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Perspective: When the cure might become the malady: the layering of multiple interventions with mandatory micronutrient fortification of foods in India

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ABSTRACT

When public health programs with single nutrients are perceived to have a poor impact on the target health outcome, the policy response can be to *supply more*, by layering additional mandatory programs upon the extant programs. However, we argue for extreme caution, because nutrients (like medicines) are beneficial in the right dose, but potentially harmful when ingested in excess. Unnecessary motivations for the reactionary layering of multiple intervention programs emerge from incorrect measurements of the risk of nutrient inadequacy in the population, or incorrect biomarker cutoffs to evaluate the extent of nutrient deficiencies. The financial and social costs of additional layered programs are not trivial when traded off with other vital programs in a resource-poor economy, and when public health ethical dilemmas of autonomy, equity, and stigma are not addressed. An example of this conundrum in India is the perception of stagnancy in the response of the prevalence of anemia to the ongoing pharmacological iron supplementation program. The reaction has been a policy proposal to further increase iron intake through mandatory iron fortification of the rice provided in supplementary feeding programs like the Integrated Child Development Services and the School Mid-Day Meal. This is in addition to the ongoing pharmacological iron supplementation as well as other voluntary iron fortifications, such as those of salt and manufactured food products. However, before supplying more, it is vital to consider why the existing program is apparently not working, along with consideration of the potential for excess intake and related harms. This is relevant globally, particularly for countries contemplating multiple interventions to address micronutrient deficiencies. *Supplying more* by layering multiple nutrient interventions, instead of *doing it right*, without thoughtful considerations of social, biological, and ethics frameworks could be counterproductive. The cure, then, might well become the malady. *Am J Clin Nutr* 2021;00:1–6.

Keywords: mandatory, fortification, supplementation, anemia, iron, micronutrients

Introduction

The concept of micronutrient deficiency as the third arm of the "triple burden of malnutrition" in low- and middle-income countries (LMICs) has gained much traction over the last decade. As a public health response to this deficiency, food fortification with micronutrients is particularly attractive to policy makers, industry, and implementation agencies, primarily because it is thought to require no behavioral modification by the

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Abbreviations used: EAR, estimated average requirement; GDP, gross domestic product; Hb, hemoglobin; LMIC, low- and middle-income country; NFHS, National Family Health Survey; TUL, tolerable upper limit.

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beneficiary, but also because it is safer and less expensive than direct supplementation. Indeed, the enthusiasm for fortification is such that the target concentrations for fortification of different nutrients in several food staples have been notified in the Indian Gazette in 2018 (1) and the choice for whether to fortify or not was dependent on the stakeholders: it was voluntary. However, fortification has been made mandatory for some micronutrients in 2020 (2). Here, the entire supply of a specific food is fortified, and it is against the law to procure or sell such foods when they are not fortified. Although food fortification has its place in alleviating specific nutrient deficiencies, it can be perceived as a panacea, and be overdone in response to apparent failures of other interventions, with the potential for excess intake, such that the cure then becomes the malady. The objective of this perspective is to consider this potential for the layering of supplementation and/or fortification programs of multiple foods targeting the same nutrient in the same population, particularly when done in a mandatory manner. Although this exploration is primarily through the prism of iron, these considerations might apply more generally to other nutrients that are supplemented and fortified.

An example of the "cure becoming the malady" is the response to the apparently "stagnant" anemia prevalence in the recently concluded Indian National Family Health Survey-5 (NFHS-5, conducted in 2019–20) (3). This has been considered a failure of the existing universal pharmacological iron supplementation program to women and children (4), and has resulted in a muscular policy thought-response, in which the central theme is "more iron delivery must be better." There is already an existing regulation for the voluntary iron fortification of salt (1) which is being considered in some Indian states (5), but the additional and recent proposal for the mandatory iron fortification of rice (6) needs careful consideration. In effect, this mandatory fortification is universal for all rice grain reaching all the beneficiaries of food subsidy programs in India, without any choice. In this layering of mandatory or voluntary fortifications, occurring on top of ongoing pharmacological supplementation programs, the cure might become the malady for several reasons. These include toxicity, but also cost and trade-offs with other important public health interventions in a country struggling with scarce resources. There are also ethical dilemmas to consider, as well as the variable, small, and possibly negligible impact of such additional efforts on anemia reduction.

The potentially low impact of fortification: an argument against layering

A core and implicit article of faith, uncorroborated by robust evidence, is that food fortification will translate into substantial functional benefits (for example, anemia) and a lower prevalence of deficiency. However, recent systematic reviews indicate that iron fortification of rice (7) and wheat flour (8) may make little or no difference to the risk of having anemia or presenting with iron deficiency. The response of iron deficiency or anemia prevalence to salt fortification in effectiveness trials has been less than satisfactory in India (4, 9). This is not universal, because effectiveness studies in other countries have shown benefits with iron fortification on anemia (10). The variable impact on anemia of iron fortification may be due to poor implementation, or uptake, or bioavailability of the fortified staple. In a trial distribution of free or subsidized double (iron and iodine) fortified salt in the state of Uttar Pradesh in India, consumer perception of the slightly "different" appearance of the salt led to their forgoing the subsidy, which resulted in low demand and compliance with usage of the fortified salt, compounded by supply-side problems (11). Thus, a simple intervention that was thought to require no behavioral change in fact requires great attention to sensory aspects, as well as extension activities like communication to convince beneficiaries to change their behavior.

There are other reasons for a lack of impact and a stagnant response, leading to calls for layering yet more interventions. A technical possibility is the apparent magnification of the prevalence of deficiency because of an inappropriate biomarker cutoff value. When fortification (or supplementation) programs are implemented in response to a mirage of deficiency, their impact will be negligible because beneficial effects are conditional on the true nutrient status of the population at baseline. An example is the use of potentially higher universal hemoglobin (Hb) cutoffs to diagnose anemia in children or pregnant women. Recent data suggest that the Hb cutoff to define anemia in Indian children and adolescents could be lower than the present WHO Hb cutoff (12). With this proposed cutoff (12), anemia prevalence in Indian children would substantially reduce to 11%, from the current 30%. In corroboration, a recent analysis of international data for pregnant women (including an Indian sample) has also proposed new Hb diagnostic cutoffs, which were ∼1 g/dL lower than the existing WHO value (13). With these cutoffs, our preliminary calculations suggest that the overall anemia prevalence in Indian pregnant women, as reported in the Indian NFHS-4 (14), would reduce by over half from its reported value of 55%. Another example is the present cutoff for serum ferritin as an indicator of body iron status, where the sensitivity of the cutoff is preferred over its specificity, such that the prevalence of iron deficiency might be presumed to be higher than its true value (15). The antecedents of the diagnostic biomarker cutoff should always be queried. A recent report from India found counterintuitively lower concentrations of iron deficiency in poorer sections of the population, and speculated that this could be either due to residual effects of unadjusted inflammation when evaluating serum ferritin (implying the need to evaluate biomarker adjustments), or an inefficient utilization of iron for Hb synthesis (implying the need for a better intake of all erythropoietic nutrients) (16).

In the same vein, a further technical possibility for magnification of deficiency prevalence is inappropriate blood sampling. Many anemia surveys use finger-prick capillary blood sampling, with attendant dilution and falsely low biomarker concentrations. A recent large and careful study in India showed that a capillary blood sample can underestimate Hb by ∼1 g/dL of blood when compared to a simultaneous venous blood sample (17). Therefore, surveys using capillary blood samples could overestimate the prevalence of anemia and this partially explains the substantial differences in anemia prevalence (56% compared with 41%) in 1- to 4-y-old children in 2 national surveys in India: the NFHS-4 (14) and the Comprehensive National Nutritional Survey (CNNS) of Indian children (18), which used capillary and venous blood samples, respectively. Again, with a mirage of high prevalence of deficiency, no change in response to an intervention will be forthcoming. Thus, the interpretation of iron biomarkers,

influenced by local factors and concurrent inflammation, as indicators of deficiency must be done with care.

Finally, when layering single nutrient interventions in reaction to a stagnant response, a clear etiological framework may not have been considered. For example, the lack of response of anemia to iron fortification is possibly due to other nutrient deficiencies and inflammation (19); consideration should then also be given to improving the absorption of iron by the intake of vitamin C–rich fruit with meals (20) and the diversification of food intake to meet all nutrient requirements (21) as well as an improved environment, rather than simply adding more iron-fortified foods, or other reductionist interventions.

The motivation for layering multiple food fortification programs

Notwithstanding the lack of impact, as aforementioned, the motivation for layering interventions can be fueled by overestimating dietary inadequacy. The true prevalence of dietary nutrient inadequacy should be estimated from simultaneous measurements of nutrient requirement and intake at the individual level, which is usually impossible in practice. Populations are therefore evaluated by comparing the distribution of their habitual dietary intakes with their theoretically or experimentally estimated distribution of nutrient requirements. Unfortunately, the requirements may be overestimated for a variety of technical reasons, as has happened in India with the iron (and other nutrients like vitamin A) requirement; more rigorous requirement values are now available (22, 23). In addition, these errors were compounded with the incorrect use of the single RDA instead of the estimated average requirement (EAR) value to estimate the risk of population dietary inadequacy.

In a population, one can only measure the *risk* of nutrient inadequacy. In an ideal setting, where normal healthy individuals consume their minimum requirement, which is used efficiently by the body, the intake and requirement distributions would reasonably overlap, yielding a 50% risk of inadequate nutrient intake in the population. This is the "status quo" by standard probability theory, and should be the target for normalcy. See **Supplemental Text 1** for definitions and calculation of risk of inadequacy and deficiency, and **Supplemental Figures 1** and **2**. A supporting corollary for this line of thought comes from examining the risk of inadequacy that would occur in exclusively breastfed infants, who, by definition, should receive all their nutrient requirements exclusively through breast milk. A WHO report on the nutrient adequacy of exclusive breastfeeding showed that the *mean* intake of human milk protein met the *mean* (empirically determined) protein requirement of healthy infants (24), which imputes a 50% *risk* of inadequacy in these healthy infants.

However, it has been suggested that the target normal population nutrient intake should result in a risk of dietary inadequacy that is well *below* 50%, to a value of ≤5% (25). With this approach, there is an enhanced risk of *excess* nutrient intake for a significant proportion of the population, with attendant activation of homeostatic mechanisms for detoxification/excretion of the excessive nutrient while adjusting to these higher than required intakes, and wasteful expenditure. It is also important that normal populations are able to meet their target nutrient requirement through their *habitual* intake of a natural and diverse food matrix. Setting high target intakes, like the RDA for a low risk of dietary inadequacy, can make it impossible to plan rational natural food intakes, particularly with plant-based diets, and especially when several important micronutrients are considered together (see **Supplemental Text 2** and **Supplemental Table 1**). In effect, this elevates the demand for chemical fortification or supplementation even in normalcy.

Therefore, if target population nutrient intakes are set high and then delivered by the state through subsidized (yet mandatorily) fortified foods, it is critical that unequivocal and robust evidence of their benefit and safety is available for this motivation. If so, it is time for India to set correct targets of nutrient intake and therefore the appropriate fortification concentrations of nutrients in different foods, because nutrient (in this case, iron) requirements have now been published (26), with explicit determinations of the EAR and distribution of requirements, as well as of the tolerable upper limit (TUL) of intake.

The potential harm of excess micronutrients: more is *not* better

There are defined upper limits of intake for each nutrient (26), which should not be exceeded by public health nutrition efforts. That could happen when fortifying multiple foods on top of nutrient supplementation (layering), or when the regulatory concentration of nutrient fortification in foods is set too high (because of the incorrect use of the RDA as the average requirement, or incorrect estimations of habitual food intake), or when target population intake is set to achieve a very low population risk of nutrient inadequacy.

Adverse consequences can also result when single nutrient intakes are much higher than their requirement in otherwise *poor-quality* diets. It is important to point out that this high intake need not exceed the TUL. This might particularly be relevant to LMIC populations that are being targeted for a high (single) nutrient intake through layering multiple fortifications and supplementation. Half a century ago, Harper et al. (27) showed that adverse consequences, like impaired growth or fatty liver, occurred when imbalanced additions of single amino acids were made to low-protein diets in rats. In the same period, Gopalan (28) noted the potential pellagragenic effect of high-leucine but low-protein, low-quality diets in a low socioeconomic group in India, subsisting on a millet called *jowar* (*Sorghum vulgare*). It has also been shown that a high iron intake may adversely affect fetal development and birth outcome (29), as well as the microbiome (30) and the risk of chronic disease (31).

When the distribution of nutrient intake is right-skewed (as for iron), high target intakes for the population could result in a significant proportion being at risk of exceeding the TUL (22). In some Indian states, it has been calculated that the consumption of a *single* iron-fortified staple food, layered on iron supplements, would result in a significant proportion of the population (≤54% in the state of Rajasthan) crossing the TUL (22). This risk can be similar for other nutrients (even if they are not the focus here); one such is vitamin A, where hypervitaminosis could occur when both supplementation and fortification programs are in place (32). Iodine fortification is also worth reflecting on, where, of the 28 states in India, the median daily urinary iodine excretion

was more than adequate among preschoolers, schoolers, and adolescents in 16, 9, and 10 states, respectively, and was even in frank excess in 1 state (18).

When manufacturers voluntarily fortify their food products as a "value add" to generate functional or health claims (as is common with iron in India), the situation takes a turn for the worse, because the advertising and marketing of fortified food products are very successful across all socioeconomic sections (33), adding to multiple avenues of nutrient intake. The most worrisome aspect is that there is no system to periodically monitor for and intervene in situations of excess nutrient intake and related adverse effects, and indeed to provide compensation for those afflicted.

The cost of layering mandatory iron fortification and iron supplementation

Through the prism of iron deficiency, the conservative cost implication, and probably an avoidable wasteful expenditure, of mandatorily adding iron-fortified rice to existing Indian food subsidies is estimated to be ∼$350 million per fiscal year. This cost estimate is the product of the incremental cost of the fortified rice (∼$0.01/kg) and the estimated national demand of rice into which it is intended to be mixed, of 33.9 million tons for government schemes annually (34, 35). The cost is of the fortificant premix alone (iron, vitamin B-12, and folate) and not of the rice delivered by the program (35). This is ∼0.012% of gross domestic product (GDP) for 2019–2020, compared with the expenditure of 1.5% GDP for health and 0.53% GDP for food subsidies in the same year. These estimates are subject to changes in the cost of premix and the exchange rate. This is also in addition to the existing ∼$130 million cost of the Anemia Mukt Bharat program for supplemental iron (36). When considering program costs, policy makers should also consider the added cost of unforeseen adverse health effects. In the long run, when fortified products will penetrate into open markets, the potential health risk costs will be even greater. When resources are scarce, the high cost of mandatory fortification also represents an unnecessary trade-off with other health and nutrition programs. An example is the much-needed distribution of high-quality foods through safety net programs such as the Public Distribution System, Mid-Day Meal, and Integrated Child Development Scheme. It is here that restraint is most needed.

The ethical dimensions of layering mandatory fortification on other interventions

An elegant framework of ethics, developed by the Nuffield Council for Bioethics (37), discusses how public health action, in its protectiveness, can be inherently paternalistic and coercive, reflecting an ongoing conflict between a libertarian (self-benefit) and a collectivist (benefit for all) outlook. In the Nuffield framework, an ascending ladder of interventions and coercion in public health is described (37), arguing that interventions with the highest coercion eliminate "free choice" and result in the loss of an individual's *autonomy*. Such coercion in public health is instituted in response to emergencies and, well-meaning and difficult as it is, usually is temporary in nature; the (quick) end justifies the means. However, layering mandatory food fortification will take on the additional dimensions of time and permanency. The potential coercion of this program in reducing autonomy of choice could be long-term, even decadal.

Another ethical issue to consider with mandatory fortification is *equity*, where equal benefit (or risk) is conferred on the entire population. If some, owing to their better food and supplement access, including value-added food products (33), or those with hereditary anemias, are put at risk of excess intake with additional layered mandatory iron fortification, then the dilemma of inequity arises. It is important to avoid a "one size fits all" mandatory approach, because particular groups of people may differ in their health status and respond differently to particular programs (37).

The need for restraint

In summary, it is important to consider the evidence on both sides of the deficiency–excess spectrum, with careful management of conflict of interest, before fortified foods are mandated and/or layered. Attention has been drawn earlier to carefully considering how multiple overlapping strategies (38) or unregulated voluntary fortification (39) might result in excess nutrient intake, as well as to the need for adequate monitoring, but this has largely been ignored in the current context. Too much enthusiasm for simultaneous fortification and supplementation can also result in messages that lead to stigmatization and inflation of anxiety. Even if fortification purportedly requires no behavioral change in the beneficiary, it is important to consider (mandatory) fortification as a low priority in the basket of potential public health interventions for nutrient inadequacy and deficiency. In addition, with reference to the recent consideration of mandatory rice fortification, the massive logistic effort needed for fortifying rice in a country with a fragmented rice-milling infrastructure may also affect the drive to provide diverse foods in food baskets. The biggest danger is when fortification and/or supplementation tend toward programmatic permanence: when it is never rolled back or targeted in more precise ways to those in need. A false perception of a "feel-good" factor is generated, when administrators feel that *something was, and is, being done*, while the basic problem lingers on, with the potential for economic harm in resource-strapped economies.

Our perspective is that instead of layering and "adding more," the primary effort should be directed toward improving dietary diversity through the availability and affordability of high-quality foods. This is considered along with restrained fortification, provided a supplementation program does not exist and the nutrient density in the diet is extraordinarily low. Because supplementation programs use pharmacological doses and usually target vulnerable populations such as women of reproductive age, adolescent girls, and young children, layering fortification on top of supplementation needs careful consideration, where children are likely to be more at risk given their lower daily requirement and TUL (23). It is our perspective that programmatic fortification should only be used with a high "true" prevalence of deficiency biomarkers or with a high risk of dietary inadequacy (well over 50%), and only be layered onto existing programs under exceptional circumstances. Simultaneous efforts should be made to evaluate the additional impact in terms of reduction in deficiency biomarkers and the risk of dietary inadequacy, but also to evaluate the emergence

of the risk of excess intake. Three clear dangers are present: first, a fixation with a nutrient rather than a broader appraisal of the entire food system; second, an urge to simplify coverage operations and to make the fortification program mandatory and universal; and third, the lack of will to roll back interventions when things improve. Although our views are illustrated for the Indian context specifically, this perspective is relevant globally, particularly for LMICs contemplating multiple interventions to address micronutrient deficiencies.

In conclusion, the fortification of nutrients in multiple foods should be considered in a multidimensional food and nutrient framework, contextualized with local data and experiences, that includes existing supplementation programs. The layering of food fortifications by the state, with other forms of in-house fortification or supplementation, is a complex interaction of national and transnational stakeholders with different motivations. The local context-specific balance of harms and benefits, as well as ethics, must override all other considerations.

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