Iron Fortification and Iron Supplementation are Cost-Effective Interventions to Reduce Iron Deficiency in Four Subregions of the World[1]

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ABSTRACT Iron deficiency is the most common and widespread nutritional disorder in the world, affecting millions of people in both nonindustrialized and industrialized countries. We estimated the costs, effects, and cost-effectiveness of iron supplementation and iron fortification interventions in 4 regions of the world. The effects on population health were arrived at by using a population model designed to estimate the lifelong impact of iron supplementation or iron fortification on individuals benefiting from such interventions. The population model took into consideration effectiveness, patient adherence, and geographic coverage. Costs were based on primary data collection and on a review of the literature. At 95% geographic coverage, iron supplementation has a larger impact on population health than iron fortification. Iron supplementation would avert <12,500 disability adjusted life years (DALY) annually in the European subregion, with very low rates of adult and child mortality, to almost 2.5 million DALYs in the African and Southeast Asian subregions, with high rates of adult and child mortality. On the other hand, fortification is less costly than supplementation and appears to be more cost effective than iron supplementation, regardless of the geographic coverage of fortification. We conclude that iron fortification is economically more attractive than iron supplementation. However, spending the extra resources to implement iron supplementation is still a cost-effective option. The results should be interpreted with caution, because evidence of intervention effectiveness predominantly relates to small-scale efficacy trials, which may not reflect the actual effect under expected conditions. J. Nutr. 134: 2678–2684, 2004.

KEY WORDS: • *economic evaluation* • *cost analysis* • *maternal health* • *iron deficiency* • *anemia*

According to the WHO, iron deficiency is the most common nutritional disorder in the world. Iron deficiency and its anemia affect >3.5 billion people in the developing world, well over two persons out of every three (1). Iron-deficiency anemia (IDA)[3] is associated with significantly poorer performance on psychomotor and mental development scales and behavioral ratings in infants, lower scores on cognitive function tests in preschool children, lower scores in cognitive function tests and educational achievement tests in school-age children (2–4), and poor pregnancy outcome (5). Furthermore, IDA is associated with low work productivity in adults (6). Young children and pregnant and postpartum women are most commonly and severely affected by IDA because of the high iron demands of infant growth and pregnancy. Mental retardation and maternal and perinatal mortality are regarded as the most severe outcomes of IDA (7).

Current WHO and UNICEF guidelines recommend that interventions for the prevention and the control of iron deficiency should follow an integrated, long-term approach. IDA must be addressed by a multidisciplinary approach, including the following elements: *1*) increased iron intake (i.e., iron-rich diets, increasing iron absorption, and iron and folate supplements, fortification of wheat flour and other complementary foods with iron and other micronutrients, where appropriate); *2*) infection control (i.e., public health measures to control hookworm infections, malaria, and schistosomiasis); *3*) improved nutritional status (i.e., control of major nutrient deficiencies, diet diversification, and infection prevention) (2,7).

There is clear evidence of the importance of investing in nutritional interventions to reduce mortalities and morbidities [e.g. (8,9)], and to reduce the economic impact of IDA. A cost-of-illness study has shown that cognitive delays in children, lower productivity among adults, and premature births as a result of IDA may lead to significant productivity losses (10–14). Illustrative calculations for 10 developing countries by Horton and Ross (14) suggest that the median value of annual physical productivity losses due to iron deficiency is about US$0.32 per capita, or 0.57% of the gross domestic product (GDP). The benefit:cost ratio for long-term iron fortification programs would range from 6:1 to 36:1, the latter including the discounted future benefits attributable to cognitive improvements. Also, the Asian Development Bank found its benefits, in terms of reduced lost productivity, compare favorably with its costs (15).

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[1] A full list of subregions and included countries, as well as detailed cost figures, are available with the online posting of this paper at www.nutrition.org.

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[3] Abbreviations used: AfrD: African subregion with very high rates of adult and child mortality; CEA: cost-effectiveness analysis; DALY: disability adjusted life year; GDP: gross domestic product; I$: international dollar; IDA: iron-deficiency anemia; WHO-CHOICE: WHO—Choosing Interventions that are Cost Effective.

0022-3166/04 $8.00 © 2004 American Society for Nutritional Sciences.

Manuscript received 18 March 2004. Initial review completed 24 May 2004. Revision accepted 23 June 2004.

Supplemental Material can be found at:
http://jn.nutrition.org/cgi/content/full/134/10/2678/DC1

We examined the cost-effectiveness of iron fortification and of iron supplementation in iron-deficiency control in four subregions of the world; other public health measures are not included in the analysis. Costs and effects were evaluated by using a modeling approach, based upon primary data collection and a review of the literature. The analysis reported upon in this paper is based on the impact of interventions to prevent maternal and perinatal mortality only. The analysis of the impact of interventions on intellectual and mental development is beyond the scope of this paper.

We did not aim to express health benefits of iron-deficiency control in monetary terms, thereby avoiding its many methodological pitfalls (16–17). Rather, we followed standard practice in the economic evaluation of health programs by performing cost-effectiveness analysis (CEA) and by expressing outcomes in health gains, i.e., disability adjusted life years (DALY) averted (16–18). This also facilitates a comparison of the economic attractiveness of iron-deficiency control with other interventions, e.g., subjected to analysis in the WHO-CHOICE (CHOosing Interventions that are Cost Effective) program[4] (18).

METHODS

Overview of cost-effectiveness analysis

CEA in health aims to inform policy makers and decision makers on the economic attractiveness (or returns on investment) of interventions to reduce disease-related mortality and morbidity. By assessing costs and effectiveness of an intervention, a "value for money" estimate is provided. The cost-effectiveness of a given intervention is typically expressed as costs per unit of effectiveness, with costs measured in monetary terms and effectiveness measured in health metrics terms. Health metrics measure the impact of an intervention on the quality of life (morbidity) and length of life (mortality) of a population and express this as a single number such as a quality adjusted life year (17) or DALY (19). Interventions with a favorable cost-effectiveness ratio (e.g., low US$ per DALY) are said to be eligible for implementation, at least in economic terms.

CEA can be undertaken in many ways, and there have been several attempts to develop methodological guidelines to make results more comparable. WHO has developed a standardized set of methods and tools that can be used to analyze the societal costs and effectiveness of current and possible new interventions simultaneously (18,20). The WHO-CHOICE project is designed to provide regularly updated databases on the costs and the effects of a full range of promotive, preventive, curative, and rehabilitative health interventions.

Regions analyzed

Most countries do not have the capacity to evaluate all potential interventions aimed at improving given health indicators at the national and the subnational level, and global estimates are too general and of little use to any specific country. However, countries may benefit from regional evaluations of data, where data of neighboring countries with similar settings are pooled. The present analysis drew on a comprehensive examination of 14 world subregions defined by geographic proximity and epidemiology according to WHO classification. This paper only presents results for four regions selected on the basis of their diverse epidemiological patterns. The four subregions are the African subregion with high rates of adult and child mortality (AfrD), the South American subregion with low adult and child mortality (AmrB), the European subregion with low adult and very low child mortality (EURA), and the Southeast Asian subregion with high rates of adult and child mortality (SearD). A full list of subregions and included countries is available in Supplemental Table 1. Full results for all regions are available at the WHO Web site (21).

Iron supplementation and iron fortification

We estimated the cost-effectiveness of iron supplementation and iron fortification programs, each at geographic coverage levels of 50, 80, and 95%.[5]

Iron supplementation. It is becoming increasingly clear that the main target group for iron supplementation should be all women of reproductive age, leading to adequate reserves for mother and fetus during pregnancy (22). In this analysis, iron supplementation involves the provision of iron to pregnant women during antenatal visits. The assumed dose follows WHO guidelines, with daily supplementation of 60 mg elemental iron given to pregnant women for 6 mo during pregnancy, and for 3 mo postpartum (22). The effectiveness estimates of iron supplementation interventions as applied in our analysis were based on a thorough review of the burden of disease attributable to iron deficiency by Stoltzfus et al. (5) for the same 14 world subregions as applied in the analysis. For the epidemiological subregion AfrD, for example, Stoltzfus et al. (5) reported that iron deficiency contributes to 22% of all maternal mortality in women between 30 and 44 y, and to 33% of all perinatal mortality. For the purposes of this analysis, we therefore assumed that the maximum attainable health effects in women between 30 and 44 y of any iron supplementation intervention in subregion AfrD are an annual reduction of maternal mortality of 22% and of perinatal mortality of 33%. The effectiveness of iron supplementation intervention is reduced by the following: *1*) the assumed suboptimal geographic coverage level, i.e., not all pregnant women receive iron supplementation; and *2*) noncompliance to the full iron supplement regimen. Reasons for noncompliance with iron-deficiency treatment include inadequate program support (such as lack of financial support), insufficient service delivery (such as lack of supplies), and patient factors (such as misunderstanding instructions, side effects, or frustration about the frequency and the number of pills taken). Galloway and McGuire (23) estimated that noncompliance reduces the number of women with sufficient iron intake and therefore the maximum attainable health effects of iron supplementation by 33%.

Iron fortification. Iron fortification involves the addition of iron, usually with folic acid, to an appropriate food vehicle that is made available to the population at large. Cereal flour is the most common food vehicle but others, such as noodles, rice, and various sauces, have also been used (7). The present CEA is based on the addition of elemental iron powders to cereal flours. Elemental iron powders have been used for this purpose for >50 y and continue to be the most widely used iron compound (24). They have the advantage of causing few, if any, color and flavor problems in stored food vehicles. They are inexpensive and suitable for fortification of staple foods, such as wheat flour and maize flour. The analysis is based on the use of electrolytic iron ($<45\ \mu$m, 325 mesh) of which evidence suggests that it should be a useful iron fortificant (23).

There have been very few trials of either efficacy or effectiveness of iron fortification for improving iron status. In industrialized countries with high bioavailability diets, this strategy has been assumed to have a beneficial effect on iron status. In populations consuming low bioavailability diets, such as those consumed in many developing country contexts, there is some evidence of benefit, as reviewed by Allen and Gillespie (25) and also suggested in recent studies (26–28). However, the benefit may be much less, and much greater amounts of fortification may have to be added (24). For that reason, the maximum attainable health effects of fortification were considered to be

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[4] WHO seeks to provide the evidence decision makers need to set priorities and to improve the performance of their health systems. The Global Programme on Evidence for Health Policy is assembling regional databases on the costs, impact on population health, and cost-effectiveness of key health interventions. This work, known as WHO-CHOICE, started in 1998 with the development of standard tools and methods. The objectives of WHO-CHOICE are to develop a standardized method for cost-effectiveness analysis that can be applied to all interventions in different settings; to develop and disseminate tools required to assess intervention costs and impacts at the population level; to determine the costs and effectiveness of a wide range of health interventions, presented with probabilistic uncertainty analysis; to summarize the results in regional databases that will be available on the Internet; and to assist policy makers and other stakeholders to interpret and use the evidence.

[5] These coverage levels do not specifically relate to current or attainable levels for iron-deficiency control, but are standardized in WHO-CHOICE analyses to foster comparability between study results.

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TABLE 1

Calculation of maternal and perinatal mortality rates in baseline and intervention scenarios[1]

	Baseline scenario						Intervention scenario: iron supplementation at 95% coverage				
	Currently observed rate	Maximum attainable reduction of mortality[2]	Coverage of current program	Compliance to current program	Net impact of current program	Baseline mortality rate	Maximum attainable reduction of mortality[2]	Coverage	Compliance	% Reduction	Intervention mortality rate
	(1)	(2)	(3)	(4)	(5) = (2)*(3)*(4)	(6) = (1)*[1 + (5)]	(7)	(8)	(9)	(10) = (7)*(8)*(9)	(11) = (6)*[1 − (10)]
		%					%				
Maternal mortality, 30–44 y											
AfrD	0.0121	22	20	67	3	0.0124	22	95	67	14	0.0107
AmrB	0.0026	15	50	67	5	0.0027	15	95	67	10	0.0025
EurA	0.0000	10	80	67	6	0.0000	10	95	67	7	0.0000
SearD	0.0049	29	50	67	10	0.0053	29	95	67	19	0.0043
Perinatal mortality											
AfrD	0.0447	33	20	67	4	0.0466	33	95	67	21	0.0369
AmrB	0.0086	12	50	67	4	0.0089	12	95	67	7	0.0083
EurA	0.0019	8	80	67	4	0.0020	8	95	67	5	0.0019
SearD	0.0301	23	50	67	8	0.0325	23	95	67	15	0.0277

[1] AfrD, African subregion with very high adult and high child mortality; AmrB, South American subregion with low adult and child mortality; EurA, the European subregion with low adult and very low child mortality; SearD, Southeast Asian subregion with high rates of adult and child mortality.

[2] In case of an optimal iron supplementation program, based on Stoltzfus et al. (5).

only 50% of those of supplementation (personal communication, R. Stoltzfus, Cornell University). As in iron supplementation, the effectiveness of iron fortification at the population level was further reduced for two reasons. Firstly, we explored the costs and effects in the event that fortification reaches various suboptimal geographic coverage levels. Second, within these coverage levels, only a limited proportion of the population consumes the food vehicle in sufficient quantities to absorb sufficient iron levels of the targeted population.

Estimating population health effects

The effects on population health were arrived at by using a population model designed to estimate the lifelong impact of iron supplementation or iron fortification on individuals benefiting from such interventions. The model simulated the health of a population over time and allows individuals to be categorized into one of the following three mutually exclusive health states: pregnant, nonpregnant, and dead. Depending on parameters, such as fertility, maternal mortality, and perinatal mortality, individuals moved between these states. In our analysis, the baseline scenario was of a population devoid of any iron-deficiency control (20). In the intervention scenario, a single intervention was introduced, reducing the maternal and perinatal mortality rates and allowing the overall population health to improve. Differences in population health estimates between the baseline and the intervention scenario were considered a measure of intervention effectiveness, expressed in DALYs.

Baseline scenario. To establish the baseline scenario, population health in the absence of any iron-deficiency control program needs to be assessed. Therefore, the effects of any preexisting iron interventions should be removed, thereby increasing the currently observed maternal and perinatal mortality rates in each of the 14 global burden of disease subregions (19). The increase was based on the assumed effectiveness of iron supplementation programs (**Table 1**). In this scenario, we assumed that no effective iron fortification intervention exists.

For example, in subregion AfrD, the current maternal mortality rate for 30–44 y olds is 1210 per 100,000 live births, in the presence of an iron supplementation program at an assumed geographic coverage rate of 20% and an assumed adherence of 67% (23). In AfrD region, an optimal iron-deficiency program would reduce maternal mortality by 22%. The baseline maternal mortality rate, in the absence of any iron-deficiency program, would then be 1240 per 100,000 live births.[6] Baseline perinatal mortality rates were calculated in the same way. Population health in the baseline scenario was then estimated by running the disease model with baseline maternal and perinatal mortality rates.

Intervention scenarios. The present analysis provides estimates for six different intervention scenarios: iron supplementation and iron fortification, separately, each at geographic coverage rates of 50, 80, and 95%. The introduction of iron supplementation and iron fortification interventions decreases the baseline maternal and perinatal mortality rates with the extent of reduction being equal to the effectiveness of the interventions, as illustrated above (Table 1). In subregion AfrD, e.g., the baseline maternal mortality rate is 1240 per 100,000 live births. As stated above, an optimal iron supplementation program would reduce maternal mortality with 22%. The intervention, with an assumed 67% adherence (23), would lead to a maternal mortality rate of 1070 per 100,000 live births.[7] Intervention perinatal mortality rates were calculated in the same way. Population health in the intervention scenario was then estimated by running the disease model by using these intervention-specific maternal and perinatal mortality rates.

Estimating costs

Costs of all interventions are reported in international dollars (I$) to facilitate more meaningful comparisons across regions. The WHO guide to cost-effectiveness analysis (18) provides more detail. The base year is 2000.

Iron supplementation. Patient-level costs for iron supplementation include provision of iron to pregnant women during 4 antenatal visits at the primary health care facility. For the women who currently attend antenatal clinics, iron supplementation was assumed to add only five additional min to the 15 min that antenatal visits last. In other words, costs of 4 × 1/3 visit (1.33 visit) were included if iron supplementation was evaluated at a coverage level equal to or smaller than that of antenatal care in a certain region. Antenatal care coverage was based on WHO estimates (**Table 2**). For the women who do not currently attend antenatal clinics, the full 15 min of the 4 visits were included. In other words, for iron supplementation

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[6] Calculated as [0.0121 × (1 + 20% × 67% × 22%)].

[7] Calculated as [0.0124/(1 + 22% × 5% × 7%)].

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coverage levels beyond that of antenatal care in a certain region, the costs of 4 visits were included. Health facility unit cost estimates were based on an econometric analysis of a large number of hospital costing studies, reported in Adam et al. (29).

Costs of iron were estimated by following WHO guidelines on iron supplementation interventions, with daily doses of 60 mg elemental iron, for 6 mo during pregnancy, and for 3 mo postpartum (21) (Table 1). Drugs prices for A regions were retrieved from a Web-based drugstore (30); prices for other regions were retrieved from the International Drug Price Indicator (31). All prices were adjusted for regional transportation costs (32).

Iron supplementation interventions also use limited resource inputs at a level above that of the patient or the providing facility, for employing program managers at the central administration at the national level, for activities such as training, health nutrition education, and supervision (Table 2). These are labeled program-level costs. Estimated quantities of resources required to start up and then to maintain each intervention for 10 y at national, provincial, and district levels were based on a series of evaluations made by regional costing teams in the different WHO subregions and validated against the literature (categories of resource input included personnel, materials and supplies, media, transport, maintenance, utilities, and capital). Details are available in Supplemental Table 2. Unit costs estimates of program-level resource inputs, such as the salaries of central administrators, capital costs of vehicles, storage costs, offices, and furniture were obtained from a review of literature and were supplemented by primary data from several countries [the full list of unit cost estimates is available at the WHO Web site (21)]. The process and the methodology to estimate program costs have been described in detail in Johns et al. (32).

Iron fortification. Industry production costs of fortified flour were based on estimates provided by the U.S. Agency for International Development Micronutrient Program (33), including costs for scales, dosifiers and electrolytic iron fortificant. Details are available in Supplemental Table 3. The number of beneficiaries was estimated using regional population sizes and assumptions on access to fortified food (**Table 3**). Program costs at the national, provincial and districts levels include management, legislation, health nutrition education and supervision costs and were estimated in the same way as the iron supplementation intervention. Details are available in Supplemental Table 4. Average annual costs per beneficiary varied between I$0.06 and I$0.15 (Table 3).

When scaling-up iron supplementation and iron fortification interventions, the cost per beneficiary may decrease with increasing coverage because of economies of scale (e.g., shared mass media costs at the national level) or may increase because of diseconomies of scale (e.g., increased management costs per beneficiary in less populous remote areas). The approach is described in detail in Johns et al. (32).

Uncertainty analysis

Estimates of the cost-effectiveness of interventions are subject to uncertainty. This can be uncertainty related to the model structure or uncertainty related to the exact values of the input data. Uncertainty analysis in CEA has been developed as a tool to assess the impact of uncertainty on study results and therefore study conclusions. In the present study, uncertainty analysis were undertaken to consider how uncertainty of epidemiological, effectiveness, and cost parameters translates into uncertainty in the cost-effectiveness ratio. High and low estimates of maternal and perinatal mortality were defined as ±25% of the baseline values. Impacts of different interventions and costs were also varied ±25%.

RESULTS

The findings indicate that, in general, iron supplementation has a larger impact on population health than fortification (**Table 4**). Iron supplementation would avert <12,500 DALYs per year in the European subregion and almost 2.5 million DALYs in the African as well as in the Southeast Asian subregion. On the other hand, fortification is less costly than supplementation because it does not require a visit to a provider and the unit cost of supplementation increases sharply with increasing coverage.

The Commission on Macroeconomics and Health recently defined interventions that have a cost-effectiveness of less than three times GDP per capita as cost effective (34). All 6 interventions in the 4 regions are cost-effective according to this criterion. The cost-effectiveness of fortification is always lower than the cost-effectiveness of supplementation, regardless of the coverage of fortification. Therefore, in terms of cost-effectiveness, fortifi-

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TABLE 2

Annual costs of iron supplementation at 95% coverage (I$)[1]

Region	Patient level costs									
	Annual number of pregnant women receiving iron supplementation[3]	Coverage of antenatal care[4]	Cost per outpatient visit, at 95% coverage[5]	Total costs outpatient visits[2]	Costs of drugs[6]	Cost per recipient	Total costs[7]	Program level costs[7]	Patient and program level costs	Cost per pregnant women
	(1)	(2)	(3)	(4)	(5)	(6) = (4) + (5)	(7) = (1)*(6)	(8)	(9) = (7) + (8)	(10) = (9)/(1)
		%	I$							
AfrD	10,998,697	55	6.84	14.97	1.14	16.10	177,123,892	5,351,324	182,475,216	16.59
AmrB	8,623,181	71	9.90	19.88	0.90	20.78	179,193,221	5,241,404	184,434,625	21.39
EurA	4,068,145	95	25.13	33.09	12.96	46.04	187,309,461	16,766,683	204,076,144	50.16
SearD	31,597,515	57	3.85	9.25	0.87	10.12	319,741,462	9,448,557	329,190,020	10.42

[1] AfrD, African subregion with very high adult and high child mortality; AmrB, South American subregion with low adult and child mortality; EurA, the European subregion with low adult and very low child mortality; SearD, Southeast Asian subregion with high rates of adult and child mortality.

[2] For coverage levels < coverage of antenatal care, 1.33 outpatient visit is included (4 × 1/3 visit); For coverage levels > coverage of antenatal care, 4 full outpatient visit are included.

[3] Equal to 95% of annual region specific number of life-births.

[4] As percentage of women having at least one antenatal care visit during pregnancy.

[5] Costs vary with coverage rate. For derivation, see Adam et al. (29).

[6] See text for sources and derivation.

[7] Costs figure is for single year. Costs vary over implementation period of 10 y and are discounted.

TABLE 3

Annual costs of iron fortification at 95% coverage[1]

Region	Industry level costs					Program level costs[2]	Industry and program level costs	Cost per beneficiary
	Total population	Access to fortified food	Beneficiaries	Industry level cost per beneficiary[2]	Total costs			
	(1)	(2)	(3) = (1) × (2)	(4)	(5) = (3) × (4)	(6)	(7) = (5) + (6)	(8) = (7)/(3)
		%			*I$*	*I$*	*I$*	
AfrD	334,580,563	60	190,710,921	0.009	1,684,893	23,203,578	24,888,471	0.13
AmrB	442,130,339	75	315,017,867	0.007	2,211,272	18,919,306	21,130,578	0.07
EurA	411,889,100	95	371,729,913	0.006	2,206,671	53,918,268	56,124,939	0.15
SearD	1,334,810,348	60	760,841,898	0.007	5,172,913	39,023,844	44,196,757	0.06

[1] AfrD, African subregion with very high adult and high child mortality; AmrB, South American subregion with low adult and child mortality; EurA, the European subregion with low adult and very low child mortality; SearD, Southeast Asian subregion with high rates of adult and child mortality.

[2] See text for sources and derivation.

cation should be the preferred option, especially in settings where there are low levels of resource availability.

However, in scenarios where more resources were to become available, the question of whether the extra resources should be spent on achieving higher coverage levels merits exploration. To answer this question, the extra costs and effects of implementing more costly but also more effective interventions were compared and were summarized in incremental cost-effectiveness ratios (**Table 5**). In all 4 regions, the overall pattern was similar. In settings of extreme resource constraints, iron fortification is the preferred option. The incremental cost-effectiveness ratios for iron supplementation were still below the criterion of 3 × GDP, indicating that spending the extra resources to implement iron supplementation is still a cost-effective option, independent of coverage level.

Uncertainty analysis focusing on the impact of varying assumptions about epidemiology, costs, and intervention ef-

TABLE 4

Annualized costs, annual effects and average cost-effectiveness of iron deficiency control in 4 regions[1]

Intervention	AfrD	AmrB	EurA	SearD
Costs	*I$*	*I$*	*I$*	*I$*
Iron supplementation				
50%	$ 38,164,705	$ 63,385,379	$100,696,296	$ 91,685,848
80%	$119,875,245	$116,771,583	$153,062,840	$214,686,470
95%	$159,095,817	$165,492,669	$179,225,469	$286,217,588
Iron fortification				
50%	$ 15,464,385	$ 15,594,183	$ 35,273,367	$ 25,035,878
80%	$ 19,192,967	$ 16,510,432	$ 41,649,470	$ 30,155,000
95%	$ 21,867,282	$ 18,565,556	$ 49,311,983	$ 38,831,752
Effects	*DALYs averted*	*DALYs averted*	*DALYs averted*	*DALYs averted*
Iron supplementation				
50%	1,274,974	130.202	6.569	1,311,084
80%	2,039,959	208.323	10.511	2,097,734
95%	2,422,451	247.383	12.482	2,491,059
Iron fortification				
50%	570,884	72.874	4.657	587,052
80%	913,414	116.599	7.452	939,284
95%	1,084,680	138.461	8.849	1,115,400
Average cost-effectiveness	*I$ per DALY averted*	*I$ per DALY averted*	*I$ per DALY averted*	*I$ per DALY averted*
Iron supplementation				
50%	$ 30	$ 487	$ 15,328	$ 70
80%	$ 59	$ 561	$ 14,562	$ 102
95%	$ 66	$ 669	$ 14,359	$ 115
Iron fortification				
50%	$ 27	$ 214	$ 7,574	$ 43
80%	$ 21	$ 142	$ 5,589	$ 32
95%	$ 20	$ 134	$ 5,573	$ 35

[1] AfrD, African subregion with very high adult and high child mortality; AmrB, South American subregion with low adult and child mortality; EurA, the European subregion with low adult and very low child mortality; SearD, Southeast Asian subregion with high rates of adult and child mortality.

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TABLE 5

Incremental cost-effectiveness of iron deficiency control in selected regions[1,2]

Intervention	AfrD	AmrB	EurA	SearD
Cost-effectiveness	*I$ per DALY averted*			
Iron fortification 50–80%	dominated	dominated	dominated	32
Iron fortification 80–95%	20	134	5,573	49
Iron fortification 95% to iron supplementation 50%	86	dominated	dominated	dominated
Iron supplementation 50–80%	dominated	dominated	dominated	179[3]
Iron supplementation 80–95%	105[4]	1349[5]	35,762[4]	182

[1] AfrD, African subregion with very high adult and high child mortality; AmrB, South American subregion with low adult and child mortality; EurA, the European subregion with low adult and very low child mortality; SearD, Southeast Asian subregion with high rates of adult and child mortality.

[2] Incremental ratios are calculated by comparing costs and effects of interventions to their cheaper alternatives.

[3] Incremental from iron fortification at 95% to iron supplementation at 80%.

[4] Incremental from iron supplementation at 50–95%.

[5] Incremental from iron fortification at 95% to iron supplementation at 95%.

fectiveness revealed that the results were quite robust to variation in the model parameters within ±25%. The mean cost-effectiveness ratios for different strategies could, in some cases, vary by a factor of almost 2 between the high and low estimates. For example, in AfrD, if iron fortification is assumed not to be 50% but 37.5% as effective as iron supplementation, the cost-effectiveness of this intervention at 50% coverage level changes from I$27 to I$36 per DALY averted. In case iron fortification is assumed to be 62.5% as effective as iron supplementation, the cost-effectiveness changes to I$21 per DALY averted. However, the overall conclusion, that the wide range of interventions examined here would have attractive cost-effective ratios, remained largely unchanged under varying assumptions in the models.

DISCUSSION

The findings show that iron fortification has the lowest cost-effectiveness ratio and is from the economic point of view most attractive. However, one of the key processes in developing a fortification program is choosing a suitable food vehicle. This can be a challenge, especially in countries with large rural populations, with a small food industry with limited technology, and with limited access to and low consumption of processed foods. Moreover, consumption of fortified foods is generally limited to the middle- and high-income groups who are not always at greatest risk of micronutrient deficiencies. Key factors in the selection of the right food vehicle include that the vehicle must be consumed regularly and in predictable amounts, and must be affordable by the target population; it must be processed in large central mills so that quality control can be effectively implemented; the fortified food does not undergo changes in color, taste, or appearance as a result of the addition of these micronutrients; and the stability and bioavailability of the micronutrients added to the food must remain high under standard local conditions of storage and use (2,35). Present study results are based on several assumptions that should be accounted for before iron fortification programs can be implemented on a large-scale. Furthermore, the present analysis is based on the use of electrolytic iron as fortificant, but there is no consensus in the scientific community whether this is indeed the best option (24). Other fortificants have been suggested, such as ferrous fumarate or ferrous sulfate, which are more costly but also more bioavailable (24).

In settings where people's diets are not based around cereal flours or another convenient food vehicle, supplementation is still a cost-effective option. Indeed, in areas with a high prevalence of IDA, it would be very cost effective to spend the higher amounts on supplementation to achieve greater population benefits. It is less cost-effective to apply this option in areas where the burden from IDA is relatively low. Since the cost-effectiveness of switching from fortification to supplementation is below 3 × GDP per capita, it falls into the band of cost-effective interventions.

The analysis used several conservative assumptions to model the population health effects and costs of iron-deficiency control. The cost-effectiveness ratios thus obtained can also be interpreted as conservative estimates. First, the impact of iron-deficiency control programs on maternal and perinatal mortality were derived from the attributable burden of iron deficiency, as reported by Stoltzfus et al. (5). Their estimates are based on predicted shifts of the hemoglobin level that are somewhat lower than the average hemoglobin level response of pregnant women to iron supplementation in the trials summarized by Sloan et al. (36) [the latter reported shifts of 8.5–11.7 g/L, whereas Stoltzfus et al. (5) estimated shifts of 6.5 g/L in AfrD]. Consequently, resulting reductions in maternal and perinatal mortality rates can be considered to be conservative estimates. Second, recent studies have shown that the recommended daily intake of 60 mg is greatly in excess of the actual requirement for replenishing pregnant women with iron deficiency in very deficient populations (37). This would mean that iron supplementation could be provided at less cost if the period of the regimen is shortened or the quantity of drugs is reduced. Third, patient adherence to iron supplementation was assumed to be 67% in this analysis. This is a conservative assumption, considering that adherence values previously reported range from 55 to 96%, with the median in the higher end of these values (23). Fourth, while many other groups in the population are likely to benefit from iron fortification, the disease model only considered the impact of iron fortification on pregnant women. IDA in pregnant women probably accounts for >95% of total deaths averted from fortification, but some deaths in the rest of the population are also likely to be averted. Fifth, the analysis reported upon in this paper is based on the impact of interventions to prevent maternal and perinatal mortality only, and did not include the gains related to the impact of interventions on intellectual and mental development.

On the other hand, the present analysis may have overestimated the health gains from iron-deficiency control because effectiveness estimates of iron supplementation and iron fortification programs were based on data stemming from

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(mainly) small efficacy trials. There remains a significant gap between the efficacy and the effectiveness of programs at controlling iron-deficiency programs among pregnant women, as most large-scale iron supplementation programs have not been evaluated with respect to impact. Allen and Gillespie (25) listed the main operational constraints in large-scale programs: inefficient and irregular supply, procurement and distribution of supplements; low accessibility and utilization of antenatal care by pregnant women; inadequate training and motivation of frontline health workers; inadequate counseling of mothers; and low compliance of the intended beneficiaries with the supplementation regimens. Many of these deficiencies can be avoided or rectified in supervised clinical trials but, in the real world, small trail efficacy does not readily translate into large-scale program effectiveness. Our study results should be carefully interpreted in the context and are conditional on the assumption that efficacy gains also translate into effectiveness gains, although we did adjust for noncompliance and suboptimal geographic coverage.

In the absence of empirical data, the present study made several assumptions on the current coverage of iron-deficiency control interventions and accessibility to fortified food. Also, in the absence of sound evidence on the effectiveness of iron fortification, the present study assumed fortification to be 50% less effective than supplementation. More research is needed to substantiate this and other model assumptions. However, by using varying assumptions, uncertainty analyses showed that cost-effectiveness estimates were robust to variation in the model parameters. Study conclusions can thus be maintained, even in the presence of uncertainty about several assumptions.

The results of the analysis are presented at the regional level, by using regional resource utilization and epidemiological patterns. While, epidemiological patterns are generally homogeneous between countries in a certain region, resource utilization patterns are expected to vary.

The findings of this study can be used to inform resource allocation decisions in iron-deficiency control in a wide range of countries. Policy makers who wish to extrapolate the results to their own decision-making context should assess whether quantities and costs of the various inputs are also applicable to individual settings. They should then make necessary adjustments to these estimates and calculate cost-effectiveness ratios that are tailored specifically to their individual context. The models used for the calculation of costs and effects, including the raw input data, are available at the WHO Web site (21).

ACKNOWLEDGMENTS

The authors would like to thank the members of the WHO-CHOICE team for their contribution to the development of the methodological framework for the analysis. They also thank Marti van Liere for comments on an earlier version of this paper.

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