Chapter 3

Developing Zinc Intervention Programs

Once it is decided that programmatic intervention is needed, several factors must be considered for the development of suitable action. First, the evidence for zinc deficiency and its public health implications should be used to motivate the public and private sectors to develop interventions and to promote public acceptance of these actions. Based on information derived from population assessments, the distribution of zinc deficiency in the population will determine whether there is a need to reach the population as a whole and therefore establish national level programs, or whether the problem of zinc deficiency is isolated to specific high-risk groups, in which case targeted interventions may be more appropriate and efficient (section 2.1). The level of risk of zinc deficiency in the population will determine the urgency with which the situation needs to be addressed, and hence will influence the choice of intervention strategy, or combination of strategies. The choice of intervention strategies will also be influenced by the in-country resources available to develop and maintain the infrastructure and/or technology necessary to deliver and sustain the intervention. The three major categories of nutrition-focused zinc intervention strategies—supplementation, fortification, and dietary diversification/modification—are discussed in the following sections.

It is clear from the results of numerous zinc supplementation trials that a wide range of health benefits can be realized by increasing the intake of zinc where intakes were previously insufficient (section 1.4). These results argue strongly for the development of programs to improve zinc nutriture in high-risk populations. However, because it is unlikely that zinc deficiency will occur in isolation of other nutritional deficiencies and health problems, programs to address zinc deficiency should be incorporated into more comprehensive new or existing health and nutrition programs when possible. Opportunities for linking zinc interventions with existing programs are discussed in section 3.5.

3.1 Supplementation

3.1.1 General issues of supplementation programs

Supplementation refers to the provision of additional nutrients, usually in the form of some chemical (or pharmaceutical) compound, rather than in food. Supplementation programs are particularly useful for targeting vulnerable population subgroups whose nutritional status needs to be improved within a relatively short time period. For this reason, such programs are often viewed as short-term strategies. In many cases, however, supplementation programs may be the only effective strategy to reach specific target groups, such as vulnerable populations who may not be reached by fortification programs due to lack of access to processed foods, or young children and pregnant women, whose requirements for zinc may not be met, even with fortification or dietary diversification/modification programs. Even in higher-income countries, there is currently no alternative approach for pregnant women than to recommend use of iron and folate supplements. In such cases, supplementation programs need to be pursued over extended periods of time, or indefinitely. It is thus possible that supplementation will continue to be the approach of choice for some subgroups of the population and for some selected micronutrients, even in the long-term. On the other hand, for other, less vulnerable populations, targeted supplementation programs may need to be maintained only until the benefits of other longer-term approaches, such as fortification and dietary diversification/modification, begin to accrue.

For supplementation programs to be successful, a health system or other delivery channel must be able to provide a consistent supply, distribution, and delivery of the supplement to the targeted groups, and to encourage their use. All too often, supplementation programs have failed because of the absence of commitment at the national and community levels, lack of supplement supply, poor coverage, poorly designed communication messages, and poor compliance. Increased burden to already overloaded health care delivery systems is also a contributing factor [1]. Poor compliance is a key limiting factor for the success of iron-supplementation programs, and has often been linked with the onset of side effects. However, recently it has also been attributed to several important behavioral barriers that may apply equally when zinc or any other supplements or medications are recommended for long periods, such as throughout pregnancy. Examples include concerns about long-term medications being harmful to the baby or resulting in a bigger baby, thus imposing difficulties during delivery [2]. A review of the World Bank's experience with supplementation programs suggests that key elements of success include social marketing efforts to raise awareness and create a demand, effective targeting of vulnerable population subgroups, increased outreach, and improved quality of services [3]. Further qualitative research is required to understand more fully the complex reasons for poor compliance in supplementation programs. Development of more innovative delivery systems and research to identify dosage schedules and chemical forms of supplements that lessen any unwanted side effects would also be useful.

Most of the existing experience with zinc supplementation is derived from research trials; we are not aware of any attempts to deliver zinc supplements in ongoing, large-scale programs. Issues that must be considered in the development of supplementation programs include the following: (1) the physical and chemical forms of the zinc compound; (2) the dosage level and frequency of administration; (3) the possible inclusion of other micronutrients in the supplement; (4) the administration of supplements with or without foods; (5) the packaging and distribution system; and (6) any possible risk of toxicity. Specific recommendations for zinc supplementation programs are discussed in section 3.1.2.

3.1.2 Choosing a supplement type, dosage, and method of administration

Chemical form of the supplement

There are several different chemical forms of zinc that can be used in supplements. Characteristics of available chemical forms of supplements are summarized in table 3.1 [4]. The costs of some zinc compounds ($US/kg zinc) are compared in table 3.3, in section 3.2, where fortification is discussed.

The choice of a particular chemical form should be based on its solubility in water, intragastric solubility, taste, cost, side effects and safety [5]. Water-soluble compounds are preferable because they are absorbed more efficiently. A number of studies have been conducted to assess the absorption of different chemical forms of supplemental zinc (zinc acetate, aminoate, ascorbate, citrate, gluconate, histidine, methionine, oxide, picolinate and sulfate), although results have been variable and sometimes conflicting in terms of their relative absorption [6–9]. In general, water-soluble compounds, such as zinc acetate, zinc gluconate, and zinc sulfate, are considered to be more readily absorbable than compounds with limited solubility at neutral pH. Some studies suggest that zinc oxide is poorly absorbed because its low solubility at the basic pH of the small intestine may prevent it from dissociating in the gastro-intestinal tract [8–10]. However, this may only present a problem when gastric acidity is reduced, as may occur in malnourished children. In a study of pregnant adolescents receiving prenatal supplements containing iron and elemental zinc as oxide or sulfate, plasma zinc levels of those

TABLE 3.1. Characteristics of zinc compounds available for supplementation (adapted from [4])

Compound	Color	Taste	Odor	Solubility in water (20°C)
Zinc acetate	White/slightly efflorescent	Astringent	Slight odor of acetic acid	Soluble
Zinc carbonate	White	Astringent	Odorless	Insoluble
Zinc chloride	White	Astringent	Odorless	Soluble
Zinc citrate	White		Odorless	Slightly soluble
Zinc gluconate	White		Odorless	Soluble
Zinc lactate	White		Odorless	Slightly soluble
Zinc methionine	White	Slightly sour and bitter	Vanilla odor	Soluble
Zinc oxide	White, gray, yellowish white	Bitter, astringent	Odorless	Insoluble
Zinc stearate	White		Faint	Insoluble
Zinc sulfate anhydrous	Colorless		Odorless	Soluble
Zinc sulfate heptahydrate	Colorless	Astringent	Odorless	Soluble

receiving the supplemental zinc oxide (25 mg zinc) remained at levels comparable to those of the unsupplemented women; only those receiving the zinc sulfate supplement (20 mg zinc) had increased plasma zinc levels [10]. Zinc methionine and zinc histidine have also been suggested [7, 11] because the amino acid ligands facilitate zinc absorption. However, the possible benefit of improved zinc absorption from these compounds may not justify their higher costs. More research needs to be carried out to compare the relative absorption, cost, and acceptability of various zinc compounds for use as supplements.

Physical form of the supplement

For infants and small children, zinc supplements have often been given in the form of a flavored syrup. Chewable tablets containing micronutrients with and without zinc (as amino acid chelate) have been used for school children [12]. Newer formulations provide tablets that are either chewable or dispersible in liquids. Recently, zinc has also been included in a mixture of micronutrients provided as a high-fat spread to be consumed alone or added to certain component(s) of the existing diet [13]. Another approach is the use of single-dose sachets of dry micronutrients (sprinkles), or crushable tablets that are added to food at the time of serving.

The optimal physical form of the supplement depends on the age of the target group, cultural preferences, and the possible desirability or need to include additional nutrients in the supplement. Young children will need to receive a liquid preparation or one that can either be made into a liquid in the household or added directly to foods, such as the sprinkles referred to above. In contrast, dry supplements (tablets, capsules or powders) are less expensive, more stable and permit inclusion of a broader range of nutrients. Recent trials with high-fat, micronutrient-fortified spreads suggest that these may provide another option for supplementation programs, although more experience is needed to assess their acceptability, efficacy, and impact on consumption of the usual household diet.

Considerations for providing zinc supplements with other supplemental nutrients or meals

Zinc supplements can be given alone or as an additional component of multi-nutrient supplements, such as prenatal iron and folate preparations. These supplements can be provided either with or between meals. In general, when minerals are consumed in the fasting or post-absorptive state, absorption is substantially greater because dietary components, particularly phytate, do not interfere with absorption [14].

When formulating multi-nutrient supplements, it is recommended that salts that are readily absorbed should be selected to avoid antagonistic interactions between zinc and other minerals. Interactions between zinc and calcium [15], zinc and iron [16], and zinc and copper [17, 18] have been described. When multi-micronutrient supplements are consumed with food, the presence of ligands in food appears to minimize the inhibitory effect of non-heme iron on zinc absorption [19–21] and vice versa [18, 22, 23]. Nevertheless, total zinc absorption is likely to be greater when the supplements are given apart from meals because of the inhibitory effect of many foods on zinc absorption. Interestingly, in one study Sandstrom et al. [19] gave iron and zinc supplements in a water solution with and without added histidine. Iron inhibited zinc absorption when the solution contained a high (25:1) iron:zinc ratio, but not when histidine, a ligand known to assist the absorption of zinc, was added to the solution.

Very few of the available zinc supplementation trials have provided details on whether the supplements were given with or without food. Therefore, it is difficult to assess whether the meals may have affected the efficacy of the interventions. In many of the studies of children, zinc supplements were given under the supervision of teachers, health care workers, or field staff, so it may be assumed that they were given without food. However, direct comparisons are needed to determine the implications of nutrient/food interactions on zinc absorption, and to assess the efficacy of various zinc dosage levels according to method of administration.

Frequency of administration

Zinc supplements probably should be given frequently, as most of the zinc in the human body exists in non-labile pools (e.g., muscle and bone) and is not readily released in response to zinc deprivation [24]. Nevertheless, some evidence suggests that providing zinc supplements less often than once daily may be efficacious. A supplementation trial among Gambian infants, for example, provided 70 mg zinc as zinc sulfate twice weekly for 1.25 years [25]. A significant improvement in arm circumference and a reduction in malarial incidence were observed. No significant effects were observed on the biochemical indices of zinc status or linear growth, but it is not certain whether zinc was the first growth-limiting nutrient in these infants. A supplementation trial among Vietnamese infants compared the efficacy of daily (5 mg) versus weekly (17 mg) zinc supplements [26] in a multi-micronutrient formulation containing vitamin A and iron. A comparable positive impact of both dosing regimens on linear growth among initially stunted children and a comparable improvement in serum zinc concentration were observed. Thus, it is conceivable that the functional impact of temporary improvement of zinc status lasts longer than the period during which the rapidly exchangeable pool of zinc is expanded. The only study to counter these findings is a study in rats, which showed that daily rather than intermittent doses of zinc were required to produce a growth response that fully compensated for a previously deficient zinc intake [27]. Given the level of uncertainty and paucity of studies making direct comparisons of efficacy between daily and weekly supplements, daily provision (5–7 days/week) of zinc supplements is recommended at this time. Further studies are needed to compare the efficacy of different dosing regimens with zinc alone, or zinc in combination with other nutrients.

Recommended daily dosage levels

The appropriate dose of supplemental zinc for the prevention of zinc deficiency in different age groups and clinical conditions has not been studied systematically. Therefore, tentative recommendations have been derived based on the RDA for zinc (section 1.6) and with consideration of the dosages used in published clinical trials of zinc supplementation in various age groups. The suggested daily dosages of supplemental zinc are summarized by life stage group in table 3.2. These have been planned to avoid the possibility of chronic overdosage, as described in section 1.7.

The recommended doses for children 7 months to 3 years (5 mg/day), and for those greater than 3 years (10 mg/day), were derived by considering the RDAs (section 1.6), the NOAELs or upper limits (section 1.7), and dosage levels used in zinc supplementation trials. A meta-analysis of randomized, controlled zinc supplementation trials measuring effects of supplemental zinc on growth among children 6 months to 10 years of age showed an overall positive growth response to zinc among growth-retarded children with dosage levels that ranged from 1–20 mg/day [28]. There was no apparent association between dosage level and magnitude of the growth response, therefore suggesting that the lower zinc dosage levels, which approximate the recommended daily intakes, may be equally efficacious as higher doses in preventing growth retardation due to zinc deficiency. For young children recovering from severe malnutrition (weight-for-height Z-score < –3), a higher dose is recommended (10 mg/day) to cover the increased requirements for catch-up growth. Assuming that tissue accretion is approximately 30 g/day and 20 μg zinc is required per g of accrued tissue, the total physiologic zinc requirements are approximately doubled. As a result, the recommended daily dosage level for zinc was doubled for young children recovering from malnutrition. For pregnant women, doses of 15–30 mg elemental zinc per day (generally as zinc sulfate) have been used most frequently (table 3.2).

As noted in the foregoing sections, available evidence suggests that the absorption of supplemental zinc is much lower (approximately half) when given with foods or supplemental iron than when consumed in their absence. These recommendations may be modified upward if the supplements are designed to be administered with foods, particularly foods with high levels of inhibitors of zinc absorption, such as phytate (section 1.6). However, a specific recommendation for higher dosage levels when zinc supplements are to be given with food or iron containing supplements is pending, as direct comparisons of the efficacy of different zinc dosage levels in relation to the method of supplementation are currently lacking. There is presently very little information on the prevalence of copper deficiency in lower-income country populations. However, in populations or high-risk groups where copper

TABLE 3.2. Daily dosages of supplemental zinc by lifestage suggested by IZiNCG

Age/sex	Range (median) of zinc doses (mg/day) used in controlled trials	Number of trials represented	RDA suggested by IZiNCG (mg zinc/d)[a]	No Observed Adverse Effect Level suggested by IZiNCG (mg zinc/d)	Dose of zinc supplements recommended by IZiNCG (mg/day)
7–11 mo	5–20 (10)	9	3/5	6	5
1–3 yr	5–20 (10)	13	2/3	8	5
4–8 yr	3–10 (10)	7	3/5	14	10
9–13 yr	15–18 (17)	3	6/9	26	10
14–18 yr, M	—	—	10/14	44	10
14–18 yr, F	—	—	8/11	39	10
Pregnancy	20–30 (25)	2	11/15	39	20
Lactation	—	—	9/12	39	20
≥ 19 yr, M	—	—	13/19	40[b]	20
≥ 19 yr, F	—	—	7/9	40[b]	20
Pregnancy	9–45 (23)	11	9/13	40[b]	20
Lactation	15	1	8/10	40[b]	20
Severe malnutrition (children < 4 yr)	5–50 (40)	3	—	—	10

a. RDAs for mixed/refined vegetarian, or unrefined, cereal-based diets, respectively
b. Represent upper limits for zinc intakes

deficiency is suspected, possible adverse effects of zinc supplementation on copper status may be avoided by including copper in the supplement. Molar ratios of zinc:copper in the supplements should be ~ 10:1, up to a maximum of 1 mg/day of copper.

3.1.3 Zinc supplementation as adjunctive therapy for diarrhea

Results of several randomized clinical trials have shown consistently that zinc supplementation reduces the duration and severity of diarrhea in children [29]. Moreover, results of one metabolic study indicate that there is excessive fecal loss of zinc during diarrhea [30]. For both reasons, it seems worthwhile to include zinc supplements in the treatment regimen of children with diarrhea, particularly in settings where there is an elevated risk of zinc deficiency in the population. A group of experts in the management of childhood diarrhea who participated in a recently convened meeting on this topic concluded that, "There is now enough evidence demonstrating the efficacy of zinc supplementation on the clinical course of diarrhea, with regard to the severity and duration of the episode" [31]. They further recommended that zinc supplementation should be provided at a dose of about two times the age-specific RDA per day for 14 days, both to reduce the severity and duration of the episode and to replenish excessive zinc losses. As noted in section 1.8, it is possible that diarrhea or other conditions that affect intestinal health increase intestinal losses of endogenous zinc, thus increasing zinc requirements. Therefore, it is also conceivable that other programs to prevent or treat diarrhea may reduce the risk of zinc deficiency by decreasing excessive losses of zinc via the intestine.

3.1.4 Cost of including zinc in ongoing supplementation programs

Given the similar requirements for frequent administration of supplemental iron for prevention of iron deficiency, and possibly other micronutrients, it would be most feasible to include zinc in programs already delivering daily or weekly nutrient supplements. The only additional costs in delivery of supplements with zinc included are the cost of the zinc compound, additional costs of quality control during supplement manufacturing, and additional costs of measuring program impact in terms of improved zinc status. Based on an average cost of zinc as zinc sulfate of US$25.7 per kg (table 3.3), the additional cost of zinc would range from US$0.05–0.19 per person per year. Previously estimated costs of an iron supplementation program were in the range of US$3.17–5.30 per person per year [3]. While the cost of programs to provide daily supplements needs to be updated, it demonstrates that the additional cost of including zinc in an existing program is minimal. If program monitoring is to be included, the cost-model for wheat flour fortification programs (table 3.4) can be used to derive an estimate. This hypothetical model program was designed to reach 1,290,000 preschool children and include a sample of 1,500 children in the evaluation activities (three surveys over 5 years). This amounts to an additional US$6,000 per year for biochemical analysis of zinc status. Therefore, the additional costs for monitoring zinc status in such a population would amount to less than US$0.01 per person per year.

TABLE 3.3. Cost of zinc compounds (US$) in 2001

Compound	Cost per kg compound	Cost per kg zinc
Zinc acetate	10.2	28.6
Zinc carbonate	16.0	30.7
Zinc chloride[a]	32.5	67.8
Zinc citrate	8.0	23.4
Zinc gluconate[a]	20.9	145.6
Zinc methionine	25.4	83.4
Zinc oxide[a]	4.5	5.6
Zinc stearate[a]	4.9	47.4
Zinc sulfate[a]	10.4	25.7

a. Listed by the US Food and Drug Administration as "generally regarded as safe" (GRAS)

3.2 Fortification

3.2.1 General issues of fortification programs

Food fortification is defined as the addition of nutrients to commonly eaten foods, beverages or condiments at levels higher than those found in the original food, with the goal of improving the quality of the diet. In higher-income countries, fortification has played a major role in increasing the dietary intake of those micronutrients for which deficiencies are common and of public health concern; the contribution of fortification programs to the virtual elimination of micronutrient deficiencies in these countries is widely acknowledged [32].

In lower-income countries, fortification is increasingly recognized as an effective strategy to improve the micronutrient status of the population. Relative to other approaches, fortification is thought to be the most cost-effective means of overcoming micronutrient malnutrition [3]. Programs are designed such that success does not require changes in the dietary habits of the population, nor any personal contact with recipients. Public education is still required, however, to create a demand for the fortified products. Once a suitable fortification program is developed and established, it can be easily sustainable. Fortification programs represent long-term strategies that may effectively prevent the development of nutrient deficiencies among their recipients, although fortification alone may not be adequate to treat existing deficiencies.

Where the micronutrient deficiency is widely distributed in the population, universal or national level fortification of centrally processed foods is an appropriate strategy. An example of a country with a nationwide zinc fortification program is Mexico, where zinc and other micronutrients are added to wheat and lime-processed corn flours that are used in preparing bread and tortilla, the two principal staples in the country. In the case where large segments of the population at risk do not have ready access to centrally processed foods, fortification may also be implemented at the community level. With the latter strategy however, quality assurance and control are more difficult to achieve.

Targeted fortification programs can be developed to increase the intake of zinc or other nutrients by specific segments of the population who are at elevated risk of zinc deficiency, such as infants, young children, or pregnant and lactating women. In this case, special-purpose foods, such as infant cereals, other processed infant foods, or foods distributed in school lunch programs, can be fortified and distributed or made available in the regular marketplace. There are several examples of the addition of zinc to foods in targeted fortification programs. In higher-income countries and in some lower-income countries infant formulas, infant cereals and ready-to-eat breakfast cereals are currently fortified with zinc. Several Latin American countries, including Guatemala, Peru, Colombia, and Mexico have used or are currently using centrally processed complementary foods for children that are fortified with zinc and other micronutrients [33]. Mexico also has developed a fortified, milk-based, beverage mix targeted toward pregnant and lactating women [33].

The government, food industry, research community, and consumer groups all play key roles in developing successful fortification programs; cooperation among these groups is extremely important for programmatic success and should be sought at an early stage of program development. A committee comprised of representatives of these groups should be created for planning, designing, promoting and regulating the fortification program. The government generally plays a vital role as the initiator, coordinator, and monitoring agency. The scientific community should be involved in determining the prevalence of zinc deficiency, the absorption and sensory acceptability of the chosen zinc salt, and the efficacy and effectiveness of the zinc-fortification program. If results from scientific studies indicate that zinc fortification is an efficacious and effective strategy to reduce zinc deficiency, the government should create legislation to implement an intervention program. The food industry can help researchers in defining feasible, affordable fortification strategies, in the identification of appropriate food vehicles and fortificants, in the definition, development and implementation of quality assurance systems and in educational efforts to reach target populations. Consumer groups are able to represent any users' concerns regarding the suitability of the fortified products.

Technical issues of specific relevance to the inclusion of zinc in food fortification programs are discussed in section 3.2.2 below. Considerations for the costs of including zinc in existing fortification programs are discussed in section 3.2.3.

3.2.2 Technical considerations for zinc fortification programs

Selection of the food vehicle(s)

Ideally, a sizable proportion of the target population should consume a proposed food vehicle in relatively constant amounts so that the fortification will result in a predictable and fairly stable level of intake of the added nutrient. The food should be able to be processed in units large enough to permit controlled fortification, should not have any objectionable changes in taste, color or appearance after fortification, should retain appropriate levels of the added nutrients after further processing or cooking and should not be consumed in amounts that present a risk of consumption of toxic levels of the fortificant in any segment of the population [32]. Information derived from dietary surveys used in the initial assessment of a population's risk for zinc deficiency can be used to identify appropriate food vehicles and usual amounts of foods consumed by different segments of the population or target group. Food vehicles that are candidates for universal fortification include staples such as rice, wheat, and maize, or condiments, like salt, that are consumed by a large proportion of the population.

Selection of the form of zinc fortificant

There are several zinc compounds that are available for fortification (table 3.1). Of these, zinc chloride, zinc gluconate, zinc oxide, zinc stearate, and zinc sulfate are listed by the US Food and Drug Administration as generally recognized as safe (GRAS). There is no consensus as to which of the GRAS compounds is most appropriate for fortification programs, especially when gastric acid production is reduced, as may occur more frequently in lower-income countries. Zinc salts vary in their solubility in water and range from very soluble (zinc acetate, zinc chloride, zinc gluconate, and zinc sulfate), to slightly soluble (zinc citrate and zinc lactate), to insoluble in water (zinc carbonate, zinc oxide, and zinc stearate). Water-soluble compounds are generally better absorbed than less soluble or insoluble compounds. As mentioned above, the chemical form of zinc chosen for fortification must not alter the organoleptic characteristics of the final product. Finally, the zinc compounds mentioned above vary in their cost, which should also be taken into account during the selection (table 3.3). Zinc sulfate and zinc oxide are the GRAS salts that are least expensive and most commonly used by the food industry. Of these, zinc sulfate theoretically should provide more reliable absorption because of its greater solubility, although it is more expensive than zinc oxide. Despite these theoretical concerns about zinc solubility, two recent studies found no difference in zinc absorption from wheat products fortified with either zinc oxide or zinc sulfate [34, 35].

Determining the level of zinc fortificant

The proper level of zinc fortification is that which would increase the intake of zinc by the targeted individuals, without imposing a risk of excessive intake on the rest of the population. The IZiNCG SC recommends an intake of no more than 40 mg of zinc per day by adults. To determine the appropriate level of fortification, it is necessary to measure or estimate the amount of the food vehicle being consumed by different segments of the population. If, for example, adult men and women consume a mean of 100 g of cereal flour/day and pre-school children consume 50 g/day, fortification of the flour with 60 mg zinc per kg of flour would provide 40%, 67%, and 100% of the respective RDAs, assuming that the diet is based mainly on unrefined cereals (table 1.10). To reach daily zinc intakes that are considered excessive, adults would have to consume approximately 667 g/day of cereal flour fortified at this level and children would have to consume approximately 267 g/day of the fortified flour, both of which seem unlikely. Recently, participants of a conference on zinc in human health concluded that the appropriate levels of zinc fortification of cereal staples generally should be between 30 and 70 mg of zinc per kg of flour [11].

Consumer acceptability of zinc-fortified foods

Sensory trials are necessary to determine whether the chosen zinc compound and level of fortification alter the organoleptic qualities of the fortified product and to assess consumer acceptance. For example, Saldamli et al. [36] found that fortifying wheat flour with 300 mg of zinc as zinc acetate per 100 g of flour did not affect the rheologic or baking properties of the wheat dough and that the sensory properties of the breads were acceptable. Sensory trials can also be used to compare organoleptic qualities and consumer acceptance of products fortified with different forms of zinc and at different levels of zinc fortification. For example, the sensory acceptability of wheat products made from wheat flour fortified per kg of flour with 30 mg of iron as ferrous sulfate alone, or both iron and either 60 or 100 mg of zinc as either zinc sulfate or zinc oxide were assessed [37]. The authors concluded that zinc-fortified bread and noodles were well accepted, regardless of the chemical form of zinc, even at 100 mg of zinc/kg of flour, although noodles fortified with iron and zinc oxide were slightly less acceptable than those fortified with iron and zinc sulfate, especially at the higher levels of zinc fortification.

Determining the absorption of zinc from fortified foods

Some potential food vehicles may have high amounts of inhibitors of zinc absorption, such as phytate, which can affect the absorption of zinc fortificants added to these foods. Since experience with zinc fortification is still limited, it is worthwhile to conduct absorption studies, using either radioisotopes or stable isotopes of zinc, to quantify the absorption of different fortificants used in candidate vehicles before final selections of fortificants and vehicles are made. Available techniques to measure zinc absorption are summarized in appendix 3.

Monitoring and evaluation issues

Once the fortification program is in place, the effectiveness of the program to reduce zinc deficiency in the target group must be monitored and evaluated. A system should be created to monitor changes in population zinc status, using the same indicators described in chapter 2. The quality of the fortified product also must be monitored on a regular basis, both at the level of the production site and at the point of purchase, to ensure that it contains an appropriate amount of the fortificant. General information on monitoring programs can be found in section 3.6. Published guidelines set for monitoring and evaluation of iron fortification programs [38] may be consulted for useful information that is also relevant for monitoring zinc fortification programs.

3.2.3 Cost of including zinc in ongoing fortification programs

Estimating costs is an important step in planning a food fortification program. Such estimates must include both industry costs (e.g., capital investment and recurrent costs, such as the purchase of fortificant) and public sector costs (e.g., quality control, monitoring and evaluation).

Zinc fortification is unlikely to occur independently of other micronutrient fortification programs. Wheat flour is the most widely fortified staple food product, and iron is the most frequently added nutrient in large-scale fortification programs. The cost of a national program to fortify wheat flour with iron has been estimated [32, 38] and this detailed estimation is used here as a model to determine the additional costs of adding zinc to an existing program.

The cost of establishing a national wheat flour fortification program will vary according to factors such as the number and size of mills, existing quality

TABLE 3.4. Estimated hypothetical costs (US$) of wheat flour fortification with iron and zinc[a]

	Annual cost of iron fortification	Additional annual cost of including zinc	Total annual costs
A. Industry Costs			
1. Capital investment	820	0	820
2. Recurrent Costs			
Equipment (maintenance, depreciation)	600	0	600
Ferrous sulfate fortificant[b]	57,090	—	57,090
Zinc sulfate fortificant[c]	—	102,600	102,600
Quality control	7,920	2,880[d]	10,800
Total industry costs	66,430	105,480	171,910
Cost per MT fortified wheat flour	0.66	1.05	1.72
B. State Costs			
1. Capital investment and maintenance	2,625	0	2,625
2. Mill inspection and monitoring (salaries & transportation)	3,500	0	3,500
Laboratory analysis and reports (including technician salaries)	1,000	96[e]	1,096
Quality assurance and monitoring training	1,500	500[f]	2,000
3. Program monitoring (dietary intake; travel, per diem, analysis, reports)	1,400	0	1,400
4. Evaluation			
Travel, per diems, and collection of biological samples	3,000	0	3,000
Laboratory analysis and reports (including technician salaries)	5,000	3,600[g]	8,600
Total State costs	18,025	4,196	22,221
Total program costs	84,455	109, 676	194,131
Cost per MT fortified wheat flour	0.84	1.10	1.94

a. Adapted from [38]
b. Cost of ferrous sulfate (US$8.65/kg elemental iron, including additional 33% for shipping) added to 100,000 MT wheat flour at 66 ppm
c. Cost of zinc sulfate (US$34.20/kg elemental zinc, including additional 33% for shipping) added to 100,000 MT wheat flour at 30 ppm
d. Additional costs of zinc analysis: 10 samples fortificant premix (5 samples per lot @ 2 lots per year) @ $4 per sample = $20; 2 analyzed samples per day, 360 d per year @ $4 per sample = $2,880 annual (semi-quantitative analysis of iron from samples taken every 2 hours should serve to ensure presence of zinc once zinc content of premix is analyzed)
e. Additional cost of analyzing fortified flour samples collected at market; one sample per month analyzed in duplicate, 12 months/year @ $4 per sample = $96
f. An additional 50% of the cost of quality assurance and monitoring training was included for zinc assessment.
g. Program evaluation for serum zinc analysis based on a sample of 1,500 preschool children @ $4 per sample = $6,000 per assessment; assessments conducted three times in a 5-year period (baseline, 12–15 months, and 5 yr post-program initiation) = $18,000/5-year period or $3,600 annually

assurance facilities, functional regulatory and food inspections, and the quantity of micronutrients being added [38]. The estimated annual cost of a program that fortifies 100,000 metric tons (MT) flour per year with 66 ppm (parts per million) elemental iron in the form of ferrous sulfate at one mill using a continuous fortification system is US$84,455, considering amortization of the capital investment over 10 years. In this example, the cost of the iron fortificant is 68% of the total program cost. The additional cost of including zinc in this program will be the cost of adding zinc fortificant in the iron premix, quality control in production, and monitoring and evaluation. Current prices of zinc fortificants in the international market are given in table 3.3. The cost for a particular industry in a specific country should include the product cost plus shipping to the country, importation taxes, and the cost of transportation within the country.

Although most costs can be shared with the cost for quality control, monitoring and evaluation of the iron fortification program, some additional cost should be added to account for the laboratory analysis for both quality control determination and for zinc determination in biological samples during program monitoring and evaluation. The estimated additional costs, US$4,196 per year, are detailed in table 3.4.

Table 3.5 provides a summary of the estimated additional annual costs of including zinc in a wheat flour iron-fortification program using either zinc oxide or zinc sulfate as the fortificant forms. Each fortificant type was included at two different levels, 30 and 70 ppm zinc, representing the lower and upper levels of the recommended range for addition of zinc fortificant. The price of mixing the zinc and iron is assumed to

TABLE 3.5. Estimated additional program cost of adding zinc to iron-fortified wheat flour

Zinc source	Cost of zinc fortificant (US$/kg zinc)	Plus 33% shipping costs	Fortification level (ppm)	Additional cost per MT of flour (US$)	Additional cost for 100,000 MT of flour	Total additional cost (including quality control and evaluation)[a]	% of cost of iron fortification program[b]
Zinc oxide	5.6	7.4	30	0.22	22,200	29,276	35
			70	0.52	51,800	58,876	70
Zinc sulfate	25.7	34.2	30	1.03	102,600	109,676	130
			70	2.39	239,400	246,476	292

a. The additional cost of quality control and evaluation of zinc fortification was estimated at US$7,076/year

b. The total cost of iron fortification of 100,000 MT of wheat flour with ferrous sulfate at 66 ppm, including quality control, monitoring and evaluation was estimated at US$84,455 (adapted from [38])

be negligible and therefore the increase in the cost of the zinc/iron premix is due only to the cost of the zinc fortificant. In the example of adding zinc sulfate to provide 30 ppm zinc, the fortificant cost was estimated at US$25.70 per kg zinc (table 3.3) plus an additional 33% for shipping, giving US$34.20 per kg additional cost to the plant. The additional cost per MT flour (US$34.20/kg × 30 kg zinc/1000 MT ×1 MT/1000 kg) is US$1.03 per MT or US$102,600 for the 100,000 MT. After accounting for quality control analyses at the industry level, and costs for equipment and monitoring and evaluation (US$4,196), the total program cost increases from US$84,455 to US$194,131. It is clear that the majority of additional program costs are due to the cost of the zinc fortificant; therefore reduction in zinc fortificant prices that may occur with increased demand would contribute substantially to limiting the additional costs of including zinc in an existing fortification program.

3.3 Dietary diversification/modification

3.3.1 General issues of dietary diversification/modification programs

Strategies to diversify or modify the diet aim to enhance the access to, and utilization of, foods with a high content of absorbable zinc throughout the year. These strategies can involve changes in food production practices, food selection patterns, and traditional household methods for preparing and processing indigenous foods. Dietary diversification/modification represents a sustainable, economically feasible, and culturally acceptable approach that may be used to improve the adequacy of dietary intakes of several micronutrients simultaneously with limited risk of antagonistic interactions.

Dietary diversification/modification strategies encompass a wide variety of approaches, but all are generally regarded as long-term strategies in terms of development, implementation, and potential for impact. They are often described as a sustainable approach because the process empowers individuals and households to take ultimate responsibility over the quality of their diet through self-production or acquisition of nutrient-rich foods and informed consumption choices [39]. Once the expected behavior changes are achieved, it is also expected that inputs will be minimal as the practices become self-perpetuating through the natural mechanisms of information sharing. Because impacts are likely to be achieved only in the long term, however, these strategies should be implemented jointly with other shorter-term approaches, such as supplementation and fortification, as required, to address the needs of specific target groups.

As discussed in section 1.6, diets in lower-income countries are often based predominantly on cereals and legumes or starchy roots and tubers, while consumption of foods with a high content of readily absorbable zinc, such as meat, poultry, and fish, is often limited because of economic, cultural and/or religious constraints. Dietary strategies described herein are directed toward improving intakes of absorbable zinc, some of which aim to increase the total intake of zinc, whereas others aim to enhance zinc absorption by altering the levels of food components that modify zinc absorption. Some strategies can be implemented at the level of agricultural production, whereas others are directed toward community or household level application.

The conditions for success of dietary diversification/modification strategies will vary depending on the specific approach used. For example, new agricultural strategies must not compromise crop yield, they must not involve additional costs for farmers, and they should not significantly alter the organoleptic and overall nutritional quality of the products. Dietary interventions involving changes in production, processing or consumption patterns must be practical, culturally acceptable, economically feasible, and sustainable for the target group. At the household level, they must not increase the cost or result in increased time and workload required by the caregiver, or require substantial changes in the types and quantity of foods consumed. Specific strategies that may be directed to improving total or absorbable zinc intakes are summarized in the sections below.

3.3.2 Agricultural strategies to increase total and/or absorbable zinc content in staple foods

Several strategies can be used to increase the zinc content of plant-based staples. These include the use of zinc fertilizers and plant breeding and genetic modification techniques. Although these methods appear promising, more research is needed to evaluate their economic, environmental, and health effects before these strategies can be recommended for implementation. These techniques, referred to as "field fortification," are described below.

Zinc fertilizers

When applied to zinc-deficient soil, zinc-containing fertilizers can increase the zinc content of cereal grains, and this technique is used extensively to enhance yields under these conditions. For example, in Turkey the zinc concentrations in wheat grains (7–12 mg/kg) are well below the accepted critical levels of zinc for adequate plant nutrition, and application of zinc to the soil at a rate of 22 kg of zinc per hectare raised the mean concentration of zinc in the plant from 8 to 13 mg/kg [40].

Plant breeding

Plant breeding can produce new cereal varieties that have higher grain zinc concentrations than pre-existing wild strains and that better tolerate zinc-deficient soils. These zinc-efficient genotypes are also more disease resistant and have improved seedling vigor, enhanced germination, and a higher grain yield [41]. Hence, their use will not decrease crop productivity or increase costs to farmers.

The identification of crop varieties that naturally contain high levels of specific micronutrients has been aided by the germplasm screening approach. Research has focused on five main crops (rice, wheat, maize, beans, and cassava) and on three micronutrients (iron, zinc, and β-carotene). All crops show significant genotypic variation in mineral content of up to twice that of common cultivars. In one study of rice grains, for example, zinc concentration averaged 24.5 ppm with a range of 13.5 to 41.6 ppm [42]. The range of genotypic differences in zinc (and iron) concentration measured in maize was around 50% of the mean value.

Plant breeding has also been used to develop mutants of corn, barley, and rice with more than 50% reduction in levels of phytate phosphorus in the kernels [43]. A 78% increase in average zinc absorption was reported in a study of five adults when fed a corn-based polenta diet in which the phytate content of the corn was reduced by 55–63% of the parent, wild-type variety [44]. Iron absorption from a low-phytate maize mutant was also improved by 50% (i.e., from 5.5% to 8.2% of intake) compared with the wild-type strain maize [45].

The amino acids methionine and cysteine form soluble ligands with zinc, and thus enhance its absorption [46]. Maize has shown some genetic variability in content of these amino acids, the highest being about 50% above the lowest levels [42, 47]. Only a small increase in the concentration of these amino acids in the diet may be needed to enhance the absorption of zinc (or iron), and therefore it is unlikely to be a constraint for plant functions [47]. At this time, there is little information about the agronomic advantages or disadvantages to increasing the concentration of sulfur-containing amino acids in staple foods. The efficacy of this modification in improving total zinc absorption in humans should be quantified in comparison with the other strategies mentioned above.

Genetic modification

Genetic engineering has recently been employed to produce rice grains containing an increased content of iron as well as a significant amount of β-carotene in the endosperm [48]. With additional research, this technique could be applied to enhance the zinc content of rice and other cereal grains.

Genetic modifications can also be used to incorporate phytase enzymes (myo-inositol hexaphosphate phosphohydrolases) into staple crops. This would dramatically decrease their phytic acid (myo-inositol hexa phosphate:IP6) content; phytase enzyme hydrolyzes phosphate groups from the inositol ring to yield intermediate myo-inositol phosphates (bi-, tri-, tetra-, and penta-phosphates; [49]). As noted in section 2.3.1, myo-inositol phosphates with less than five phosphate groups (i.e., IP-4 to IP-1) do not inhibit zinc absorption [50].

Genetic modification can also be used to increase the level of promoters of zinc absorption in plant-based staples. A gene that codes for a sulfur-rich metallothionein-like protein has recently been introduced into rice *(Oryza sativa)* to increase iron absorption [51]; zinc absorption would be expected to improve simultaneously.

3.3.3 Strategies to increase production and/or intake of zinc-rich foods

To increase the zinc content of diets, small-livestock husbandry, aquaculture, and production of other indigenous zinc-rich foods can be promoted, where feasible. Education and behavior change strategies can also be used, either alone or in combination with production activities, to promote greater intake of zinc-rich foods.

Small livestock production

Production of a variety of small livestock (e.g., guinea pigs, poultry, rabbits, and small ruminants) can be promoted to increase the availability of these zinc-rich foods within a community or household. Education is key to the success of these interventions, and efforts must be made to ensure that the livestock produced is not entirely sold for cash. Some of the food that is produced should be reserved for household consumption and targeted to those household members at higher risk of inadequate zinc intake. Regrettably, evidence from Bangladesh and Ethiopia suggests that the increases in household income achieved through increased livestock production do not necessarily translate into improved dietary quality among producer households [52, 53]. Nutrition education and behavior change interventions seem to be essential in achieving nutritional impact because the increases in income may be invested in basic necessities or consumer goods other than food [39]. It is also important to ensure that small livestock are not regarded by producer households as ceremonial foods (e.g., guinea pigs in highland Ecuador) that are only consumed on special occasions. A limitation of this type of intervention is that animal product intake is sometimes constrained by cultural or religious factors that prohibit their inclusion in the diet.

Aquaculture

Aquaculture may be a more suitable strategy in countries where economic, religious, and/or cultural factors prevent the consumption of meat and poultry. Inclusion of fish (whole) can increase the content and density of zinc and other nutrients (fat, iodine, iron, selenium, niacin, and riboflavin) in the diet. Use of whole dried fish is more desirable as it contains more zinc than fish flesh without bones [54, 55] and also does not require refrigeration. Fish flour or meal prepared from small, whole dried fish, including the bones, can be used to enrich cereal-based porridges for infant and child feeding. A new farmer-focused, systems approach has been carried out successfully in Bangladesh and Malawi whereby aquaculture was incorporated into existing farming systems with the minimum of investment [56]; further exploration of these methods is recommended. As was described for small livestock production, promotion of aquaculture must also include educational efforts to ensure that increased production translates into greater intakes by vulnerable groups.

Indigenous zinc-rich foods

Agronomic and genetic improvements have led to the development of higher-yielding genotypes of some indigenous wild plants (e.g., wild fruits, nuts, seeds, leaves), as well as varieties that are resistant to drought or heat stress, tolerant of poor soils, and easily cultivated and accepted by local rural communities [57]. In some regions (e.g., Korea, Vietnam, Sahel in Western Africa, Zambia), an inventory of certain edible species has been compiled and some analyses of minerals undertaken [58]. Sago grubs, which are consumed in Papua New Guinea, and locusts, which are consumed in Malawi during certain seasons, are rich sources of zinc [59]. More information is required on the content of zinc and zinc absorption modifiers in local indigenous foods to identify those that might be suitable sources of absorbable zinc.

Processed snacks

The absorbable zinc content of processed food products such as chips or noodles can be enhanced by incorporating zinc-rich food items, such as dried fish, fish liver, and other organ meats. In Thailand, for example, beef or chicken livers are used to enrich a popular, locally produced snack food prepared from a 2:1 mixture of sago flour and tapioca flour and processed by steaming to enhance vitamin A retention [60].

3.3.4 Household food processing methods to increase absorbable zinc in the diet

At the household level, reduction in the phytate content of the diet can be achieved in two ways: (1) by inducing activity of plant-associated phytase (myo-inositol hexaphosphate phosphohydrolases; EC 3.1.3.26) and the enzymatic hydrolysis of phytic acid (myo-inositol hexaphosphate) through germination, fermentation, and soaking; and (2) via diffusion of water-soluble phytate through soaking.

Germination

Most cereal grains and legumes contain some endogenous phytase, but the activity varies among species and varieties. Endogenous phytase activity is high in rye and wheat, but very low in maize and sorghum, and is negligible in dry or dormant seeds. Germination increases the activity of endogenous phytases in cereals and legumes as a result of *de novo* synthesis or activation of the enzyme, although the extent of this increase also depends on the species and variety [61]. After 2 to 3 days of germination, the hexa-inositol phosphate content of cereals is reduced by 13–53% in cereals and 23–53% in legumes [62, 63]. Soaking also activates endogenous cereal phytases, and the level of activity varies with temperature and pH [62].

Flours prepared from germinated grains can be added to ungerminated flours to promote phytate hydrolysis during food processing. For example, addition of 10% germinated maize flour to maize dough decreased the phytate content of *kenkey* (a traditional maize dough in Ghana) by 56% [64]; even greater phytate reductions can be achieved if these doughs or flour slurries are incubated at the optimal temperature, pH, and time to maximize phytase activity. A similar process can be applied to lower the phytate content of porridges used in infant and young child feeding. In this case, use of germinated flour has an added advantage in that denser porridges can be prepared (e.g., with 20–28% dry matter and a comparably higher zinc density), as the high amylase content of the germinated flour decreases water-binding capacity of the starch and lowers the viscosity of the porridge to that of a porridge with lower dry matter content (e.g., 7–10% dry matter). The result is a porridge with higher energy and nutrient density and a lower phytate:zinc molar ratio.

Care must be taken when using amylase-rich foods to ensure that the porridges are decontaminated by heating prior to use. Germination may increase the concentration of *Enterobacteriaceae*, fungi, *bacillus* species, etc., including potentially pathogenic and toxinogenic species [65]. If germinated cereal grains are not thoroughly dried before being milled into flour, they may become contaminated with aflatoxin, which is produced by *Aspergillus flavus*, *A. parasiticus*, and *A. nomius* when storage conditions are poor (i.e., 88–95% relative humidity; 25–30° C) [58].

Fermentation

Fermentation can induce phytate hydrolysis via the action of microbial phytases (EC.3.1.3.8), which can originate either from the microflora on the surface of cereals and legumes or from a starter culture inoculate [66]. The levels of phytate reduction reportedly achieved by fermenting cereal-based flour slurries or porridges are variable, but reductions of about 50% appear to be achievable [67]. A number of factors within the lactic acid fermenting system probably influence microbial phytase activity, and hence the level of phytate reduction achieved, including the types of fermenting organisms present, pH, incubation temperature, and ratio of solids to water [68]. High tannin content in cereals (e.g., bullrush millet, red sorghum) also appears to inhibit phytase activity [69].

In the future, commercial phytase enzymes prepared from *Aspergillus* o*xyzae*, A. *niger*, *or A. fumigatus* may be available for human use. Only the phytase prepared from *A. fumigatus* is heat stable, and hence can be incorporated into the staple food prior to cooking. The high cost of these enzymes is likely to preclude their use in many lower-income countries at the present time.

Soaking

Soaking can reduce the phytate content of certain cereals (e.g., maize and rice) and most legumes because their phytate is stored in a relatively water-soluble form, such as sodium and potassium phytate, and hence can be removed by diffusion. Levels of water-soluble phytate in legumes and cereals vary widely, ranging from only 10% in defatted sesame meal to as much as 70–97% in California small white beans, red kidney beans, corn germ, and soy flakes [70, 71]. Removal of water-soluble phytate can be achieved more effectively by soaking legume flours rather than whole legumes.* Reductions in IP5 + IP6 content ranging from 51–57% have been achieved, when maize flour is soaked and the excess water is removed by decanting [67]. In Malawi, a method of soaking pounded maize was found to be well accepted, and a nearly 50% reduction in phytate content of maize flours was achieved by the rural participants [72]. Soaking may also remove other antinutrients such as saponins and polyphenols. The potential loss of water-soluble nutrients following this procedure needs to be quantified.

Zinc absorption from cereal-based foods by humans has been improved by employing some of these processing methods to reduce phytate content, such as the fermentation of bread [73], and the germination and soaking of oats [74]. Animal studies have shown greater femoral zinc in rats fed diets containing fermented soybean meal than those fed regular soybean meal, due to the increase of zinc solubility in the small intestine [75]. Increases in *in vitro* levels of soluble iron have also been reported after fermenting porridges prepared from white sorghum and maize with a starter culture, with and without the addition of commercially prepared wheat phytase enzyme [69].

To date, the efficacy of these interventions to improve human zinc status has not been extensively tested. One community-based intervention study using a quasi-experimental design employed a range of dietary strategies to increase the content of micronutrients (including zinc) and to enhance the absorption of zinc among a group of Malawian children with maize-based diets and a high prevalence of stunting. The strategies were implemented using formative research and included promotion of the consumption of animal source foods, notably whole, dried, soft-boned fish, and reduction of the phytate content of the maize-based porridges. The latter was accomplished primarily by soaking maize flour prior to cooking, and also by encouraging the fermentation of porridges and the addition of germinated cereal flour during the preparation of the porridges [62]. After 12 months, which included a six month intervention period, Z-scores for mid-upper-arm circumference and arm muscle area ($p < 0.001$), although not weight or height Z-scores, were greater in the experimental group compared with the control group. After controlling for baseline variables, the incidence of common infections was lower in intervention children compared to controls, although with no change in malaria or hair zinc status [76]. These results corresponded to dietary changes in the treatment group, which resulted in diets that supplied significantly more animal source foods, especially soft-boned fish, and less phytate ($p < 0.01$), and in higher median intakes of absorbable zinc, and a reduction in the

* L. Perlas, personal communication.

prevalence of inadequate zinc intakes ($p < 0.01$) [77].

3.3.5 Programmatic experience with dietary modification/diversification strategies to increase micronutrient intake and status

During the past few decades, home gardening and nutrition education interventions using social marketing techniques have been popular food-based strategies, especially for the control of vitamin A deficiency [39, 78, 79]. More recently, a few innovative programs have been designed to address multiple micronutrients, including iron and vitamin C in addition to vitamin A (see Ruel and Levin [39]). None of the programs aiming at increasing the production and/or intake of micronutrient-rich foods, however, has specifically addressed zinc as a target nutrient, even those focusing on multiple micronutrient deficiencies. This opportunity should be pursued in the future. Interventions to increase production/intake of animal sources of iron, such as small livestock production and aquaculture, could also provide an opportunity for adding zinc as a target nutrient without any additional costs.

Plant breeding strategies are also suitable approaches for addressing iron and zinc deficiencies simultaneously because positive correlations between zinc and iron concentrations (and other trace minerals) have been consistently found when screening for genetic variability [80]. Again, adding zinc as a target nutrient could be achieved at no additional cost.

Programmatic experience with the promotion of home processing techniques to increase absorbable zinc in the diet is surprisingly limited, considering the large amount of literature showing their effectiveness in reducing phytate and in increasing zinc absorption in clinical studies. Several small-scale studies have documented that amylase-rich foods improve the nutrient density of the diet, and the potential usefulness of these approaches for increasing the micronutrient concentration of complementary foods for young infants has been shown [81–83]. There is, however, little evidence of the efficacy or effectiveness of such approaches for the control of zinc or other micronutrient deficiencies, with the exception of the Malawian study discussed above. Research in this area is urgently needed to determine the potential of these approaches to contribute to the alleviation of zinc deficiency among vulnerable groups. There is no information available on the cost or cost-effectiveness of dietary modification/diversification strategies.

3.4 Formative research for program planning

Formative or consultative research is an approach that has been developed to design effective programs to improve infant and young child feeding [84, 85]. The approach has also been used in diarrheal disease control programs [86, 87], in the design of vitamin A interventions [88], including a successful social marketing program to promote intake of vitamin A–rich foods in Thailand [89], and in a dietary intervention to enhance micronutrient adequacy of rural Malawian diets [62]. The formative research methodology is based on the premise that community nutrition programs will be more effective in modifying child feeding practices and in improving child nutrition if communities are directly involved in their design and formulation. Program planners need to understand the behaviors, practices, culture and constraints faced by the population targeted by their program [84]. The methodology involves the following steps:

1. Define the key problems and practices.
2. Identify simple and effective actions within the household.
3. Test the recommended practices in the homes to determine which ones are most practical and culturally acceptable.
4. Develop an effective strategy for the promotion of the selected practices among the targeted population.

Formative research is largely based on qualitative methods adapted from anthropology, market research, and nutrition education, which may be complemented by some semi-quantitative or quantitative methods as appropriate. The ultimate objective is to understand "what people say, believe, do, and want to do" [84, page 1], and to use this knowledge for improved program planning and effectiveness.

Although experience in the use of formative research for the design of micronutrient programs is rather limited, recent efforts by Helen Keller International to adopt this methodology for vitamin A programs should provide useful guidelines for its use in the design of zinc interventions [88]. The approach could be particularly useful to design food-based interventions, in particular the strategies aimed at increasing the content or the absorption of zinc in the diet through changes in household purchasing, preparation, and processing techniques, or intra-household allocation of resources. Approaches previously developed for use with other micronutrients could be adapted to explore available, culturally acceptable, and affordable food sources of zinc at the community level. For example, a detailed protocol was previously developed to assess natural food sources of vitamin A at the local level, using focused ethnographic studies [90, 91]. Other interventions requiring a behavior change component, such as promoting the use of a fortified product, or even motivating the population to comply with a supplementation program, could also benefit from using a formative research approach for program design.

3.5 Linking zinc interventions with other nutrition and health programs

To reach the specific target groups with a particular intervention, such as zinc supplements or educational messages to promote dietary modification, an appropriate delivery mechanism must be identified. For example, infants might be reached through well-baby clinics or growth monitoring programs if these have suitably high population coverage. Educational messages for pregnant and lactating women might be delivered through community-based women's groups, antenatal clinics, or religious organizations. Formative research is generally needed to select the optimal delivery mechanism. Obviously, if a successful micronutrient program is already in progress, it might be most prudent to link zinc activities with the existing program. A listing of existing health and nutrition programs and opportunities for the inclusion of specific types of zinc interventions is summarized in table 3.6.

The number of asterisks (*) in each cell of this table reflects the potential of a particular program to serve as a vehicle or distribution mechanism for three broad types of interventions to control zinc deficiency. One asterisk (*) represents a possible opportunity, but one that is not likely to be the most effective. Two asterisks (**) represent an opportunity that has limited usefulness because the frequency of exposure to the intervention is too limited or irregular. An example of this is immunization. Although the immunization schedule has the advantage of starting very soon after birth, thus allowing an early first contact of the infant with the health system, the immunization schedule does not allow for providing a supply of zinc supplements monthly. The same is true for other interventions that bring mothers to the health center infrequently, such as vitamin A supplementation, which is repeated only once every 6 months. For zinc supplementation, monthly contacts with the health services, such as to receive a monthly supply of supplements, would be ideal, although bi-monthly provision of zinc supplements could be similarly effective and even more efficient by reducing the burden on health centers imposed by monthly delivery. Three asterisks (***) are given to interventions that theoretically bring mothers to the health center on a monthly basis, but high compliance to the monthly schedule would need to be achieved for the intervention to be an optimal approach for zinc supplementation. Four asterisks (****) are given to interventions that are prime opportunities for the particular zinc intervention considered. Examples include iron supplementation programs for women, which could easily add a zinc supplementation component. Similarly, existing food fortification programs could add zinc as one of the nutrients included in the fortification process. The cost implications of adding zinc to supplements or food fortification programs have been discussed in sections 3.1.4 and 3.2.3, respectively.

Education interventions to promote increased zinc intake or the use of home processing techniques to increase zinc absorption can be included in any nutrition or health education program curriculum. It is particularly relevant in the context of programs promoting exclusive breastfeeding and optimal complementary feeding practices for young infants. In situations where effective prenatal care programs are in place and bring mothers in frequent contact with the health system, increased zinc intake could also be promoted among mothers and their families.

Finally, agricultural programs combining increased production of animal products and education to promote greater intake by vulnerable groups are the ideal mechanism to target multiple micronutrients, including zinc, at little additional cost.

3.6 Evaluation of zinc interventions: surveillance and monitoring

Monitoring and evaluation are essential components of intervention programs and thus should be integrated into the overall program strategy development. Monitoring and evaluation are key to ensuring that programs are implemented as planned, that they are reaching their target population in a cost-effective manner, and that they are having the expected impact.

Evaluative research has been defined as the systematic collection of information on the design, implementation, and effect of projects on targeted populations [92]. Monitoring is usually referred to as the component of evaluative research that addresses the implementation aspects of a program, whereas evaluation is concerned with the program's effects or impacts. Because their objectives are different, monitoring and evaluation require different methodologic approaches, although many of the general concepts related to the selection of designs and indicators apply to both.

Monitoring implies the continuous collection and review of information on project implementation activities, coverage and use, which can be used to re-design or re-orient the program and to strengthen its implementation and the quality of service delivery in an ongoing fashion. A monitoring system can be used to assess service provision (availability, accessibility, and quality), utilization, coverage, and cost [93]. More specifically, monitoring can help assess the following [94]:

- delivery of the service or intervention (whether or not it is delivered)
- timeliness of service delivery
- quality of service delivery
- coverage of the intervention (the degree to which targeted individuals and communities are reached)

» appropriateness of the intervention and the level of use of the services by the targeted populations
» costs of implementation
» overall effectiveness of implementation of the different activities (whether the actual implementation follows the implementation plan)

Evaluation seeks to determine the extent to which the project goals and objectives have been achieved and whether the intervention is having the expected impact on the targeted population. Clearly, in order to achieve impact, program performance must be achieved, and this should be ensured through an effective monitoring system.

TABLE 3.6. Opportunities for linking interventions to control zinc deficiency with existing maternal and child health and nutrition programs

Maternal and child health and nutrition programs	Opportunities for linking with interventions to control zinc deficiency		
	Supplementation	Fortification	Dietary diversification/ modification
Child health and nutrition (prevention)			
Malaria control (bed nets, education, prophylaxis drugs)	contacts with health services may be too infrequent and irregular*		combined education programs*
Immunization	may allow early exposure to health services during first few months of life**		
Growth monitoring/well-baby clinic	good vehicle if once/ month***		education as part of growth monitoring***
Education and behavior change interventions			
Promotion of exclusive breastfeeding	may allow early exposure to health services**		promotion of exclusive breastfeeding is an excellent food-based strategy for children 0–6 months****
Education on complementary feeding practices	timely because of increased needs of infants from 6 months of age**	excellent for promoting the use of processed, fortified complementary foods, if available locally****	excellent for the promotion of home preparation and processing techniques to increase zinc content and absorption****
Hygiene, prevention of illnesses	may be too infrequent or irregular*		education regarding fermentation (improved zinc absorption/diarrhea prevention)*
Control and treatment of infectious diseases	may be too infrequent or irregular for prophylaxis* opportunity to include zinc in treatment regime***		
Deworming	may be too infrequent or irregular; possible to provide shorter term supply (e.g., 1–2 months)*		
Vitamin A capsules distribution	too infrequent: every 6 months*		
Iron supplementation	excellent: zinc can be included in supplement****		
Food distribution programs	good opportunity if once per month***	excellent opportunity to fortify with zinc if food donations are fortified locally****	

continued

TABLE 3.6. Opportunities for linking interventions to control zinc deficiency with existing maternal and child health and nutrition programs *(continued)*

Maternal and child health and nutrition programs	Opportunities for linking with interventions to control zinc deficiency		
	Supplementation	Fortification	Dietary diversification/ modification
Child health (curative)			
Treatment of ARI	opportunity to treat severe zinc deficiency*		
Treatment of diarrhea	treatment should include zinc***		
Treatment of severe PEM	opportunity to treat severe zinc deficiency***		
Maternal health, nutrition and care			
Prenatal care	timely, but may be infrequent**		if contacts are frequent enough, can be a good vehicle for education**
Prevention and control of iron-deficiency anemia (supplementation)	supplementation programs can include zinc****		
Family planning, reproductive health	may be too irregular and infrequent*		
Vitamin A supplementation	too infrequent: every 6 months; possible to provide shorter term supply (e.g., 1-2 months)*		
School girls/adolescent girls nutrition and health programs	depends on the nature of the program*		
School feeding programs (food for education)	good vehicle for supplementation****	can be a good vehicle for distribution of fortified foods****	can increase zinc intake, depending on foods provided and menu****
Other			
Food fortification (of staples)		zinc can be included****	
AIDS prevention	depending on frequency of exposure*		
Agriculture programs (e.g., promotion of animal products [fish ponds, small livestock]) combined with education			opportunity to promote home production and intake of animal products****

*Selecting evaluation designs and indicators**

Although the distinction between monitoring and evaluation is useful from a programmatic point of view, this section will use the general term "evaluation" because the principles described apply to both monitoring and evaluation designs.

Two main questions must be asked when selecting an evaluation design: What is the purpose of the evaluation? And what is the level of precision needed by the users of the information?

* This section draws extensively on the work of Habicht and collaborators [93, 95].

Purpose of the evaluation and appropriate indicators

The specific purpose of the evaluation, or what the evaluation intends to measure, is the first consideration in the choice of an evaluation design. For example, results of evaluations can be used to make decisions about whether or not to continue a program, expand it, modify and/or strengthen it, or discontinue it.

Habicht, Victora, and Vaughan [95] classify evaluation objectives into four categories: provision, utilization, coverage, and impact. Relative to the distinction made previously between monitoring and evaluation, the first three objectives would refer to monitoring and the fourth one to impact evaluation. A fifth objective could be added to this list: evaluation of the cost of the program. Examples of indicators to address these five objectives for the three main types of interventions to address zinc deficiency (supplementation, fortification, dietary modification) are presented in table 3.7.

TABLE 3.7. Examples of indicators that can be used for different evaluation purposes and different types of interventions for the control of zinc deficiency

	Types of interventions for the control of zinc deficiency		
Objective of evaluation	Supplementation	Fortification	Dietary modification (Education, home processing and production interventions)
Provision and availability of services	Number of programs or facilities offering supplements Number of supplements available for target population	Number of food products fortified Number of markets with fortified products available	Number of education sessions provided Number of inputs distributed to promote small animal husbandry or fish ponds
Accessibility of services	% of the population living at reasonable distance from distribution point	% of the population with access to markets where fortified products are available	% of the population who could be reached by education or distribution of inputs
Quality of services	% staff trained in intervention (importance of zinc, vulnerable groups, supplementation dosage, schedule)	Quality control of product: level of fortification, stability during storage	Quality of the education, communication, behavior change: Number of staff trained, duration of training, knowledge of staff Duration and intensity of education sessions Quality of inputs provided, amount and quality of education provided with production intervention
Utilization of services by targeted population	Number of individuals coming to receive supplements	Number of families who purchase fortified product in sufficient amounts Number of individuals who receive fortified product with regular frequency	Number of families who have heard messages or attended education sessions Number of families who have received and used production inputs
Coverage of the targeted population	% at-risk individuals who take supplements with recommended frequency	% of at-risk population consuming sufficient amounts and right frequency of fortified product	% of at-risk population who have received education and other inputs
Impact on the targeted population	Assessment of changes in biochemical, clinical, functional indicators of zinc deficiency in targeted individuals	Amounts and frequency of intake of fortified product by targeted individuals Changes in biochemical, clinical, functional indicators of zinc deficiency in targeted population	% of targeted population with increased knowledge % of targeted population who adopted recommended practices or production activity Changes in amount of food (animals, fish) produced and/or consumed Changes in amount and frequency of intake of sources of bioavailable zinc Changes in biochemical, clinical, functional indicators of zinc deficiency

For all three types of programs, the indicators used to assess the provision of services refer to operational issues such as whether the program is providing the inputs and services in a timely fashion to the right population and with adequate quality. To assess for coverage, the indicators should reflect what percentage of the targeted population (based on need and vulnerability) actually receives the intervention as planned, and for service utilization, appropriate indicators include the percentage of the population who actually use the inputs provided.

Impact indicators, in the case of zinc interventions, can include final outcomes such as biochemical, clinical, and functional signs of zinc deficiency, or intermediary outcomes such as changes in knowledge and attitudes, changes in dietary intakes of zinc or zinc-rich foods, or adoption of recommended home processing techniques or animal or fish production activities (table 3.7).

Level of precision needed for evaluation

Following the approach described by Habicht, Victora, and Vaughan [95], the next question to be answered in selecting an evaluation design is, what is the level of precision required for decision makers to have sufficient information about the performance and/or impact of their program? Or, more specifically, how confident do program planners and decision makers need to be that the effects observed are due to the intervention, or what is the level of inferences required? The three levels of inferences defined by Habicht [93] are adequacy, plausibility, and probability. Taking zinc interventions as an example, an adequacy evaluation would refer to assessing the prevalence of zinc deficiency relative to some pre-determined criteria. For example, it may be that the overall goal of a country is to reduce the prevalence of zinc deficiency among children to 10% or less (or any cut-off point used to define a public health problem). Thus, adequacy would be achieved if the evaluation showed that the prevalence of zinc deficiency at the time of the evaluation was lower than the 10% pre-established cut-off point. Adequacy evaluations are usually the simplest and least costly types of evaluations because they do not require randomization or the use of a control group (table 3.8). They do, however, require the same level of scientific rigor as other types of evaluation.

Plausibility and probability, on the other hand, require more resources and a more sophisticated design because they have to demonstrate with some certainty that the achievements in reducing the prevalence of zinc deficiency are related to the intervention being evaluated. For an evaluation to be plausible, it must be able to demonstrate that the zinc intervention program seemed to have an effect above and beyond other external influences that may also have affected the prevalence of zinc deficiency (such as, for example, increased income and resulting improvements in

TABLE 3.8. Types of intervention designs recommended to achieve various levels of inferences (focusing on impact evaluations)[a]

Type of inferences	Purpose of the evaluation	Types of designs
Adequacy	Determine whether the current prevalence of zinc deficiency is adequate (according to some pre-determined criteria, which could be the level considered as representing a public health problem, if there was one).	Cross-sectional survey of the prevalence of zinc deficiency at a certain point in time, and comparison of prevalence findings with pre-established criteria of adequacy
Plausibility	Determine whether it is plausible to conclude that the zinc intervention contributed to current prevalences of zinc deficiency or to the observed changes in the prevalence of zinc deficiency.	Quasi-experimental and other designs that can be used: » Cross-sectional survey with treatment and comparable control group » Longitudinal study with before and after measurements (looking at changes in treatment group only) » Longitudinal-control study, with both a comparison group and before and after measurements » Case-control study with measurement of cases, compared to matched comparable controls
Probability	Determine, with a pre-established level of probability, that the impact on zinc prevalence is due to the intervention	Double-blind, randomized experimental design: » Randomization of the intervention » Before and after measurements » Intervention and control group » Both subjects and researchers are blind to the treatment during the intervention and the analysis

a. Based on Habicht [93].

dietary quality that were not related to the specific zinc intervention). This is achieved by effectively controlling for these potential confounding factors and biases through a careful selection of evaluation design and appropriate multivariate data analysis methodologies. Quasi-experimental or case-control designs are the designs of choice for achieving plausibility (table 3.8).

Finally, probability evaluations are the types of evaluations that provide the highest level of confidence that the intervention caused the outcome, or in the case of zinc, that the zinc intervention is responsible for the reduction in the prevalence of zinc deficiency. This is usually achieved by using a randomized, controlled, double-blind experiment. The probability design is based on the premise that there is only a small known probability (usually < 0.05) that the observed difference in the prevalence of zinc deficiency between treatment and control communities (or individuals) is due to other factors, such as confounding factors or biases, or to chance alone. Probability designs are the reference standard of efficacy* research; they require randomized, double-blind, placebo-controlled designs, which are the only types of designs that can be used to establish causality.

Table 3.8 summarizes the types of intervention designs that can be applied to achieve these different levels of inferences for impact evaluations of zinc interventions. For more details and for examples of designs to address other evaluation objectives (provision, utilization, and coverage), see Habicht, Victora, and Vaughan [95].

Additional discussions on the choice of evaluation designs and indicators and on the design and implementation of monitoring and evaluation systems can be found in several published documents on monitoring and evaluation [92, 94] and in the vitamin A literature [96, 97].

3.7 Summary

Three possible direct approaches may be taken to improve zinc intakes in whole populations or particular subgroups that are at risk of zinc deficiency: supplementation, fortification, and dietary modification/diversification. Given the small amount of programmatic experience to date in the control of zinc deficiency, research efforts need to be directed toward the study of the efficacy, effectiveness, cost-effectiveness, and acceptability of different strategic approaches. A considerable amount of research is still required to produce the necessary scientific evidence for designing effective interventions.

Although there is much experience with zinc supplementation in small-scale, controlled research trials, there is as yet very limited experience in ongoing, large-scale supplementation programs that include zinc. Nevertheless, a series of specific recommendations have been proposed for zinc supplementation programs, based on currently available information. For example, research suggests that soluble forms of zinc salts (e.g., zinc acetate, zinc sulfate, zinc gluconate) should be used in the supplement formulation, that the supplements should be administered between meals to maximize absorption, and that the supplements should be offered daily. Suggested daily dosage levels for supplemental zinc have been derived (table 3.2), considering the IZiNCG RDAs, the NOAELs or upper limits for zinc intake, and dosage levels used in controlled trials of zinc supplementation that are considered to be effective and have no apparent adverse clinical effects. In areas or subgroups that may be at risk of low copper status, it is recommended to include copper in the zinc supplement (zinc:copper molar ratio 10:1, to a maximum of 1 mg/day copper), so as to minimize the possible risk of altered copper metabolism. Supplemental zinc is also recommended as an adjunct therapy during the treatment of diarrhea in children, where the recommended daily dosage is equivalent to two times the age-specific RDA, for 14 days. Direct studies are needed to better define the optimal doses (amount, frequency, and duration) of zinc supplements for different age and physiologic status groups, and the implications on dosage levels of modifying the method of administration, such as giving the supplement with or between meals and combining zinc with other micronutrients in the supplement. The effects of different chemical and physical forms of supplements on zinc absorption and the cost, shelf life, and acceptability of the supplement also require evaluation. Cultural and behavioral factors that influence adherence to the proposed dosage schedules should also be assessed, and studies are needed of the effectiveness and efficiency of different distribution systems.

Experience with the fortification of foods with zinc is, at present, largely represented by the fortification of infant formulas, infant cereals, and ready-to-eat breakfast cereals. Several Latin American countries are using or have used centrally processed complementary foods fortified with multiple micronutrients, including zinc. Mexico currently has a national, voluntary fortification program for wheat and lime-processed corn flours (the efficacy of this program in preventing zinc deficiency in Mexico has not yet been evaluated). It is recommended that the selected food vehicle for zinc fortification be one that is widely consumed in stable and predictable amounts, and that it is processed on a reasonably large scale to permit adequate quality control. Further, its organoleptic properties should not be affected by the

* An efficacy trial is one that applies an intervention under controlled conditions to determine the magnitude of effect that can be achieved under the best possible circumstances [93].

addition of zinc fortificants and it should be able to retain appropriate levels of the zinc fortificant during processing, storage, and preparation. Examples of candidate zinc fortification vehicles include rice, wheat, and maize or condiments such as salt or fish sauce. Selection of the fortificant form of zinc should take into consideration its acceptance for use (e.g., listed as GRAS by the US Food and Drug Administration), its solubility, lack of effect on organoleptic properties of the food vehicle, and cost. Both zinc oxide and zinc sulfate are relatively inexpensive and have been used as zinc fortificants. Zinc oxide may be less well absorbed in humans than zinc sulfate because it is not water-soluble, although current evidence suggests that zinc absorption from these two fortificants does not differ appreciably. Nevertheless, this needs to be confirmed in additional human studies in populations with high rates of enteropathy and/or hypochlorhydria. Although the appropriate level of zinc fortificant to be added to a food vehicle should be assessed in each specific case, a suggested range for fortification of cereal staples is 30–70 mg zinc per kg of flour. Further information is required on the absorption of zinc, sensory acceptability, shelf life, and final product cost, when different chemical forms of zinc are added to different food vehicles. The latter studies should also consider these outcomes when zinc is included with other micronutrient fortificants to take possible interactions into account. Studies of both the efficacy and effectiveness of fortified food products, including fortified complementary foods, in improving zinc status are needed.

There are several possible strategies for increasing the intake of total zinc and/or absorption of zinc from the diet. These include the following: (1) agricultural strategies to increase the total zinc content, or decrease the content of phytate, of staple food crops using zinc fertilizers, plant breeding, or genetic modification techniques; (2) community or home-based strategies to increase the production and/or intake of zinc-rich foods, such as through promotion of small-livestock production, aquaculture, indigenous zinc-rich foods or processed snacks; and (3) household food processing methods to increase the amount of absorbable zinc in the diet. Examples of household food processing techniques include germination, fermentation, or soaking procedures to reduce the phytate content of cereals or legumes. Experience with these strategies in intervention studies or small-scale programs is still limited. All possible dietary diversification/modification strategies need to be evaluated in terms of their efficacy, acceptability, effectiveness, and cost-effectiveness. In addition, agricultural methods to increase the zinc content of foods and/or improve zinc absorption from foods need to be evaluated in terms of their possible economic and environmental impact.

All of the program options for improving zinc intakes would benefit from the use of formative research, because all methods require some degree of behavior change. Qualitative methods already developed for use in other health and nutrition programs may be adapted and applied to improve the effectiveness of zinc interventions.

Given the likelihood of the coexistence of several micronutrient deficiencies, intervention programs to address zinc deficiency should be linked to programs that address other problem micronutrients to make more efficient use of resources. Intervention programs that address other health issues may also be used as opportunities to include the delivery of zinc-related interventions. Some of the many possibilities, as summarized in table 3.6, include incorporation of nutrition education to improve intakes of dietary zinc in child health and nutrition prevention programs (e.g., growth-monitoring clinics, programs to promote exclusive breastfeeding, improved complementary feeding practices, or improved hygiene practices); inclusion of supplemental zinc in diarrhea treatment programs; inclusion of supplemental zinc where other micronutrient or food supplements are distributed; and inclusion of zinc in fortification programs with other micronutrients.

As with all program interventions, monitoring and evaluation activities should be included in zinc intervention programs. Several indicators can be incorporated into these activities for all types of program strategies. Examples of possible indicators include evaluation of the provision of services, the utilization of services, the coverage of the program in the target population, and its impact on population zinc status or other functional outcomes (table 3.7).

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