Geoffrey Rose and the precautionary principle: to build the quaternary prevention in the prevention

Prevention has been medicalized leading to frequent iatrogenic harms. This calls for quaternary prevention (P4) in prevention: to avoid unnecessary medicalization/interventions and its associated iatrogenic harms. We present a conceptual articulation which guides P4 in prevention. Geoffrey Rose shows the difference between "reductive" preventive measures (reduce risks derived from modern life, such as reducing sedentary and ultraprocessed food) and "additive" (add protective artificial factors such as vaccinations, screenings, lipid-lowering drugs). The great potential harms of additive preventive measures require systematic application of the precautionary principle (PP). The PP advises that persisting scientific doubts about significant potential harms of preventive interventions, the State should actively discourage them by requiring the proponents to provide the appropriate evidence of their effectiveness/safety, exploring harmless alternatives, and increasing public participation in decision-making process. Unfortunately, this approach does not often occur in potentially iatrogenic preventive measures.

Keywords: Quaternary prevention. Disease prevention. Primary health care.
Introduction

Quaternary Prevention (P4) is an action taken to identify people at risk of overmedicalization, to protect them from excesses of biomedical interventions, and to offer them ethically acceptable alternatives. P4 has slowly grown in relevance in primary care and public health settings. It differs from other levels of preventive actions as it focuses on institutional/professional ethos and practice, instead of diseases and environmental issues.

P4 is important in prevention, especially in primary health care (PHC) and public health, for several reasons. Firstly, the background of main concern is the great potential of harm and medicalization of clinical-sanitary actions. Secondly, preventive actions in asymptomatic individuals are a sui generis situation, in which large numbers of people are exposed to potential adverse effects without potential benefits. Thirdly, primary prevention actions (such as vaccines and reduction of risk factors [Lipid-lowering drugs and antihypertensive drugs]) and secondary prevention actions (such as disease screening) have been proliferating in both public health and clinical settings; where frequently, preventive treatments are confused with clinical care.

Fourthly, disease mongering (trafficking or marketing of diseases and risks) turns healthy people into sick ones - people who consider themselves to be ill and are thus treated this way by professionals - turning them into chronic consumers of preventive interventions. This conversion is achieved by lowering the cut-off points for high-risk, using flexible diagnostic criteria of diseases/disorders, as well as through preventive technologies advertising. This process interferes with the culture and production of clinical and preventive knowledge, increasing the medicalization of prevention and its harms.

Fifthly, there is greater tolerance to the harms of preventive actions. Such harms are being watered down in the ocean of tolerated common adverse effects of biomedical treatments. For instance, it is impossible to perceive part of these harms due to overdiagnosis phenomenon. Overdiagnosis happens when people have a correct diagnosis of a disease, which would not cause clinical symptoms or be a life-threatening condition in the future. These people are treated (in this case, overtreated) because they are indistinguishable from those diagnosed who would eventually get sick.

Overdiagnosis and overtreatment occur in large proportions in disease screening, generating the paradox of popularity: Overdiagnosed and overtreated people believe that they were saved by screening even though they were actually harmed. This context is interpreted as beneficial, i.e., the adverse effects are supposedly offset by the “cure” of the chimerical disease/risk factor. There is a range of side effects that comprise: (a) drug costs and treatment follow ups; (b) body mutilation, in the case of some cancers; (c) frequent impacts on patients’ subjectivity/mental health and their families (e.g., anxiety, depression, fear of disease relapse, etc.). These effects on the social imaginary create a growing self-feeding wave of blind beliefs in the need for more disease screening and preventive treatments. Overdiagnosis is a relevant public health problem which demands P4.
Finally, the harm tolerance in preventive actions has also been induced by policymakers, and more recently, by biotechnology through the promotion of preventive actions, associated with the intense process of social biomedicalization.16,17

The P4 in PHC is a necessity. In clinical care, it can be operated through the interpretation of clinical contexts and negotiation of treatments via: (a) the use of judicious words; (b) the adoption of dynamic explanatory models in handing out professional interpretations (diagnoses) to patients; (c) the singularization of therapies; and (d) the distinction between present/future disease clinical care, i.e., care of an ill person versus future disease (prevention). This distinction is crucial for P4 in prevention.

For instance, in the clinical care of a suffering patient who demands treatment, it is acceptable some tolerance to medicine interventionism, presupposing great confidence in biomedical knowledge, biotechnologies, and professional expertise. Preventive actions in asymptomatic patients require the opposite attitude: resistance to biotechnological interventionism; disbelief of medical-scientific knowledge and expertise; requirement of high quality scientific empirical evidence of on final outcomes of the proposed preventive action, comparing harms and benefits.

In clinical care, the therapeutic action is not obstructed by the absence of such evidence, although it is growingly required. In prevention, on the contrary, such absence, a doubtful or only weakly favorable balance between harm and benefit, should suffice to contraindicate the intervention, due to the prominence of non-maleficence in prevention, in relation to beneficence.7,20 (Figure 1).

**Figure 1. Differences between illness and prevention in asymptomatic patients**

* Evidence = scientific evidence of good quality and convergent on final outcomes, showing significant and broad benefits (systematic reviews and meta-analyses) and few harms. Source: adapted from Tesser and Norman.7
This article articulates three concepts in order to contribute to the orientation of P4 in prevention. Two of them were proposed by Geoffrey Rose\textsuperscript{21,22}, the ‘reductive’ and ‘additive’ preventive measures. The former refers to “removing or reducing some unnatural exposure in order to restore a state of biological normality”\textsuperscript{22} (p. 148). The latter means: “adding some other unnatural factor in the hope of conferring protection” (idem). The third concept is the precautionary principle (PP), developed in environmental law, based on contemporary ecological problems\textsuperscript{23,24}. It points out that confronted with significant potential hazards and damages arising from an activity or product presenting scientific doubts, the State must act to avoid them\textsuperscript{25}.

In the next topic we approach the concepts of additive and reductive prevention from the conception of Rose, then highlighting the consequences of this distinction for the practice of P4 in prevention. Next, we present and discuss the PP, in order to articulate it to the two previous concepts.

Geoffrey Rose, in the book “The Strategy of Preventive Medicine”\textsuperscript{22}, characterizes and discusses two preventive strategies: high-risk and population. He points out advantages and disadvantages of each and concludes that the population approach is more effective and radical. In analyzing it, the author distinguishes in one page two types of interventions: reductive and additive preventive measures, without further development of this distinction. Due to its great relevance and regardless of the preventive strategy considered, it deserves to be expanded and analyzed separately.

**Preventive reductive and additive measures**

Preventive reductive measures are actions aimed at reducing artificial exposures in the way of living, known to be pathogenic, of higher risk or detrimental to health, especially in industrialized societies\textsuperscript{22}: “Stopping smoking, avoiding severe obesity, taking regular exercise, reducing the dietary intake of saturated fat and salt, and reducing chemical contamination of foods and of the environment” (p. 148).

Rose\textsuperscript{22} (p. 148) says that these actions are aimed at restoring biological normality, defined as “conditions to which we are thought to be genetically adapted through our evolutionary history.” They take the form of clinical actions (guidance, counseling), public health and social organization, such as reducing economic inequalities\textsuperscript{26}, promotion of sustainable mobility and physical activity (cycle lanes, walking paths and leisure green areas), policies to promote cultivation and distribution of food without pesticides and without multiprocessing, urban sanitation (housing, drinking water and sewage collection), universal schooling, health legislation and regulation, etc. Such measures are theoretically consistent and corroborated by the available scientific knowledge and evidence\textsuperscript{27,28}. By reducing risks and pathogenic factors, several accepted social determinants of illness merge or, at least, broadly converge with health promotion\textsuperscript{29} in both the societal and individual dimensions. It relates to the restoration of environmental and social conditions and health-friendly ways of living, presenting relatively few problems regarding the scientific basis for its recommendation.

Moreover, in general, the reductive preventive measures are convergent with most of the peoples’ cultural traditions in the planet\textsuperscript{30}.

Reductive preventive actions can be considered “generally safe, and they can therefore be accepted on basis of reasonable presumption of benefit”\textsuperscript{22} (p. 148).
They are scarcely problematic from the point of view of handling the uncertainty (nonexistent), the resulting harms (null or minimal) and the guarantee of beneficial results, necessary in the prevention. This consensus supports an affirmative posture of their desirability, being relatively easy to establish their content.

Additive preventive measures are generally interventions professionally delivered in the body or in the environment, alien to the ecology-economy-physiology of the daily life of humans. They include the application of drugs, vaccines or other biological, physical or chemical products22: “Drugs (such as for the control of blood pressure or cholesterol), immunizations, and the use of unnatural doses of natural substances (such as high-dose folic acid for preventing neural tube defects, chlorination of water supplies, and “natural” food additives and preservatives)” (p. 148). This group can be expanded including screening tests that can lead to cascades of interventions.

Since most people are healthy (asymptomatic) and only a small part of them will become seriously ill in the future, additive preventive actions can result in significant and extensive harm without potential benefits for many people6,7. “This effectively rules out the use of this type of measure except where the offered benefit is rather large, i.e., in high-risk groups, or for common or serious hazards”22 (p. 148). Therefore, they cannot be considered safe and the burden of proof must fall on their proponents (professionals and health systems): “there can be no prior presupposition of safety, and hence the required evidence of benefit and (particularly) security must be more stringent”22 (id.). There must be scientific, reputable, good quality and convergent evidence that the benefits widely outweigh the harms, being zero or minimal, even if such evidence tarry years or decades to produce. Thus, a strong asymmetry is imposed in the recommendation of additive preventive measures: an unfavorable or doubtful balance of benefits is sufficient to support the suspension of the measure or to oppose its implementation, which is strictly consistent with the precautionary principle, discussed below.

In additive prevention, safety and harm-benefit ratio is obtained through evaluations of two types of studies: (a) experimental or interventional: randomized clinical trials (RCTs) and their reviews and meta-analyses, before the application in the population; and (b) observational: after application of the biomedical intervention in the population. Both should evaluate the final results of the interventions, including careful record of harms. It is important to emphasize that no evidence on intermediate outcomes concerning diseases, physiological parameters, complementary tests, etc., is accepted (evidence type DOE - disease oriented evidence31,32). Although important for the production of medical and preventive knowledge, techniques and technologies, these intermediate outcomes are insufficient for the evaluation of efficacy and safety in additive prevention. In this kind of prevention, the high-risk of iatrogeny, the rigorous management of uncertainty and the intolerance to harms (Figure 1) require distrust of individual and collective experience, both lay and professional, and even theoretical medical-scientific models. Such requirements of additive prevention demand excellent empirical evidence regarding final outcomes such as quality of life, mortality, morbidity (evidence type POEM - patient oriented evidence that matters31,32). Once an additive preventive measure (a screening, a preventive treatment or a vaccine, for example) has been implemented, observational studies should evaluate its effectiveness,
focusing on the reduction of general and specific mortality, morbidity (incidence and severity of cases) and iatrogenic harm.

Primary data on benefits and harms in evaluations (clinical trials and observational studies) of additive preventive measures should be available to the scientific community. This is necessary to allow for the verification of methodological procedures, results and conclusions in order to increase the appropriateness of the production of scientific knowledge, reducing frequent and harmful conflicts of interest\textsuperscript{33}. However, the harms of additive preventive measures have been less studied than the benefits, as in breast cancer screening\textsuperscript{34,35}. The harms are frequent in the form of overdiagnosis in the screening tests and, consequently, the cascade of interventions that are then generated (overtreatment)\textsuperscript{36}.

The results of clinical trials and observational studies are often counterintuitive and beyond the reach of clinical and patients’ experience. Therefore, the opinion of experts who treat the sick should not have a privileged position in decisions about the additive preventive actions. The difficulties and complexities of evaluating the effects of these actions and the many biases involved in this evaluation, such as screening, selection bias, lead-time bias, length-time bias and overdiagnosis, should be considered\textsuperscript{37,38}. This is reinforced by the complexity of health-disease processes, by the limitations of biomedical theoretical models and by the ignorance about the genesis and evolution of various diseases, especially chronic diseases and cancers, giving rise to many of these measures.

\textbf{Consequences of the distinction between reductive and additive measures}

The introduction of the distinction between additive and reductive actions is a watershed in preventive measures: a conceptual and attitudinal operator that facilitates decision-making on preventive reductive measures, while strengthening the criteria for recommendations of preventive additive measures. As the former reduces unnatural risk factors/exposures, there is consensual guarantee of benefits and safety making their recommendation relatively easy. The situation is reversed in the latter, where there is the introduction of unnatural products/factors not previously existent into individuals’ ecology-economy-physiology. If the technical and ethical requirements for an intervention are already greater in prevention than in patients’ clinical care\textsuperscript{7}, these requirements are further intensified for the preventive additive measures, due to the great potential of harm involved. As highlighted above, intervention studies (R.CTs) should guide implementation decisions, and observational evidence in the population should support them only if large benefits and minimal or no harm are found through high-quality research, suitability and transparency. Otherwise, due to the preeminence of non-maleficence in prevention, the introduction of the measure should be suspended.

Therefore, in the decisions about recommending or performing additive preventive measures, the differences pointed out require an emphatic skeptical, resistant and anti-interventionist attitude, only to be surpassed by the convergence of broadly favorable scientific evidence, as specified above. Such attitudinal modulation, ethically shifted towards resistance to intervention, generates an explicit preference in clinical
and public health for reductive preventive actions. This ethical-sanitary stance must be assumed and disseminated in public health, within physicians and other health professionals and populations7 (Table 1).

Table 1. Characteristics, attitudinal modulation and requirements resulting from the differentiation between preventive additive and reductive actions.

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>REDUCTIVE PREVENTION</th>
<th>ADDITIVE PREVENTION</th>
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<tr>
<td><strong>CHARACTERISTICS</strong></td>
<td>Less potential for harm and medicalization</td>
<td>Great potential for harm and medicalization</td>
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<tr>
<td>Safety and benefits accepted</td>
<td>Safety / benefits must be proven</td>
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<tr>
<td>Relatively easy consensus between theories, evidence (DOE and POEM) and common sense.</td>
<td>Scientific consensus should be produced from POEM evidence showing large benefits and zero / little harm</td>
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<tr>
<td>Little conflict of interests in the production of evidence and its application</td>
<td>Many conflicts of interest involved in the production of evidence</td>
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<td>Approaches equity</td>
<td>High medicalization</td>
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<tr>
<td>Increased sustainability</td>
<td>High cost</td>
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<tr>
<td>It partially coincides with the promotion of health</td>
<td>Does not impact social determinants of health-disease</td>
<td></td>
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<tr>
<td>It acts on general determinants of health-disease</td>
<td>Triggers cascades of interventions</td>
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<tr>
<th>ETHICAL AND TECHNICAL REQUIREMENTS</th>
<th>REDUCTIVE PREVENTION</th>
<th>ADDITIVE PREVENTION</th>
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<tbody>
<tr>
<td>Does not require intervention studies</td>
<td>Requires favorable review / meta-analysis of high quality randomized clinical trials on final outcomes involving harms and benefits</td>
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<td>It requires selection and review of observational studies, valuing consensual conclusions about risks.</td>
<td>Requires evaluative observational studies after the action is implemented, for its maintenance</td>
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<tr>
<td>Requires post-deployment monitoring</td>
<td>Requires post-deployment monitoring</td>
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<tr>
<th>ATTITUDINAL MODULATION</th>
<th>REDUCTIVE PREVENTION</th>
<th>ADDITIVE PREVENTION</th>
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<tbody>
<tr>
<td>Calm optimism without pressure</td>
<td>Anti-interventionist skepticism</td>
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<tr>
<td>Higher propensity for preventive recommendations and decisions</td>
<td>Resistance to the proposition of preventive actions</td>
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<tr>
<td>Total preference for reductive preventive actions in society and clinics in health services (especially in PHC), converging with societal, community and individual health promotion.</td>
<td>In doubt, do not hold or suspend action</td>
<td></td>
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<tr>
<td></td>
<td>Precautionary aversion to actions: burden of proof lies with proposers (who must overcome with scientific empirical data repeatedly the anti-interventionist skeptical resistance, even after implantation).</td>
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Source: Authors’ elaboration.

However, additive preventive measures have been trivialized and propagated in society, the media and the medical profession, as if biotechnological advancement made the new additive preventive technologies generally safer and more effective. This quite widespread imaginary is largely misleading39. It lacks conceptual and symbolic antidotes aimed to introduce criteria that facilitate its deconstruction and prudent reconstruction, in order to allow the rigorous scrutiny of these actions, making it easier to identify which ones are justifiable and safe. Even if the distinction between reductive and additive preventive measures is valuable, it is complemented with force and adequacy by the precautionary principle.

**Precautionary Principle**

The precautionary principle (PP) emerged in the 1970s in Germany in the face of ecological problems. It states that regulatory agencies and governments must anticipate the potential danger and prevent it from occurring. PP is applied when scientific
information is insufficient, inconclusive and/or uncertain in activities with indications that may have dangerous effects. During the 1980s, it was incorporated into various national environmental policies. In the following decade, it was spread through various international agreements and treaties, involving a variety of subjects. Its legal status is evolving and received a broad support, enough to affirm that it reflects a principle of customary law.

The PP is not only an environmental principle as it applies to the protection of human health. Public health is actually considered as a pioneer area of PP. The closing of a nineteenth-century London water pump proposed by John Snow as an action against a severe cholera epidemic is a quoted example. The medical science of the time considered that this was an airborne disease (miasmatic theory). Snow showed that people who died during a few days' period in an area, drank from a certain water pump and proposed to stop its supply, which was accepted and successful. In the following months, the Epidemiological Society of London, the Royal College of Physicians, and the General Board of Health rejected the waterborne thesis. The decision to abide by Snow’s proposal was made in an uncertain environment, based on a study by a single scientist, being considered a typical example of a precautionary decision.

The PP was born in opposition to the ecological, environmental and human damages of economic and industrial activities that introduce toxic chemical/physical products into the environment, society, food and human work processes. Most PP applications that are advocated within the realm of public health refer to the exposure to products used in activities that are generally external to clinical and health action. For example, Wardman and Löfstedt illustrate the complexities of PP application in the case of cell phone technologies, discussing sociocultural conditions and the political dynamics involved in the process.

The PP is part of a broad ethical perspective, and aims to generate measures to protect public health in the face of uncertainty. This differs from the risk assessment approach, which asks: “What harm from an activity can we tolerate?” Instead, the PP asks, “What actions can we take to prevent damage from this activity?” (p. 4). However, what often happens in public health and preventive medicine is what Kriebel called the principle of reaction, being necessary to wait until evidence of damage arising from an activity or product accumulates before measures are taken to avoid harm.

Science and evidence have a central role in achieving the objectives of PP implementation, but they have been used in a different direction. There is a tradition and tendency in preventive medicine and public health to focus on the evaluation of efficacy and risks. Martuzzi synthesizes the reasons why the evidence-based approach to risk assessment is potentially harmful: it is designed to support ‘proven’ decisions, leaving a vacuum in the absence of such evidence. It is not a realistic option in modern governance in the face of dangers and uncertainties, especially in the case of new biotechnologies. The translation of the evidence into wise decisions is fraught with difficulties. The following stand out: defining and framing the decision issue is a social process and not a specialized task; the same evidence may have different implications depending on the underlying ethical point of view - for example, relative supremacy for beneficence or non-maleficence (case of additive prevention).
evidence on the problem can be robust and abundant (DOE type), while evidence on final outcomes and harms may be sparse (POEM type); the process of identifying and processing evidence by specialists is vulnerable to manipulation by vested interests49(examples are abundant and repeated55). An important step in changing the logic of the reaction towards PP is to reduce the influence of economic interests on the production and processing of evidence in the health field49,51.

The PP has been characterized by four central components involved in its application: (1) To avoid potential damages of an activity or product in the face of uncertainty. In our case, avoid iatrogenic harm from preventive additive actions. (2) Proponents of interventions have the burden of proving their effectiveness and safety. (3) Explore harmless alternatives before arriving at an undesirable assessment of acceptable levels of activity risk. Full exploration of alternatives to potentially harmful actions is required before accepting a quantified level of minimum harms. Additive prevention is likely to be harmful and the harm-benefit ratio is unavoidable, but this component indicates strong preference for reductive preventive alternatives. (4) Increase public participation in decision-making (deserves a specific discussion, not feasible here). Another aspect involved in PP is the one referred to active surveillance. A set of implemented activities may be gradually considered harmful or uncertain as scientific knowledge and evidence advance, leading to its immediate suspension as a precaution24,42,46,48,52,53.

The PP has already been applied in high-severity medical situations. Wilson et al.54 discuss its application in transfusion medicine, in which there was a pioneer medical use of the PP, without environmental involvement45: the PP was applied to protect the risks of transmission of diseases through blood transfusion and its consequences, raising debates in the literature, with criticisms, defenses and developments56. Martuzzi48 states that PP is implicated in the principles of clinical medicine, particularly in the principle of non-maleficence. But bioethical principles have always been overlooked, while relegated to the conscience of health professionals57. However, caring for patients is an ethically complex situation, even more complex in the case of serious sickness, in which the application of PP can generate difficult situations58, more difficult than in the case of additive prevention.

Goldstein52 argues that PP should be applied to public health actions. We emphasize and argue that especially the approach of preventive additive actions should be systematically oriented by the PP. However, discussions about PP generally do not focus on common preventive actions taken in clinical care in PHC and public health programs such as vaccinations, screening and preventive treatments. Chaudry59 for example, refers only to the relationship between environmental health, occupational health and nursing in public health, without considering the preventive additive measures.

On the other hand, in present preventive issues, the subjectivity of people and populations is shaped by the information and guidelines of medicine and public health, as well as social and media values, in a context already criticized for excessive healthism or sanitary imperialism, obsessed for youth and body perfection, in which individual preventive and promotional actions have become almost irresistible social and moral imperatives60-63 in search of prevention at all costs39, irrationally distracting from the PP.
Although the requirements of the regulatory agencies’ protocols appear to be consistent with the second component of PP (requiring proponents to prove efficacy and safety), as in the case of clinical trials for approval of medicines and other products, there are several preventive actions which would probably not have been applied in millions of people or would not be performed if PP was used analyzing additive prevention (see hormone replacement therapy as primary prevention, discussed below).

The precautionary principle articulated to additive prevention

By its own definition, all additive preventive actions are candidates for using the rigorous approach posited by the PP. Although technological and health-disease complexities may occasionally produce a gray area between additive and reductive preventive measures, such a distinction is sufficiently consistent under the orientation of P4 in order to focus on additive preventive measures: activities with great potential harm and in which there is supremacy of non-maleficence. This strongly demands the systematic application of PP.

In addition, a special feature of the additive preventive measures facilitates the application of PP: such application requires simple actions to be operationalized, requires only the decision not to authorize, not to recommend and not to implement preventive additive actions whose harm-benefit ratio is unfavorable or uncertain; or not keep them functioning (suspend them) if already implemented. Additive prevention does not require alternative courses of action, although reductive prevention is always preferable and can fulfill this harmless alternative role. Additionally, in this case, the harm tends to be self-limiting, since it depends on the repetition of measures over time in people and generations. Lastly, there are no financial costs involved in reductive preventive measures, whereas this is not the case in the implementation and maintenance of costly preventive additive measures.

The application of the PP to additive preventive measures already implemented should raise a red flag, to mark them as never definitively established, since they require rigorous periodic scrutiny to prove that their maintenance is justified.

The more a clinical outcome becomes acknowledged to be avoidable by additive prevention, the greater the need for PP and P4\textsuperscript{19}. The complexity of the health-disease processes is great and the theoretical models underlying these measures are always to some degree reductionist and limited. As the intervention is usually restricted to one or a few specific factors or risks, its final results may contradict the theoretical prediction.

An example of such failure with serious practical consequences was the use of hormone replacement therapy (HRT) in women as primary prevention. In published preliminary studies HRT showed a potential cardiovascular preventive effect, by improving the lipid profile (DOE type of evidence) as well as the absence of significant harms. However, after years of widespread use of HRT, facilitated and induced by their supposed preventive actions, a large, good methodological clinical trial showed an increase in cardiovascular mortality (POEM type of evidence) in the treated group. This generated a clinical guideline explicitly contrary to HRT as a preventive measure\textsuperscript{64,65} and even an obstacle concerning its therapeutic use.
The arrogance of preventive medicine, as stated by Sackett et al.\textsuperscript{64}, still needs to be corrected. The PP applied to additive prevention is an important and necessary resource in this task. Several additive preventive activities do not stand the test of the PP. We should mention some examples even without detail or discussion, due to space limitations: mammographic screening for breast cancer has an unfavorable\textsuperscript{66} or, at least doubtful, harm-benefit ratio in the face of extensive and serious damage\textsuperscript{12,67-69}. The same occurs with the case of screening for prostate cancer\textsuperscript{70}. The use of statins as primary prevention of cardiovascular diseases, shows minimal benefits\textsuperscript{39,71-73}, the evidence is fraught with conflicts of interest and there is total lack of transparency of the patient’s primary data on the harms\textsuperscript{54,75}, appearing to be much more frequent than those reported in clinical trials and in some severe cases\textsuperscript{73-76}. The prevention of cervical cancer through anti-HPV vaccination presents no evidence of final outcomes on harm-benefit ration to the target population, showing only intermediate results for older women (16-26 years), with little follow-up in clinical trials regarding a condition with decades-long evolution. There are also systematic conflicts of interest disseminated in the production of evidence and significant potential long-term harms\textsuperscript{39,77,78}. These four additive preventive measures affect millions of asymptomatic people exposed to significant potential harms, as they face a harm-benefit ratio that is unknown, negative or uncertain, thus requiring the application of the PP.

Final considerations

Clinical activity, especially in PHC and public health need to adopt and highlight the distinction between reductive and additive preventive measures, while rigorously applying in the latter the precautionary principle to guide P4 in prevention. This distinction outlined by Geoffrey Rose emphasizes the preference for reductive preventive measures in synergy with the promotion of societal and individual health and requires the systematic application of PP to additive preventive measures. However, the public health context shows the opposite, the sparse application of PP. Vested interests and little cautious practices are producing serious harm to many people through excessive use of additive prevention, inducing overdiagnosis/overtreatment.

Conceptual developments, new clinical and institutional practices and research are needed to create the scientific, professional, institutional and social legitimacy to apply the precautionary principle to additive preventive measures.
Authors’ contributions

Charles Dalcanale Tesser conceived the paper and wrote the first version. Both authors participated in the review and critical discussion of the content, the bibliographic update, the writing up and approval of the final version of the article.

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