EPISTEMIC UNCERTAINTIES

Unfamiliarity breeds uncertainty. Epistemic uncertainties are subjective in nature and arise primarily from limited knowledge. They can take several forms. First is the universal ignorance such as regarding the cure of AIDS – for that matter even hypertension – that nobody knows how to reverse; or could be data gaps such as unavailability of risk of leukaemia in males with low ferritin level, or cause attribution of deaths in India. The former requires a long-term research whereas the latter is just a question of carrying out a survey in the relevant groups of people.

Another aspect of ignorance is that two or more treatment strategies may be equally good, or equally bad, and nobody knows yet which one to adopt and when. For example, amoxicillin and cotrimaxazole could be equally effective in nonsevere pneumonia. Mortality risk reduction in coronary artery disease by behavioural changes such as exercise, diet, lipid modification, and smoking may be similar to the other medical therapies such as aspirin, beta-blockers, and bypass surgery. Adoption of one or the other would depend on the personal preference rather than scientific considerations.

KNOWLEDGE GAPS

Ignorance permeates across all biological phenomena although degree varies. This includes parameter uncertainty regarding the factors causing or contributing to a particular outcome. Experts tend to differ, such as for aetiological factors of vaginal and vulvar cancer. Inadequate knowledge can also be for role of values that have not been observed. That lung functions are affected by pollution exposure is well known but what happens if NO_2 level reaches extreme level of 100 $\mu g/m^3$ is not fully known. In many situations the only knowledge is that the health is adversely affected by a specified exposure but exactly how much is the effect is uncertain. In fact, quantitation of the effects has remained a major epistemic bottleneck in evidence-based decisions. Also, many times it is not clear why some factors cause disease in one and not the others. An everyday example is exposure to iodine deficient water and soil that cause goiter in some people – that too of varying degrees – and not in the others residing in the same area. All such unknown factors are sometimes called **chance**.

There are instances when medical science has been practiced on a wrong premise. A recent example is peptic ulcer that was thought to be caused by excess acid produced by stress but now it has been discovered that *Helicobacter pylori* is the culprit in many cases. A similar scenario of infection origin seems to be emerging for coronary artery disease. Intake of tamoxifen for long duration is now being implicated for endometrial cancer.

Another aspect of inadequate knowledge is model uncertainty that pertains to functional form of relationship between etiologic factors and outcome. *Model by definition is a simplistic version, and it is never perfect*. Modifications that improve the model can always be suggested but the practical gain with such modification can be debated.

Rarely acknowledged aspect of inadequate knowledge is confusion about definition of various health conditions. For example, there is so much debate on the definition of an apparently simple-looking condition such as hypertension with the blood pressure (BP) cut-off starting from 130/80 mmHg and reaching to 160/95 mmHg. Isolated systolic hypertension (sysBP ≥ 140 mmHg and diasBP <90 mmHg) is no longer considered a benign condition but is considered a cardiovascular risk factor. Definition of diabetes now includes the concept of premellitus stage such as obesity that requires prophylactic weight control. Many such examples can be cited that illustrate epistemic insufficiency.

INDIVIDUAL IGNORANCE

Whereas the preceding discussion refers to collective ignorance, the second source of epistemic uncertainty is at individual level, either at the level of the clinician or at the level of the patient or the family. Physician's lack of awareness about new developments and their implications come under this category. Human fallibility is not uncommon. Even the most responsible researcher can make an honest mistake. The possibility of incomplete or wrong analysis of the data or interpretation also causes this type of uncertainty.

Patients also quite often do not know how to describe their complaints. Depending upon their education and knowledge, they adopt different styles with varying emphasis. It is not uncommon that vital information is missed. Incomplete information due to memory lapse or for any other reason also causes epistemic uncertainty that can affect research findings.

LIMITATION OF INSTRUMENTS

Third type of epistemic uncertainty arises from nonavailability of appropriate instruments. Perhaps no instrument is perfect but what causes specific concern is difficulty in measuring some characteristics such as psychological stress and positive health. How do you measure blood loss during an operation with unstandardised swabs and spilling in some cases? Surrogates are used that work only as a stopgap till such time that a more valid tool is developed. Nonavailability could be at the micro level also such as of the facility of CT scan that might be strongly indicated in a particular case, or the right laboratory facility for evaluating specific enzyme level. These facilities may not be locally available or might be too expensive for the patient.

BIASES AND ERRORS

Fourth are the biases, perceptions, and preferences. For the physician, they can intensely affect the choice of investigations and their interpretation, treatment strategies, prognostic assessment, etc. For prostate enlargement, one may give more importance to prostatic specific antigen test over the ultrasound image when they are discordant. Value judgments and errors are always epistemic. For the patient and the family, these judgments can affect their acceptability and adoption of an advice or a procedure. At the macro level, these can take the form of publication bias of the journals, and the bias present in trials.

Errors of judgment or otherwise in medical care can result in perforation, laceration or injury to an organ during an invasive procedure, unplanned return to operation theatre, infection developing subsequent to admission, and transfer of patients from general care to special care. The level of competence and expertise of the clinician is always of concern. Some are meticulous in piecing together the history, examination, laboratory, imaging and other evidence into a solid framework for management but some lack this knack. Not all are equally good in extracting relevant information from the patient. Distinguish such individual incompetence from the inherent weaknesses in universal knowledge while planning a medical research.

Faith of the patient on the care-provider and on the system can also be a significant determinant of the outcome. A related parameter is compliance. Directly Observed Therapy Short-course has been devised precisely for the problem of compliance in tuberculosis treatment, and this problem persists in many other settings such as anaemia prophylaxis. Noncompliance and nonadherance may occur with regimens for cardiovascular risk reduction programs and such other prophylactic and treatment modalities. Uncertainties arising from such inadequacies are epistemic and not aleatory.

MANAGEMENT OF EPISTEMIC UNCERTAINTIES

Although sensitivity analysis can be carried out with different plausible scenarios to assess epistemic uncertainties, their management is an uphill task. Perhaps the only effective strategy is to take preventive steps in terms of using valid tools, exercise sufficient care, be knowledgeable and objective, recognize biases, and differentiate between facts and value judgment. Many of the epistemic uncertainties go unnoticed. Some can be reduced through tools such as scoring system, aetiology diagram, and expert system. For some of these such as nonresponse and properly recognised biases, statistical adjustments are possible at the time of analysis.

We have used some statistical terms in Examples 1 and 2 that follow. Do not worry if you are not able to make full sense. The purpose of these examples is to illustrate aleatory and epistemic uncertainties.