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Managing Scientific Uncertainty in Medical Decision Making: The Case of the Advisory Committee on Immunization Practices

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This article explores the question of how scientific uncertainty can be managed in medical decision making using the Advisory Committee on Immunization Practices as a case study. It concludes that where a high degree of technical consensus exists about the evidence and data, decision makers act according to a clear decision rule. If a high degree of technical consensus does not exist and uncertainty abounds, the decision will be based on a variety of criteria, including readily available resources, decision-process constraints, and the available knowledge base, among other things. Decision makers employ a variety of heuristic devices and techniques, thereby employing a pragmatic approach to uncertainty in medical decision making. The article concludes with recommendations for managing scientific uncertainty in medical decision making.

Keywords: *ACIP, medical decision making, scientific uncertainty*

I. INTRODUCTION

Medical research is designed to explore and enhance effective treatment methods, thereby resulting in improved patient care. Researchers attempt to operationalize their experimental and laboratory results, that is, to translate newfound theoretical knowledge into practical, viable courses of treatment for the working physician. This tidy, linear design is complicated by questions of whether every gap in knowledge can be filled and whether scientific uncertainty can be managed.

The Ancient Greeks concluded that nature's mysteries could be painstakingly eradicated over time as new and better research filled in the gaps of

missing information. Absolute certainty was impossible, but a reasonable approximation could be achieved over time. Theirs was a world filled with uncertainty, but they were confident answers always were available to the diligent researcher. It was not until the Enlightenment that two philosophers, David Hume and Immanuel Kant, squarely confronted the core question of whether something can ever be known and, if so, whether limits apply to human knowledge (Jones, 1970, 121–3, 225–7; Fjelland, 2002).

As Dr. Benjamin J. Djulbegovic of the University of South Florida observed in a 2007 article in *The Journal of Medicine and Philosophy*, the crucial issue for physicians is to distinguish between types of uncertainty—between knowledge that can be acquired if enough empirical evidence is amassed and knowledge that can never be fully known owing to the nature of the inquiry—and to develop a taxonomy of clinical uncertainties to address the former. Dr. Djulbegovic (2007, 81) argued that "my main point is that once the existing uncertainty is recognized and acknowledged, further steps will be facilitated in the form of the next logical question: how do we devise an effective resolution of the uncertainty which we have now formally accepted?" He raises a salient point. Understanding how researchers engage in decision making under conditions of uncertainty and how they manage that uncertainty is crucial if medical science is to advance.

This article explores the question of scientific uncertainty using the Advisory Committee on Immunization Practices (ACIP) as a case study. The ACIP is a 15-member group of physicians that meets periodically to review data on vaccines licensed for use in the United States by the US Food and Drug Administration (FDA). Group members make recommendations to the US Centers for Disease Control and Prevention (CDC) on vaccine uses and doses for specific populations by developing written recommendations for routine vaccine administration to the pediatric and adult populations, along with vaccination schedules regarding appropriate periodicity, dosage, and contraindications. ACIP statements are official federal recommendations for the use of vaccines and immune globulins in the United States and are published by the CDC (Preboth, 2001; Thompson et al., 2003; Meadows, 2007, 25; Blazek, 2008). The ACIP is a strong case study since group members invariably make a multitude of decisions under conditions of scientific uncertainty. Where a high degree of technical consensus exists about the evidence and data, ACIP members make decisions according to a clear decision rule. If a high degree of technical consensus does not exist and uncertainty abounds, the decision will be based on a variety of criteria, including readily available resources, decision-process constraints, and the available knowledge base, among other things. In short, ACIP medical decision makers employ a variety of heuristic devices and techniques, thereby employing a pragmatic approach to uncertainty in medical decision making.

II. EPISTEMOLOGY AND UNCERTAINTY

That uncertainty exists and must be managed has been recognized by philosophers and scientists for centuries. David Hume claimed that nothing can ever be known with absolute certainty; therefore, all knowledge is suspect. Knowledge is prized owing to its utility. Metaphysical abstractions are tantamount to "sophistry and illusion" and must be "committed to the flames" (Hume, 1977, 111–12; Wallace, 1978, 10). Immanuel Kant, Hume's primary theoretical opponent, famously remarked that he was awakened from his "dogmatic slumbers" by Hume's skepticism. In Kant's view, Hume undermined the possibility of shared knowledge since utility can vary according to time and place. For knowledge to be universally useful and replicable, it must be theoretically absolute (Kant, 1987, 49). Add to this debate, the works of philosophers such as Friedrich Nietzsche, who attacked the quest for objective "truth" as a sickness in the western intellectual tradition, and a crisis in epistemology erupted in the nineteenth century (Nietzsche, 1966, 3).

Twentieth-century cognitive scientists have tried to make sense of the philosophical debate over uncertainty by explaining the boundaries of scientific decision making. As Theodore Porter argued in his book *Trust in Numbers*, proponents of universality in science divorce the concept of knowledge from its context. They champion the scientific method, with a capital "M." The Method must be clear, logical, intellectually rigorous, verifiable, and ultimately replicable. Owing to its objective features, the Method is immune to the myths and contextual influences that infect other, lesser disciplines. Moreover, if the Scientific Method is perfected, eventually mankind will solve the great problems that always plague human beings. The rise of the Method gradually has led to the glorification of quantification and data analysis as a means of ensuring accountability (Porter, 1995, 11–21).

In this same vein, Larry Laudan examined the problem of what might be called the "postmodern conundrum" in his book *Progress and Its Problems*. The Enlightenment's view of the Method allowed rational thinkers to make enormous strides in the seventeenth and eighteenth centuries, but eventually a troubling question arose. What if science—which scientists thought existed as a method outside of its context—was yet another byproduct of its context? What if the attempt to demythologize epistemology is but another myth? (Laudan, 1977).

This inquiry was especially worrisome because many scientists viewed the Scientific Method as the paramount means for rationally discovering the world. When the scientific method was attacked, people assumed that rationality was under attack. This led to an epistemological crisis because people lost confidence in the "Method," and what commentator Philip Kitcher called the "Legend" of idealized science. In the words of Kitcher (1993, 5), "Since the late 1950s, the mists have begun to fall. Legend's lustre is dimmed. While it may continue to figure in textbooks and journalistic expositions, numerous

intelligent critics now view Legend as smug, uninformed, unhistorical, and analytically shallow."

This conclusion favored epistemological relativism. In Laudan's view, it was possible to legitimize science without embracing nihilism or returning to the myths propagated by mainstream scientists who support the "Legend." The problem is that defenders of the Legend of Science have assumed that their discipline eventually can, and will, answer all important questions and encompass all useful knowledge about the natural universe. Progress is a matter of further exploring the world as we increase our knowledge and develop better equipment or more sophisticated calibrations of existing equipment. If science cannot fulfill this promise of greater explication over time, then the entire discipline is threatened because we are no longer making progress toward the goal of absolute knowledge.

Laudan suggested that this perspective confuses different inquiries. Science is an excellent means of conceptualizing problems and, consequently, it becomes an invaluable problem-solving tool. Despite the utility of science for addressing conceptual problems, supporters have tried to make it a tool for solving empirical problems. By arguing that empirical problems are the only true problems of the natural universe, they have created a culture of science that must be defended as an "all or nothing" construction. Either science has the potential to answer all questions or it completely fails as a means of conducting rational inquiry. Laudan argued that this traditional approach of the logical positivists is a mistake because it forces science to do too much and thereby creates a myopic discipline that threatens to crumble when it is attacked. Science can be a legitimate human endeavor without being the *only* worthwhile human endeavor. It is time to reject empiricism and acknowledge that science is not separate and somehow above its context, Laudan suggested.

A culture of unquestioning empiricism is ubiquitous and, as a result, its foundations often seem invisible. In *Sorting Things Out: Classification and its Consequences*, Geoffrey C. Bowker and Susan Leigh Star argued that we should examine the foundations upon which human beings build classification systems. The act of classifying things is a distinctly human enterprise. Human beings are so accustomed to classifying their world that they do not realize they are doing it. As a result, often people confuse the act of classifying something with the thing being classified. Sometimes, they do not even realize that they are classifying anything; they see it as merely examining reality (Bowker and Star, 1999).

The idea that reality exists often is an unexamined assumption that arises out of a given context. According to Helen Longino, context is socially constructed. Scientists are part of a socially constructed community. Lone geniuses laboring away in isolated laboratories do not generate scientific knowledge, despite the numerous myths that reinforce this stereotype. Instead, progress in science occurs through a process of experimentation, publication,

and consensus among a community of practitioners. Members of the community discuss their new findings, decide whether the evidence supports one hypothesis over another, and accept or reject new data. With rare exceptions, lone geniuses do not exist outside of this community. Longino's contention that scientific knowledge is the result of a complex array of social processes means that knowledge never exists independent of its context (Longino, 1990, 231–2).

Ronald Giere adopted a different approach in his book *Explaining Science: A Cognitive Approach*, but he agreed with Longino that the idealized view of science is unworkable. In Giere's view, idealized science presupposes that results reached in scientific research correspond directly with the real world. The problem with this correspondence theory of reality is that it assumes that scientific data reflect the real world, but it fails to take into account how mental models operate. A model used by scientists to understand the world does not correspond to objective reality. It is a shorthand means of understanding the world, but invariably it does not capture every fact or nuance. A model allows a scientist to create a mental representation of the world, but that is all it is designed to accomplish. Owing to what Giere called a scientist's "representation and judgment," the model can be defended as providing an accurate or inaccurate explanation of phenomena, but it does not directly reflect those phenomena (Giere, 1988, 19; see also Kasper et al., 2008).

When it comes to making decisions in light of scientific uncertainty, philosophical pragmatists contend that perspective is a key component of their philosophy. A person makes choices in life, and the sum of those choices, in large measure, determines whether the person will succeed or fail. Pragmatism is not a consistent ideology that requires adherence to supposedly immutable propositions that must be linked logically with similar syllogisms. It is an experimental approach to the world. If an individual tries a course of action and it proves to be ineffective, the individual is well-advised to try something else in its stead (Rorty, 1989). Neo-pragmatist Richard Rorty suggested that no difference exists between something that is true and something that works as a practical matter; he argued that it is nonsensical to think that objective, immutable standards exist separate and apart from the real world. The only standards that apply to people are those reached discursively. People build their lives on a foundation constructed from their language use, the rules and mores of society, and their belief in what works and what does not (Churchill, 2008; MacIntyre, 2008).

III. UNCERTAINTY AND MEDICAL DECISION MAKING

Physicians, especially those engaged in clinical research, typically are pragmatists regardless of whether they subscribe to formal pragmatist theory.

They confront uncertainty by using their background knowledge and expertise to sort through available treatment options and decide on a preferred course of action to pursue. They cannot exhaustively research all possible causes of disease or consequences of treatment or nontreatment. The probabilities are virtually unlimited. The human body is a complex organism with multiple interacting systems that combine to create challenges that may not be amenable to linear solutions involving sequential steps. Physicians recognize that uncertainties exist, but a decision must be made, nonetheless. As a rule of thumb, practitioners generally approach uncertainty in terms of (1) the frequency (probability) of an event; (2) the likelihood the probability assessment is accurate and believable; and (3) entropy, which refers to the uncertainty that results when one treatment option is not clearly superior to others (Contrera, Matthews, and Benz, 2003; Djulbegovic, 2007, 82).

According to information theory entropy, when the probability of various choices is equal, a decision-making stalemate occurs because a clear decision rule is absent. Maximum uncertainty exists because expected utility theory, which dictates that decision-makers act based on the probability that a desirable outcome can be achieved, cannot resolve doubt when probabilities are equal or risks are unquantifiable. If all desirable outcomes are more or less equal or unknown, something more is needed if a decision is to be made. This lack of information about the probability of desired outcomes is captured in the term "equipoise," which refers to "equal beliefs, or equally distributed uncertainty about the relative effects of competing treatment alternatives" (Djulbegovic, 2007, 82). Equipoise does not necessarily indicate that a precise quantitative distribution of treatment effects can never be observed. Instead, the term has a looser meaning; it expresses the difficulty in decision making that occurs when no one treatment option appears superior to others and there exists a possibility that the doubt will never be resolved satisfactorily. As medical researchers confront a novel problem, their educated guesses and elegant research hypotheses cannot suggest a preferred course of treatment. No clear decision rule exists or is likely to exist.

For many physicians, the choice of scientific methodology and analytic technique is tailored to the uncertainty about treatment effects; that is, they seek to maximize the benefits of a treatment option and minimize the risk of side effects. In an effort to resolve the uncertainty associated with treatment effects in cases where no treatment option is immediately preferred, medical researchers often rely on an experimental protocol called "randomized controlled trials" (RCTs). RCTs require patients to be enrolled in an experiment whereby one group of patients is administered a drug whereas another group is administered a placebo. Afterward, the differences between the patients' condition before and after the administration of the drug are calculated for each group, and the results are compared between the two groups (Djulbegovic, 2007).

When uncertainties about the cause and effect of competing treatments are high, it is difficult to know whether the observed effects were the result of the treatment(s) or owing to other factors such as patient selection, pre-existing conditions, unknown biases, or even random error. In situations where uncertainties are high, additional RCTs are the most efficacious means of resolving uncertainties. Presumably, additional trials will yield useful results because the RCTs eventually will provide clear data on the performance of one alternative treatment when compared with a competing alternative treatment. Clinical trials theoretically work well when equipoise exists; that is, RCTs are designed to be a tiebreaker in cases where competing treatment options cannot be evaluated effectively through intuition or heuristic devices. The choice between seemingly equivalent alternatives can be called "Alternative Futures," or the choice between discrete alternatives where the outcome cannot be predicted with a reasonable degree of reliability beforehand (Djulbegovic, 2007).

In instances where the treatment effects are dramatic or immediately recognizable—such as in the case of blood transfusions, insulin, or penicillin—RCTs are not necessary. The relationship between administration of the drug or treatment and the effect is reasonably clear. Mistakes can, and sometimes do, occur, but generally the uncertainties can be resolved. A clear decision rule exists. Unfortunately, treatment effects are not always immediately recognizable no matter how many RCTs are used (Bornstein and Emler, 2001, 98–9).

Another level of uncertainty exists in medical research, and that involves a "Range of Futures" or the possibility that no discrete alternatives exist or, in any case, the alternatives have yet to be identified. A good example of this problem is when a new drug is introduced into the marketplace. Despite the clinical trials conducted by pharmaceutical companies, often a great deal of time is needed, possibly decades, to determine whether negative side effects will occur. Because data are limited, it is possible that the range of potential side effects is greater than one might predict even when reviewing the side effects associated with similar drugs from the same family of chemical substances (Bornstein and Emler, 2001; Lankshear, Ettorre, and Mason, 2005, 375). Making comparisons and calculating risks when a Range of Futures is present are far more difficult than when Alternative Futures are involved because the former lacks precision in its data collection and analysis. Nonetheless, there is a high probability that given enough time and data, discrete categories can be developed and eventually the RCT method may allow researchers to discriminate among and between treatment options (Djulbegovic, 2007).

The worst-case scenario in medical uncertainty can be called "True Ambiguity." In these cases, the situation is so novel and knowledge about alternative treatments is so incomplete that researchers cannot begin to calculate the quantity or quality of discrete choices. Unlike a situation with a

Range of Futures, it is impossible to determine whether enough information will be collected and analyzed to improve the decision-making process. The difficulty with True Ambiguity is not simply that data are missing; a method of understanding data even if they were to be identified and collected is absent. Perhaps, the method will never be found. A researcher faced with True Ambiguity should not despair that certainty is impossible and therefore become paralyzed with indecision, but he or she should recognize the travails associated with research when uncertainties outweigh certainties (Djulbegovic, 2007, 83).

Ever since medical researchers began employing clinical trials to test the relative merits of alternative treatments, the justification for enrolling patients in the trials has been the need to resolve uncertainty among treatment options. The question naturally arises as to whose uncertainty is morally relevant. Equipoise, which describes uncertainty among individual physicians, is different from uncertainty among the community of scientists and medical researchers. In the former case, a physician may be uncertain as to the relative benefits associated with a menu of potential treatments, but the physician has the option of reading the relevant medical literature, consulting with more experienced practitioners, or referring the patient to an appropriate specialist. In a situation where the individual is uncertain but a higher degree of certainty may be available if the physician undertakes a reasonably diligent effort to discover the necessary information, enrollment in a clinical trial is not warranted.

The broader uncertainty principle that applies to the community of medical researchers presents a separate set of problems and issues. As researchers Lilford and Djulbegovic have observed, the crucial question is this: "How much uncertainty can we accept before entering a patient into a trial and by whom (patients, physicians, and community)?" (Lilford and Djulbegovic, 2001, 795). Although the debate continues, generally if the individual physician finds a genuine lack of consensus among scientists and physicians about an appropriate course of treatment, the appropriate step is to enroll the patient into a clinical trial as an efficacious means of resolving the dilemma.

Assuming *arguendo* that the enrollment of a patient in a clinical trial is seen as an acceptable method of resolving doubt as to treatment options, a difficulty can arise when the goals of the trial and the goals of the individual patient are different. The study parameters may be strictly controlled and may require a regimen that is not ideally suited for an individual patient. When a single physician was treating a single patient, the patient's health and welfare were the primary goals in the physician-patient relationship. When the patient enrolls in a clinical trial, the interests of the researchers in ensuring the integrity of the research project become factors in treatment decisions. This observation does not mean that physicians can knowingly compromise a patient's health in the interests of a higher good, but it does mean that making exceptions for a particular patient presents problems that

may not be resolved in the context of a clinical trial (Bornstein and Emler, 2001).

Researchers have recognized the potential conflict of interest that exists between the researcher who must protect the integrity of the clinical trial and an individual patient who may need something that is not provided for in the trial. One way to resolve the conflict is through the use of game theory. According to this view, the players are the patient and the researcher. The solution to the game is to find an equilibrium point at which each player's game strategy is optimal when compared with other players' game strategy. In the context of an RCT, equilibrium is reached when the probability of random allocation at which both the patient and the researcher will most likely achieve their goals occurs. If one treatment is obviously superior to competing treatments, neither patient nor researcher is well-served by randomization. If the results cannot be predicted in advance and if there are no clear guidelines for determining which treatment to superior to the alternatives, both the patient's and the researcher's most rational course of action is to randomize (Tarrant, Stokes, and Colman, 2004).

Statistical tools can be employed to investigate alternative treatments and their probable rates of success. In fact, some researchers have found a typical bell-shaped curve in testing new treatments, suggesting that such treatments used in RCTs are, on average, as likely to be inferior as they are to be superior to standard treatments. In other words, because there is no clear standard for differentiating among and between experimental treatments, randomization is the preferred course of action for resolving uncertainty (Djulbegovic, 2007).

Resolving uncertainty through RCTs remains a crucial endeavor for scientists, but one medical researcher cautions against extending the effort too far:

> As inevitable and unpleasant as many uncertainties are, one can argue that patients (and their doctors) should not even strive to completely eliminate uncertainties. Although the role of scientific method is to reduce uncertainties, a total elimination of uncertainty would be undesirable, since, it has been argued, it would lead to deterministic life—meaning that all events would be known in advance, in turn implying no hope, no ethics, no freedom of choice. (Djulbegovic, 2007, 95)

Desirable or not, eliminating uncertainty is not a realistic objective. Instead, researchers and practitioners alike must focus on managing uncertainty. This task involves determining when uncertainty exists, the cause of the uncertainty, and the likely consequences of uncertainty. Even if uncertainty cannot, and should not, be banished from the realm of science, it can be managed.

In a medical setting, managing uncertainty can be especially troubling because the consequences of failure may be calamitous. Uncertainty can be resolved by overtreatment. "Uncertainty also propels activity—doctors have a propensity to resolve uncertainty and ambiguity by action rather than

inaction," one researcher has noted. "Such activity may lead to increased hospital admissions and may be the cause of excessive ordering of tests, although this result has not always been found. Increasing diagnostic uncertainty also leads to a reluctance to withdraw intensive care therapy" (Hall, 2002, 218).

IV. THE ACIP AND MEDICAL UNCERTAINTY

The ACIP presents an excellent case study to understand uncertainty in medical decision making owing to the nature of research on vaccines. With some vaccines—for example, smallpox, polio, and measles—a high degree of technical consensus exists about the evidence and data and a reasonable degree of certainty exists. These vaccines have been shown to perform safely and effectively over time. Other vaccines—for example, those involving human immunodeficiency virus, autoimmune diseases, and certain types of prenatal infections—are controversial because evidence is divided over whether they are safe and effective when administered in certain dosages to certain populations. In these cases, great uncertainty exists, and it is unlikely to be resolved satisfactorily in the near future (Szilagy et al., 1994; Blazek, 2008; Gentile, 2008; Gilca et al., 2008; La Torre et al., 2008; Ramsey, 2008).

As with any group of medical professionals, ACIP members are forced to confront uncertainty in their deliberations; they frequently find themselves faced with cases involving equipoise. Interviews with ACIP members indicate that the group harbors no illusions about the limits of scientific data. Laudan's insight that science can provide guidance in conceptualizing problems even if it cannot answer all questions empirically is widely regarded as accurate. If the medical professionals who staff the ACIP can provide a likely diagnosis and propose a reasonable course of treatment through vaccine recommendations, they believe that uncertainty can be managed effectively. The first step, of course, is to draw on existing sources of knowledge as the basis for formulating an effective problem statement or research hypothesis. Setting up the problem and appreciating its parameters are crucial initial steps.

A large knowledge base supports the group's activities. The overall goals of the ACIP are to provide advice to government agencies for reducing the incidence of vaccine preventable diseases and to increase the safe usage of vaccines and related biological products. In the United States, immunizations have resulted in the eradication of a variety of diseases, including smallpox, polio, measles, and rubella. Disease rates from vaccine-preventable diseases have been reduced by 99% (Henley, 2003; Blumenthal, 2004; March, 2004; Schmidt, Kroger, and Roy, 2004; McCaffrey, Pugh, and O'Connor, 2007; Meadows, 2007, 25–6; Smith and Shay, 2006; Ramsey, 2008).

The ACIP decision-making process that leads to the formulation of an effective problem statement includes review of labeling and package inserts,

review of the scientific literature on the safety and efficacy of vaccines, assessment of cost effectiveness, review of the morbidity and mortality associated with the disease, review of the recommendations of other groups, and consideration of the feasibility of vaccine use in existing programs (Blumenthal, 2004; Bridges, 2004; Gentile, 2008). At meetings, the ACIP may vote to include new vaccines into the national program or to modify existing vaccine schedules. The CDC then acts on the recommendations (Schmidt, Kroger, and Roy, 2004; ACIP, 2008; Luman, Shaw, and Stokley, 2008; US Department of Health and Human Services, 2008, 13).

The decision-making process commences when an issue is placed on the ACIP agenda either from ACIP-affiliated entities such as the CDC or the executive secretariat or via a third party such as other medical research agencies or entities or the general public. A disease that sweeps through the world and garners considerable media attention or a highly touted, promising new vaccine heavily promoted by the pharmaceutical industry may be ripe for ACIP attention as well. Sometimes, the ACIP seeks out issues for consideration and sometimes the issues cry out for attention (ACIP home page, ACIP, 2011).

The ACIP is not well-known to the general public. Consequently, the issues that appear on the group's agenda typically do not originate in a public arena. The relative obscurity of the committee can be a blessing. High-profile agencies sometimes become targets of public anger or hysteria, especially when they produce study results that challenge long-held beliefs or trigger scrutiny from suddenly interested, but technically unsophisticated policy makers. The ACIP is not the only agency or committee to participate in decision making with respect to vaccine recommendations; to the extent that public pressure concerning vaccines exists, the CDC or the FDA serves as the first line of defense.

After an issue is placed on the agenda, the entire ACIP assigns it to an appropriate committee subset or working group. The majority of the research and investigation of a vaccine occurs within the framework of the working

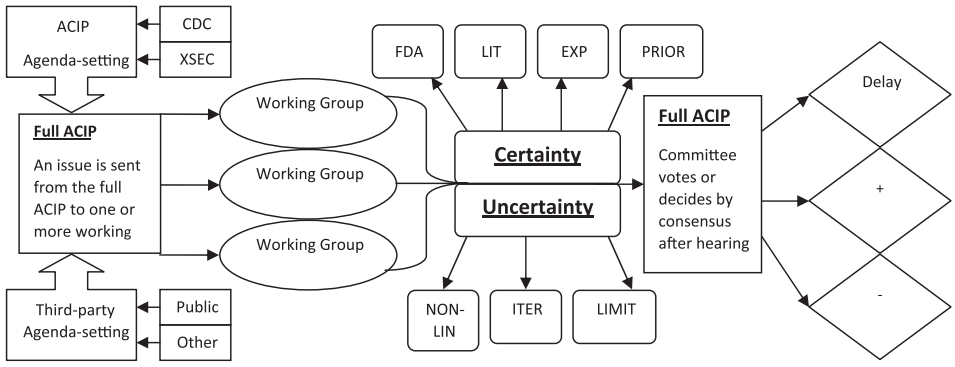

Fig. 1. A model of ACIP decision making under conditions of uncertainty.

groups. A working group immediately begins by framing and occasionally reframing the question at hand. This statement may seem intuitively obvious, but it raises a crucial point. Sometimes, the way a problem is conceptualized and stated can determine the methodology and approach, which affect everything that follows. This is the stage at which handling uncertainty is crucial; if the statement of the problem is flawed, vaccine recommendations will be ineffectual and costly. Concomitantly, working group members must define the parameters of what they know, what they do not know, and what they need to know. Some tried-and-true sources of information include the FDA's files and records used to approve the vaccine for sale in the United States. A literature search also can provide data and published information on studies on the safety and effectiveness of the vaccine. ACIP members and staffers even search beyond the narrow confines of medical literature on vaccines because a broadened search can yield new insights into relevant fields and bodies of knowledge (Carpenter, 2004; Blazek, 2008; Dempsey et al., 2008).

If an issue is relatively straightforward and a large quantity of high-quality data already exist, a case does not require prolonged consideration because stating the problem is reasonably clear-cut. By the same token, an issue where great uncertainty exists, deliberations may stretch across multiple meetings and, in extreme cases, a final decision may be postponed until more data or information can be compiled. The committee's actions do not depend on rote requirements or specific timetables established ahead of time. The committee moves as quickly or slowly as the issue warrants. If the disease burden is high and a vaccine is desperately needed to stem the rising tide of a pandemic, the committee will act with greater dispatch than if the disease burden is low and the need for the vaccine is less pressing. Prior ACIP decisions in similar instances can shed light on the appropriate course of action. As with virtually any deliberative body, the ACIP affords great weight to its past decisions. When other avenues of decision making are foreclosed or have produced few useful results, determining how the group decided similar past issues will help to guide decision making in the instant case (ACIP home page, ACIP, 2011).

The ACIP consciously adopts a pragmatic approach. Working group members consult whomever and whatever they need to conceptualize the problem and develop a recommendation. After a working group wrestles with uncertainties, it reports back to the full ACIP in advance of a full ACIP meeting. When the full ACIP meets to discuss the vaccine, the working groups present information and their conclusions. At that point, the ACIP must reach a decision on whether it should recommend dissemination and administration of the vaccine. The decision can be the result of consensus or, in cases where the group cannot reach consensus, a vote may be taken. The decision can be one of three choices: (1) delay making a decision pending receipt of new data; (2) a positive recommendation suggesting that the vaccine be administered in a particular way; or (3) a negative recommendation

indicating that the vaccine should not be administered, or at least not administered to a certain population in a certain manner (Blazek, 2008).

Uncertainties occasionally will require the ACIP to postpone the decision-making process while the group searches for new data or new data sources. Implicit in this decision-making process is the understanding that uncertainty always exists and must be handled. No serious thought is given to the idea that the issues are so imprecise and the data so incomplete that a decision can never be made. ACIP members generally reject the True Ambiguity scenario because it leads to the "no action" alternative in each instance. If so many variables are missing that a decision cannot be made, the committee will defer the decision—treating it as a Range of Futures issue where discrete alternatives do not yet exist—but the deferment cannot exist indefinitely. At some point, a recommendation on a vaccine and the appropriate doses must be made even when a Range of Futures exists. The ACIP has rejected the epistemological position that some answers can never be found. In some cases, the decision-making process may have to be refined by reframing the question and approaching the problem from a new perspective. Examining and reexamining treatment effects, especially after a question has been reframed, can yield fresh insights.

Even when ACIP members believe they have framed a question appropriately, they may need to revisit a recommendation at a subsequent time if new information comes to light or if data gaps require future research. Thus, a decision, once reached, is not irrevocable. The iterative nature of the decision-making process and ongoing vaccine research means that uncertainty need not paralyze the ACIP's efforts. In cases where the problem statement as it was conceptualized originally leads to a dead end, the committee may return to the initial problem and reframe the question (Djulbegovic, 2007; Blazek, 2008; Dempsey et al., 2008).

Like most modern scientific researchers, ACIP members generally do not subscribe to the "crucial experiment" school of thought. The public often believes that a lone, heroic scientist working in a laboratory will experience a "Eureka" moment, or a series of moments, after which all becomes clear and science can solve a problem. Medical researchers understand that such dramatic breakthroughs are rare. Instead, data are accumulated by a community of researchers over time and, in many cases, the effects of the data are unknown. Later researchers working with those data may find an application that was previously unknown or they may interpret the data in new ways that provide insight into other research, perhaps filling in the gaps in data sets. ACIP members realize that the decision-making process can be made linear, but the data-generation process is more iterative and piece-meal owing to the nature of the scientific method (Pope, Ziebland, and Mays, 2000; Michaels, 2005; Green and Glasgow, 2006). In the words of one researcher, "it is very rare to find determinative experiments in environmental health sciences. A single, well-constructed experiment almost never resolves a critical issue on the cause of disease" (Krimsky, 2005, S129).

Because each vaccine is different and the quality and quantity of the data that come before the ACIP are different, the focus will vary from one case to the next. In the case of a vaccine where a great deal of information and consensus exists, the certainties outweigh the uncertainties. For a new vaccine, the data may be incomplete because scientific studies cannot yet evaluate potential side effects. Such uncertainties may be acceptable if the disease treated by the vaccine is virulent and the need for treatment is urgent. In those cases, ACIP members accept the risks inherent in making a positive recommendation because the probable benefits are so high. If they turn out to have been mistaken in their recommendation, they can revisit the decision at a subsequent ACIP meeting (Lave and March, 1993, 19–34; Nexoe, Halvorsen, and Kristiansen, 2007; Crout, Tarsitano, and Wood, 2009).

Costs and tradeoffs are always factors that influence ACIP vaccine recommendations. Is it preferable to spend millions of dollars on a vaccine that prevents or retards only one potentially fatal disease in a narrow population or should the funds be used to treat diseases that affect many more people but which may not be as dangerous to a larger cohort? Analogously, is it preferable to plan for events that seldom occur or, if they do occur, affect only a few people (but to an extraordinary degree) or is it preferable to plan for events that occur frequently and affect a large number of people only slightly? Interviews with ACIP members indicate that they always weigh costs as part of the variables that affect their decisions, recognizing that the committee is not primarily charged with an accounting function.

V. CONCLUSION: MANAGING SCIENTIFIC UNCERTAINTY IN MEDICAL DECISION MAKING

Although the ACIP represents a small, relatively homogenous body of medical researchers, some generalizations can be drawn from studying the ACIP decision-making model. Care must be taken not to overgeneralize, of course; as long as the presuppositions are clearly stated and the biases are known, the generalizations can help to explain how scientists and medical researchers deal with uncertainty.

Managing Uncertainty Requires a Problem Statement to Be Conceptualized Appropriately

A researcher or physician must properly formulate a "problem statement" in the face of uncertainties. This endeavor requires great skill and sound judgment. If the problem statement is formulating too quickly or based on expected outcomes and preconceived biases, the resultant diagnosis and treatment will be flawed. The researcher or physician must gather data to the extent that it exists and follow its logical conclusions, regardless of where

they lead. At the same time, data may be missing, unavailable, and/or ambiguous; the researcher or physician must take care not to suffer from analysis paralysis. At the point at which no further data are forthcoming or useful, the problem statement must be conceptualized.

Pragmatism Can Be Used to Conceptualize a Problem Statement

Pragmatism is first and foremost a heuristic tool that can help cut the Gordion knot of scientific uncertainty. Caution is in order, however; intellectual laziness must not pass for pragmatism. Reliance on intuition can cause physicians to fall back on clichés such as "this is the way I always treat this kind of case" in lieu of appreciating differences in a new case or investigating new scientific advances or more efficacious treatment options. Employing pragmatism and recognizing the limitations of knowledge, as discussed by cognitive scientists, does not require decision makers to eschew efficacious methods. Where statistics and quantitative tools are available, for example, they can assist in decision making (Fisher, 2003).

Pragmatism as a philosophical construct can be employed as a tool for conceptualizing a problem statement and, afterward, reviewing options for developing an effective treatment regimen. Analogizing among and between cases, consulting with peers, and familiarizing oneself with the medical literature are crucial steps. As outlined in figure 1, ACIP members have established a series of procedures that allow members to employ these pragmatic tools. If uncertainty exists after going through these procedures, relying on intuition and professional experience would be appropriate.

Tradeoffs Involving Costs Always Exist and Are Largely Uncertain

As crass as it sounds to the general public, costs, monetary and societal, are always factors in the medical decision-making process. Moreover, because costs are not always quantifiable beforehand, to some extent the tradeoffs among and between costs generally are uncertain. ACIP members are not tasked with directly considering monetary costs in decision making, but an awareness of budget deficits and the scarcity of resources cannot, and perhaps should not, be avoided. In the normal course of business—for example, when a chemical is marketed and it has not only a high degree of risk but also a high degree of financial reward for the manufacturer—the marketplace may absorb the cost and a company may be willing to accept the burden for any potential damage occasioned by the company's product. Even if a pharmaceutical company invests a great deal of time and money in drug trials that do not produce a marketable product, the company sometimes can absorb negative externalities because it still earns a large return on investment through the marketing of effective drugs. In the case of a successful vaccine, the costs can be passed on to the customer (in this case, the patient and/or the patient's health care provider). An expensive new drug

that initially is funded by a pharmaceutical company and eventually is financed through the health care system—thereby allowing the drug maker to recoup the investment as well as earn a profit—is a prime example of a well-functioning health care system (Ghosh, 2008).

In market failure situations, government may need to step in to ensure that the burden is not too daunting for the private sector, especially under conditions of uncertainty. For vaccines, where risks and uncertainties abound, the pharmaceutical companies bear the burden of a vaccine's success or failure. If the market for a new drug is small, but the needs are high—for instance, if a new acquired immunodeficiency virus (AIDS) vaccine is developed, few people need it, the costs are high, but the people who need it must have it soon or they might die—a pharmaceutical company may be unwilling to market the drug. There is an opportunity cost in offering a drug that few people will use when the company could be offering a drug that would help a larger number of people. As a matter of public policy, government may decide that it is in the best interests of everyone in the polity to ensure that the number of terminal AIDS cases declines. If government desires the drug to be available, it will have to assume the risk by assuring the private sector that the risks will not fall entirely (if at all) on an individual pharmaceutical company (Pearce and Turner, 1992; O'Connor, 1997; Gollier and Treich, 2003; Nexoe, Halvorsen, and Kristiansen, 2007).

ACIP decision makers recognize that their recommendations and the repercussions can determine whether drug manufacturers continue to conduct research into vaccines and offer them for sale in the United States. Although the group is not charged with responsibility for determining whether the pharmaceutical company will bear the costs and risks of developing a new vaccine or whether a third party, including government, will pay, the reality is that any decision-making body, especially one that is making recommendations with a substantial impact on the public, cannot avoid considering costs.

Reconceptualizing a Problem Can Sharpen Insights

The way a problem is stated can determine the answers the research will generate. Sometimes, the research question must be refined even if it was well thought-out in the initial stages of development. As ACIP members have discovered on occasion, when a research agenda seems to be unproductive because the data are missing or important variables are poorly understood, it makes sense to restate the problem. This revision is not designed to avoid the hard questions; it seeks to get at a problem in new ways. A fresh approach or a separate set of issues can lead to insights and information that was not forthcoming previously. In some instances, bringing in new experts and undertaking an additional literature review to educate medical researchers on the salient issues raised by the new research questions can

trigger progress, to say nothing of possible insights gleaned through serendipity.

Science Is Iterative

A well-framed question can lead to a rigorous research agenda that yields valuable insights into fundamental questions about vaccines and treatment effects, ideally lessening the disease burden on the target population. Even when such insights are lacking, the incremental advance that the ACIP working groups make in understanding part of a medical problem can lead other researchers to make advances. In cases where the ACIP answers a question it has posed, the answer can raise more questions and not only lead to more uncertainty but also lead to further advances. This never-ending cycle of questions and answers amounts to iterative "progress."

Avoiding Scientific Manipulation

In a public health setting, the demand for quick, easy-to-understand, and cost-effective progress is immense and occasionally unrelenting. Medical decision makers have an obligation to report their findings in a proper context with appropriate caveats and qualifications, but the pressure to produce demonstrable, viable results may lead policy makers to minimize nuances in the service of a political objective. Such machinations undermine, rather than advance, medical science and must be minimized, to the extent possible. Third parties often ask for certainty in medical decision making because they do not fully understand the nature of scientific progress. Sometimes, they ask because they have a political agenda. Science can, of course, be politicized (Costanza and Cornwell, 1992; O'Riordan and Jordan, 1995). Moreover, public organizations are hardly bastions of objective, neutral information, and scientists are not always seekers of truth (Carpenter, 2004; Anonymous, 2006; Intemann and De Melo-Martin, 2008; Pielke, 2008). They, too, have a vested interest in the outcome of scientific studies as these organizations attempt to establish and maintain a domain, compete for scarce resources, and play the games of bureaucratic politics (Anonymous, 2004, 2005; Wise, 2006; Whitford, 2007; Rose, 2008; Van Der Wal, De Graaf, and Lasthuizen, 2008).

ACIP members are trained as medical professionals, but they all recognize that they exercise policy-making influence. Any governmental entity that is charged with addressing scientific issues ultimately will feed its decisions into the policy-making process. Otherwise, there is no point in government organizing such a committee. When medical professionals make policy decisions, in one sense they close the science-policy gap because they must use their knowledge and expertise to reach sound decisions that are both scientifically accurate, to the extent possible, and defensible within the public policy realm (Bradshaw and Borchers, 2000; Dempsey et al., 2008).

Aside from the politics, conscientious scientists realize that uncertainty is a feature of all information and data and must be confronted without illusion. Although researchers in the medical community can live with doubt and ambiguity in their research, the lay public often clamors for absolute precision. It is therefore incumbent upon researchers to communicate the idea that boundaries exist for human knowledge and invariably limitations exist. This is far easier said than done because the public often does not understand the intricacies of the scientific method and the limitations in the data (Kinzig et al., 2003, 330–1).

Because it does not operate within the public eye, the ACIP has avoided the controversy that sometimes swirls around high-profile public agencies. Nonetheless, committee members must communicate their recommendations to agencies such as the CDC and the FDA that do have public constituencies. The use of vaccines can be contentious, especially among citizens who mistrust government and medical elites and who believe, for example, that childhood vaccinations cause harm out of proportion to the benefits they provide. The ACIP could find itself under the glare of the public spotlight at any time, although that has not happened in the past (Blazek, 2008).

Uncertainty Cannot, and Should Not, Be Eradicated; It Should Be Managed

Uncertainty is ever present (Beresford, 1991; Reckhow, 1994). As Benjamin S. Halpern and his colleagues wrote in 2006, "there are essentially two types of numerical uncertainty—one type can be removed with more data and the other type cannot." In their view, "although the treatment of uncertainty can seem daunting . . . people have long accepted it in many aspects of their daily lives. We fly in aeroplanes, we drive across bridges, and we manufacture and use chemicals" (Halpern et al., 2006, 13).

These researchers raise an excellent point. The difficulty that most nonscientists have when they grapple with uncertainty is that often they do not understand the context in which decisions are made. Scientific and medical issues are so complex and usually require so much background information that the average person cannot make sense of the issues and data. The task for policy makers who make decisions in a highly technical, complex field is to help nonscientists understand the context (Trautmann, Vieder, and Walker, 2008). For science professionals and physicians who seek to communicate as much accurate data as possible, the difficult chore also is to find the most appropriate means of translating scientific information into easily understood messages that do not misrepresent the data or hide the uncertainties (Reckhow, 1994). The difficulty of the task does not obviate the need to complete the task. As Halpern et al. (2006, 13) write, "there is no single best tool for dealing with uncertainty--the best choice will depend on the management context and the quality and quantity of data available."

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