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Evidence-based primary prevention?

by Paolo Vineis, MD¹

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Key terms anthropology, degree of evidence, ethics, high-risk groups, population impact.

Public health can benefit considerably from the new wave of “evidence-based medicine”, gaining in clarity with respect to objectives and in awareness with respect to the evidence that is available, or not available, in favor of different forms of preventive intervention. In the meantime, a reductionist approach to primary prevention would be extremely dangerous. This type of approach would consist in the sole consideration of scientific evidence and on the establishment of a very high threshold for such evidence (eg, randomized controlled trials, which are not always adequate for evaluations of effectiveness with respect to public health). Instead, we have to be aware that, with exceptions, prevention involves changing the habits and behavior of large groups of people. Such changes cannot be made without adequate consideration of ethical and even anthropological aspects. In addition, a creative approach to prevention — not solely influenced by the “gold standard” of randomized-controlled trials — has still to be developed. In brief, primary prevention clearly requires the integration of several skills and disciplines, none of which has to be considered sufficient in itself.

In my contribution, I critically consider the role of the different disciplines that have to be integrated in order to practice effective evidence-based primary prevention: (i) how evidence-based primary prevention might differ in scope and methods from evidence-based medicine, (ii) the specificity of systematic reviews and guidelines aimed at prevention, (iii) how systematic reviews differ from guidelines and recommendations, (iv) the relevance of different measures of efficacy (odds ratio, number needed to treat), (v) the practical and ethical implications of different preventive strategies (high-risk groups versus general population), (vi) the anthropological context in which each preventive action has to be evaluated.

What is evidence-based medicine and how does it differ from evidence-based primary prevention

Evidence-based medicine has become popular among clinicians and epidemiologists as a tool with which to facilitate the translation of scientific research into clinical practice.

The principles of evidence-based medicine include the use of quantitative estimates of efficacy, including confidence intervals, reference to randomized controlled trials as the “gold standard” of medical evidence — at least as far as efficacy is concerned — the conduction of systematic reviews of evidence, usually based on meta-analyses (eg, the Cochrane Library), the use of scores to assess the qualitative level of the studies, the search for publication bias (use of funnel plots and similar approaches) and other sources of bias, and systematic and rational approaches to the transfer of research into practice (evidence-based guidelines). Concerning randomized-controlled trials, it is, in fact, a commonly held misbelief about evidence-based medicine that the only gold standard is the randomized-controlled trial. Instead, evidence-based medicine does not advocate randomized-controlled trials for all questions, but it rather values different types of proof according to their own merits.

Evidence-based medicine was born at the patient’s bedside. Evidence-based health care was introduced soon afterwards. Evidence-based primary prevention, however, is still in its infancy. It has the following problems in comparison with evidence-based medicine and evidence-based health care:

1. It requires 2 steps, one comprising the evaluation of evidence on cause-effect relationships (eg, the protective effect of fruits on carcinogenesis) and the other referring to the efficacy and effectiveness of preventive activities (eg, the different ways in which the consumption of fruit

¹ Unit of Cancer Epidemiology, Dipartimento di Scienze Biomediche e Oncologia Umana and Centro per la Prevenzione Oncologica, Torino, Italy.

can be modified in living populations). The 1st point differs from usual systematic reviews in evidence-based medicine because randomized-controlled trials are seldom available, so that systematic reviews have to be based upon lower-level evidence, such as case-referent and cohort studies. In addition, the extent of publication bias may be uncertain. Randomized-controlled trials are sometimes available for the 2nd point; however, they are difficult to organize and may be complex, are often based on cluster randomization and therefore may be difficult to interpret, are strongly influenced by (cultural) contexts and therefore may give conflicting results.

2. A systematic discrepancy between theoretical efficacy and effectiveness in preventive practice is to be expected. The effectiveness of health education and similar preventive tools depends strongly on many aspects of the context, for example, the organization of health services and communities, the cultural background (eg, degree of understanding of and tolerance to risk), and economic and ethical aspects. A positive, well-conducted randomized-controlled trial provides strong evidence of preventive effectiveness, while a negative study is more difficult to judge because of all the complexities involved.

Systematic reviews versus recommendations

Basically, evidence-based medicine consists of (i) the conduction of systematic reviews of the evidence and (ii) setting rules for the use of evidence in clinical decisions, for example, through the elaboration of guidelines for clinical practice. It should be clear that these aspects are 2 distinct steps, the 1st being primarily based on scientific principles for causal assessment and the 2nd involving extra-scientific elements, such as reference to values. Typically, the 1st step consists of a meta-analysis of the available randomized clinical trials, while the 2nd step leads to recommendations. There is not necessarily a strict link between the two. As the guidelines of the American Society for Clinical Oncology suggest, a high level of scientific evidence can be followed by a low-level recommendation (because the drug is expensive or not tolerated by the patients) and vice versa.

It is my opinion that such a distinction between the assessment of evidence and decision making is essential and very fruitful for public health as well. Although decision making should be clearly based on the degree of evidence, action can be taken even with a low degree of evidence, depending on the circumstances. To give an example, drugs have been banned because of a weak suspicion — based on case reports — of a toxic effect (ie, on the basis of poor evidence) if their benefit proved to be modest or absent. This is the case for gangliosides and the risk of Guillain-Barré syndrome. The important prin-

ciple underlying evidence-based medicine is to summarize all the available evidence, to create awareness about the areas in which evidence is lacking, and to use the best evidence transparently in decision making.

Are the same concepts of evidence-based medicine applicable to public health?

Public health can certainly follow the same principles, but there are some additional difficulties and peculiarities. At least the following 3 different steps are involved: (i) systematic reviews of the evidence on causal relationships, (ii) systematic reviews of the evidence on the effectiveness of preventive practices, (iii) setting evidence-based guidelines for prevention. The last step is doomed to be strongly value laden.

Methodology of systematic reviews

There are several ways to perform a systematic review, depending on the aims. Until recently, reviews in the health sciences have not been systematic. However, many journals now insist on reviews being systematically conducted, and the methods of conducting a systematic review have been published in several places (1–3).

We have examples of systematic reviews that are relevant both to the evaluation of causal evidence and to the evaluation of effectiveness of action (prevention or cure).

An approach to cause-effect assessment is represented by the monograph series of the International Agency for Research on Cancer (IARC), in which the summaries of studies are prepared in a relatively free form (ie, a descriptive, narrative text). These are brief comments on the quality of individual studies and no formal meta-analysis is usually produced. Extensive searches of the papers are made. There are no explicit criteria for the selection of the papers at the beginning, although only the “informative” ones are summarized or included in the evaluation. Before the working groups convene, IARC staff provide them with the primary studies, and background papers are prepared. Then the evidence is assessed by the group according to the aforementioned criteria at the time of the meeting. There are no explicit criteria for selecting the participants of the working groups. The epidemiologic evidence on the association between a risk factor and cancer is then categorized according to discrete categories (sufficient, limited, inadequate, no evidence). The distinctions among the categories are chiefly based on (i) the reproducibility of the evidence, (ii) validity (absence of bias and confounding), and (iii) the role of chance.

Other protocols are now available for etiologic epidemiology, for example, MOOSE (“Meta-analysis of Observational Studies in Epidemiology”) for the evaluation of observational studies (ie, studies in which the risk factor cannot be randomized) (4). The authors of the pa-

per propose a checklist of all steps of a review (background, searching, methods, ways to report results, reporting of discussion, reporting of conclusions).

To give an example, a comprehensive bibliographic search would include the following: (i) qualified searchers (eg, librarians, investigators), (ii) an explicit search strategy including the identification of key words, (iii) an effort to include all available studies, (iv) searching of bibliographic databases and hand searching in libraries, (v) inclusion and exclusion criteria for the selection of articles, (vi) inclusion of non-English reports, abstracts and unpublished studies, and (vii) a completely reported search strategy to allow replication.

A rather different approach is used in the systematic reviews prepared by the Cochrane collaboration working groups. They are more relevant to the assessment of the effectiveness of preventive or (more often) curative action. In this case a strict selection of the papers is made. Only randomized controlled trials are used (with exceptions), and only good-quality studies are considered for review. The quality of the studies is assessed on the basis of predefined criteria, and a score is assigned. This procedure restricts the base of evidence. Then meta-analysis is used to summarize the evidence, on the premise that only randomized-controlled trials are considered. Assessments are made of the reliability of the single studies. The whole process requires some kind of training and compliance with the rules set by the Cochrane collaboration network. The outcome of the Cochrane meta-analyses is a meta-odds ratio with a confidence interval (ie, a quantitative assessment) accompanied by a commentary by the authors of the review. The Cochrane Library mainly includes systematic reviews and meta-analyses on drugs, although a notable exception is represented by a series of reviews on different actions to induce smokers to quit. Unfortunately, we have very few other examples of systematic reviews on the effectiveness of preventive actions.

Guidelines for decision making — from scientific evidence to social context

Medicine uses tools and concepts derived from the natural sciences, particularly biology, but it is deeply immersed in a social "milieu". Most, if not all, medical or preventive acts have a social component — in addition to the technological one — which may consist, for example, of the development of a proper approach when an environmental problem within a community is dealt with. The relationships between the technological and social components of medicine or public health warrant adequate investigation, in order to avoid both a "reductionist" view or a naive approach to social aspects. I will describe a situation in which the use of rational protocols is surrounded by a complex context (an environmental crisis), and I will propose a theoretical framework to

encompass such a situation. The main message is that, although a scientific approach is highly valuable, to stick only to it (ie, to an "evidence-based" paradigm) would have strong limitations.

How much evidence do we need?

In spite of several attempts, including the IARC monographs, to establish "sufficient" levels of evidence, the degree of scientific evidence and the threshold for preventive action are relatively independent or asymmetric. A high level of evidence needs action, ie, it always requires intervention (it would be morally unacceptable not to intervene), but a low level of evidence does not necessarily have to be dismissed. According to the "precautionary principle", the suspicion of harm, particularly if it would occur in the long term, with cumulative and irreversible consequences, should be followed by action. Of course, how much "suspicion" is necessary is a matter of political debate, and it depends on the circumstances. Therefore, there is no fixed threshold of scientific evidence below which no preventive action is due. Not only does the threshold vary according to circumstances, but it also changes over time as the awareness of society increases.

Degree of evidence versus population impact

Most systematic reviews of the literature use the odds ratio as a measure of effectiveness (see, eg, the already mentioned meta-analyses on anti-smoking devices in the Cochrane library). However, a simple relative measure of effectiveness may be misleading; although it is appropriate for causal assessment, it is not appropriate for estimating the overall impact of prevention.

Let us imagine that an intervention reduces mortality by 20% (ie, the odds ratio is 0.8). If the absolute risk of death in the population is 1%, then the reduction of such risk is 0.002 (that is, 1% multiplied by 20%). The intervention will be able to avoid 2 deaths per thousand persons treated. If the death rate is 30%, then the deaths avoided will be 30% multiplied by 20% (ie, 6%) meaning that we will avoid 6 deaths for every 100 persons submitted to the intervention. The inverse of the prevented deaths is called the number needed to treat (NNT), which is $1/0.002$ (=500) for the 1st example and $1/0.06$ (=17) for the 2nd example. We need to treat 500 subjects to avoid 1 death in the 1st case versus only 17 in the 2nd. Clearly, the NNT conveys much more information than the odds ratio, since it includes the absolute frequency of the event (in this case the death rate).

The NNT is particularly valuable for comparisons. Let us suppose that there is a certain amount of money for an intervention program in a developing country. One strategy could aim at screening all young women (age 35–44 years) for cholesterol. This procedure would imply screening 20 000 women to avoid 1 death (NNT

Table 1. A simple ethical evaluation (6).

Groups	Values		
	Beneficence	Decisional autonomy	Equity
Exposed subjects	?	(A)	(B)
Unexposed subjects	?	?	(C)
Medical staff	?	?	?
Others	?	?	?

20 000). With the same money, however, we could implement a strategy aiming at providing fresh water in a town of 20 000 inhabitants. In this way, we could reduce the risk of intestinal infection from 20 000/20 000 in an untreated town to 18 000/20 000 in a treated town, leading to a prevention of 2000 cases of intestinal infection (or 100/1000 for an NNT of 10). In both cases, however, the odds ratio would be 0.8.

High-risk groups versus a population-based approach

Geoffrey Rose, in an important book called *The Strategy of Preventive Medicine* (5), has stressed that we should expect greater gains, in preventive policies, from strategies aimed at large sectors of the population rather than at small, high-risk groups. Rose's idea is simple and typically utilitarian on moral grounds: the vast majority of the cases of disease do not occur in the minority of subjects who have extreme exposures, but in those with average or low exposures. Moreover, if we compare whole populations like the Japanese and the Finns for the level of cholesterol, the differences between them concern the whole distribution of the values. It would have very little meaning to try to cut the tails of extreme levels in both populations, whereas the most meaningful public health intervention would be to shift the whole Finnish distribution to the Japanese level.

Although Rose's point of view makes a lot of sense if we want to be really effective, there are the following potential objections: (i) to try to reduce the average level of exposure may be extremely ineffective because the target is the general, undifferentiated population, (ii) even worse, we can blame widespread behavior such as moderate alcohol drinking and thus introduce a kind of "puritan" or moralistic attitude towards habits that are rooted in a culture (eg, wine in the French culture), or (iii) we risk inducing changes only in the most privileged sectors of society, those that are less refractory to educational messages.

These considerations introduce us to the ethics of primary prevention.

Ethical evaluation

Ethical evaluation of preventive practices is far from trivial. Prevention can easily violate a person's decisional autonomy or introduce inequalities among the population.

Tore Nilstun & CG Westrin (6) have proposed a simple way to deal with ethical issues in medicine. Their proposal has the advantage of revealing the tensions and conflicts that characterize any medical activity and of making the underlying ethical models explicit. Let us consider table 1, which includes both the key values at stake and the groups affected by the decision.

The table illustrates only some of the potential ethical conflicts that can arise in preventive action. Case A refers to an infringement of decisional autonomy for the exposed persons. This is the case of the imposition of the helmet for motorcycle drivers or the introduction of speed limits. Case B refers to inequalities in resource allocations that affect, in particular, the exposed persons, for example, if anti-smoking activities are considered to be more cost-effective than the reduction of occupational exposure to carcinogens. People exposed to occupational carcinogens may argue that they are a minority whose exposure is not self-inflicted but is dictated by profit or societal concerns, and it invokes a problem of equity or social justice. This is the main reason why a strictly utilitarian approach based on cost-effectiveness reasoning tends to fail on ethical grounds. In addition, a problem of justice can be invoked by the unexposed (say, nonsmokers, case C) if they argue that too much public money is spent on anti-smoking campaigns and medical care for smokers.

Ethical evaluation is not easy. On one hand, it must be done on a case-by-case basis, since each situation has its own specificities. On the other, each ethical judgment needs to refer to general ethical models. For example, utilitarianism will put much emphasis on cost-effectiveness and the number of lives saved, libertarianism on the infringement of basic liberties, and egalitarianism on distribution issues and social justice.

Anthropological aspects and an example

To stress the importance of integrating also an anthropological evaluation into risk assessment, I will consider a case of environmental pollution, the one which occurred in Love Canal. Thousands of tons of potentially hazardous chemicals were discarded in a place where a large community, including children, moved to live. Three contrasting attitudes developed when pollution was discovered. On one hand, the state epidemiologists undertook investigations aiming to ascertain whether any damage to the population was apparent. Therefore, they computed incidence rates for cancer, malformations, and other severe conditions (7). According to their reasoning, if the number of adverse events occurring in the area was equal to the number expected, on the basis of the state incidence rates, then no harm had been done. This is conventional epidemiologic reasoning, which can be easily summarized in a protocol, including the estimation of an expected number of events based on a proper compari-

son population, the enumeration of cases of disease in the local community, the comparison between the observed and the expected frequency of disease, a statistical test of the difference, and a consideration of alternative explanations (bias, confounding). Of course the observed to expected comparison would be completed by a review of the relevant toxicologic or epidemiologic literature. If this sequence gives a negative result (ie, no disease excess can be demonstrated) then the epidemiologist (usually the county or state public health officer) concludes that no harm has been done, particularly if there was no a priori reason to suspect a toxic effect.

But how does the community itself reason? In the Love Canal episode there were 2 opposite views in the community, according to anthropologists (8). Those who had nothing to gain from moving away from the area (ie, elderly people who had already paid for their homes) denied that any danger to community health occurred. On the contrary, young couples with children were considerably worried about pollution and tended to attribute both vague symptoms and serious disease (such as cases of leukemia among the children) to chemical intoxication. It is clear that the community response to the discovery of pollution was heavily influenced by extra-scientific values. It would be wrong, however, to label these values irrational; in fact, in a way, all 3 reactions (from the epidemiologist and from the 2 community groups) were "rational" since they gave different weights to the same elements of the picture. It is obvious that it would make no sense to summarize community attitudes in a protocol. The main characteristics of these attitudes can be simplified as follows: for the epidemiologists value conflicts are set apart, while they are clearly recognizable in local community attitude; the evaluation of the episode is performed according to a protocol by the epidemiologists, while in the community it depends on age, income, social role, and other anthropological characteristics; criteria for evaluation are mainly associated with short-run and long-run personal consequences, according to an implicit system of weights, for the community, while objectivity and internal validity prevail for scientists; finally, the evaluation process is linear for the latter, while it occurs in a circular way in the community, being at each run influenced by both new events (facts) and the discussion within the community.

One of the main characteristics of community response is that no univocal definition of the risk is given. The risk run by members of the community is defined one moment on the basis of some health outcome (excess of leukemia among children) and at another moment according to economic and social consequences (loss of the house) or according to an anthropological view of the relationships between the environment and health. The group which would suffer most of the consequences of pollution (young couples) are also those who tend to give

a general interpretation of the episode in which either unusual symptoms or isolated cases of leukemia are attributed to the chemically polluted environment. These people have both a holistic view of the problem (which cannot be easily simplified into an epidemiologic protocol) and a "polythetic" definition of risks (ie, risk is not defined exclusively on the basis of single and simple nosological entities). The epidemiologist, on the contrary, has a "monothetic" definition of risk, an excess of the observed over the expected frequency.

Concluding remarks

Compared with evidence-based medicine, evidence-based primary prevention has peculiarities that deserve some emphasis. Although methods for systematic reviews may be the same, evidence-based primary prevention involves the evaluation of mainly nonexperimental studies on cause-effect relationships, plus studies with variable designs concerning the efficacy of different preventive actions. There is a specificity of guidelines and recommendations aimed at prevention, deriving from the emphasis on populations rather than on individual persons, concerning (i) the relevance of different measures of efficacy (odds ratio versus number needed to treat), (ii) the practical and ethical implications of different preventive strategies (high-risk groups versus the general population), and (iii) the anthropological context in which each preventive action has to be evaluated.

A particularly relevant issue is how much evidence we need for action, since the degree of scientific evidence and the threshold for preventive action are relatively independent or asymmetric. A high level of evidence always requires intervention, but a low level of evidence does not necessarily have to be dismissed. However, how much "suspicion" is necessary before intervention is undertaken is a matter of political decision, not only of scientific evaluation, and it depends on the circumstances. This issue is typical of prevention, and it is complicated by a further difficulty in that, while in medical care we can weigh benefits and risks for the same individual, in public health sometimes those who run the risks (eg, workers) differ from those who get the benefits (consumers, society at large). Therefore, equity might be an ethically relevant issue more often in prevention than it is in medical care.

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