is suspected of causing diarrhea. The Bayesian method provides a feasible, efficient, and logically satisfying answer to the causality assessment problem. It also gives new insights and increased understanding into the problem of assessing adverse drug reactions.

Key words: adverse drug reactions, causality assessment, Bayes Theorem, probability

INTRODUCTION

In the first paper of this series [1] we presented a Bayesian approach to the problem of assessing causality in suspected adverse drug reactions. Using the odds ratio form of Bayes Theorem we showed how the posterior odds in favour of drug causation can be obtained by multiplying the prior odds by likelihood ratio terms for each of five separate elements of the case information: History (Hi); Timing (Ti); Characteristics (Ch); Dechallenge (De); and Rechallenge (Re).

$$(1) \frac{P(D \rightarrow E | B, C)}{P(D \not\rightarrow E | B, C)} = \frac{P(D \rightarrow E_t | B)}{P(D \not\rightarrow E_t | B)} \times LR(Hi) \times LR(Ti) \times LR(Ch) \times LR(De) \times LR(Re)$$

Posterior Odds = Prior Odds x Likelihood Ratio terms

D is the suspected drug.

E is the adverse event.

E_t is the generic type of the adverse event.

$D \rightarrow E$ indicates that the drug caused the adverse event.

$D \not\rightarrow E$ indicates that the drug did not cause the adverse event.

B is background information.

C is the case information.

We argued that in principle, this approach provides a coherent framework for dealing with the multiple uncertainties and complexities of the adverse reaction causality problem. In this paper we describe techniques for applying this approach in practice. In Section A we discuss general techniques for

probability evaluation. In Section B we describe how to implement the Bayesian approach and demonstrate the approach using a case of diarrhea after amoxicillin use.

A. GENERAL TECHNIQUES FOR PROBABILITY EVALUATION

In this section we describe four general techniques for evaluating probabilities that can be used to advantage in the causality assessment context. They are: conditioning; analogy; the use of frequencies; and the use of models.

Conditioning: Sometimes, evaluating the probability of a proposition can seem difficult because the assessor's thoughts about the proposition depend on which of several other propositions are true. For example, if an assessor wants to determine the probability that an event of type E_t will occur as an adverse reaction to a drug D within a day of receiving a specified dosage of D, he might find that his assessment of this probability depends on the mechanism of the reaction (whether the reaction is immunologic or dose-dependent, for example). Or again, in assessing the probability that an event of type E_t , which is not caused by D, will occur in a specified time period, the evaluator might want to consider separately each possible alternative cause for the event.

In such cases, the Law of Total Probability (see Appendix I) can frequently be applied. First, the various possibilities on which the evaluation depends must be listed in such a way that one and only one of them can be true (for example, the mechanism for the reaction may be immunologic, dose-dependent, or "other"; or the alternative, nondrug causes for the event might be a viral infection for which the patient is being treated, some

other, nondiagnosed infection, or another "unknown" cause). Then, the assessor must evaluate the probability of the proposition in question, conditional on each listed possibility. Next he must evaluate the probability for each of the possibilities he has conditioned upon; this evaluation involves inherently unobservable propositions, but in our experience assessors often have little trouble partitioning their belief among a set of mutually contradictory mechanistic theories (the trickiest part is to decide how much probability to assign the catch-all "other" or "unknown"). Finally, the assessor puts together these two sets of evaluations according to the Law of Total Probability. An example of this procedure will be presented in Section B below.

Analogy: As explained in the first paper of this series, probability is just a measure of the assessor's uncertainty. Thus, it is sometimes possible for an assessor to evaluate a probability for a proposition by thinking about some other proposition about which his uncertainty is comparable and whose probability is easier to appraise.

For example, suppose you believe that the pharmacological mechanisms by which two related drugs can cause a particular kind of adverse reaction are very similar. Then it may be reasonable to suppose that the timing distributions for events of this type as adverse reactions to the two drugs are similar (in particular, say, the probability that E occurs within one day after receiving D_1 , given that D_1 caused E, would be nearly the same as the same probability with respect to D_2). But the assessor may have much more experience with one of the drugs than with the other, in which case he might be quite confident about his assessment of the timing distribution corresponding to the familiar drug, which he can then transfer (perhaps with minor modifications) to the less familiar one.

As another example, suppose an assessor needs to evaluate his probability that the next infant receiving a course of therapy with a new "cillin"-type antibiotic drug will develop diarrhea. He can base this evaluation on the knowledge that reported incidences of diarrhea following therapy with other drugs in this group range from about 5 to 25%, with a mode of about 10% [2,3]; and so, if he is unaware of any feature of the new drug that would distinguish it from others in its class with respect to its propensity to cause diarrhea, he should assess the required probability, by analogy, at about 1/10.

Frequencies: Sometimes, an assessor may have access to observed frequencies that are clearly relevant to a probability evaluation problem he is trying to solve. For example, he might want to evaluate his probability that the next infant receiving a specified course of amoxicillin therapy will develop diarrhea, and he notes that a study monitoring outpatients in a large pediatric teaching hospital reported 130 cases of diarrhea out of 1320 patients within two days of beginning amoxicillin therapy [2]. Should he necessarily evaluate his probability as 13/132?

In general, the answer to this question is no. There are two primary reasons for this. The first has to do with the similarity between the patients for whom the probability evaluation is relevant and the patients upon whom the observed frequencies are based. The class of patients to which the probability evaluation refers is precisely specified by the conditions that appear to the right of the "|" in the statement of the probability. For example, if the probability in question, $P(E_t | D, M)$ (the probability that a patient with clinical condition M who receives D in a specified way will experience an event of type E_t) the class consists of all patients who have the clinical condition defined by M and receive the course of therapy denoted by D. Differences in such factors as age, sex, severity of M, comorbidity, or

the dosage of D, however, may limit the applicability of frequencies reported in the literature to the specific class of patients for which probabilities are being assessed.

The second reason that probabilities may differ from observed frequencies has to do with chance variation. Even if the patients for whom frequency information is available are characterized precisely, the probability and the observed frequency need not coincide, since the observed frequency reflects to some extent the vagaries of chance, especially if the sample size is small.

Now, if the frequency information is based on patients in the class defined by the probability evaluation problem, and these patients have no other special defining characteristics and their number is large, then any coherent evaluation of the probability must be very close to the observed frequency. Otherwise, adjustments have to be made. Correcting for sample size is easy; dealing with the difference between the classes to which probability evaluation problems and observed frequencies refer is not.

Informally, we suggest the following solution to the problem. Use observed frequencies, when available, to provide an "anchor" or initial solution to a probability evaluation problem. Then think about the ways in which the class to which the frequency information refers may differ from the class relevant to the probability evaluation, and decide what direction these differences suggest for changing the initial solution. (For example, if the observed frequencies for diarrhea following amoxicillin therapy were based only on infants in day-care centers, among whom one expects to find an elevated incidence of gastroenteritis, the frequencies should be adjusted downward to apply to the general infant population.) Finally, adjust the probability evaluation in the appropriate direction.

Sometimes, it is possible to use the connection between probability and frequencies to help evaluate probabilities, even when relevant observed frequencies are not available, by the following psychological ploy: the device of imaginary results. Suppose that an assessor has a great deal of clinical experience with a particular kind of adverse event, and, for example, he must evaluate the probability that an event of this type will occur within one day of beginning D-therapy, given that it occurs sometime in the month after the therapy begins. Such an assessor might find it useful to draw upon his experience by imagining a great number of patients in the relevant class who have an event within a month after beginning D-therapy, and asking himself what proportion of those patients he thinks will experience the event in the first day. If he can answer this question, he should use this proportion as his answer to the required probability evaluation problem.

Models: A model is a formal and general approach to probability evaluation. Models can be viewed as systematic applications of the ideas of conditioning and analogy. Because they can be constructed in accordance with the rules of probability theory, they give a framework for the coherent merger of different kinds of relevant information. As an example of the kind of model that would be helpful in the causality assessment context, think of the time of onset of a dose-dependent adverse reaction to drug D. This time cannot be predicted with certainty, but it depends in part on certain pharmacological properties of the drug, physiological aspects of the reaction, and specific attributes of the patient. A model for time to onset would specify how the mean reaction time depends on a particular set of drug-event-patient parameters, and it would also specify the pattern of the residual variability (which is not determined by the specified parameters). If such a model were constructed, the causality assessor would only need to specify the values of the input parameters for the particular case at hand, and he could then use

the model to compute the probability that an event of type E_t caused by drug D would occur just when the event E undergoing assessment occurred (which is the numerator of the likelihood ratio for timing).

Such models would be of great benefit in implementing the Bayesian strategy, because they would reduce the number of probability evaluations that an assessor would have to perform in carrying out any particular causality assessment, they would substantially reduce the subjectivity in each of the remaining evaluations, and they would permit general predictive tests that would substantiate the models' and hence the whole Bayesian procedure's validity. We do not yet have such models, but one of the great advantages of the Bayesian approach is that it makes clear what models need to be developed, and it allows their incorporation into the causality assessment procedure as they are developed.

B. HOW TO IMPLEMENT THE BAYESIAN APPROACH: EXAMPLE OF AN APPLICATION TO A CLINICAL CASE

In this Section, we apply the Bayesian approach to a case of suspected amoxicillin-induced diarrhea. The analysis is not based on an exhaustive review of the literature; rather, it represents the clinical consensus of the authors of the paper, only one of whom (M.S.K.) has special expertise in this area. Nonetheless, we believe that the analysis provides a good introduction to the Bayesian approach and that the conclusion we draw is both essentially correct and consistent with all our opinions relating to the problem.

THE CASE

B.L. is a 17-month-old male day-care center attendee who on December 10 developed signs and symptoms of an upper respiratory tract infection with rhinorrhea and cough, but without fever or gastrointestinal symptoms. On the third day of his illness, his temperature rose to 39.4°C, he became irritable, and he began to pull at his ears. He was seen by his pediatrician on that day and was diagnosed as having bilateral otitis media. Treatment was initiated with amoxicillin suspension in a dose of 125 mg t.i.d. Over the next 24 hours, B.L. had three watery bowel movements. By the fifth day, he was afebrile; the diarrhea continued, but without exacerbation. His mother telephoned the pediatrician, who suggested continuing the medication and encouraging fluid intake. B.L. remained afebrile and became less irritable and more playful, but the diarrhea persisted. The amoxicillin was discontinued after a 10-day course, and the diarrhea resolved within two days following dechallenge and did not recur.

ANALYSIS

The analysis is performed in six steps that are shown in table 1. The six subsections that follow each deal with one step in the analysis. Each subsection begins with a general discussion of the issues involved. This is followed by direct application to the case outlined above.

TABLE 1 GOES HERE

1) The Case "Parameters"

a) The Clinical Condition (M) and the Adverse Event Type (E_t): The Bayesian strategy requires that the patient's clinical condition M and the type of adverse event E_t be unambiguously defined and that the definitions then be consistently applied in every subsequent probability evaluation. The level of specificity of these definitions can make a difference in how easy it is to carry out probability evaluations in which they play a role.

b) The Time Horizon: It is usually a good idea to attach a definite time horizon to the definition of the event type (that is, the definition of the event type is modified to include the requirement that the event occur sometime within a fixed amount of time -- the time horizon -- after the administration of D). Specifying the time horizon is particularly useful in assessing the prior odds and the distribution for time to onset of the event as a function of the cause of the event. As a rule of thumb, we usually take as the horizon for a relatively common event a period at least as long as a "reasonable" time period for the event to occur as an adverse reaction to the suspect drug D, while for an uncommon event, the horizon might be much longer. For example, if the event is diarrhea (as in the example), an appropriate time horizon might be one or two weeks; if the event is Stevens-Johnson syndrome the horizon might be one year. The time horizon chosen can facilitate the assessment, but it does not affect the evaluation of the posterior odds in favor of drug causation. More accurately, we should say it should not affect the evaluation, and would not, if the assessor were coherent. Changing the time horizon will change the values of the different components of the posterior odds, but the changes compensate (see Appendix III). For example, shortening the time horizon typically increases the prior odds in favor of drug causation, but proportionately lowers the likelihood ratio for timing.

c) The Possible Causes of E: The assessor must make a list of the possible causes for E that he wishes to consider in his evaluation. Since the Bayesian method works by partitioning the total probability, 1, between the listed causes it is important that the items on the list be mutually exclusive and exhaustive. Note that the first item in the list, drug-causation, has a very specific meaning in this context. The proposition $D \rightarrow E$ means that E would not have happened as and when it did had D not been administered; this does not rule out the possibility that some aspects of the patient's clinical condition were also necessary for E to occur. Thus, if there is an interaction between the effects of the drug and other non-drug causes for E, the interaction is credited to drug causation.

The Case "Parameters": Application

The Clinical Condition M: M is the upper respiratory tract infection (presumably viral), which by the third day is accompanied by fever and bilateral otitis media.

The Adverse Event Type E_r : A bout of frequent, loose stools, which we shall hereafter refer to as diarrhea.

The Time Horizon: One week from initiation of D-therapy.

Possible Causes of E: (1) Amoxicillin (denoted D hereafter); (2) Late-occurring GI symptoms secondary to the original infection (that is, M); (3) Coincidental gastroenteritis.

2) Collecting The Relevant Case Information

The Bayesian approach requires the assessor to list the relevant case information in each of five classes, in response to the prompts given in Table 2 (the questions in Table 2 are posed with respect to a particular suspect drug D; if more than one drug is a possible cause of D, repeat the questions with respect to each of them). Note that the relevant information is not the whole case report but only those aspects of it that are useful for distinguishing drug from non-drug causation. Also, the quantity of information in each of the five classes can vary widely from case to case. In particular, for most cases, H_i and T_i contain important and sometimes abundant data. On the other hand, many events are irreversible, and so dechallenge and rechallenge cannot occur. Even if E is reversible, it may be sufficiently serious that rechallenge is not ethically feasible and so does not take place.

The Relevant Case Information: Application

H_i: There is no information about the patient's previous experience with D or events of type E_t but two aspects of the case places the patient at special risk for diarrhea from a non-drug cause (cause 2 or 3 above) he is a day care-attende, and the diarrhea occurred in December.

T_i: E began within one day after D-therapy was initiated.

Ch: The only relevant information in this category is the duration of E; the diarrhea persisted for ten days before dechallenge took place.

De: The diarrhea resolved within two days after dechallenge.

Re: No rechallenge occurred.

3) Evaluating The Prior Odds

$$(2) \quad \begin{array}{l} \text{Prior} \\ \text{Odds} \end{array} = \frac{P(D \rightarrow E|B)}{P(D \not\rightarrow E|B)} = \frac{P(E_t|D) - P(E_t|D^c)}{P(E_t|D^c)}$$

As previously demonstrated in [1], the prior odds can be regarded as a function of two incidence probabilities, $P(E_t|D)$ and $P(E_t|D^c)$, the first giving the incidence of events of type E_t among patients with M who receive the specified course of D -therapy, and the second giving the same incidence for an otherwise similar group of patients who do not receive D . Usually, such incidences are not known precisely. However, the assessor can always use the following tactic, whose precise formulation and probabilistic justification are presented in Appendix II: first, he expresses his uncertainty about the "true" incidences in the form of a probability distribution for these two quantities; then, he uses the appropriate midpoints of these distributions as his probabilities $P(E_t|D)$ and $P(E_t|D^c)$; finally he computes the prior odds as a function of these probabilities according to the formula shown above.

It is frequently possible to employ this tactic in a more informal way, particularly when the assessor has access to reasonably extensive and relevant frequency information (as is often the case for the incidence of events of

type E_t when D is not administered, because estimates for the incidence of such events in the general population can frequently be obtained from the medical literature). When such frequency estimates exist, they can be used to evaluate the relevant probabilities directly, without constructing distributions for the "true" incidences, as in the discussion above on the general relation between probabilities and frequencies. But the cautions issued there hold: the assessor may need to make adjustments to the observed frequencies, since he is interested in the incidence among patients with clinical condition M , not the general population. If patients with M are at greater or less than average risk for events of type E_t , the assessor needs to modify the general incidences accordingly. Also, if the use of the drug D is high in the general population, the population incidence of events of type E_t represents mixtures of the incidences with and without D , and some adjustment is necessary before the observed frequencies can be used to give estimates of $P(E_t | D^c)$ alone.

Another informal method that sometimes works when information about the "true" incidence is limited involves applying the analogy technique for evaluating probabilities. For example, the assessor may believe that the connection between the drug D and the event E of interest is the same range as some other drug-event associations, whose incidence figures are reasonably well-estimated in the literature, and he can adjust these incidences figures to give his $P(E_t | D)$.

But suppose neither of the informal substitution methods discussed in the previous two paragraphs works, and the assessor feels quite vague about what the "true" incidence for events of type E_t really is. As suggested in the first paragraph of this section, he should then try to assess a distribution that describes his uncertainty about the relevant "true" incidence. For example, he may believe that the "true" incidence for events of type E_t

following administration of D is somewhere between, say, 1/1000 and 1/10,000, but he cannot discriminate any more finely than this. Assuming that his uncertainty is approximately uniform over the "order of magnitude" scale, the argument given in Appendix II suggests that he should assess $P(E_t|D)$ as 1/2558 (this is the mean of a distribution that is uniform in the log, or order of magnitude, scale, between 1/1000 and 1/10,000). The point is that the fact that the assessor's information is quite diffuse does not preclude evaluating a prior odds that accurately reflects his uncertainty.

Of course, when information is very diffuse and the assessor's opinion is correspondingly vague, his prior odds can change substantially if he gets access to new data that allows the "true" incidence to be estimated much more sharply. This in no way implies that the kind of calculation described above is "wrong"; only that the value of new information can be high when little is known.

The Prior Odds: Application

To calculate the prior odds, we estimate the numerator and denominator of the ratio on the right hand side of equation (2), using observed frequencies obtained from a study monitoring antibiotic-associated gastrointestinal symptoms in pediatric outpatients in Montreal (B.L.'s home) (some results from this study, but not the raw data that we use, are presented in [2,3]). In addition, we use data from Maricopa County, Arizona, presented in [4,5].

The first quantity we need to estimate is $P(E_t|D) - P(E_t|D^c)$; this difference estimates the "true" incidence of D-caused cases of events of type E_t . In the Montreal study, about 10% of the more than 1,300 patients

receiving amoxicillin suffered from diarrhea within a week of beginning therapy. How many of these were drug-induced? To answer this question, we would like to know what the incidence of diarrhea in the same period would be among patients with M if they were treated with a drug as effective as amoxicillin that could not induce diarrhea as a side effect. Of course, no such drug exists. However, the lowest incidence of diarrhea in the study followed trimethoprim/sulfamethoxazole therapy, and was of the order of 2.5% in the first week of therapy. Thus, we estimate that the incidence (per child) of amoxicillin-caused diarrhea in the first week of therapy is at least $0.1 - 0.025 = 0.075$. However, this is probably an underestimate, since some of the diarrhea following trimethoprim/sulfamethoxazole may represent adverse reactions to this drug. Thus, we must adjust our estimate of the incidence in nondrug-induced diarrhea downward somewhat, and as a result increase our estimate of the incidence of amoxicillin-induced diarrhea.

To decide how much of an adjustment to make, we argued along different lines. A lower bound for the incidence of nondrug-induced diarrhea can be obtained by thinking about the spontaneous occurrence of diarrhea in which no drug involvement is possible because the affected child was taking no drugs prior to the outbreak of the diarrhea. We assume that one to two-year old children experience approximately one such episode per year on average (this estimate is based primarily on the data in [4]), which is equivalent to an incidence (per child) of about 0.019 per week. This figure must be increased somewhat, since it does not condition on the children having a viral infection (M), which increases the probability of developing diarrhea. We have thus estimated the incidence (per child) of nondrug-induced diarrhea among children with M, in the week following initiation of amoxicillin therapy, to be greater than 0.019 and less than 0.025, and we adopt the value of 0.02. Thus, our estimate of the incidence (per child) of drug-caused

| diarrhea among such children in this time period is $0.1 - 0.02 = 0.08$: this |
 | is our assessment of $P(E_t|D) - P(E_t|D^c)$. |

| Thus, applying equation (2), we evaluate the prior odds in favor of |
 | causation as |

$$| \text{Prior Odds} = [P(E_t|D) - P(E_t|D^c)] / [P(E_t|D^c)] = 0.08/0.02 = \underline{4.0} |$$

4) Evaluating The Likelihood Ratio Factor for History

To evaluate the likelihood ratio factors, it is necessary to assess the probability for all the differentially diagnostic information elicited in response to the questions summarized in Table 2, given the contradictory hypotheses that D did and did not cause the adverse event E.

There is a conceptual difference between LR(Hi) and the other factors. Each of the other factors involves thinking in the forward direction, from a cause to its observable effects, while the information in Hi occurred before the event E, and so it is more difficult to think about how likely the events in Hi were to happen, conditional on the cause of an event that occurred after it did.

The representation for LR(Hi) given in equation (3, below) requires the assessor to think in "reverse chronology" (conditioning on the cause of E to evaluate the probability of an event occurring before E), which is difficult.

$$(3) \quad \text{LR(Hi)} = \frac{P(\text{Hi} | D \rightarrow E, B)}{P(\text{Hi} | D \not\rightarrow E, B)}$$

Thus, it is easier to think about LR(Hi) in terms of the following alternative representation:

$$(4) \quad LR(H_i) = \frac{P(D \rightarrow E_t | H_i, B) / P(D \not\rightarrow E_t | H_i, B)}{P(D \rightarrow E_t | B) / P(D \not\rightarrow E_t | B)}$$

In words, LR(Hi) is just the ratio of the odds in favor of the drug causation taking into account the information in Hi (and no other case information) to the prior odds in favor of drug causation (ignoring the information in Hi). Seen in this way, the information in Hi serves as an adjustment to the prior odds, based on additional information about the patient that predates the occurrence of E. In effect, the relevant "reference set" in which to place the patient shifts from the general set of patients with M who experience an event of type E_t after the specified course of D-therapy, to those who share the same relevant history as the particular patient whose case is the subject of the assessment.

The adjustments to the prior odds required to evaluate LR(Hi) are often quite subjective, because the information that must be taken into account is too specific to expect to find readily assimilable observed frequencies based on large numbers of cases in the literature. Thus, it is useful to realize that certain types of historical information, which seem to affect the incidence of events of type E_t, can be disregarded. In particular, according to equation (3), a datum in Hi will make LR(Hi) differ from 1 only if it affects the incidence of events of type E_t differentially between drug and nondrug causes. That is, if, say, the patient had some special attribute that doubled his risk for events of type E_t no matter what the cause, and the possession of this attribute by the patient was the only information in Hi, LR(Hi) would be 1. Thus, any such attributes can be disregarded in calculating LR(Hi).

The Likelihood Ratio Factor for History: Application

We assume that day-care center attendees are 1.4 times as likely to suffer from non-drug-induced diarrhea (because of the greater exposure rate as the general pediatric population (this estimate is primarily based on data in [5]), while they are at no added risk for drug-induced diarrhea. But we must also include in our analysis the fact that the diarrhea occurred in December. Based on evidence presented in [5] and general pediatric experience the incidence of non-drug induced diarrhea is approximately twice as high in the fall and winter as the yearly average. The season would be expected to have no effect on drug-caused diarrhea. Thus, because of the history of day-care attendance and occurrence in the December the term $P(D \rightarrow E_t | H_i, B)$ in equation (4) is larger than $P(D \rightarrow E_t | B)$ by a factor of $1.4 \times 2.0 = 2.8$. On the other hand, since these elements of history have no effect on the rate of drug-induced diarrhea, $P(D \rightarrow E_t | B, H) = P(D \rightarrow E_t | B)$. Using these results in equation 4 we get:

$$\begin{aligned}
 LR(H_i) &= \frac{P(D \rightarrow E_t | B) / P(D \rightarrow E_t | B) \times 2.8}{P(D \rightarrow E_t | B) / P(D \rightarrow E_t | B)} \\
 &= 1/2.8 = \underline{0.36}
 \end{aligned}$$

5. Evaluating Other Likelihood Ratio Factors

The likelihood ratio factors for timing, characteristics, dechallenge and rechallenge can best be evaluated by determining, separately, their numerators and denominators. In carrying out these evaluations, the techniques of conditioning and analogy will be frequently applied. In particular, the probabilities given drug causation will depend on the mechanism of the adverse reaction, and the probabilities given nondrug causation will typically depend on what the alternative etiologies are; in both cases, conditioning on the appropriate entities is required.

The calculations involved in evaluating these factors are relatively straightforward, compared to the prior odds and $LR(H_i)$, and further discussion will be deferred to the example. Here, we consider only one issue. Notice that the information in chronologically preceding categories is conditioned upon when the probability for information in succeeding categories is calculated, as required by the multiplicative condition for coherence (see Appendix I in [1]). For example, when calculating the probability that sulfonamide-induced Stevens-Johnson begins, say, three days after onset of therapy, it is necessary to condition on historical information, like the fact that the patient under consideration is atopic. This successive conditioning at first sight seems to introduce a great deal of complexity to the evaluations, but in fact this is not generally so. All the probability evaluations required for these likelihood ratio factors are conditional on the cause of the event E (D, or some other cause); and conditional on the cause, the sets of information in the various categories are often independent, as would surely be the case with the timing information and the fact that the patient is atopic in the Stevens-Johnson example. When this conditional independence does not obtain, of course, the

relevant conditioning information must be taken into account for a valid probability evaluation. This point is amply illustrated in the case analysis below.

Other Likelihood Ratio Factors: Application

LR(Ti): Recall that we condition on (as part of B) the information that the event E begins after D-therapy is initiated. Taking this into account, the pediatrician in our group (M.S.K.) assessed the following distributions for time to onset of an event of type E_t starting from the beginning of D-therapy, in a patient with M, given (because of the time horizon) that an event of this type occurs within one week of the beginning of D-therapy:

| <u>Day of onset (i)</u> | <u>P(day i D → E)</u> | <u>P(day i M → E)</u> | <u>P(day i E coincidental)</u> |
|-------------------------|-------------------------|-------------------------|----------------------------------|
| 1 | .33 | .33 | .14 |
| 2 | .33 | .22 | .14 |
| 3 | .20 | .15 | .14 |
| 4 | .07 | .11 | .14 |
| 5 | .04 | .09 | .14 |
| 6 | .02 | .06 | .14 |
| 7 | .01 | .04 | .14 |

It should be noted that none of these timing distributions depend on the fact that B.L. attended a day-care center or that the diarrhea occurred in December; that is, the information in T_i and the information in H_i are independent, given the cause of E. The distribution for $P(\text{day } i | M \rightarrow E)$ was induced from the following distribution, which represents the probability of getting diarrhea beginning the first day of M: .25 first day, .25 second day, .15 third day, .1 fourth day, .07 fifth day, .05 sixth day, .04 seventh day, .03

| eighth day, .02 ninth day, .04 tenth day or later. The distribution shown in |
 | the table above is obtained from this one by conditioning on the diarrhea |
 | beginning between the third day (when D-therapy began) and the ninth day, a |
 | week later. |

| Since E actually began within 24 hours of initiating D-therapy, the |
 | numerator of the likelihood ratio factor for timing is .33. To evaluate the |
 | denominator, we need to evaluate two additional quantities, the probabilities |
 | for $M \rightarrow E$ and "E coincidental", given that D did not cause E. By the addi- |
 | tion rule, these two numbers sum to 1. Knowing that (i.e., conditioning |
 | upon) the patient had a viral U.R.I. (M), our pediatrician (M.S.K.) estimated |
 | that among the two possible nondrug causes, M would be approximately three |
 | times likely as coincidental gastroenteritis. Thus, the denominator of the |
 | likelihood ratio for timing, using the Law of Total Probability, is ob- |
 | tained as follows, where "day 1" is short for "onset of E occurs within 24 |
 | hours" and every probability is conditional on background information B: |

$$\begin{aligned}
 | P(\text{day 1} | D \not\rightarrow E) &= [P(\text{day 1} | M \rightarrow E) \times P(M \rightarrow E | D \not\rightarrow E)] + \\
 | & \quad [P(\text{day 1} | E \text{ "coincidental"} \times P(E \text{ "coincidental"} | D \not\rightarrow E)] \\
 | &= (.33 \times .75) + (.14 \times .25) \\
 | &= \underline{.28}
 \end{aligned}$$

| Thus, |

$$\begin{aligned}
 | LR(T_1) &= P(\text{day 1} | D \rightarrow E) / P(\text{day 1} | D \not\rightarrow E) \\
 | &= .33 / .28 \\
 | &= \underline{1.2}
 \end{aligned}$$

Note that in the calculation for $LR(T_i)$, the only part of the three timing distributions that was actually used was the probability they assigned to day 1, the day on which E actually occurred. Thus, if another assessor gives the same probabilities to day 1 but differs with us about the probabilities assigned to other days, the answer that the assessor obtains for $LR(T_i)$ for this case will agree with ours. The reason for assessing the entire distribution is that it provides a context for the one evaluation that counts, the probability assigned to what actually happened.

LR(Ch): To evaluate this factor, we need to calculate the probability that an event of type E_t persisted unabated for the duration of D-therapy given the hypotheses of drug and nondrug causation. Again, given the cause of E, the information whose probability we need to assess is independent of the information in T_i and H_i .

Assuming that D caused E, M.S.K., based on his clinical experience, assessed the probability that an event of type E_t would last at least 9 days, given that the event was an adverse reaction to D, as .7.

Assuming that D did not cause E, we believed that whether M caused E or E was coincidental to M, the distribution for time to resolution was the same. This distribution was assessed by the pediatrician M.S.K. as follows: the probability that the diarrhea would end before 7 days is .60; in 7 days, .10; in 8 days, .08; in 9 days, .06; in 10 days, .05; in 11 days, .04; and longer than 11 days, .07. Therefore, the probability that an event of type E_t would last at least ten days, given a nondrug cause, is $.06 + .05 + .04 + .07 = .22$

$$LR(Ch) = 0.7 / .22 = \underline{3.2}$$

LR(De): We need to calculate the probability that the diarrhea will resolve two days after dechallenge with D, given the hypotheses of drug and nondrug causation and given that the diarrhea had persisted until the time of dechallenge. These calculations are handled just as were the corresponding ones relative to the timing information. First, as explained in the discussion of Ch, we decided that there would be no differences in our distribution for the duration of the diarrhea whether it was caused by M or by a coincidental gastroenteritis. Using the distribution for duration of diarrhea above, conditioned to last at least 9 days, the probability that the diarrhea would resolve within two days after dechallenge (ie., 10-11 days after onset) given nondrug causation, is $(.05 + .04) / .22 = .41$. The time distribution for resolution given drug causation was judged by M.S.K. to be similar to the distribution for time of onset (see above). Consequently, the probability of resolution within 2 days of dechallenge was estimated as $.33 + .33 = .66$. Thus:

$$\text{LR(De)} = .66 / .41 = \underline{1.6}$$

LR(Re): Since no rechallenge occurred, this factor is equal to 1.

6. Calculating the Posterior Odds

According to equation (1), to calculate the posterior odds in favor of D causation, we must multiply together the prior odds and the likelihood ratio factors.

Posterior Odds: Application

A summary of the case analysis and the resulting posterior odds is shown in Table 3. As shown, the posterior odds (obtained by multiplying the prior odds by each of the likelihood ratio terms) is 8.85 and the posterior probability of drug causation is .90.

TABLE 3 GOES HERE

Note that one of the strongest pieces of evidence was simply how long the diarrhea lasted before dechallenge occurred; had the amoxicillin been immediately discontinued, the case for drug causation would have been far less convincing -- and had in addition the drug been trimethoprim/sulfamethoxazole instead of amoxicillin, so that the prior odds in favor of drug causation would be substantially lower, the posterior odds would have favored a nondrug cause for the diarrhea.

DISCUSSION

The techniques for implementing the Bayesian approach described in this paper, which are based on the rules of probability theory, provide considerable help in doing an assessment although they do not, as yet, constitute a standardized system. Nonetheless, they should allow an interested reader to use the approach, and the main characteristics of the Bayesian method should be clear. We believe that it provides a coherent framework for dealing with the multiple uncertainties and complexities of the causality assessment problem. Because it deals with the problem in all its "real world" uncertainty and complexity, the Bayesian approach requires more in-depth analyses than other methods and in its current form is not suitable for rapid filing of large

numbers of case reports. The extra time spent to use the Bayesian approach is amply justified however, when the answer to the individual causality assessment problem at hand really "matters". Moreover, we believe that with further work it will be possible to standardize the approach and make it easy to use without sacrificing what we see as its essential correctness.

In the first paper of this series [1], we argued that the method meets criteria that allow the consumer of an assessment to understand and believe the results in a way not possible with other methods. Similar features make the method attractive from the assessor's point of view. First, the method provides a way to incorporate all his ideas relevant to a particular causality assessment problem. Thus, in the example presented, ideas as different as the rate of diarrhea in an epidemiologic study, the increased risk of diarrhea in the winter months and in day-care attendees, the possibility that the diarrhea was caused by the patient's viral disease or was "coincidental", and the probable duration of diarrhea from different causes can all be incorporated and combined in a satisfying way. Second, by providing a logical framework for using the different sources of diagnostically useful information, the method allows the assessor to focus his attention on the elements of the evaluation, rather than on how they should be combined. This frequently allows important insights into the real significance of elements that might be ignored with other methods. The diagnostic importance of the duration of the diarrhea before dechallenge is an excellent example of this phenomenon in the case presented. Although it turns out to be important information differentiating drug from non-drug cause, we completely missed the significance of the duration of the diarrhea when we performed our first informal evaluations of the case.

Third, the method for combining the results allows easy identification of which elements drove the assessment. This allows the assessor to evaluate his

"confidence" in the final result very quickly. His overall confidence is primarily determined by his confidence in the few elements that drove the assessment. This also makes further research to increase confidence much more efficient by allowing these activities to focus only on the "important" elements of the case.

Finally, and most importantly, because the method follows logical rules for combining probabilities, it makes sense of this complex problem. Thus, rather than just accepting how the component assessments produce the final result, the assessor can understand why. This should allow him to learn much more effectively from such assessments than if he employed the "black box" of global introspection or the arbitrary scoring rules of the published standardized method (see [6] or [7], for instance).

This unique "explanatory" feature of the Bayesian approach can also be used to help understand a causality assessment result arrived at by any method. This can be achieved by reversing the direction of the Bayesian assessment: instead of estimating the prior odds and likelihood ratio terms and determining the posterior odds from them one can start with a posterior odds and determine what prior odds and likelihood ratio terms such a result would imply. More precisely, since all the component elements (including the posterior odds) are tied together mathematically any single term in the assessment can be inferred from a knowledge of the others. We believe that application of the Bayesian approach, either in the forward direction to assess causality, or in the reverse direction to learn what any given causality assessment result implies, should have widespread applicability, not only in assessing adverse drug reactions, but in medical differential diagnosis in general.

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TABLE 1Application of the Bayesian Approach:The Steps in the Analysis

1. Identify the case "parameters"
2. Collect the relevant case information
3. Evaluate the prior odds
4. Evaluate the likelihood ratio for History
5. Evaluate the other likelihood ratio factors
6. Calculate the posterior odds

TABLE 2
Eliciting Case Information

The assessor should answer each of the following questions. If he is unsure of the correct answer, he should state the grounds and extent of his uncertainty (in probabilistic terms). While the answers to these questions will provide all of the relevant case information for many cases, any additional case information that can help differentiate between drug and nondrug etiological candidates in a particular case under review should also be noted in the appropriate chronological period.

1. Hi:

a. Has the patient taken D or similar drugs before? How frequently? On how many of these occasions did he experience an event of type E_t or another possible adverse reaction? Describe, if different from E_t .

b. How frequently has the patient previously experienced events of type E_t without exposure to D or related drugs?

c. Are there are attributes of the patient that place him at special risk to events of type E_t from any cause? If so, what are they, and from which causes is he at special risk?

2. Ti: When in relation to the course of D-therapy did the patient experience the event E? If available, give the time-course of all prodromal events.

3. Ch:

a. Are there any data about levels of D in tissues or body fluids during the time the patient experienced E? If so, what are they?

b. Are there any distinctive details in clinical presentation, laboratory results, pathological findings, or duration that can help differentially diagnose the cause of E? If so, what are they?

c. Did the symptoms of E abate before dechallenge occurred? If so, how long after the time of onset of E?

4. De:

a. Was D discontinued or its dosage reduced after the onset of E? If so, describe how and when.

b. If dechallenge occurred, did the manifestations of E abate? If so, to what extent and when?

c. Were the manifestations of E treated directly? Was a specific antagonist to D administered? What was the result?

5. Re:

a. If dechallenge occurred, was the patient subsequently rechallenged with D? If so, when and in what dosage?

b. If rechallenge occurred, did the manifestations of E recur? If so, to what extent and when?

TABLE 3
Summary of Results

| <u>Term Assessed</u> | <u>Odds</u> | <u>Cumulative Odds</u> | <u>Cumulative Probability</u> |
|----------------------|-------------|------------------------|-------------------------------|
| Prior | 4.0 | 4.0 | .80 |
| History (Hi) | .36 | 1.44 | .59 |
| Timing (Ti) | 1.2 | 1.73 | .63 |
| Characteristics (Ch) | 3.2 | 5.53 | .85 |
| Dechallenge (De) | 1.6 | 8.85 | .90 |
| Rechallenge (Re) | 1.0 | " | " |

POSTERIOR ODDS IN FAVOUR OF DRUG CAUSATION = 8.85

POSTERIOR PROBABILITY IN FAVOUR OF DRUG CAUSATION = .90

APPENDICES

Appendix I: The Law of Total Probability

Suppose A_1, A_2, \dots, A_n are mutually contradictory propositions such that one of them must be true. Then for any proposition C , the Law of Total Probability states that:

$$P(C|B) = [P(C|B \text{ and } A_1) \times P(A_1|B)] + \dots + [P(C|B \text{ and } A_n) \times P(A_n|B)]$$

The Law of Total Probability is derived as follows. First, since the propositions A_1, \dots, A_n are mutually contradictory and one of them is true,

$$C = (C \text{ and } A_1) \text{ or } (C \text{ and } A_2) \text{ or } \dots (C \text{ and } A_n).$$

By the additivity condition, which obviously extends to n mutually contradictory propositions,

$$P(C|B) = P(C \text{ and } A_1|B) + \dots + P(C \text{ and } A_n|B)$$

Now apply the multiplicative condition (see Appendix I in [1]) to each term on the right:

$$P(C|B) = [P(C|B \text{ and } A_1) \times P(A_1|B)] + \dots + [P(C|B \text{ and } A_n) \times P(A_n|B)].$$

Appendix II: Predictive Probability and the "True" Incidence

A probability distribution for the "true" incidence gives values for the assessor's probabilities $P(a \leq \text{"true" incidence} \leq b)$, for all a and b between 0 and 1. A distribution is usually specified by means of a density function, a nonnegative function f defined on the interval $(0,1)$, such that $P(a \leq \text{"true" incidence} \leq b)$ is obtained as the area under the graph of f between a and b (The total area under the graph of f is 1).

The tactic discussed in Section B under "Evaluating the Prior Odds" derives from the following theorem, due to de Finetti:

Suppose $X_1, X_2 \dots$ is a sequence of $(0,1)$ -valued random variables, whose distribution is invariant under any reordering of the variables. Then

$$(1) \quad P(X_1 = 1) = \int_{[0,1]} y \, dG(y),$$

where G is the distribution function for the random variable Y and

$$Y = \lim_{n \rightarrow \infty} [(X_1 + \dots + X_n) / n]$$

(It is a conclusion of the theorem that this limit exists.)

The expression on the right of equation (1) is called the mean of the distribution G . If G has a density function g , then

$$\int_{[0,1]} y \, dG(y) = \int_{[0,1]} y \, g(y) \, dy.$$

To interpret the theorem in the context of this paper, X_1, X_2, \dots represents a sequence of future patients with clinical condition M who, say, are to receive a specified course of D -therapy and of whom nothing additional is known (that is, "generic" patients with the two stated properties). Because of their "genericness", the assessor's probability distribution for which of these patients will experience an event of type E_t does not depend on their labelling, so the theorem applies. Y represents the "true" incidence. Thus, the theorem implies that if the assessor evaluates his distribution G for the "true" incidence, his predictive probability that the next patient will experience an event of type E_t (that is, that $X_1=1$), or $P(E_t | D)$, is just the mean of the distribution G .

Appendix III: To a coherent evaluator, the posterior odds does not depend on the time horizon

The time horizon adds an additional conditioning proposition to all the probabilities calculated in a causality assessment: that the event E occurs in a specified time interval — say T — initiated by administration of the drug D. Refer to this proposition as "E in T". Now as long as the actual time that E occurred, say t, is in the interval T, then any probability already calculated conditionally on case information C — which includes the proposition "E at t" — is unaffected by also conditioning on "E in T", which adds no new information. In particular, the probabilities that appear as the numerator and denominator of the posterior odds are conditional on C and hence on "E at t", and so are unaffected by the time horizon, so long as t is in the time horizon interval T.

It is of interest to see how the other terms that are evaluated in a causality assessment depend on the time horizon. For convenience, suppose there is no information in H_i (that is, all H_i information is already included in B, as specification of M). Then, the only terms affected by the time horizon are the prior odds and the likelihood ratio for timing, since all subsequent likelihood ratio terms are calculated conditionally on T_i , that is, on "E at t".

Using Bayes' Theorem, the following relation can be shown to be true:

$$1) \frac{P(D \rightarrow E | B, E \text{ in } T)}{P(D \not\rightarrow E | B, E \text{ in } T)} = \frac{P(D \rightarrow E | B)}{P(D \not\rightarrow E | B)} \times \frac{P(E \text{ in } T | B, D \rightarrow E)}{P(E \text{ in } T | B, D \not\rightarrow E)}$$

That is, the prior odds calculated with the time horizon T is the product of the prior odds without the time horizon, multiplied by another factor that derives from the timing distribution for the event, with and without drug causation.

Similarly, the likelihood ratio for timing can be written:

$$(2) \quad LR(T_1) = \frac{P(E \text{ at } t | B, D \rightarrow E, E \text{ in } T)}{P(E \text{ at } t | B, D \not\rightarrow E, E \text{ in } T)}$$

Using the multiplication law the numerator of this expression can be rewritten as: $P(E \text{ at } t | B, D \rightarrow E) \times P(E \text{ in } T | E \text{ at } t, B, D \rightarrow E) / P(E \text{ in } T | B, D \rightarrow E)$. So long as we choose the time horizon (E in T) to be longer than the actual time interval of occurrence (E at t) then the expression $P(E \text{ in } T | E \text{ at } t, B, D \rightarrow E) = 1$. Thus the numerator of (2) becomes: $P(E \text{ at } t | B, D \rightarrow E) / P(E \text{ in } T | B, D \rightarrow E)$

Applying the same logic to the numerator and denominator of the likelihood ratio for timing we get:

$$(3) \quad LR(T_1) = \frac{P(E \text{ at } t | B, D \rightarrow E) / P(E \text{ in } T | B, D \rightarrow E)}{P(E \text{ at } t | B, D \not\rightarrow E) / P(E \text{ in } T | B, D \not\rightarrow E)}$$

$$= \frac{P(E \text{ at } t | B, D \rightarrow E)}{P(E \text{ at } t | B, D \not\rightarrow E)} \times \frac{P(E \text{ in } T | B, D \not\rightarrow E)}{P(E \text{ in } T | B, D \rightarrow E)}$$

That is, the likelihood ratio for timing with the time horizon T is the product of the likelihood ratio for timing without the time horizon, multiplied by a factor that is the reciprocal of the factor appearing on the right hand side of equation (1). Multiplying the left and right-hand sides, respectively, of equations (1) and (2) shows that the product of the prior odds and $LR(T_i)$ remains the same, with and without any time horizon T that contains the actual occurrence time t .