The Precautionary Principle, epidemiology and the ethics of delay

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Summary

Ethics tells us: do good and do no harm and invokes the norms of justice, equity and respect for autonomy in protecting and promoting health and well-being. The Precautionary Principle, a contemporary re-definition of Bradford Hill's case for action, gives us a common sense rule for doing good by preventing harm to public health from delay: when in doubt about the presence of a hazard, there should be no doubt about its prevention or removal. It shifts the burden of proof from showing presence of risk to showing absence of risk, aims to do good by preventing harm, and subsumes the upstream strategies of the DPSEEA (Driving Forces Pressure Stress Exposure Effect Action) model and downstream strategies from molecular epidemiology for detection and prevention of risk. The Precautionary Principle has emerged because of the ethical import of delays in detection of risks to human health and the environment. Ethical principles, the Precautionary Principle, the DPSEEA model and molecular epidemiology all imply re-emphasizing epidemiology's classic rôle for early detection and prevention. Delays in recognizing risks from past exposures and acting on the findings (e.g., cigarette smoking and lung cancer, asbestos, organochlorines and endocrine disruption, radiofrequency, raised travel speeds) were examples of failures that were not only scientific, but ethical, since they resulted in preventable harm to exposed populations. These may delay results from, among other things, external and internal determinants of epidemiologic investigations of hazard and risk, including misuse of tests of statistical significance. Furthermore, applying the Precautionary Principle to ensure justice, equity, and respect for autonomy raises questions concerning the short-term costs of implementation to achieve long-term goals and the principles that guide compensation.

***Key words*: Precautionary Principle, epidemiology, ethics, delay**

"The time is short, the work is great, the master of the house is waiting, the workers are lazy, and it is not for you to finish the job, but you are not exempt from beginning"
"If not now, when?"
The Talmud[3]

"Epidemiology is merely a tool for helping people in trouble"
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Introduction

Ethics tells us: do good and do no harm. It invokes the norms of justice, equity, and respect for autonomy as values governing relationships between human beings as individuals[1, 2] (Table 1). The preservation, protection and promotion of life is the norm by which we judge the worth of all activities (Talmud)[3]. It follows that we endorse activities that bring us closer to this norm and reject activities that do not – a viewpoint common to classic theologic and humanistic traditions[4]. These traditions exhort us to protect the weakest and most vulnerable. Social contracts and laws seek to translate these ethical norms into systems of justice, laws and social organization. Right to know, right to act, informed consent and compensation are some of legal tools these systems use. Failure to use these tools leads to abuse of these ethical norms[5, 6].

The Precautionary Principle restates common sense rules for doing good by preventing harm: "better to be safe than sorry" or "when in doubt about the presence of a hazard, there should be no doubt about its prevention or removal"[7]. Bradford Hill's term – the case for action – the need for intervention when there is uncertainty concerning definitive proof of causation, anticipated the Precautionary Principle[8].

The Precautionary Principle repudiates waiting for result of complete assessment of past risk, especially when the results are severe, and not doing everything possible to anticipate future risk, so as narrow the time gap between suspicion and verification[9]. In other words, time is of the essence.

The major components of the Precautionary Principle are: defining the risk to be prevented, shifting of the burden of proof from demonstration of risk to demonstration of absence of risk, reducing risk through substitute technologies or removal or modifying a hazardous technology exposure at the source, and promoting modal shifts and substitution, and using interventions proportionate in cost to the costs of the prevented hazards and risks. There is also emphasis on rigorous evaluation of the efficacy of interventions, in terms of benefits versus the risks, or the risks of doing something as opposed to waiting and doing nothing[9-12] (Table 2).

The strategies of the Precautionary Principle mesh with those of the World Health Organization (WHO) model for DPSEEA for doing good by preventing harm. The DPSEEA model is utopian; it promotes "upstream" change in social,

Table 1 - Ethics, norms, and legal tools

Ethics
Do good
Do no harm
Norms
Justice
Equity
Respect for autonomy.
Legal tools
Right to know
Right to act
Informed consent
Compensation

Table 2 - Precautionary Principle

Aim:	Do good by preventing harm
Implication:	When in doubt (about the presence of a hazard), there should be no doubt (about its prevention or removal)
Redefinition:	Bradford-Hill's case for action
Ethical Issues:	Delay, benefits vs. risks, risks vs. risks

economic and technological systems to prevent creation of hazard and risk in the first place in a time line going from driving force→pressure→stress→exposure→effect→action[11]. But the Precautionary Principle also subsumes molecular epidemiology, which though it restricts itself to the "downstream" detection of effects of exposures inside living systems, offers promise of preventing delay by earlier – i.e., faster – detection of risk[13, 14].

Epidemiology's missions are the early detection and prevention of risk and the study of the distribution and determinants of disease[15]. The first mission tells us time is short and the message is to hurry up. The second tells us not to rush into premature conclusions. The two missions are based on contrasting interpretations of the adage "better to be safe than sorry"; the first from the risks of delays from doing nothing and accepting a false negative, the second from the risks of prematurely doing something and accepting a false positive (fig. 1).

DPSEEA: "Upstream": Before The Black Box
("Fixing the System"):

Driving Force ---> Pressure ——> Stress ——> **Exposure ——> Effect ——>** Action

Molecular Epidemiology – "Downstream": Inside the Black Box:
("Finding the victim")

Exposure ——> Absorption ——> Internal Dose ——>
Biologically Effective Dose ——> Early Response ——>
Altered Structure Function **——> Effect**

Fig. 1. Time lines of DPSEEA and molecular epidemiology

Epidemiology and risk assessment, because they deal with public health, are not ethically neutral disciplines in the same way that mathematics, musicology, and archeology are. No human lives were lost because mathematicians required 300 years to solve Fermat's theorem. In public health and environmental epidemiology, delay in identifying and acting to reduce risks itself may create risks to health and environment. Is the precautionary principle the *deus ex machina* for rescuing public health from delays in recognizing risk and our inability to deal with uncertainty?

Ethics, the Precautionary Principle, epidemiology and the dimension of time

Ethical imperatives for preserving, protecting and promoting life and preventing damage, depletion or destruction of life-support systems in our environment drive us towards use of what some call the Precautionary Principle and others call precautionary strategies. In public health, delay in recognizing risk is of ethical import, and therefore, in the broadest sense, indicates negligence. We suggest that delay too often derives from a disproportionate emphasis on the use of epidemiology as an instrument for definitive proof of the distribution and determinants of disease rather than as a tool for early detection and warning of preventable risk.

The most extreme recent example of the acutely catastrophic human cost of delay comes from the epidemiology of genocide[16]. In Srbnice, officials ignored early warnings and interventions that would have prevented the massacre of 8,000 Bosnians – in one day in 1995 –

which came one day too late; the resignation of the Dutch Government seven years later, in 2002, was seven years and one day too late.

The very title of the Document of the European Environmental Agency – *Late Lessons from Early Warnings*, and the timelines for its case studies underscore the ethical import of delay for public heath[17]. The 50 to 100 year delays in assimilating, accepting and acting on the early evidence on risks from ionizing radiation, benzene, asbestos, DES, and sulfur dioxide and mad cow disease were catastrophic, even if not in an acute manner[17]. Our own work on health risks from lead[18, 19], asbestos[20], solvents, and cancer in university laboratory workers[21], cancer in naval divers with underwater exposures to toxicants[22] and increased speed limits[23] documents examples of epidemiologic delay and their human costs in occupational medicine and public health in Israel. More recently, proposal to remove chalk containing silica, arsenic, cadmium and chromate from classrooms following presentation of sentinel cases of lung cancer and impairment of pulmonary diffusion in school teachers is an example of the application of the Precautionary Principle in the face of uncertain and preliminary knowledge about possible risk, resulting mainly from rapid delivery of information of concern to the population at risk[24].

If the ethical case for the Precautionary Principle is the human cost of delay, then the time interval between emergence of risk and its detection and removal is a surrogate measure of this cost of delay. Conversely, saving time by shortening this interval saves lives. But saving time is what drives much technological change and brings innovations that sometimes create new risks. For example, promoting increased speeds of vehicular travel, which means time saved, was the pretext for one of the worst decisions against public health in the 20th century: the addition of lead to gasoline, to make motor vehicles go faster. This step, which in its day was promoted as "progress" in saving economic time, not only produced massive neurotoxic damage to tens of millions of children[25], but even worse, resulted in increases in road deaths owing to the exponential relationship between the fourth power of increases in speed and road deaths and emissions of pollutants. Here we have an example of how an econometric definition of progress through time saved was catastrophic as defined by criteria derived from classic theologic and humanistic traditions – and could have been prevented if society had applied the Precautionary Principle.

The epidemiology of delay

The determinants of delay in epidemiology are two-fold: external barriers and methodologic errors of commission and omission (Table 3).

Elsewhere, we have commented on the external determinants (suppression, repression, funding, and publication bias), proposed institutional reforms to reduce their occurrence[26] and reported on a mechanism for protection of investigators subject to pressures that produce these biases[27].

Table 3 - Barriers to detection of risk

External
Suppression
Repression bias
Funding bias
Lamppost epidemiology
Not asking the right questions

Table 4 lists some errors of methodologic commission inherent to epidemiologic studies that are reasons for lateness.

Table 5 lists errors of commission associated with ignoring biologic evidence and divorcing epidemiology from collateral information on biologic plausibility.

Table 4 - Why epidemiology is late: some errors of commission: methodologic reasons

- Small studies→low power
- Large studies→big numbers→exposure misclassification→bias towards null (radar studies?)
- Looking for grey hair in third graders: truncated follow-up of outcomes (“Small is not beautiful”)
- Dismissing effects associated
  with P>0.05 from small studies and clusters Chance does not favour the prepared mind: Bonferroni vs Pasteur: automatic dismissal of positive findings on sub-groups hypothesized to be at special risk; phantom confounding
- Failing to correct for the healthy worker effect

Table 5 - Why epidemiology is late: some errors of commission: ignoring the biologic sentinels

Underuse of ecological markers:
– Organophosphates and bee mortality[28]
– DNA changes, endocrine disrupters and developmental defects in fish[22]
– Herbicides and lymphomas in dogs[29]
– Electrical and magnetic fields from high tension lines and milk productivity in cows[30]

Table 6 - Why epidemiology is late: errors of omission

Non-use, underuse or non-investigation of
– Sentinel events→groups at risk[31]
– Early cases of cancer with short induction periods[32]
Increases in case fatality
– Early effects of raised speed limit on deaths[23]
– Increased case fatality from leukemias in residents near radio and TV antennae[33]
– Non-use of proportional incidence and mortality when denominators not available
– Ignoring disproportionate number of multiple primaries[34]
– Failure to assess natural experiments from ecological associations
– Road deaths: 40% drop in UK vs absence of drop in USA during 1990s[35]
“Fallacy of ecological fallacy” [36]

Table 6 list errors of omission that derive from not going beyond the rigid structures of hypothesis testing confined to case control and cohort studies. The other papers in this conference address most of these issues.

External pressures on the content and direction of epidemiologic research produce delays in recognition of risk, as does an excessive preoccupation with statistical modes of reasoning divorced from the ABC’s of biologic plausibility. These trends accounted for resistance of Ronald Fisher, the greatest biostatistician of his time—and a consultant for the British Tobacco Trust, to recognizing the cause-effect relationship between cigarette smoking and lung cancer[37]. As Bradford Hill himself noted, the failure to use collateral lines of evidence, and the inherent delays and uncertainties associated with discovering new knowledge, are other reasons for delay.

How to speed up epidemiology’s response time

Ethical principles, the Precautionary Principle, the DPSEEA model, and molecular epidemiology all imply re-emphasizing and strengthening epidemiology's classic rôle for early detection and prevention. Can we reduce the time lag between suspicion of risk and intervention, in keeping with the principle of the case for action? Strategies for enhancing epidemiology's effectiveness for earlier detection and prevention of risk or avoidance of Type II errors involve addressing the errors of commission and omission we have just listed in Tables 4-6. The first strategy is to address the distortions in direction and content of epidemiologic research resulting from external pressures associated with repression, suppression, and funding biases. The other strategies include: investigating sentinel events and cancer cases with short latent periods, recognizing that certain exposures (single or mixed) produce multiple outcomes (e.g., cancer, reproductive, neurotoxic), using partial data sets when there are barriers to access to data, and making greater use of ecologic comparisons of time trends on population-wide impacts. Finally, there is the issue of greatest substantive and symbolic importance: abandoning the *routine* use of $p<0.05$ as a criterion for not making a Type I error when outcomes are catastrophic.

Ethics of delay and the context of tests for significance testing

Bradford Hill, when he invented the term, the case for action, warned against the dangers of misusing tests for statistical significance as pretexts for delay:

> "The χ^2 test is an excellent servant and a bad master".
> "No formal tests of significance can answer those questions [regarding causality]…they contribute nothing to the "proof" of our hypothesis".
> "To decline to draw conclusions without standard errors can surely be…silly…we waste a great deal of time, we grasp the shadow and lose the substance, we weaken our capacity to interpret data and to make reasonable decisions whatever the value of P. And far too often we deduce "no difference" from "no significant difference"[6].

Tests of statistical significance are criteria for judging the reproducibility of an experimental association between exposure and risk. They are not guides for making decisions about life and death under conditions of uncertainty for assessing either rare catastrophic events or long-term large population risks. For rocket science, we want a p of zero in estimating error of a landing site on the moon; for deciding whether or not to close a shaky bridge, any p value short of 1.00 carries unacceptable risk. The decision to operate on a patient with RLQ pain, nausea, vomiting, fever, tenderness at McBurney's point and rebound is not guided by significance testing, but a weighing of the benefits and risks of operating versus not operating dictated by the diagnosis of appendicitis, a potentially fatal medical emergency.

Ethical constraints

Invoking the Precautionary Principle is, by itself, not an exercise in validation of efficacy of an intervention for doing good, preventing harm and not causing harm. We can ask: does applying the Precautionary Principle ensure justice, equity and respect for autonomy? How is good defined? Who decides? And for whom? And who pays the short-term costs of implementation to achieve long-term goals? All environmental dilemmas can be reduced to several bottom-line principles: everything is interrelated, everything has to go somewhere,

Table 7 - Ethical constraints: principles: justice, equity, respect for autonomy of individual

Questions:

Who decides?
For whom?
Good for all?
Costs: who pays and how?

Justice?
Protection of weakest→protect all
Greatest good for greatest number?
Abuse: casting as susceptibles
Costs of preventing false positives

there is a cost to everything, and someone has to pay, in one form or another (Table 7).

The social costs and dangers of the Precautionary Principle

Implementation of the Precautionary Principle means there will be social costs associated with turn-arounds. For example, terminating many industrial processes, and substitution, and therefore, the loss of work and livelihood for large cohorts of workers, produces a scenario of better public health for many and worse social stress for some. If doing no harm and promoting equity are two principles of ênvironmental ethics, then it follows that policies to apply the Precautionary Principle presuppose compensation of those worker populations deprived of employment by its application[1]. The attached commentary, prepared by Colin Soskolne, defines the ethics of distributive justice and compensation of those losing work as a result of application of the Precautionary Principle.

Furthermore, as Goldstein has shown[38], there is a need to apply a precautionary strategy in evaluating the impact of intervention strategies that themselves can produce risk. Invoking the Precautionary Principle to do no harm means that when there is an intervention to prevent a health risk, its effect must be evaluated. It therefore follows that if to predict is to prevent, then the use of the Precautionary Principle to explicitly repudiate risk assessment – the everyday tool for practicing public health – carries the potential for doing harm.

Above all, equity, justice, and respect for individual autonomy dictate against invoking the Precautionary Principle to misuse molecular epidemiology – the major danger from its misapplication. Its capacities for the early detection of special risks in sub-groups should not mutate into search for susceptible sub-castes. As Geoffrey Rose has shown, such strategies presuppose acceptance of low-level exposures with lower risks, but more victims in the larger group[39].

Conclusion

Is the move to the precautionary principle driven by a sense that epidemiology has lost its soul? But at the same time, are there dangers from using the Precautionary Principle to ignore or discredit evidence-based risk assessment when it is properly carried out in a transparent and open manner.

The lag time between preventable risk and the discovery of its cause measures the gap between the Precautionary Principle and certainty of proof. Ethics suggests that time and delay equate with harm, and medicine tells us, above all, to do no harm. Irving Selikoff, on his deathbed, confessed his regret over waiting so many years before he worked to get asbestos banned – and wondered whether the years he spent in research were misspent: “I could have saved a lot of those boys instead of waiting”[40].

Comment: Ethics and the Precautionary Principle: the ethics of distributive justice (by Colin Soskolne)

Compensation for those people suffering untoward side effects from the application of any new approved substance or technology ought to be built into the notion of precaution. We protect all by protecting the most vulnerable. But it is the most vulnerable who are often those first or most harmed. While the herd is protected or enjoys the benefits of new technologies, should the herd not compensate the vulnerable or susceptible minority that experiences some ill effect, and provide them with, say, access to free health care and compensation for lost income? The rationale underlying an affirmative response to this question is that if the vast majority enjoys benefits, then those enduring harms should be compensated, because it is at their expense that the herd will have derived its benefits. This rationale fits well with the ethical core principle of "distributive justice"[41].

The notion of whether compensation would be acceptable under the Precautionary Principle is very much a matter of context. If the principle is applied in a context of "egalitarian theory/values", as in Canada, then compensation would likely be acceptable. However, in the context of "libertarian theory/values", as exists in the USA, compensation likely would not be favoured. Finally, there is the utilitarian principle of "the greatest good for the greatest number". This ethically problematic theory guides much of every day public health. Under "utilitarian theory", the intent of any public health action is to achieve the greatest good for the greatest number. This theory accepts that some will be harmed. Distributive justice would require that those harmed deserve to be compensated by those not harmed. Under the Precautionary Principle, one aims to reduce the risk of harm to zero, or more practically speaking, to minimize as far as possible harm in the presence of uncertainty.

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