

# LARGE-SCALE FOOD FORTIFICATION: AN OVERVIEW OF TRENDS AND CHALLENGES IN LOW- AND MIDDLE-INCOME COUNTRIES IN 2017



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On behalf of the Micronutrient Forum

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## ABBREVIATIONS

ASEAN	Association of Southeast Asian Nations
CDC	Centers for Disease Control and Prevention
Codex	The Codex Alimentarius (FAO/WHO)
CSOs	Civil Society Organisations
DALYs	Disability-adjusted life years
DHS	Demographic and Health Surveys
EAR	Estimated Average Requirement
EDTA	Ethylenediaminetetraacetate used in fortification as the sodium iron salt (NaFe(III)EDTA)
eLENA	e-Library for Evidence for Nutrition Actions
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FFI	Food Fortification Initiative
GAIN	Global Alliance for Improved Nutrition
GDP	Gross domestic product
HDI	Human development index
HIV	Human immunodeficiency virus
ICCIDD	International Council for Control of Iodine Deficiency Disorders
IDA	Iron deficiency anaemia
IDD	Iodine deficiency disorder
IGN	Iodine Global Network (previously ICCIDD)
INACG	International Nutritional Anemia Consultative Group
IVACG	International Vitamin A Consultative Group
IZiNCG	International Zinc Nutrition Consultative Group
LMIC	Low- and middle-income countries

**ABBREVIATIONS (CONTINUED)**

MeSH	Medical Subject Headings
MNF	The Micronutrient Forum
NaFeEDTA	Sodium iron ethylenediaminetetraacetate
NGO	Non-Government Organisation
NI	Nutrition International
NTD	Neural Tube Defect
PVO	Private voluntary organisation
QA	Quality assurance
QC	Quality control
RDA	Recommended Dietary Allowance
RR	Relative risk
SDGs	Sustainable Development Goals
SEARO	South East Asia Region
SUN	Scaling Up Nutrition
UL	Tolerable upper intake levels
UN	United Nations
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USI	Universal Salt Iodisation
VAD	Vitamin A deficiency
VMNIS	Vitamin and Mineral Nutrition Information System
WFP	World Food Programme of the UN System
WHA	World Health Assembly
WHO	World Health Organization

# Abstract

Global micronutrient deficiencies are estimated to affect 1.6 billion people and cause economic losses ranging from 2 - 5% of gross domestic product (GDP) in low- and middle-income (LMIC) countries. Large-scale fortification is of proven effectiveness along with (and part of) the broader nutrition, health and development agenda that is being promoted by the Sustainable Development Goals (SDGs), the Scaling Up Nutrition (SUN) Movement, World Health Assembly (WHA) goals and the Global Nutrition Report, amongst others. Two distinguishing features of food fortification are the multisectoral nature of the intervention, as well as the close relationship with the private sector (which does the actual fortification under government responsibility for legislation, regulation and compliance, and with other stakeholders).

This report provides an objective overview of the state of large-scale food fortification in the world, with emphasis on gaps and challenges to the scaling-up of the fortification of staple foods to populations that would benefit. Building on the historical experience of more than 80 years, the review focuses on perspectives of the continuing micronutrient gap in many LMIC populations, and the role of large-scale fortification to address these dietary gaps. Despite considerable attention to micronutrient deficiencies by governments, donors and their partners over the last 25 years, there is a relative paucity of data for some vulnerable populations and countries. Existing large-scale fortification of staples, oils and condiments and their accompanying policies and programmes are outlined, along with monitoring and evaluation and the challenges of adequate compliance and enforcement. The rationale for adopting such programmes in terms of cost-effectiveness, efficiency and sustainability are discussed using both affluent country experience and more recent low- and middle-income experiences.

Large-scale (mass) fortification is usually mandatory but voluntary programmes are included where appropriate. Other methods of food fortification (e.g. of condiments) that have the potential to reach a wide target group of consumers likely to be micronutrient-deficient, such as iodised salt, sugar with vitamin A and fortified cooking oil, are discussed as well as micronutrient-fortified condiments like fish sauce and soya sauce. Fortified complementary foods for young children or commercially-fortified, processed foods such as breakfast cereals are not discussed, as they are well-covered elsewhere.

Currently, 86 countries have legislation to mandate fortification of at least one industrially-milled fortified grain (85 countries plus the Punjab for wheat flour; 16 for maize; 6 for rice) (as identified by the Food Fortification Initiative in 2017). Costa Rica and the USA do so for all three. Whereas 84 countries mandate both iron and folic acid, Australia does not include iron and five countries do not include folic acid. Such programmes have resulted in the fortification of 30% of the world's industrially-milled wheat flour, 48% of maize flour and 1% of rice.



There have been recent advances in technical aspects, and on identifying and filling evidence gaps, and these will contribute to further prioritising the additional information and stronger evidence needed. Implications of the findings, such as the development of a tracking tool to increase accountability, a food assessment coverage tool, identification of data needs and appropriate biomarkers, the possibility to use more modelling, and so on, will be identified. More in-depth country experiences and systematic analyses of efficacy and effectiveness were presented in greater detail in the report of the Food Fortification Summit (#FoodFortification) held in Arusha, United Republic of Tanzania in September, 2015, along with recommendations and a call to action. The Arusha Statement on Food Fortification that came out of the Summit in 2015 (<http://www.gainhealth.org/wp-content/uploads/2015/05/Arusha-Statement.pdf>), defined five critical areas of action [1].

1. Modest but new investment is essential.
2. A major effort is needed to improve oversight and enforcement of food fortification standards and regulations - poor compliance with laws and regulations limits potential for impact and undermines effectiveness.
3. More evidence must be generated to guide fortification policy and programme design, to continually improve programmes and demonstrate impact.
4. Progress requires more transparent accountability and global reporting. We support the call for a global observatory or annual report of the state of fortification.
5. Continuing advocacy is a high priority for all stakeholders such as the SUN movement and African Union to advocate for greater attention by governments.

# 1

## Introduction

Deficiencies of micronutrients – and the negative consequence of a diet lacking in essential vitamins and minerals/trace elements – continue to pose significant public health problems in much of the world, especially in women and young children in low- and middle-income country (LMIC) populations [2] and female adolescents [3]. Overall, micronutrient malnutrition has widespread and important health and economic consequences [4-7] with a small but important contribution to the total global burden of disease [8-10]. The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) have identified four main strategies for improving micronutrient malnutrition:

- Nutrition education leading to increased diversity and quality of diets
- Food fortification
- Supplementation
- Disease control measures [11]

It is now also widely recognised that without parallel changes in socio-economic and socio-cultural norms, these strategies are unlikely to be fully effective or sustained [12]. An increasingly important strategy is the large-scale fortification of staple foods regularly eaten in diets consumed around the world.

### 1.1 SIZE OF THE PROBLEM OF MICRONUTRIENT DEFICIENCIES

Over 1.6 million people globally are estimated to be at risk of micronutrient deficiencies such as those that cause anaemia [13]. A systematic review of all studies published between 1988 and 2008 that reported on micronutrient intakes of women in resource-poor settings found that the reported mean/median intakes of all the micronutrients measured in over half of the studies were below recommended intakes (except for vitamins A and C and niacin, and even they were 29%, 34% and 34% of Estimated Average Requirement (EAR) respectively) [14]. While regional differences were apparent, overall the review identified that women living in resource-poor settings of LMIC commonly have inadequate intakes of one or more micronutrients [14], confirming earlier studies [2, 15], particularly in pregnancy [16] and incur considerable social and economic costs, usually with a negative gender bias against females [17].

## 1.2 HISTORICAL PERSPECTIVE

Food fortification has been an important and effective public health intervention for well over 80 years, and continues to play an important role in the current nutritional health and well-being of populations in most affluent countries [18-20]. Historically, iodine rich foods have been recommended since ancient times [21] and in 400 BC, the Persian physician Melanpus suggested iron filings be added to wine to increase the potency of soldiers [4]. Starting in the early part of the 20th century, fortification was used to target specific health conditions: goitre with iodised salt; rickets with vitamin D-fortified milk; and beriberi, pellagra and anaemia with B vitamins and iron-enriched cereals.

During the 1930s and 1940s, grain milling removed most of the micronutrient content from the common cereal crops. In the southern states of the USA, most available land was being used for non-food crops such as cotton and tobacco. As corn products were the major dietary staple, and the resulting poor diets were deficient in niacin, the deficiency disease pellagra was endemic [19]; in the late 1920s, pellagra was the eighth or ninth highest cause of death in the USA [22]. An initial decline in early 1930s was likely due to the distribution of yeast and high protein foods rich in niacin and other B vitamins as a public health response but this plateaued as the programme faltered during the Depression. The second large decline (of both pellagra and iron deficiency anaemia) started in 1939 after bakers volunteered to enrich flours and bread with high-vitamin yeast in 1938 [4]. By 1960, pellagra was largely eliminated, partly due to improving socio-economic conditions and more varied diets, but most importantly by the enrichment [19]. Nevertheless, niacin deficiency was still a public health problem in parts of Africa, China and India in the 1970s [23] and still exists in some areas. Other examples, among many, include the Chicago House of Correction in 1948-49, where a large decrease in the incidence of B vitamin deficiencies followed enrichment, and in China, the "remarkable remission in signs of riboflavin and niacin deficiencies among troops of the Chinese National Army" followed the introduction of enriched rice [19]. The United States' Food and Drug Administration (FDA) established its Food Fortification Policy in 1980 [24]. Iodised salt was introduced in the USA in 1924, although only half of USA household salt is currently iodised [25].

Canada had a similar history as the United States. In the early 1900s, beriberi from thiamine (vitamin B<sub>1</sub>) deficiency, as well as blindness and at least one sign of vitamin A deficiency (VAD), were present in 21% of schoolchildren in populations in British Columbia, Saskatchewan, Newfoundland and Labrador, and about 50% of schoolchildren had evidence of past rickets (from vitamin D deficiency) [26]. Recognition of these deficiencies led to the mandatory addition of calcium (as bone meal), iron and B vitamins to flour, and vitamin A to margarine in the 1940s [26]. Slightly later in 1949, following experience in Switzerland in 1923 and a year later in the USA [4], iodisation of salt became mandatory, and subsequently largely eliminated goitre in Canada [26]. Canadian regulations were amended in 1965 for the mandatory addition of vitamin D to (fluid) milk, which largely eliminated the widespread problem of childhood rickets. Nevertheless, Canada's first comprehensive nutrition survey, conducted in 1970-1972, found many segments of the population had dietary intake inadequacies, especially of iron, calcium, vitamin D and protein. These findings emphasised the need for continuous monitoring and evaluation of micronutrient programmes including fortification.

Like the United States, Switzerland was an early pioneer in the adoption of iodised salt. Starting in 1925, many European countries also had voluntary fortification of margarine, but with the advent of the Second World War in 1939, some governments made this compulsory – justified by the fact that margarine was replacing butter in the diet [27]. There is now mandatory addition of vitamins A and D to margarine and fat spreads in most northern European countries [27]. France has recently identified a series of micronutrient deficiencies – deficiency in calcium and magnesium mainly in adolescents and older people, and deficiency in iron and vitamin C in women – and is using this collection of data to prepare for optimal fortification [28].

In the 1970s, Australia evaluated a 6.5 month wheat flour fortification programme that sought to address micronutrient deficiencies, especially thiamine, seen in the diets of outback Australian Aborigines [29] and later the prevention of Wernicke-Korsakoff Syndrome. Almost 30 years later, the first author subsequently went on to write an article on the “repeating history of objections to the fortification of bread and alcohol” [30].

By 1995, 17 countries in Latin America were routinely fortifying with one or more micronutrients [31, 32]. The region’s experience of fortifying sugar (as the most appropriate vehicle) with vitamin A in the 1970s was an innovative intervention spearheaded by Guatemala and subsequently adopted by other Central American countries [33] and in Zambia [34]. In the 1950s, Chile was the first Latin American country to fortify wheat flour with iron (to be consistent with North American standards rather than explicitly for anaemia control) and with thiamine in the prevention of Wernicke-Korsakoff syndrome [35].

Legislation on restoration of vitamins and/or minerals removed by processing was passed by a number of South American countries in the 1960s but rarely enforced although some manufacturers went ahead anyway [35]. In 1993, Venezuela mandated iron and B vitamins to be added to wheat flour, and for maize flour to have vitamin A, B vitamins and iron added; by the end of the decade most countries in Central and South America had similar legislation. Fortified maize and its products are found in many Latin American countries and now, in 17 African countries and territories [36, 37]. Fortification of cereal flour was initiated in the Kingdom of Saudi Arabia in 1994 along with, on a small scale, in Afghanistan, and then subsequently Oman in 1996, and by the early 2000s, Bahrain, Iran, Iraq, Jordan, Kuwait, Morocco, Palestine, Qatar, and Yemen. Today, only eight countries in the Middle East do not fortify cereal flour [38]. Mandatory fortification programmes are also in place in five Central and Eastern European countries (Kazakhstan, Kyrgyz Republic, Moldova, Turkmenistan and Uzbekistan [39]). South Africa has mandatory food fortification for maize (corn) meal for iron, zinc, folic acid niacin, riboflavin, thiamine, and vitamins B<sub>6</sub>, B<sub>12</sub> and A. Fortified maize and its products are found now in many countries in Africa with mandatory fortification in 12 Sub-Saharan African countries [36, 37]. It is no coincidence that the recent Summit on global mass fortification was held in Tanzania in 2015 [1].

A relative lack of appropriate centrally-processed food vehicles, less developed commercial markets and relatively low consumer awareness and demand delayed by almost 50 years the widespread adoption of mandated fortification of staples as a viable option for low- and middle-income countries [20]. With the experience of both voluntary and mandatory fortification over

many decades in many Western countries and Japan, it is now increasingly being implemented in LMIC. This has been largely due to expanding commercial markets, increased centralisation of industry, increased demand and awareness of benefits, and improved (while often still inadequate) quality assurance and control measures. While fortification in the more affluent countries was initially used effectively to prevent specific micronutrient deficiency diseases, it is now increasingly being used in those countries especially, to correct or prevent population nutrient intake inadequacies, balance total nutrient profile of a diet, restore nutrients lost in processing and more recently, to appeal to consumers wishing to supplement their diet [24]. However, this is not the case in many LMIC where the risk of deficiency diseases remains relatively high, especially in women and children.

### 1.3 THE BROADER NUTRITION, HEALTH AND DEVELOPMENT AGENDA

Micronutrient malnutrition remains an important problem globally - differentially and negatively affecting women, including adolescents, and children and those sub-populations of lower socio-economic status and/or disadvantaged in other ways, including internal inequities within low-, middle- and high-income countries. In the relatively recent past, when such problems were identified, they tended to be addressed by single nutrient, vertical approaches. This approach had considerable success in addressing iodine deficiency and relatively little success with iron deficiency anaemia [40]. With new evidence and analysis, there has been a shift in the last decade towards an intersectoral approach in public health nutrition. This shift occurred because of a recognition that single nutrition approaches tend to be less sustainable and a less efficient way of using resources, along with accusations of donor-driven priority setting in countries. An impressive example of integration has been the inclusion of vitamin A supplementation into Child Health Days and Weeks, along with immunisation and other child public health interventions [41]. Fortification is an increasingly important part of the armamentarium to fight against micronutrient deficiencies with its relatively long experience, growing evidence base and advantages in terms of sustainability.

The nutritional status and resulting health of both individuals and societies exist as the outcomes of immediate, underlying and basic social, political and cultural aspects [42-44], as well as genetic and environmental, even ancestral, factors [45]. Not surprisingly, the most effective interventions, when scaled up, are often those that address more than one of these factors - and different mixes of interventions are often more effective - depending on the problem they are addressing and the national situation and resources [46]. Fortification is a proven cost-effective intervention (Section 5) that complements programmes that aim to improve dietary quality and diversity, and large-scale supplementation of micronutrient(s) when appropriate. Each of these strategies has a place in eliminating micronutrient malnutrition and together the appropriate mix of strategies addresses more widely both "nutrition-specific" and "nutrition-sensitive" interventions [6]. While fortification is often seen as one of the simpler interventions, it is now recognised that all the interventions have their own complexities and advantages, and in varied populations with different needs, different mixes of interventions may be needed to address different population segments at both national and sub-national levels. For example, a recent study from rural Bihar in India found that despite universal

supplementation programmes existing for some time, maternal anaemia levels remained high and levels of iron-folic acid receipt (37%) and consumption, remained low [47]. Given the slow rate of change in improvement for women in such a situation, an approach such as fortification has potential benefits, both for prevention and coverage.

This report shows how fortification is contributing to these changes and remaining challenges. Somewhat disappointingly perhaps, the new Sustainable Development Goals (SDGs) have only one goal directly targeting nutrition (“Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture”. <http://www.un.org/sustainabledevelopment/hunger/>), but at least 12 of the 17 SDGs are directly linked to nutrition [48] and it is hard to see how this would be achieved without the contribution of fortification to helping to eliminate micronutrient deficiencies.

#### **CALL OUT BOX 1: IMPLICATIONS OF FOOD FORTIFICATION FOR HEALTH AND ECONOMIC DEVELOPMENT OF NATIONS**

Anticipated public health and economic benefits derived from fortification include:

- Prevention or minimisation of the risk of occurrence of micronutrient deficiencies in a population or in specific population groups
- Contribution to the correction of a demonstrated micronutrient deficiency in a population or in specific population groups
- Potential for an improvement in nutritional status and dietary intakes that may be, or may become, sub-optimal as a result of changes in dietary habits/lifestyles
- Plausible beneficial effects of micronutrients consistent with maintaining or improving health [11]
- Increase in country’s GDPs: micronutrient deficiencies have been estimated to cost an annual GDP loss as high as 5% GDP [49]
- Increase in productivity and earnings due to correction of iron deficiency anaemia (IDA) alone. IDA is estimated to cause a 17% reduction in productivity in heavy manual labour, as well as an estimated 2.5% loss of earnings due to lower cognitive skills [50]
- An estimated 2.4-9% reduction in the global burden of diseases due to correction of iron deficiency anaemia (IDA), iodine deficiency disorder (IDD), vitamin A and zinc
- Given the burden on already often under-resourced health systems, the cost-effectiveness, and role of the private sector, savings can be expected

# 2

## Food Fortification Defined and Scope of Review

### 2.1 METHODOLOGY

This review addresses the strategy of large-scale fortification of staple foods regularly eaten in diets consumed around the world as a means of addressing micronutrient deficiencies. A wide-ranging search for references in both the formal literature and the grey literature [especially by NGOs that focus on this area such as the Food Fortification Initiative (FFI), the Global Alliance for Improved Nutrition (GAIN), Nutrition International (NI), and the Iodine Global Network (IGN), was conducted, along with national reports. This was underpinned by a formal literature search of articles and reports over the last 15 years, in English only, through the University of Sydney Fisher Library. Key words used were: “Fortified food\*”, “Enriched food\*”, “Supplemented food\*”, and for Medical Subject Headings (MeSH)-Medline (via OvidSP) “Food, fortified//ae- adverse effects”. As the review focuses on mandated mass fortification predominantly, complementary key words also used were: “Government program\*”, “Government sponsored program\*”, “Nutritional policy”, “Government health promotion”, “Food fortification program\*”, “Policymaker\*”, “Health policy\*”, “Mandatory program\*”, and under MeSH: “Health promotion/og”, “Nutrition policy/”, “Health policy/”, “Mandatory programs/”, “Policy making” and “Legislation, Food/”. In addition, references were added by a process of forward citation searching, for example, identifying relevant references of key articles such as the WHO/FAO 2006 guidelines [11], following them up, and then repeating the process with each article used. Clarifications and unpublished data from persons involved in global fortification activities were also sought.

During recent years, several summary reports on food fortification have been published. In 2006, the WHO published evidence-informed guidelines for various aspects of fortification. These guidelines included the appropriate selection of vehicles and fortificants; how to determine fortification levels; and the implementation of effective and sustainable food fortification programmes [11]. An initial expanded version of this report was presented at the #FutureFortified Global Summit on Food Fortification, which took place in Arusha, Tanzania in September 2015. Based on the initial report version and the outcomes of the Arusha meeting, a synopsis report was published by the Micronutrient Forum in October 2016. In early 2017, a Food Fortification Global Mapping study was published by experts from the European Committee and the Global Alliance for Improved Nutrition (GAIN). This report included a summary of experiences with national food fortification programmes [51].

The current report will provide the most comprehensive overview of large-scale food fortification in the world to date, and has been updated with new data since the original report in 2015. It includes references to original articles from the relevant literature as well as evidence gaps and recommendations for programmes and research as identified during the Arusha summit and in the other publications [52]. This report focuses on mass fortification and does not address home fortification, biofortification or specialised fortified foods for specific target groups (for example, fortified complementary foods for infants and young children who typically cannot consume enough of fortified family foods to match their dietary requirements [53]).

## 2.2 DEFINITIONS

**Food fortification** is defined as the practice of “deliberately increasing the content of essential micronutrients<sup>1</sup> in a food so as to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health” [11]. The Codex *General Principles for the Addition of Essential Nutrients to Foods* defines fortification (or synonymously “*enrichment*”) as “the addition of one or more essential nutrients to a food whether or not it is normally contained in the food, for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the populations or specific population groups” (Codex 1987) [54]. The following definitions are all shortened versions of text from the WHO/FAO manual [11] generally citing the Codex Alimentarius general principles for the addition of essential nutrients to foods (Codex 1987) [54].

**Mass (or universal) fortification** fortifies foods that are widely consumed by the general population and is usually mandatory and regulated by government, which has often instigated the intervention. An important distinction when discussing large-scale fortification of staple foods is between *mandatory fortification* and *voluntary fortification*, self-evident policies, which are discussed further in [Section 5](#).

**Targeted fortification** fortifies foods for specific population groups such as complementary foods for young children or rations for displaced populations, and can be mandatory or voluntary. These can also be considered as supplements that are added to fortify complementary foods such as micronutrient powders (e.g. Sprinkles™) and are usually consumed by targeted individuals at the household level (or in displaced persons settings).

**Voluntary, market-driven fortification** allows food manufacturers to voluntarily fortify foods available in the marketplace but which are subject to regulatory limits.

Further definitions can be found in the Codex Alimentarius along with the basic principles of fortification for public health outcomes. Some further relevant key definitions are the following.

Besides fortification or enrichment, **restoration** means the addition to a food of essential nutrient(s) which are lost during the course of good manufacturing practice, or during normal

<sup>1</sup> “Essential micronutrients” in this context are those vitamins, minerals and trace elements that are normally consumed as a constituent of food and which are needed for growth and development and the maintenance of healthy life and which cannot be synthesised in adequate amounts by the body (Codex Alimentarius Commission as amended in 1991).



storage and handling procedures, in amounts which will result in the presence in the food of the levels of the nutrient(s) present in the edible portion of the food before processing, storage or handling (Codex 1987) [54]. Nutrients may be added to foods, such as with restoration of nutritional value where nutrients lost during processing (e.g. iron, niacin, riboflavin and thiamine) are added back. In some cases, foods may also be fortified with nutrients not normally present, such as the addition of calcium to orange juice [24]. *Restoration* is not the focus of the review but has historical and current importance. *Nutritional equivalence* is when an essential nutrient is added to a product that is designed to resemble a common food in appearance, texture, flavour and odour in amounts such as the fortified product has a similar nutritive value, in terms of the amount and bioavailability of the added essential nutrient, such as vitamin A in margarine. *Appropriate nutrient composition of a special purpose food* such as meal replacement or a complementary food for young children, while obviously important, are beyond the scope of this review.

Nutrients can be added to foods at different points along the value chain from the foods' production, its processing and finally to its ingestion "from field to mouth". Horticulturally and in agriculture, nutrients can be added by the plant breeding process of biofortification or adding nutrients to fertilisers or water supplies. Nutrients can be added at virtually any stage of processing both home-based or in factories, or at the household and individual level such as home-based fortification with micronutrient powders. These are briefly discussed below but the focus of the review is large-scale or mass fortification.

The Codex document defines *special purpose foods* (foods that have been designed to perform a specific function, such as to replace a meal), and other terms such as *nutrient density* (the amount of nutrients in metric units per stated unit of energy in MJ or kcal) and *standardisation* (the addition of nutrients to a food in order to compensate for natural variations in nutrient level). Codex also specifies fortification basic principles such as "that the essential nutrient should be present at a level which will not result in either an excessive or an insignificant intake of the added essential nutrient considering amounts from other sources in the diet", and that the addition of an essential nutrient to a food should not result in an adverse effect on the metabolism of any other nutrient (Codex 1987) [54]. Importantly, they include methods of measuring, controlling and/or enforcing the levels of added essential nutrients in foods that should be available.

Even though market-driven foods that are fortified, such as breakfast cereals, can provide a significant amount of micronutrients in the national diet in countries like Australia, Canada, parts of Europe and USA [24, 55], the current review is largely addressing mandatory large-scale or mass fortification. However, targeted fortification will be considered where the target population is large and the delivery aspects are similar. Voluntary market-driven fortification will be addressed where foods, usually condiments like soup bouillon cubes (West Africa) and iron-fortified soy (China) or fish sauce (Vietnam), are aimed at the general population for an identified public health nutrition problem. Even when voluntary, these are regulated by government, although the effectiveness of this depends on the degree to which compliance is achieved [56].

Targeted fortification (e.g. nutrient-fortified complementary foods for children aged 6–24 months) is important for sub-groups of nutritionally vulnerable populations and populations in emergency situations whose nutrient intake is insufficient through the family diets that are available to them [6]. Targeted fortification is also effective in resource-poor settings where family foods do not include animal source foods that are typically necessary to meet nutrient requirements of young children [6, 11, 20]. Home fortification involves addition of nutrients directly to food consumed by women or children, or both, in the form of micronutrient powders or small quantities of food-based fortified lipid spreads (e.g. lipid-based nutrient supplements). Such targeted fortification is recommended for emergency situations [57] and is increasingly being tried in broader health systems, for example, in Chhattisgarh, India [58]. However, the addition of micronutrient powders to prepared foods does have some of the challenges of supplementation (logistics, sustainable compliance) as opposed to foods fortified at source [6] and has been found to require quite a significant nutrition education effort to mothers, for example in Aceh after the Tsunami [59].

Biofortification, the term for a plant breeding approach of food crops, has been promoted as a sustainable, and ultimately cheaper, alternative to more usual fortification interventions and has had some considerable technical success, particularly in increasing iron, beta-carotene (provitamin A), zinc, and folate contents in staple foods [6, 60, 61]. Basically, biofortification involves the breeding and genetic modification of plants to improve their (micro)nutrient content and/or absorption [11] and is not further considered in the review.

### 2.3 LARGE-SCALE OR MASS STAPLE FOOD FORTIFICATION

While the focus will be a concentration on mandatory staple food fortification, the definition of what constitutes a “staple”, commonly wheat and maize flour and rice, can vary by history and culture, for example sweet potato, cassava, millet and plantains are considered staple foods in some, but not all societies. Ideally, fortified foods fill identified gaps in dietary micronutrient adequacy that have been identified by food intake studies in target population groups [62]. The main advantage of the mass fortification of staple foods with vitamins and minerals as a public health intervention is that the increased micronutrient content in staple foods or condiments is added at the processing stage, before they are introduced to the market, and so is largely invisible as a means to improve the nutritional quality of the population’s diet [63]. Expanding urban populations in LMIC are facing the challenge of growing rates of urban malnutrition and chronic disease. The urban poor were found to be particularly susceptible to the high price of foods when these accelerated in 2007–08 [64]. It has been suggested that food fortification is particularly relevant for the urban poor because of this population’s high consumption of centrally processed foods, limited access to micronutrient-rich foods, disproportionately high burden of disease, and a strong reliance on a consolidated food delivery system [65].

The fortificant needs to be one that is both adequately bio-available, does not interact with other food constituents and nutrients, and is of acceptable cost [62]. As noted, there has been considerable success globally, for example with 86 countries now having mandatory fortification of wheat or maize flour [39]; and for iron and iodine fortification especially, having a high effectiveness-to-cost ratio [63, 66]. However, challenges remain [Section 7]. In the past, mass fortification programmes were launched backed with insufficient evidence on the appropriate fortificant, interaction with other food components and other critical factors for effectiveness. Therefore, even as recent as 2010, Hurrell and colleagues [67] predicted that only nine of 78 national programmes they reviewed at that time “could be expected to have a positive impact on iron status”. Consequently, there has been extensive work on aspects of components of mass fortification, especially the fortificant used, that increase the chances of success of programmes [Section 5]. Examples are the interim consensus recommendations in 2009 [68], and more recent recommendations emerging from several processes including the Arusha meeting [1, 69] and WHO eLENA [70, 71].

While the Codex Alimentarius definitions have stood the test of time, the guidelines of WHO/FAO by Allen et al. [11] extended the interpretation of public health needs beyond addressing widespread deficiency diseases, so that it also incorporated plausible public health benefits that may be derived from increased micronutrient intakes, based on “new and evolving scientific knowledge”. The public health significance of “the potential benefits of food fortification is primarily a function of the extent of the public health problem”[11].

The scope of this review is therefore to establish the current state of large-scale fortification globally – of the fortification of staple foods in particular, the rationale for fortifying, and the expected benefits to public health expected. The complexity of the topic will be examined using the parameters of public health need, technical aspects, and political and social determinants. The review will note gaps in the current information and available evidence, and the challenges and uncertainties, while recognizing the great public health successes that have been achieved using fortification to date.

### CALL OUT BOX 2: GENERAL FOOD FORTIFICATION RESOURCES AND FURTHER READING

Fortification is the practice of “deliberately increasing the content of essential micronutrients in a food so as to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health” [11].

The Codex General Principles for the Addition of Essential Nutrients to Foods defines fortification (or synonymously “enrichment”) as “the addition of one or more essential nutrients to a food whether or not it is normally contained in the food, for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the populations or specific population groups”.

Fortification includes:

- **Mass fortification** is the addition of one or more micronutrients to foods commonly consumed by the general public such as cereals, condiments or milk and is usually instigated, mandated and regulated by the government sector [11], in response to demonstrable micronutrient deficiencies or where a population, or even a sub-population, may benefit.
- **Targeted fortification** is the fortification of foods aimed at specific sub-groups to increase their intake rather than the population as a whole, such as complementary foods for infants and children, and emergency feeding and special biscuits for children and pregnant women.
- **Market-driven fortification** is when a food manufacturer takes a profit-driven initiative to add specific amounts of one or more micronutrients to processed foods, usually voluntarily but under government regulations.
- **Other types of fortification** such as: household and community fortification also known as point-of-use, micronutrient powders such as Sprinkles™, and biofortification.

# 3

## The Gap in Micronutrient Intakes at Population Level and the Resultant Deficiency Outcomes Being Addressed

Annually, the cognitive and motor development of 40%-60% of 6-24 month old children growing up in LMIC are at risk due to iron deficiency [66]. Iron deficiency may account for about half the world's anaemia burden, although with much geographic variation [72], causing the loss of 19.7 million disability-adjusted life years (1.3% of global DALYs) [66]. A lack of iron has been estimated to contribute to over 600,000 stillbirths or neonatal deaths and over 100,000 maternal deaths during pregnancy [73]. Some 18 million newborns are estimated to be born intellectually impaired as a result of maternal iodine deficiency - leading to estimated intellectual losses of from 7.4 [74] up to 15 IQ points [75]. Insufficient intake of vitamin A results in some 350,000 cases of childhood blindness (with half of those affected dying within 12 months of losing their sight) and compromised immune system leading to at least 157,000 early childhood deaths due to diarrhoea, measles, malaria and other infections each year [76]. It has been estimated that each year, 1.1 million children under the age of five die because of vitamin A and zinc deficiencies [68]. In 2006, some 300,000 children were estimated to be born each year with severe birth defects due to maternal folate deficiency [77]. Micronutrient deficiencies alone have been estimated to cost an annual GDP loss of 2% - 5% (in LMIC) [50, 78, 79] with direct costs estimated between US\$20 to \$30 billion every year [78]. For example, anaemia from all causes has been estimated to lead to 17% reduced lower productivity in heavy manual labour and an estimated 2.5% - 4% loss of earnings due to lower cognitive skills [50].

Other outcomes of the relatively poorer diets, and compromised well-being and health in women and young children in many LMIC are the substantially higher rates of maternal mortality, stillbirth and neonatal mortality in the lowest compared to the highest income countries: 98% or more of these adverse outcomes occur in low-income countries [80, 81]. Within countries, costs of micronutrient malnutrition differ between socio-economic status of sub-populations. For example, in the Philippines costs attributed to micronutrient deficiencies in the poorest third of households were estimated to be five times higher than in the wealthiest third [82]. Such disparities add increased financial burdens to often already overloaded and under-resourced health systems [83, 84]. While reasons for disparities are not always known, they at least partly relate to differences in access to health care and resources, as well as behavioural factors such as poor "care-seeking behaviours" to both health care and specific interventions [85]. Consequently, interventions like fortification that apparently require less active health and nutrition-seeking behaviours, and/or increases availability or access to improved dietary intakes, could be expected to have an important impact [2].

### 3.1 IRON DEFICIENCY AND ANAEMIA

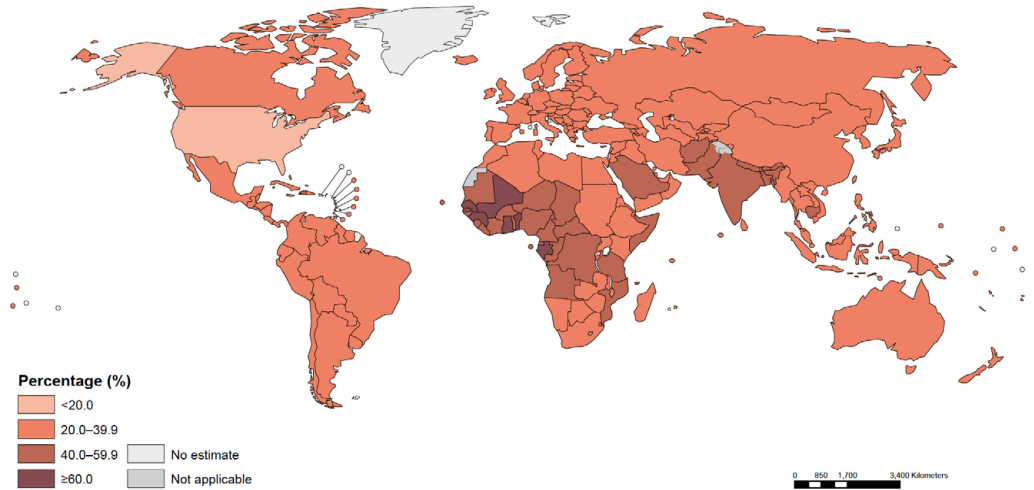
Anaemia is the most common and widespread nutritional disorder in the world, affecting millions of people in both affluent countries and LMIC. Iron deficiency occurs when physiological demands are not met due to inadequate intake, absorption or utilisation, or excessive iron losses [86], and has negative impacts even before developing into IDA. While iron deficiency is thought to be the most common cause of anaemia globally [72], anaemia can also be caused by other nutritional deficiencies (particularly folate, vitamin B<sub>12</sub>, vitamin A, copper); parasitic infections (including malaria, helminths, and schistosomes such as hookworms); chronic infection associated inflammation including HIV; and genetic disorders, such as haemoglobinopathies like sickle cell disease [87].

Recently estimated global anaemia rates are 29% (496 million) of non-pregnant women, 38% of pregnant women (32 million) and 43% of young children under five years (273 million), but the ranges vary enormously [88] by socio-economic status and geographical location. Most of the estimated total 1.62 billion people currently estimated by WHO to be affected by anaemia [89] are women of reproductive age or young children [88-90]. Such figures mean that in LMIC, every second pregnant woman and about 40% of preschool children are anaemic. Anaemia rates for children under five years of age go as high as 70%, 74% and 80% in South Asia, East Africa and Central and West Africa respectively as compared with 11% in high-income regions [88]. Similar figures for anaemia prevalence in pregnant women range from 23% in high-income countries compared to 53%, 46% and 61% for South Asia, East Africa and Central and West Africa. In Latin America and the Caribbean, prevalence rates of anaemia among children under 6 years of age ranged from the lowest 4% in Chile and moderate levels in Nicaragua, Brazil, Ecuador, Panama, and Honduras, to over 40% in Guatemala, Haiti and Bolivia, indicating a severe public health problem. The prevalence of anaemia among women of childbearing age similarly ranged from 5.1% in Chile to 40% in Panama while Haiti (45.5%) had the highest reported prevalence rates, and so overall, anaemia remains a public health problem in most Latin American and Caribbean countries for which data are available [91].

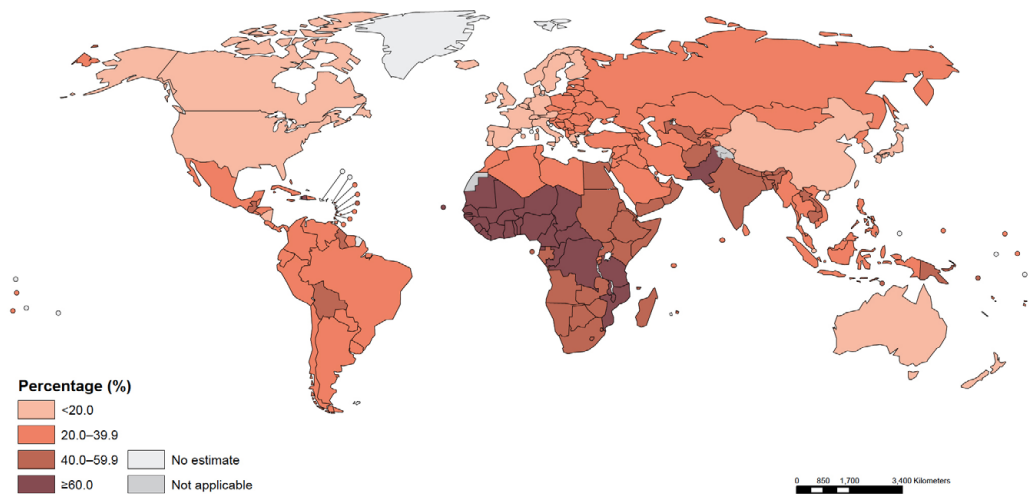
It has been estimated that an average of 50% of anaemia is due to iron deficiency in women rising to 60% for pregnant women, whereas in children about 42% of anaemia is due to this deficiency [88]. However, the proportion directly attributable to iron deficiency is geographically variable, and a recent review suggests there is large heterogeneity between countries. Therefore, the percentage of anaemia attributable to iron deficiency may be more in the range of 25% for children and 37% for non-pregnant WRA [72]. Consequently, although population iron deficiency rates are greater than those of anaemia [92], there is little consistent correlation between the two globally. Estimates of anaemia prevalence derived from the haemoglobin concentration alone do therefore not allow to separately assess the contribution of iron deficiency against the contribution of other causes of anaemia. Currently available iron indicators are more difficult to interpret in populations in LMIC due to this multifactorial aetiology of anaemia [93]. Current estimates, using haemoglobin levels, are nevertheless shown in *Figure 1* as they reflect the severity and geographic extent of the problem, even imperfectly.

**Figure 1: Global estimates of the prevalence of anaemia (2011)**

**a) In pregnant women aged 15–49 years**



**b) In infants and children aged 6–59 months**

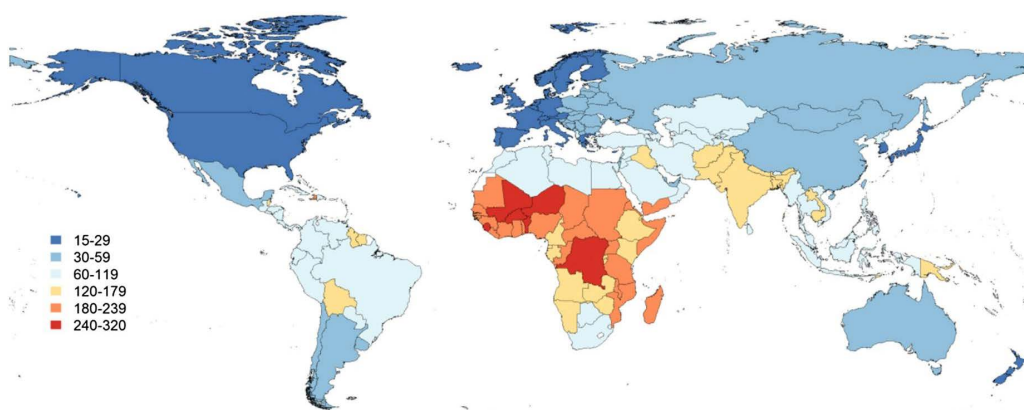


Taken with permission from the WHO Report “The global prevalence of anaemia in 2011” [90].

### 3.1.1 Health and economic consequences of anaemia and iron deficiency

The health and economic consequences of these high prevalences of anaemia are considerable [94]. *Figure 2* shows the years lost to disability (DALYs) due to anaemia [95]. Iron supplementation or fortification can increase productivity in adults - by up to 17% for heavy manual work [78] - and boost cognitive development in children, particularly for those who were initially iron-deficient or anaemic [5]. While the early stages of iron deficiency are often asymptomatic, functional consequences even in the absence of anaemia include increased maternal and perinatal mortality, low birth weight, impaired cognitive performance and poorer educational achievement as well as reduced work capacity [96, 97] with serious economic impact on families and populations [98]. One estimate was that the median annual economic loss because of iron-deficiency anaemia in 10 LMIC was \$US16.78 per capita (in 1994 US dollars) or 4% of gross domestic product [94]. This means there is an ongoing need to deal with the possibility of iron-deficiency anaemia in LMIC women, especially in pregnancy [16] and where populations experience a greater infectious burden and systemic inflammation, both of which can increase iron loss and concomitantly reduce iron absorption and utilisation [99].

**Figure 2: Total years lived with disability due to anaemia per 10,000 population, by country (2010)**



Taken with permission from Kassebaum et al. [95].



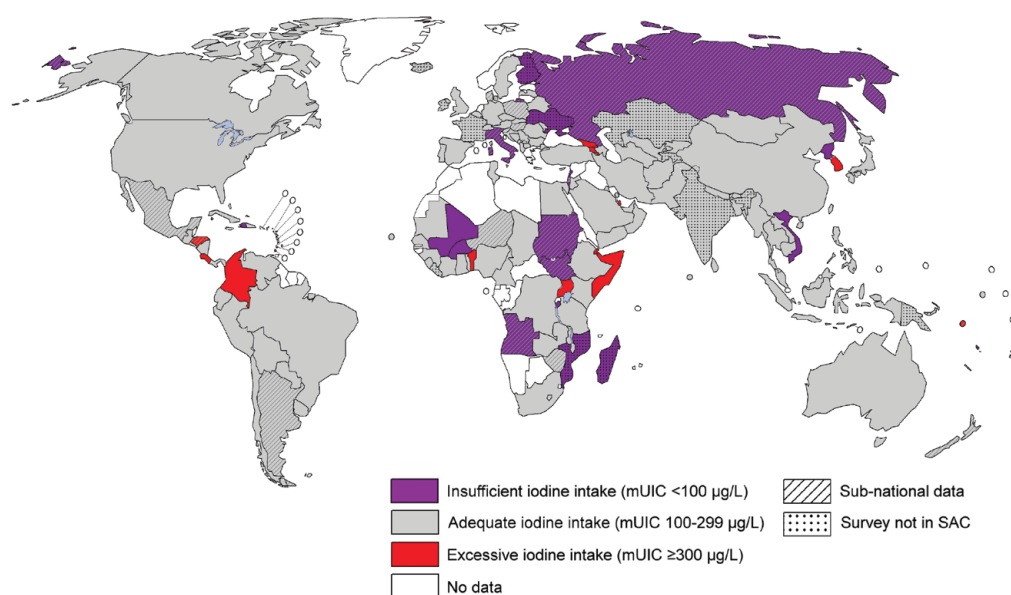
### 3.1.2 The gap remaining and the strategies to reduce the gap

There are several strategies to reduce and/or treat iron deficiency and iron-deficiency anaemia: dietary modification and diversification that aims to increase the content and bioavailability of iron in the diet [100]; preventive or intermittent iron supplementation through tablets, syrups or drops; fortification with effective iron compounds of staple foods (typically maize, soy and wheat flour; and biofortification [11]. Deworming in conjunction with other interventions, such as malaria control interventions, is effective in some situations in reducing anaemia and in increasing the efficacy of interventions, that increase iron intakes [101, 102]. Mass large-scale fortification of staple foods or condiments is a preventive strategy aimed at reducing the risk of developing iron deficiency and pre-existing iron-deficiency anaemia through increased dietary iron [103]. Iron fortification can be, and often is, accompanied by other micronutrients (i.e. folic acid, vitamin B<sub>12</sub> or vitamin C) that may enhance the effectiveness of the intervention [92]. Mass targeted or market-driven food fortification with iron has been used with various vehicles: soy sauce, fish sauce, salt, milk, sugar, beverages, bouillon cubes, maize flour, and complementary foods [11]. Although the effectiveness of flour fortification in reducing anaemia prevalence has been considered equivocal [104], recent studies and a systematic review of iron fortification of foods have found an association with increased haemoglobin, improved iron status, and reduced anaemia across populations [105] and support the intervention's effectiveness.

An earlier joint statement on anaemia from WHO and UNICEF emphasised an integrated approach consisting of iron supplementation, iron fortification of food, treatment of co-existing pathological conditions, dietary diversification and improved nutrition, improved sanitation and access to clean water, improved access to health care and nutritional education of consumers [70]. Nevertheless, there has been little progress. Since 1995, the global prevalence in all groups has fallen only slightly. For example, the global prevalence of anaemia fell by only 0.02% to 0.3% per year between 1993 and 2013 [89]. WHO has set a 50% reduction of anaemia in women of reproductive age (from 2011 prevalence) as the second global nutrition target for 2025 [106].

## 3.2 IODINE

Deficiency of iodine, resulting in a reduction in the production of thyroid hormone, is an ancient problem [21] resulting in a spectrum of iodine deficiency disorders (IDDs) including goitre, intellectual impairments, growth retardation, neonatal hypothyroidism, and increased pregnancy loss and infant mortality [75]. Prior to the widespread salt iodisation in LMIC, there were few countries in the world where some degree of iodine deficiency had not been a public health problem [5]. Considerable progress has been made since then, but the problem remains in many LMIC countries (and much of Eastern Europe) as can be seen in [Figure 3](#) [107-109].

**Figure 3: Global map of iodine nutrition**

Taken with permission from the Iodine Global Network (IGN) [107, 108]

### 3.2.1 Health and economic consequences of iodine deficiency

Iodine deficiency is the world's single greatest cause of preventable mental retardation. Deficiency is especially damaging during the early stages of pregnancy and in early childhood leading to (in its most severe form): cretinism, stillbirth and miscarriage, and increased infant mortality [110]. Even mild deficiency can cause a significant loss of learning ability, a frequently-quoted 13.5 intelligence quotient (IQ) points at a population level [111] but now considered to range from 8 to 13.5 IQ points [112]. Iodine deficiency consequently results in a loss of economic productivity [113]. It has been estimated by the World Bank that each (US) dollar dedicated to IDD prevention would yield a productivity gain of US\$28 [21].

### 3.2.2 The gap remaining and the strategies to reduce the gap

Tremendous progress has been made through salt fortification over the last two decades – the proportion of households in the developing world consuming adequately iodised salt has risen from less than 20% in 1990 to over 74% today [114], and the number of countries classified as iodine deficient has fallen dramatically from 110 in 1990 to 25 in 2015 [108]. Although substantial progress has been made over the last several decades, iodine deficiency remains a significant health problem worldwide and affects both industrialised and developing nations [115]. Currently 26% of LMIC households still do not consume iodised salt [116] and 25 countries remain iodine-deficient (defined as median UIC < 100 µg/L). Of these 25 countries,

seven are considered moderately deficient and 18 are mildly deficient, while no countries are currently considered to be severely iodine deficient [107] (*Figure 3*). These figures are currently being updated [108] (Gorstein personal communication).

Iodine deficiency remains a particular threat to the health and development of some vulnerable populations such as those with higher iodine requirements (weaning infants, preschool children, and pregnant and lactating women), and those that are “difficult-to-reach” due to restricted access to iodised salt or in countries in conflict situations. The IGN’s global scorecard for 2014 estimates of “still-unprotected infants” exceed 38 million. While more information has become available over the last few years, data are still missing from 41 countries including the Democratic Republic of the Congo, Iraq, Israel and Syria [108]. Where salt iodisation alone is not sufficient for control of iodine deficiency in vulnerable populations, iodised oil supplementation can be a viable and often complementary option, and especially for women of reproductive age should be regarded as an option. In some more affluent countries, mild iodine deficiency is reappearing in women of reproductive age [112]. All alternative strategies to Universal Salt Iodisation (USI) however, are likely to be more costly in delivering adequate iodine.

### 3.3 FOLATE AND NEURAL TUBE DEFECTS

Neural tube defects (NTDs), which include anencephaly, spina bifida and encephalocele, are congenital malformations that arise during the structural development of the neural tube, a process that is completed in 21 to 28 days after conception [117]. NTDs are conservatively estimated to have an incidence of >300,000 new cases a year, resulting in 2.3 million DALYs exhibiting a social gradient with the most economically disadvantaged populations in countries having the highest incidence [117].

The distinction is made between folate, the naturally occurring vitamin, and folic acid, the synthetic form most commonly used as a fortificant. Folate is a water-soluble B vitamin present in legumes, leafy green vegetables (such as spinach and turnip greens) and some fruits (such as citrus fruits and juices). In general dietary terms, on average, usual folate intakes are often insufficient to achieve a folate status associated with the lowest risk of NTDs [118]. The bioavailability of folic acid is approximately 70% higher than that of folate naturally contained in foods, although there are wide variations depending on the methodology used in the measurement [119].

#### 3.3.1 Health and economic consequences of folate deficiency

Clinical folate deficiency itself results in megaloblastic anaemia, the second most common cause of anaemia during pregnancy [120]. Insufficient periconceptional folate is also associated with a number of birth defects that may relate to genetic and environmental factors operating before conception or during early pregnancy [121]. Impaired methylation capacity interferes with the genes regulating neural tube closure [122] and leads the increased risk in incidence of NTDs. Folic acid derivatives are essential for DNA synthesis, DNA methylation, cell division, and tissue growth with methylation enabling proper gene expression and chromosome structure

maintenance, all critical biological processes, and especially for foetal development [123]. Low levels of both folate and vitamin B<sub>12</sub> (and associated hyperhomocysteinaemia), have been identified in mothers of children with NTDs [124]. While increased maternal intake of folate and folic acid is specifically associated with a decreased risk for NTDs, folic acid supplementation does not have a clear effect on other birth defects [125].

The health and economic consequences of folate deficiency are not the same as the consequences of those suffering from neural tube and related defects, especially as the latter involves the affected individual, his/her family and the community; health system support will be very different depending on the socio-economic conditions. Folate and the metabolically related B vitamins, vitamin B<sub>12</sub> and riboflavin, have received both increased scientific and public health interest in recent years [118] because evidence is now suggesting other potential roles for folate and/or related B vitamins in protecting against cardiovascular disease (especially stroke) [126], certain cancers, cognitive impairment and osteoporosis, beyond the well-established role in preventing NTDs, but any exact relationships remain to be confirmed [127].

### ***3.3.2 The gap remaining and the strategies to reduce the gap***

A recent review for the BOND Initiative on folate deficiency worldwide compared surveys of folate status published between 1995 and 2005, and highlighted the need for more population-based studies specifically designed to assess folate status, consensus on the best indicators for assessing folate status, and agreement on the appropriate biomarker cut-off point to define the severity of deficiency to gain a better understanding of the magnitude of folate deficiency worldwide [127]. In the report [127], folate and vitamin B<sub>12</sub> status were most frequently assessed in women of reproductive age (34 countries), and in all adults (27 countries), respectively. No relationship between vitamin concentrations and geographical distribution, level of development, or population groups could be identified. Consequently, the estimation of a public health gap in folate deficiency can only be measured by the number of countries with neither folic acid fortification of staples nor periconceptional folic acid supplementation. The Food Fortification Initiative estimates that currently 77 countries have introduced folic acid fortification legislation [39]. Besides folic acid fortification, supplementation with folic acid is internationally recommended to women from the moment they are able to actively begin trying to conceive until 12 weeks of pregnancy [128] but has limited effectiveness. Another option, also recommended by the WHO e-Library of Evidence for Nutrition Actions (eLENA) [71], is that women of reproductive age take weekly preventive iron and folic acid supplements, especially in populations where the prevalence of anaemia is above 20%.

### 3.4 VITAMIN A DEFICIENCY

Relative poverty remains the predominant underlying cause of vitamin A deficiency (VAD) as a public health problem. Populations that regularly consume diets of poor quality with little access to sources of the generally more bio-available, but relatively expensive and so less accessible, retinol-rich source foods are particularly susceptible [129]. Beta-carotene, a precursor to vitamin A is generally found in plant sources and while cheaper, is much less bio-available [76, 130]. The 1995-2005 WHO estimates classify 122 countries as having a moderate to severe public health problem based on biochemical VAD in preschool-age children (*Figure 4a*); while 88 countries are classified as having a problem of moderate to severe public health significance with respect to biochemical VAD in pregnant women (*Figure 4b*) [131].

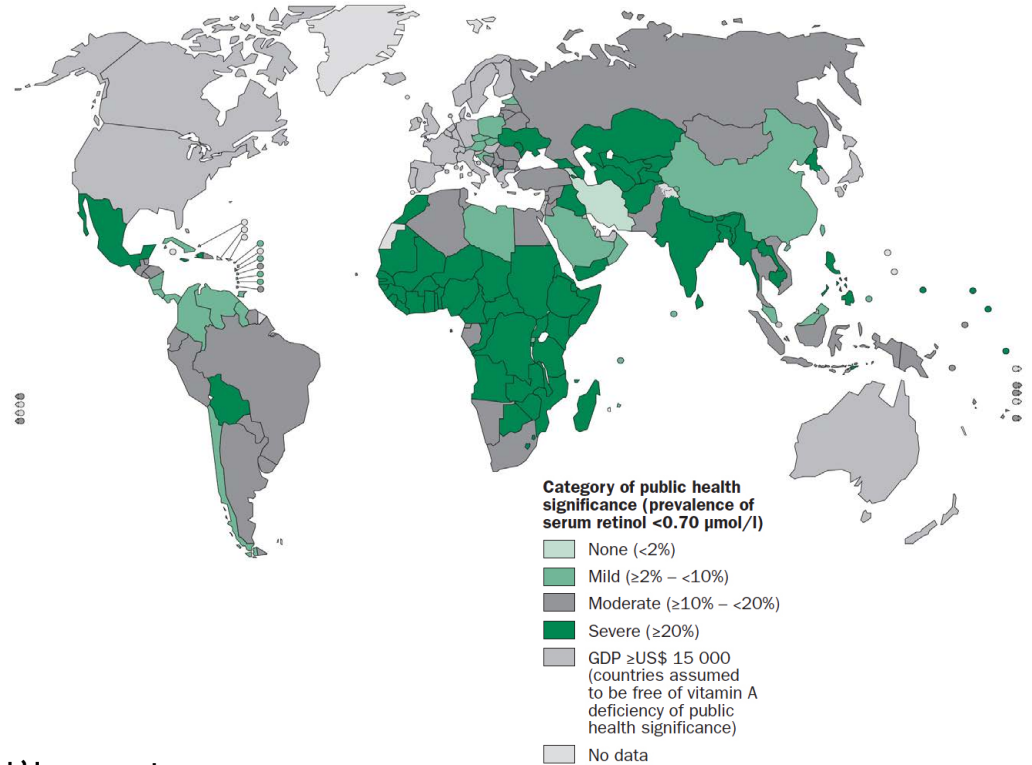
Globally, night blindness (an early clinical sign of VAD) is estimated to affect 5.2 million preschool-age children (95% CI: 2.0-8.4 million) and 9.8 million pregnant women (95% CI: 8.7-10.8 million), corresponding to 0.9% and 7.8% of the population at risk of VAD, respectively. Low serum retinol concentration (<0.70 µmol/l) affects an estimated 190 million preschool-age children (95% CI: 178-202 million) and 19.1 million pregnant women (95% CI: 9.30-29.0 million) globally. This corresponds to 33.3% of the preschool-age population and 15.3% of pregnant women in populations at risk of VAD, globally. The WHO Regions of Africa and South-East Asia are the most affected by VAD for both population groups [131]. The challenges include identifying the best biomarkers and their relationship to co-existing infectious diseases, and the body's homeostatic mechanisms regulating vitamin A in the body [130].

#### 3.4.1 Health and economic consequences of vitamin A deficiency

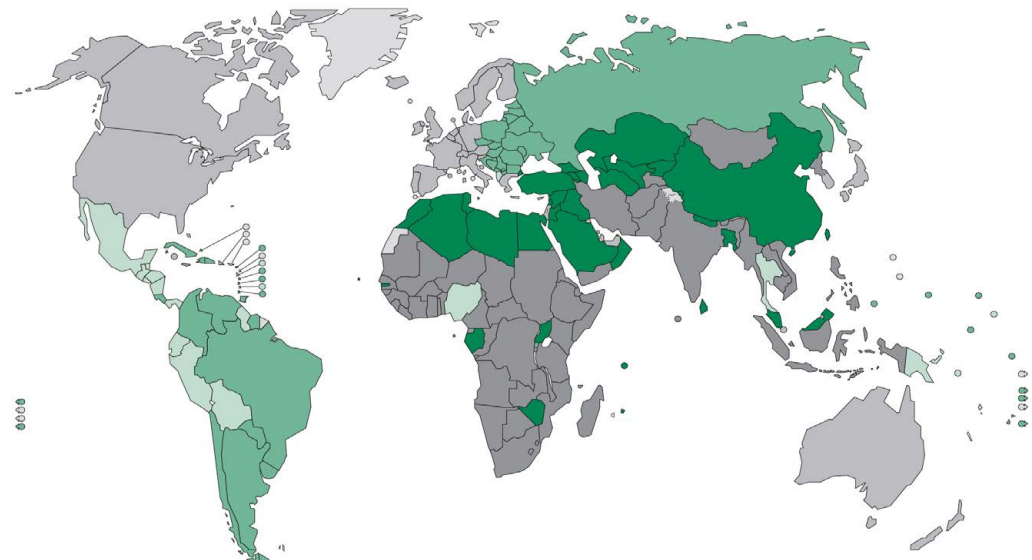
Clinical conditions caused by VAD range from blindness due to xerophthalmia (the leading cause of preventable childhood blindness), anaemia, and a weakened host resistance to infection by childhood infectious diseases, increasing their severity and increasing the risk of mortality to young children by nearly a quarter [129]. Poor diets, along with high prevalence of infectious disease and poor environmental conditions lead to low body stores and a failure to meet physiologic needs for which vitamin A is necessary, such as supporting tissue growth, normal metabolism and resistance to infection [76, 128, 130]. An estimated 250,000 to 500,000 vitamin A deficient children become blind every year, half of them dying within 12 months of losing their sight [71]. The most vulnerable are young children, and pregnant or lactating mothers [131]. For vulnerable pregnant women, VAD (as evidenced by the high prevalence of night blindness in affected populations) occurs especially during the last trimester when demand by both the unborn child and the mother is highest [71].

**Figure 4: Category of public health significance of vitamin A deficiency (1995-2005)**

**a) In preschool-age children**



**b) In pregnant women**



Used with permission from the WHO [131]

### *3.4.2 The gap remaining and the strategies to reduce the gap*

Overwhelmingly, it is the reduced resistance to infectious disease that makes VAD such a devastating public health problem and that has led to the global attention it has received. Supplementation with high doses of retinol in oil, two to three times a year has been a major public health intervention and has been the intervention of choice with considerable funding implications (mainly from the Government of Canada through Nutritional International). Nevertheless, most recommendations have noted the need for complementary actions such as improving diets (for example through home gardening) often in female-headed households, and addressing infectious diseases [132]. Obviously, improving the quality of diets in affected populations will also reduce other micronutrient deficiencies, but especially it is commonly recommended for vitamin A programmes, because of (perceived) sustainability, or the ready availability of beta-carotene in most diets. This requires nutrition education to change dietary habits, as well as providing better access to vitamin A or provitamin A (beta-carotene)-rich foods where possible, but can include most of the orange-fleshed fruits such as mango, papaya, or vegetables (not least the bio-fortified orange sweet potato) or dark green leafy vegetables. Encouraging home gardening or local cooperatives to grow such foods has had considerable success including on empowerment of women in some settings, such as Bangladesh [132].

Although there has been a long history of vitamin A fortification in margarine and milk in northern Europe [4], fortification has only recently been seen as an option for LMIC. National supplementation with high dose vitamin A has been the main focus in affected countries. However, there is current questioning of the reliance on likely unsustainable national supplementation programmes – for example if the very few donors involved stop supporting the intervention – and because many consider a regular intake in smaller quantities, as fortification could provide, is more physiological, and more effective [133]. In a recent review of vitamin A policies, Mason and colleagues [134] assert that the remarkably slow decline in VAD in low- and middle-income countries is due mainly to the failure to apply scientific evidence to policy. They make a case for a phased move towards frequent intakes of vitamin A in physiological doses, such as via the fortification of staple foods. There is strong evidence that VAD can be alleviated by this method [134].

Increasing the dietary intake of vitamin A through fortification of a staple food or condiment with vitamin A has been the primary strategy for reducing VAD in Central and South America, where sugar began to be fortified with vitamin A four decades ago [33, 135]. Since the fortification of sugar with vitamin A in 1974, it is estimated that now only a very few of the poorest families do not have adequate vitamin A intake [24, 33]. Fortifying with vitamin A is already gaining momentum as increasing numbers of other potentially fortifiable foods such as edible oils become centrally produced or processed under controlled conditions and penetrate broader socio-economic markets in LMIC.

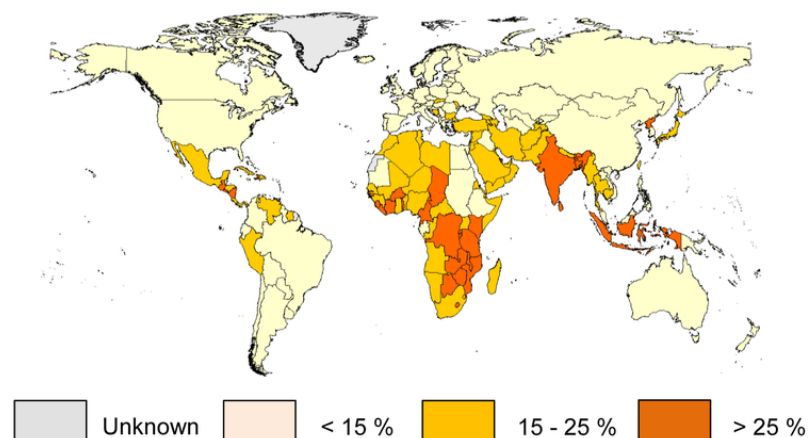
### 3.5 ZINC

Zinc is essential for multiple aspects of metabolism and severe zinc deficiency is historically associated with poor growth. Zinc is important for cellular growth, cellular differentiation and metabolism, and deficiency limits childhood growth and decreases resistance to infections [136].

While it is suspected that there is a great deal of zinc deficiency, biomarkers to assess this are problematic [137]. Physiologic signs of zinc depletion are linked with diverse biochemical functions rather than with a specific function, a situation which does not lend itself to specific biomarkers of zinc nutrition [138]. Although more national surveys now include the assessment of plasma zinc concentration, there are still insufficient data on the global prevalence of zinc deficiency. Consequently there has been a use of surrogate markers such as linear growth, using plasma zinc concentration and/or dietary zinc intake in countries identified at high risk of zinc deficiency based on a high stunting prevalence or high prevalence of dietary zinc availability [137].

Wessells et al. [139] estimated the prevalence of inadequate zinc intake based on the apparent absorbable zinc content of the national food supplies as derived from national food balance sheet data obtained from the FAO. A “best-estimate” model, comprised of zinc and phytate data from a composite nutrient database and the International Zinc Nutrition Consultative Group (IZiNCG) physiological requirements for absorbed zinc [137], estimated the global prevalence of inadequate zinc intake to be 17.3% [139] depending on which methodological assumptions were applied and the estimate used here of global stunting, which is thought to somewhat reflect zinc deficiency (*Figure 5*). The regional prevalence of inadequate intake ranged from 6% - 7% in high-income regions and Latin America and the Caribbean to 30% in South Asia. WHO [71] estimates approximately 165 million children under five years of age are stunted (height-for-age < -2 SD below the WHO Child Growth Standards median), with the vast majority living in Africa and Asia.

**Figure 5: Prevalence of nutritional stunting in children under 5 years of age**



Taken with permission from IZiNCG [140]



### **3.5.1 Health and economic consequences of zinc deficiency**

Given the presumed relationship of zinc deficiency and growth, it would seem likely that the effects of poor growth due to zinc deficiency could certainly contribute to stunting, and all the economic and health consequences that lead from stunting. As with other micronutrient deficiencies, zinc deficiency is more likely during pregnancy due to increased nutrient requirements of the mother and the developing foetus.

### **3.5.2 The gap remaining and the strategies to reduce the gap**

The available evidence suggests that zinc supplementation during pregnancy may help to reduce preterm births in low-income settings, but does not prevent other sub-optimal pregnancy outcomes including low birth weight or pre-eclampsia [136]. Although there is good evidence of the efficacy of zinc in treatment of diarrhoea, and some studies have shown mortality, morbidity and growth benefits, there remain a number of information gaps as to the extent of the effects and the optimal pattern of intervention [137]. The consequences of the population zinc gap cannot therefore be accurately known [136]. Zinc as an incremental cost in diarrhoea management however is very cost-effective, with an average cost of \$73 US per DALY gained and \$2,100 US per death averted. Currently there are no estimates for zinc coming into the diet through fortification. Supplements taken separately from food result in a rapid increase in plasma concentrations, whereas consuming a food fortified with zinc will have a more gradual effect on blood concentrations because of the presence of the food matrix [141]. The available evidence is inconsistent, but suggests that zinc supplementation may help to improve linear growth of children under 5 years of age [71]. WHO has adopted an interim consensus statement on wheat and maize flour with a variety of micronutrients, including zinc [136]. In the absence of more definitive recommendations, some countries such as Fiji have gone ahead with including zinc as a fortificant [39].

## **3.6 OTHER MICRONUTRIENTS**

As information in different populations becomes more available, other micronutrients, at least in some sub-populations, are likely to become of greater public health interest. Folate and zinc both became widespread public health targets only over the last decade or so. There is now increasing evidence that vitamins B<sub>12</sub>, D and E, as well as calcium and selenium, and perhaps others, should be assessed for their public health significance and whether fortification is an option. Vitamin B<sub>12</sub> deficiency is quite consistently thought to be under-rated as a problem [15], probably particularly in populations that consume a vegetarian diet. However, not all micronutrient deficiencies are necessarily suitable for addressing through fortification [4].

### 3.6.1 Vitamin B<sub>12</sub>

As a group, the B vitamins have been used as fortificants, through yeast initially, since early fortification programmes, when niacin was being used to help eliminate pellagra as a public health problem in endemic areas [19]. Especially in terms of women's general health, besides the established concern with megaloblastic anaemia and neurological damage, there are good reasons to increase vitamin B<sub>12</sub> intakes [45]. It has been shown, for example, that vitamin B<sub>12</sub> status differs among pregnant and lactating women (PLW) compared to non-PLW and which appears to reflect the enhanced vitamin B<sub>12</sub> supply to the foetus [142]. Large surveys in the USA and the UK show that vitamin B<sub>12</sub> deficiency is not uncommon and the prevalence increases with age [143]. Approximately 6% ≥60 y were vitamin B<sub>12</sub> deficient (plasma vitamin B<sub>12</sub> < 148 pmol/L), with almost 20% having marginal status in later life [144]. In LMIC, vitamin B<sub>12</sub> deficiency is even more common, starting in early life and persisting to old age across the life span due to a low consumption of animal source foods. In older persons, food-bound cobalamin malabsorption becomes the predominant cause of vitamin B<sub>12</sub> deficiency, at least in part due to gastric atrophy, but importantly, it is likely that most elderly can absorb the vitamin from fortified food [143]. So, while fortification of flour with vitamin B<sub>12</sub> is likely to improve the status of most persons with low stores of this vitamin, intervention studies are still needed to assess efficacy and functional benefits of increasing intake of the amounts likely to be consumed in flour, including in elderly persons with varying degrees of gastric atrophy [144].

It has also been suggested that pregnant and lactating women may benefit from intakes exceeding current recommendations [142], particularly so in some populations that have low intakes such as largely vegetarian populations, and the authors further suggest that fortification may be an important source of this additional vitamin B<sub>12</sub>. The potential population thought to be at risk is expanded by a recent study showing that vitamin B<sub>12</sub> deficiency in children in Colombia was associated with grade repetition and school absenteeism, independent of folate, iron, zinc, or vitamin A status biomarkers [145]. There is some indication that high rates of low or marginal vitamin B<sub>12</sub> status remain in most locations and across population groups in Latin America and the Caribbean [146]. There is also evidence that riboflavin status is generally low in the UK population, and particularly so in younger women; this warrants further investigation [118]. In countries with mandatory folic acid fortification of cereal flour, folate deficiency no longer appears to be a public health problem (prevalence < 5%). Adding vitamin B<sub>12</sub> as a fortificant with folic acid has been suggested as a strategy in areas where vitamin B<sub>12</sub> deficiency is an established concern. However, at this point, not enough is known on prevalence of deficiencies of the B vitamins, especially B<sub>12</sub> in LMIC, and whether fortification with vitamin B<sub>12</sub> would be an effective measure to reduce the deficiency. In wealthier countries, vitamin B<sub>12</sub> fortification of flour is most likely to lower the prevalence of inadequacy in the elderly (except for the 2% - 4% suffering from pernicious anaemia), in those who consume low amounts of animal source foods (ASFs) and fortified cereals, and in non-users of supplements [144]. The prevalence of low serum vitamin B<sub>12</sub> status (in the absence of anaemia or macrocytosis) does not appear

to increase after mandatory folic acid fortification [147]. In LMIC, flour fortification would potentially improve vitamin B<sub>12</sub> status in a much larger proportion of the population because of low usual intake of the vitamin in ASFs. Here, individuals could likely benefit across the life span, especially pregnant and lactating women, children and the elderly, but, as yet, there is currently too little experience to know for sure [144].

### 3.6.2 Vitamin D

Similar to the B vitamins, vitamin D has provoked a great deal of increased interest and attention over the last decade or so. Historically, vitamin D deficiency has been associated with rickets, a disease now largely under control [148]. However, there are periodic reports of immigrants to northern Europe being deficient, especially if dark-skinned and/or if cultural practices such as full-body cover-up or infant swaddling are prevalent [147, 148, 150]. Rickets was controlled in affluent countries after the Second World War by a combination of vitamin D and vitamin A being added to milk, better diets in general and better living conditions including less industrial pollution. However, vitamin D deficiency does appear to be a worldwide health problem to an unknown extent that is now of concern because it affects not only musculoskeletal health, but is increasingly being associated with a wide range of acute and chronic diseases [148, 149, 151] such as a possible increased risk of Type 1 diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmune diseases, and even frailty [152-155]. Global estimates of vitamin D deficiency are scarce and appropriate biomarkers and their cut-off points are uncertain [154]. A 2011 systematic review on vitamin D deficiency concludes that there is some indication that vitamin D insufficiency may be a public health problem in Latin America and the Caribbean, but the exact magnitude is currently unknown [156]. The only country with a nationally representative sample was Mexico, which found 24%, 10%, 8%, and 10% prevalence rates of vitamin D insufficiency (25-hydroxyvitamin D < 50 nmol/L) in preschoolers, schoolchildren, adolescents, and adults, respectively [156]. Maternal vitamin D deficiency, variously quoted with a prevalence of 8% to 100% depending on the country of residence and the definitions of vitamin D deficiency, predisposes to low vitamin D stores in the newborn and increases the risk of infantile rickets because the mother is the only source of vitamin D during pregnancy [150].

### 3.6.3 Vitamin E

Marginal intake of vitamin E is relatively common in the USA but there is little information about this condition globally. Data from NHANES 2003-2006 indicate that the average dietary intake of alpha-tocopherol from food (including enriched and fortified sources) among Americans 2 years and older was 6.9 mg/day [157], which is well below the current Recommended Dietary Allowance (RDA) of 15 mg/day. At this level of dietary intake, more than 90% of Americans would not be meeting daily dietary recommendations for vitamin E [157], but fortification with vitamin E is likely to continue to be voluntary in commercially sold retail foods. Figures for LMIC are not currently available.

### 3.6.4 Selenium

Although there are well-recognised areas globally where the soils are selenium-deficient, including Australia, China, Finland, New Zealand and Russia, it appears that other factors need to aggravate the deficiency before a clinical syndrome such as Kaishin-Beck's disease or Keshan disease is manifest. Selenium deficiency is known to exacerbate iodine deficiency increasing the chance of cretinism [158]. China has used fortification of salt plus other measures to address the disease in the northwest part of the country, but it seems unlikely this would become more widely used [159], although Finland does "fortify" its fertilisers.

#### **CALL OUT BOX 3: SUMMARY OF THE SIZE OF THE PROBLEM AND THE GAP BETWEEN NEED AND PROGRAMMES**

- The global gap between micronutrient deficiencies and effective measures to address them remains large (common estimates suggest around 1.6. to 2 billion people to be micronutrient deficient).
- Women, young children and adolescents are particularly at risk, especially in disadvantaged settings.
- The actual figures of the gap are not known with accuracy, partly because of insufficient data in recent years, a lack of national and sub-national surveys, and often inadequate biomarkers, meaning that much of the current data are incomplete or out-of-date.
- There are fewer national surveys (e.g. for VAD) being conducted today than a decade ago.
- An attempt to construct a Table of the prevalence of different populations by conventional age groupings (including adolescents) and gender was not possible because of insufficient data.
- Rapid survey methodologies for assessing disaggregated national deficiency levels, as well as coverage of fortification (and other interventions such as dietary diversity and supplementation) are urgently needed to provide evidence of coverage among diverse geographic and income groups.
- Similarly, increased resources are required that would lessen the data gap and would help to lessen the existing gaps between programmes and need.

# 4

## Global Overview of Current Large-Scale Fortified Foods

This overview of the commonly fortified staple food vehicles and nutrient fortificants includes considerations such as the choice of both nutrient and the food vehicles, forms of nutrients, and the many technical aspects for the choice of all of these in different socio-economic and cultural environments. The overview will be organised in three broad sections: (1) large-scale or mass fortification of cereal staple foods; (2) large-scale fortification of condiments including salt and sugar; and (3) edible oils and other food vehicles.

### 4.1 LARGE-SCALE FORTIFICATION OF STAPLE FOODS

The continuing high prevalence of iron-deficiency anaemia among pregnant women globally [88] and the poor rates of improvement [89] have helped push the iron fortification of various flours. Similarly, the continuing risk of NTDs in countries without folic acid fortification and its proven effectiveness has provided an incentive for further expansion. The Copenhagen Consensus in 2008, when commenting on the cost-effectiveness of fortification and the considerable effort at that time being devoted to scaling up the iron fortification of flours with iron and folic acid, noted that the aim was for 70% of all roller mill wheat flour to be fortified the end of 2008 (using the 2004 baseline of 20%) [5]. Considerable progress has been made but current coverage by 2016 is estimated to be 30% of the world's industrially milled wheat flour, 48% of industrially milled maize flour, and 1% of industrially milled rice as fortified with at least iron or folic acid through both mandatory and voluntary efforts [39]. The successes and failures have helped drive the expansion but programme effectiveness and measurement of impact are now getting more attention [160]. The Food Fortification Initiative continuously updates these data ([ffinetwork.org](http://ffinetwork.org)) [39].

#### 4.1.1 Wheat

Wheat is the third largest cereal produced in the world, after maize and rice, and is the second most consumed in the diet after rice. It is estimated that about 65% of the wheat crop is used for food, while 17% is used for animal feed and 12% is used in industrial applications, including bio-fuels [161]. Various varieties are eaten, and all of these varieties belong to the genus *Triticum aestivum*. By 1950, 26 USA states (out of 48 at the time) and three territories had instituted mandatory laws requiring the enrichment of cereal flour and bread, and during the Second World War, enriched bread became the temporary law of the land [18]. Although there are FDA standards for both "flour" and "enriched flour", most flour currently sold in the USA has B vitamins, including folic acid, and iron. Globally, WHO now comfortably describes it as "feasible,

well tolerated and potentially very effective strategy to prevent and reduce iron deficiency and iron-deficiency anaemia” [11]. Wheat flour is the primary staple food in a large number of countries in Europe, North America, the Middle East and North Africa [39, 161]. Increasing consumption with the globalisation of diets makes it an optimal vehicle for fortification with iron and other vitamins and minerals.

The majority of wheat is milled into flour through the mechanical extraction of the core endosperm of the kernel (which consists mainly of the bran, the germ and the endosperm), and which contains the bulk portion of the kernel’s protein and carbohydrates [162]. In broad terms, the cost average of grain (supplied to FAO by the International Association of Operative Millers) accounts for about 81% of the total cost of flour, while the rest is for electricity cost (6.5%), labour cost (4%), expendable materials and other costs (8.5%) [162]. The wheat flour is then used to prepare different breads and baked goods. The extent to which wheat flour is sifted to separate the fine-grain endosperm is the extraction rate, with higher extraction rate indicating higher retention of the bran and germ. Most of the vitamins and minerals from wheat are found in the bran or germ, and flours of 80% or lower extraction rates have a significantly reduced nutrient content. However, high-extraction flour contains higher levels of phytates, which chelate minerals and thus interfere with intestinal absorption of iron [163], although a recent study suggests this may be less of a problem, at least in anaemic women with sub-optimal iron stores, than previously thought [164]. Another recent study suggests that zinc absorption may not be related to dietary phytate intake in infants and young children based on modelling from combined data from multiple studies [165]. Depending on cultural norms and traditions, there is an enormous variety in the wheat flour products made, some leavened and others unleavened, and cooked and processed in a variety of ways. For example, in India, wheat flour is used to produce unleavened flat bread such as batura, chapati, naan, paratha, phulka, puri and tandoori roti [166]. More technical details on the processing of flour from wheat are available from the Cochrane review of Peña-Rosas et al. [103] and other technical sources [167].

Since wheat flour is consumed in such large quantities and by entire populations, it is by far the most commonly used food vehicle in large-scale iron fortification programmes [39] with 86 countries (plus the Indian Punjab Province) having legislation to fortify wheat flour produced in industrial mills. All the countries with mandatory legislation fortify wheat flour with at least iron and folic acid except Australia, which does not include iron, and the Democratic Republic of Congo, Nigeria, Philippines, UK and Venezuela, which do not include folic acid [39]. Five countries (Democratic Republic of Congo, Gambia, Namibia, Qatar, and United Arab Emirates) fortify at least half their industrially milled wheat flour through voluntary efforts [39]. Mandatory fortification of wheat flour has been reported as a key success in Morocco and Uzbekistan, with the latter having wheat flour enriched with iron and folic acid at half of the nation’s flour mills [168]. In Egypt’s national wheat flour fortification programme, ferrous sulphate and folic acid are added to all wheat flour produced under the national food subsidy programme for baladi bread, a traditional bread in Egypt that reaches an estimated 50 million Egyptians on a daily basis [169]. In 2009, Kyrgyzstan introduced the law “On the Enrichment of Bread Flour” that envisages a phased transition of all mills to mandatory production of enriched flour [170].

The benefit from, and sustainability of, an iron fortification programme depends not only on factors such as regular consumption of the chosen vehicle across the entire population, the quantity of added iron and its bioavailability, but also on the organisation of the industrial sector in a given country. More specifically, there must also be a balance between intake of vehicle (wheat flour) and amount of iron added to achieve an estimated effective daily iron absorption of about 1 to 2 mg per day [171]. Fortification of staple foods such as flour with iron can be done at a cost of only \$0.10-0.12 US per person per year, with a cost-benefit ratio calculated to be 8.7:1 [24]. As with all fortification, even with the best available data at baseline, continuing monitoring needs to be done.

The flour used to make bread has been used as vehicle for several fortificants. It has been a public food vehicle for iodine (Australia, Denmark), niacin (USA), folic acid (Australia), vitamin A (Philippines) and others. In the elimination of pellagra, the initial enrichment of bread with vitamin-rich yeast was critical and sufficiently convincing that by 1941, about 30% of the white bread and flour produced in the USA was voluntarily enriched [18], and by the end of 1942, following promulgation of federal enrichment regulations, along with the enactment of mandatory fortification by two Southern USA states, over 75% of all family flour and baker's white bread produced in the country was enriched [172].

The rationale for the fortification of staples with folic acid is the prevention of NTDs, although it will also contribute to a reduction in some anaemias. Maternal consumption of milk, fresh fruits and nuts before and during the first trimester of pregnancy has been associated with reducing risk of NTDs in offspring, which emphasises the need to recommend dietary measures to complement fortification. However, in most countries without mandatory fortification, women are not consuming the recommended 0.4mg of dietary folate per day. Despite a strong evidence base and extensive public health campaigns encouraging periconceptional daily supplementation of folic acid, such programmes have not been especially successful; not least because the most vulnerable are unplanned pregnancies affecting young women and those of lower socio-economic status and educational attainment [173]. Voluntary fortification improves the situation but is insufficient [173]. The folic acid fortification level recommended for flour by WHO is between 1 and 5 ppm depending on the estimated per capita flour availability [171]. The final amount of folic acid to be used as the fortificant has been described as "an accommodation of both effectiveness and safety" [24]. Where initiated, mandatory fortification has substantially improved folate (and homocysteine) levels and NTDs rates have fallen significantly [117, 174]. A review of the prevalence of NTD cases in 27 studies, pre- and post-flour fortification and the percentile distribution of folic acid content in flour (2005–2009) using data from Argentina, Brazil, Canada, Chile, Costa Rica, Iran, Jordan, South Africa and the USA found consistent reductions in NTD prevalence. Nevertheless some countries have chosen not to fortify, despite the continued evidence of impact, for concern of other adverse effects of long-term, relatively high intakes of folic acid [173]. Priority research needs have recently been identified, including around appropriate folate biomarkers most useful in assessing nutritional health status and development [175]. As noted above, concerns have also been consistently raised about the

risk of neuropathies among vitamin B<sub>12</sub>-deficient persons being masked by the fortification with relatively high levels of folic acid [176]. There have been ongoing concerns of vitamin B<sub>12</sub> deficiency being masked by folic acid fortification but which, in fact, appears not to be a practical problem [147].

A New Zealand Ministry for Primary Industries report estimated that the percentage of children with inadequate iodine intakes had dropped from 30% to 4% because of iodine fortification. Since October 2009, regulations have required that non-iodised salt be replaced with iodised salt in all bread except organic breads, salt-free breads, and bread mixes for making bread at home (although manufacturers can choose to voluntarily add iodised salt to bread mixes). Nevertheless, Australia, New Zealand, USA and several countries in Europe have seen a re-emergence of mild to moderate iodine deficiency, especially in pregnant women [177-179]. Australian and New Zealand health authorities such as the Australian Institute of Health and Welfare are monitoring the effectiveness of the increased amount of iodine in the food supply. Denmark continues to have mild low iodine status but has seen a decline in iodine deficiency (as assessed by urinary iodine excretion) following a multiple action intervention since 1997 involving changes in milk intake, iodine supplementation and fortified bread [180]. Australian millers are also required to add folic acid to wheat flour for bread-making purposes (although the New Zealand Government has opted for a voluntary fortification standard). All plain, fancy and sweet breads, rolls and buns, bagels, focaccia, English muffins, flat breads made with yeast and flour mixes or flour for domestic bread making must now contain folic acid [181].

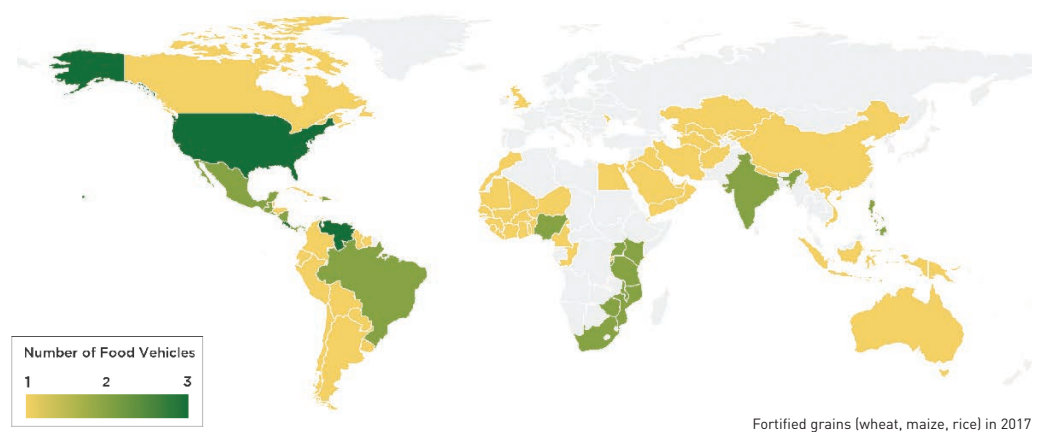
Many manufacturers now voluntarily choose to fortify other foods with folic acid, which has become a common practice especially in breakfast cereals in many countries, and it must be listed in the ingredient list on the labels. Based on all available scientific evidence, adding folic acid to bread is safe [181]. The efficacy of vitamin A-fortified wheat flour buns (pandesal) was established in young Filipino school-aged children whose vitamin A status was significantly improved in those with marginal to low initial serum retinol concentrations [182], although to our knowledge this has not been widely adopted. Bread has also been suggested as a suitable vehicle for fortification with vitamin D [183], again because it is such a common part of diets worldwide. Whereas the bioavailability of cholecalciferol from bread is not known, a study in Finland reported both fortified low fibre wheat and high fibre rye bread increased serum 25-hydroxyvitamin D concentration as effectively as a cholecalciferol supplement and so concluded that the fortified bread would be a safe and feasible way to improve vitamin D nutrition [183].

Overall, using one staple or another, the Food Fortification Initiative estimates that currently 77 countries have introduced folic acid fortification legislation and that nearly a third (30%) of the world's commercially-milled wheat flour, 48% of industrially milled maize flour, and 1% of industrially milled rice is fortified with at least iron or folic and is estimated to reach more than two billion people [39]. Iron fortification is now reaching increasingly distant localities such as Fiji and the Solomon Islands in the South Pacific. The Solomon Islands' Food Fortification National Committee has begun arrangements for a public-private partnership to help address



the three largely preventable problems of anaemia, NTDs, and longer term stunting [39] using iron, folic acid and zinc fortification for all rice and flour from industrial mills. Fiji has gone the next step in actually evaluating the impact of using fortified flour over 11 years. Despite some methodological issues, this evaluation showed that over the time of fortification, the prevalence of anaemia, and iron, zinc and folate deficiencies significantly declined in Fijian women of child-bearing age [39].

**Figure 6: Mandatory and voluntary cereal (wheat, maize, rice) fortification programmes globally**



Source: Global Fortification Data Exchange (GFDx) 2017.

[www.fortificationdata.org](http://www.fortificationdata.org)

#### 4.1.3 Maize (*Zea mays*)

More than 200 million people rely on maize, in its many forms, as a staple food [184], especially in Sub-Saharan Africa, Southeast Asia and Latin America. Estimates suggest that maize provides approximately 20% of the dietary energy (calories) consumed in the world [63, 184, 185]. Maize flour and corn meal are used here as generic terms covering various types of maize flour and corn meals that are produced and consumed in different ways [184]. Although in countries where maize is a staple, corn flour or maize meal are consumed by population groups across the social gradient, regardless of age, sex, socio-economic position, or place of residence, those populations from lower socio-economic strata and those living in less urbanised areas are the more likely to have a more heavy reliance on maize products as their dietary staple [63].

There are two basic categories applied to the processing of corn, essentially differing in particle size [186]. The cooking and processing methods used when consuming the resulting flour products vary greatly from country to country. In the wet milling process, not used for small-scale or direct consumption, maize is separated into relatively pure starch, protein, oil and fibre [187]. Industrial dry milling includes particle size reduction of whole maize, retaining all

or some of the original maize germ and fibre resulting in meal, flour, pre-cooked meal, dry masa and hominy flour [186]. In many settings, maize kernels are cooked in a dilute alkali solution (traditionally limewater, ash or lye) and after washing, are then dehulled by removing the pericarp leaving the endosperm and germ [188]. In the domestic processing of tortillas, the grain is steeped for up to 12 hours, then washed and ground to a fine dough and cooked as flat cakes. Lime concentration and cooking times both have an impact by reducing phytic acid and increasing calcium content whereas iron and zinc contents are not affected by this nixtamalisation processing [188]. In nutritional terms, a potential constraint is that the high phytate and fibre volume affects absorption [186, 189, 190], although as noted elsewhere, in women with low iron stores, this may be less of a problem than conventionally thought [164]. Cooking procedures, including nixtamalisation and fermentation, can increase accessibility of micronutrients such as niacin [185]. More information on maize home and commercial processing is available from the review by Nuss and Tanumihardjo [185], Pasricha et al. [184] and the proceedings of the meeting “Technical considerations for maize flour and corn meal fortification in public health” [186].

Although the fortification of maize flour and corn meal has less experience on which to draw compared with the fortification of wheat flour, there are now 16 countries doing so [39, 103]. Mandatory fortification is in place in Brazil, Costa Rica, El Salvador, Kenya, Mexico, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, the United States and Venezuela while Ghana, Malawi, and Mauritania have voluntary fortification [39]. Recommendations have been made by an Inter-Agency group [68] and guidelines continue to be updated internationally [103]. Although it is estimated that 48% of industrially milled maize flour is currently fortified [39], one of the main challenges is that many consumers mainly consume locally-produced, unprocessed (and unfortified) maize meal milled at the village level or in small-scale mills using hammer mills [186]. Consequently the number of small mills without fortification technology in a country will affect whether the fortification of maize flour is a feasible option for that particular country [186]. This contrasts to urban and other populations with their greater access to commercially fortified products. Sustainability of fortification programmes is difficult in contexts of extreme and extended poverty and lack of opportunities, and so poverty reduction programmes and other social intervention policies and social protection schemes often need to be put in place to support the impact of maize flour fortification [63].

WHO held a consultation on technical considerations for maize flour and corn meal fortification in public health with the Sackler Institute for Nutrition Science and the Flour Fortification Initiative in April 2013, and some of the suggested research priorities arising from the consultation are included in [Section 7](#).

#### 4.1.4 Rice

Of the 222 million metric tonnes of rice that are industrially milled each year, less than 1% is fortified with essential vitamins and minerals. While this might be “considered an untapped opportunity for food fortification” [39], it has been a considerable technical challenge to fortify rice successfully, although attempts have been made for at least 30 years. Japan had fortified grains to add to rice before being cooked decades ago (on the market since 1981) but the concept has not really been implemented elsewhere on a large-scale despite an even longer period of development since the 1940s in the USA and the Philippines [191], although the newer technology development may be changing that [192]. Rice differs from other fortified food staples, such as maize or wheat, in that the grain needs to be fortified directly rather than the sub-products (e.g. flour or porridge) [193], and some technological and technical barriers remain. The stakes are high – more people eat rice than any other staple and many are at risk of micronutrient deficiencies. Currently six countries have mandatory rice fortification (Costa Rica, Nicaragua, Panama, Papua New Guinea, Philippines and the USA), and Brazil, Colombia and the Dominican Republic have large-scale voluntary rice fortification programmes while there are three sub-national programmes in Africa, two in Europe and 15 in the Americas; and globally, at least six countries (Bangladesh, Burundi, Cambodia, China, Egypt and Indonesia) are in the planning stages [39].

The main approaches have been either covering rice grains with a micronutrient-rich rice-adhesive mixture, or by adding micronutrients to formulated rice granules made up of rice flour to be indistinguishable from other grains [194]. Technical challenges in fortifying rice have included discolouration (most consumers judge rice quality on its whiteness, unless specifically seeking brown, less polished forms) and perceptions of taste differences. Rice is known to be a highly culturally sensitive commodity with growing, selecting and cooking of rice grains all subject to regional, national and even local preferences. These differences can affect, to different degrees, the micronutrient retention and the final amount of vitamins and minerals that will be consumed [193]. Rice differs from other fortified food staples, such as maize or wheat, in that the grain needs to be fortified directly rather than the subproducts (e.g. flour or porridge) [193] and the main approaches have been either covering rice grains with a micronutrient-rice adhesive mixture by dusting, coating or extrusion, or by adding micronutrients to rice granules made up of rice flour to be indistinguishable from other grains [194]. An example is Ultra Rice® which uses formulated rice grain analogues of microencapsulated iron pyrophosphate and other micronutrients including thiamine, zinc, vitamin A, folic acid, and other B vitamins, mixed with rice flour [192]. When these grains are blended with traditional rice (typically at a ratio of 1 to 100) the result is fortified rice that is nearly identical to unfortified rice in aroma, taste, and texture [192]. More technical aspects can be found in a review article by Steiger et al. [194] covering current technologies (coating, dusting and the various extrusion technologies). The main focus in extrusion methods is on cold,

warm, and hot extrusion technologies, including process flow, required facilities, and size of operations, and the advantages and disadvantages of the various processing methods are also discussed in the review article.

An efficacy study of fortified rice in Mexico in non-pregnant, non-lactating women between the ages of 18 – 49 found that the average iron fortificant ingested was 13mg/day and that, compared to the control women, mean plasma ferritin concentration and estimated body iron stores became significantly higher, and transferrin receptors were lower [195]. Mean haemoglobin concentration was significantly increased only in those women with a lower baseline haemoglobin <12.8g/dl (as might be expected) and the overall prevalence of anaemia was reduced by 80% [195]. Studies in the Philippines of Filipino children with iron-fortified rice have also demonstrated efficacy [196]. The baseline prevalence of anaemia of 100% in all three groups in the study was significantly reduced to 51% (using ferrous sulphate), 54% (using ferric pyrophosphate) and 63% in the control group [196]. After six months, the two intervention groups showed significant further improvement whereas the control group stayed the same. Since early 2000, there have been 13 largely positive efficacy studies [197].

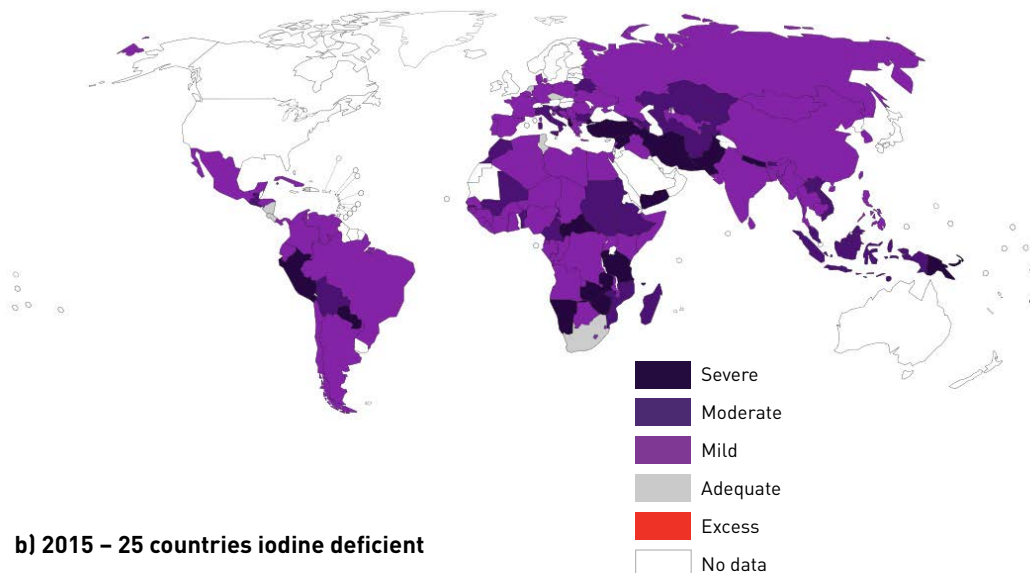
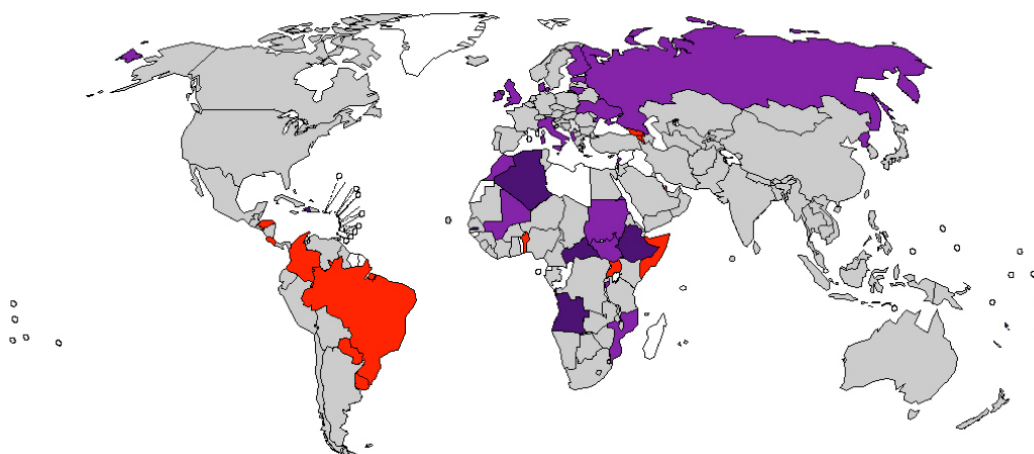
A recent overview of evidence and recommendations for effective large-scale rice fortification [197] concluded, that it is “not necessary to conduct additional efficacy trials prior to the introduction of rice fortification”. In a workshop in Bangkok in 2014, the following micronutrients were recommended for rice fortification: iron, zinc and vitamins A, B<sub>1</sub>, B<sub>3</sub>, folic acid and B<sub>12</sub> [197]. Acceptable organoleptic properties have been established in Cambodian and Vietnamese children in a promising study [198]. Effectiveness studies included those in the Philippines during 1947-49 which used a coated rice fortified with thiamine, niacin and iron and where there was a reduction in cases of beriberi [199]. Another effectiveness study came from Costa Rica which has a long history of large-scale fortification and attributed the reduction of NTDs to its “food fortification experience, its centralized rice industry, government leadership, and private sector support” [200]. The proceedings of the Bangkok meeting also noted that more specific rice fortification guidelines are in development [201]. The WHO, in collaboration with GAIN, convened a consultation on “Technical Considerations for Rice Fortification in Public Health” in Geneva, Switzerland on October 9-10, 2012 to provide technical inputs to the guideline development process, particularly with reference to feasibility and implementability [193]. At the same time a Cochrane systematic review of the fortification of rice with vitamins and minerals for addressing micronutrient malnutrition was performed [202]. These expressions of great interest in the fortification of rice reflect both the need and the challenges.

## 4.2 LARGE-SCALE FORTIFICATION OF CONDIMENTS INCLUDING SALT AND SUGAR

### 4.2.1 Salt

Iodine was not discovered as an element until the early 19th century in France [21]. However, ancient Chinese medical writings from approximately 3600 BC recorded decreases in goitre size when people ate seaweed and burnt sea sponge [203]. Although goitre was certainly recognised at that time, along with the accompanying intellectual retardation, the whole range of IDD was not recognised and described until relatively recently [113]. IDD continues to be a problem of public health significance in many parts of the world [75, 108, 204] although much improved since the widespread application of salt fortification with iodine. In the 1830s, the French nutritional chemist, Jean Baptiste Boussingault, observed that the prevalence of goitre was increased in areas where naturally occurring iodised salt was infrequently consumed and recommended the distribution of naturally iodised salt for public consumption. Although there were early attempts at this time to implement iodine prophylaxis in the USA, Switzerland, France, and other areas, adding iodine to the diet, largely through the fortification of table salt, did not begin at a large scale until the early 1920s, initially in Switzerland and the USA [203]. After fortification was initiated in the United States in 1924, when iodine was voluntarily added to salt, the incidence of goitre decreased significantly in those parts of the United States known as the “goitre belt,” (where 26-70% of children had clinically apparent goitres) [203]. Among children in Michigan, the incidence of goitre is recorded as having decreased from 35% to 2.6% between 1924 and 1935. Although iodine fortification of salt is now mandatory in 120 countries worldwide [108], including Canada and Mexico, it remains voluntary in the United States, and the USA FDA does not mandate the listing of iodine content on food packaging [203]. Russia and much of Europe also have voluntary codes [107, 110].

Universal iodisation of salt is the preferred strategy for the control of IDD in most countries [177] and salt is the vehicle of choice for fortification for the following reasons: (i) it is consumed by nearly everyone at roughly equal amounts throughout the year; (ii) salt production is often limited to a few centres, which facilitates quality control; (iii) addition of iodate or iodide does not affect the taste or smell of the salt; and (iv) iodisation is cheap (less than 0.01 USD per day) [205]. While iodine deficiency is most devastatingly seen in the mental retardation of cretins, whole populations have in the past not reached their optimal functioning due to less apparent iodine deficiency in the population and thus pregnant women. This has had enormous consequences both for individuals and communities, and for economic development of whole regions. Iodine deficiency and IDD have been considerably reduced due to iodisation of salt [115, 205] and is recognized as one of the great public health nutrition achievements. As shown in [Figure 7](#), the world has moved from 110 countries iodine deficient in 1993 to now only 25 countries deficient [107, 108]. The second figure also shows one of the current challenges in which 10 countries and some counties in China are now showing iodine excesses [107, 115].

**Figure 7: Iodine deficient countries in 1993 and 2015 (Iodine Global Network [108])****a) 1993 – 110 countries iodine deficient****b) 2015 – 25 countries iodine deficient**

Taken with permission from Iodine Global Network (IGN) [107, 108]

Although there is recognition of the importance of iodisation of salt, some 30% of LMIC households are still not consuming iodised salt. There is especially low coverage in some European and Central European countries, as well as in South Asia and some Sub-Saharan countries [115]. One estimate of global insufficient iodine intake is approximately two billion individuals, and approximately 50% of continental Europe remains mildly iodine deficient [206]. Iodine intakes in other industrialised countries, including the USA and Australia, have fallen in recent years and mild iodine deficiency has reappeared due to declining iodine residues in

milk products, and changing salt consumption patterns due to concerns about hypertension and manufacturing use. Approximately 90% of salt consumption in industrialised countries is from purchased processed foods, and so the iodisation of household salt only will not supply adequate iodine unless the food industry uses iodised salt [206].

Where salt iodisation programmes do not appear to be feasible, or not reaching at-risk groups, other strategies are needed, such as the supplementation of targeted populations with iodine [177, 207]. The fortification of other food vehicles with iodine has also been suggested and tested [11]. Although salt is by far the most common and successful vehicle for iodisation, other potentially suitable staple food vehicles for iodine fortification in public health programmes have included: water, sugar, fish sauce, edible vegetable oils and fats, cereal grains such as rice, wheat and maize flours, condiments and seasonings including bouillon cubes, and powdered or liquid milk [11], all of which have been tested with varying degrees of success. Experimental or quasi-experimental studies have been conducted to assess the effects of iodine fortification of water in Thai schools, milk in Northern Europe, the UK and US, sugar in Sudan and animal fodder in Finland [11]. There have been attempts to introduce double-fortified salt (iodine and iron) [208] and even triple-fortified with vitamin A [209]. While technically feasible, this approach has not taken off as a public health measure – partly because it requires a high degree of salt purity. The possibility of potassium-enriched (sodium-reduced) iodised salt has been raised as a potential area for further development to address concerns about hypertension and salt consumption [207]. A meeting on iodine fortification strategies in public health suggested areas of integration between salt reduction (to prevent hypertension) and iodine fortification strategies in policy development, communication and advocacy and monitoring and surveillance [210].

#### 4.2.2 Sugar

Another condiment with a long history of being fortified with successful results is sugar. In the Central American country of Guatemala, vitamin A has been added to sugar since 1974 [211] with significant results. In a country where children were widely vitamin A deficient, the current serum concentrations of retinol in children and women in the poorest part of Guatemala are the same as in the United States [24]. Only a very few of the poorest families are now considered not to have adequate vitamin A intakes [24, 33]. The fortification of sugar with vitamin A was based on the consideration that 70% of the population consumed about 60 g of sugar per day and so sugar could be fortified with vitamin A at 12 mg/day [211]. Studies in Guatemala showed that vitamin A-fortified sugar was an effective strategy for improving the vitamin A status, providing children with about a third of their recommended intake of vitamin A, and increasing the amount of vitamin A in the breastmilk of lactating women. A similar finding was later reported from a study in Zambia [34]. One of the challenges in Guatemala, despite the success of sugar fortification with vitamin A, is that the Guatemalan government still supplies additional vitamin A in the form of supplements every six months to the children of Guatemala, and micronutrient powders also include this vitamin [24]. Other micronutrients have been added to vitamin A fortified sugar with mixed results: addition of folic acid accelerates the degradation of vitamin A [212] while addition of sodium iron ethylenediaminetetraacetate (NaFeEDTA) to sugar was found to be stable and efficacious [213].

Although other fortification vehicles could be considered to deliver vitamin A [33], sugar remains the most cost-efficient for Central America, and has been adopted in virtually all the Central American countries. However, the support from both government and industry has fluctuated. A review of the experience and lessons learned found that to be successful, besides technical considerations, communication and advocacy, it was necessary to have adequate legal or statutory instruments, including a fortification law, standards of identity, technical regulations, and universal labelling [135]. Establishment of legal criteria regarding the nutrient content of the fortificant in terms of a minimum acceptable level for the consumer was found to be preferable to establishing criteria to govern the production process [135]. In the Central American context, the harmonisation of legislative instruments and technical regulations among neighbouring countries was needed to satisfy free trade initiatives and agreements [135] with possible lessons for other emerging regional trade pacts. Following the success of the fortification of sugar in Central America, the process was encouraged (largely by USAID) in Zambia. The programme has not been properly evaluated unfortunately. After initial difficulties with enforcement of the Statutory Instrument on sugar, difficulties with unfortified sugar being imported and under-selling the fortified sugar, and the low purchasing power of many households, which led, amongst other things to repackaging of sugar into smaller packets with a loss of quality and an increase in price [34, 214]. Nevertheless, the fortified sugar packets are now prominently displayed in supermarkets suggesting that they are indeed being bought and consumed.

### 4.3 EDIBLE OILS AND OTHER FOODS

#### 4.3.1 *Edible oils including margarines*

There is a long history in Europe and some other countries of fortifying margarine with vitamin A and D to ensure nutritional equivalence with butter. After the introduction of vitamin-A fortified margarine in Denmark in 1917, the number of cases of xerophthalmia reported at Copenhagen Hospital fell by more than 90% and had been eliminated by 1918 [215, 216]. Similar results were reported when Newfoundland, Canada fortified its margarine with mandatory vitamins A and D (in the USA, it remains voluntary) [217]. In the UK, vitamin A was first added to margarine voluntarily and later mandatorily during the Second World War with vitamin D to achieve nutritional equivalency to butter [4]. In the past decade, there has been renewed interest in fortifying edible oils – including margarine – with vitamin A in LMIC, especially as policy-makers look for alternatives to high-dose vitamin A supplementation. The production of vegetable oils (canola, corn, cottonseed, coconut, olive, palm, peanut, safflower, soybean and sunflower) is high throughout the world, and consumption is increasing, especially among lower socio-economic groups [216]. With the increasing incidence of non-communicable diseases and the recognised benefits of Mediterranean-type diets, consumption of vegetable oils, especially olive oil, are also increasing amongst more affluent populations globally.

Along with the criteria normally used for assessing suitability for fortification, oil fortification has the attributes of technical feasibility in terms of forming a true solution leading to uniform



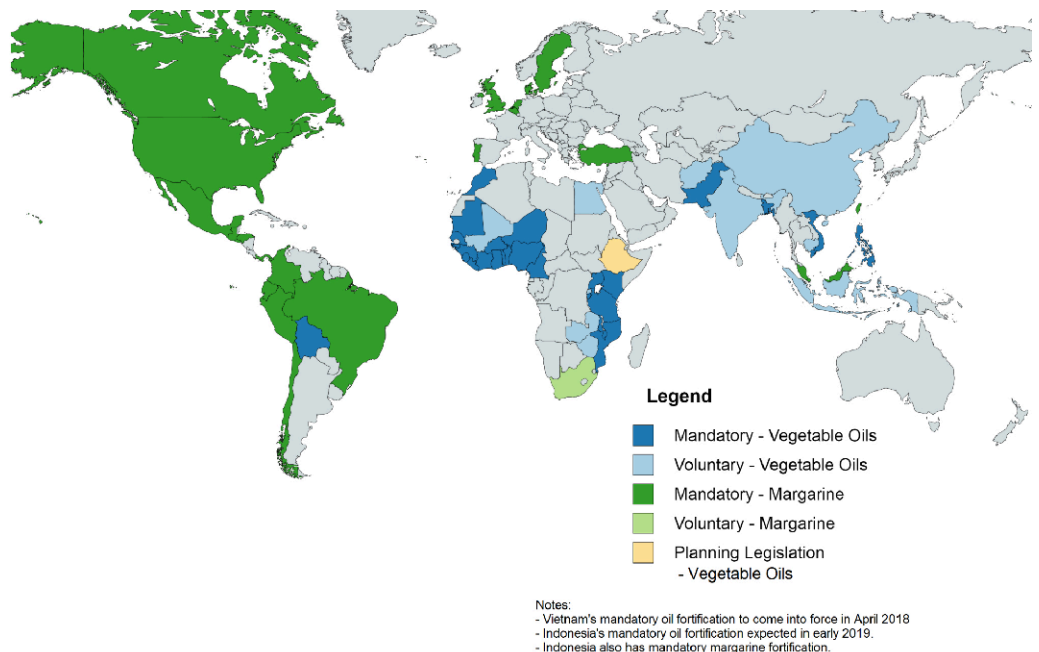
distribution in oil, stability of vitamin A in oils and the benefit that stabilised vitamin A forms remain largely active in the end product, even when used for frying, as well as organoleptic suitability (at low concentrations) [216]. Edible oils are usually consumed by almost everyone in a particular geographic population at somewhat uniform rates in a particular culture (10-20g/day in African countries and up to 70-90 g/capita/day in Asia) [216]. Oil milling is also usually capital intensive with a few oil mills serving the majority of national demand; self-sufficient home-growing and crushing of oil seeds is only a small fraction of oil use. Economically sustainable fortification has been identified as part of oil fortification with the cost increase amounting to only 0.1%-0.3% of the retail price [216], allowing producers to absorb the costs of fortification. Issues of stability are key to the effectiveness of oil fortification. While vitamin A is sensitive to light, oxygen, moisture and to some extent heat, if in sealed, light-proof containers, it is sufficiently stable to be used domestically.

One of the best examples comes from the Philippines where Star® margarine, a hydrogenated margarine product that had been popular in the country since 1931, and was consumed by poorer socio-economic groups as it did not need refrigeration, has been successfully fortified with vitamin A [11]. The initial study to determine the stability of beta-carotene and vitamin A (retinol palmitate) in the product showed high percentages of vitamin A retention and good thermal stability even when heated. Later, a double-blind, randomised community trial of children between the ages of 3 and 6 also showed an increase in mean serum retinol in the experimental group (and a decrease in the control group) after six months of daily consumption of the product. The prevalence of low serum retinol (<20mg/dl) significantly decreased from 25.7% to 10.1% [218]. Despite its vitamin A content having to be increased so that each serving of one tablespoon now provides 100% of the RDA for Filipino young children, the marketed product has remained affordable to consumers and has been made more accessible by reducing container sizes. It has also received the Department of Health seal of recognition as a product that meets national fortification standards [218].

In North America and Europe, margarine fortified with vitamins A and D is mandated. Current fortification programmes for vitamin A in fats and oils shows global distribution of 41 countries and there are likely to be others. Of these 41 countries, well over half have mandatory fortification of margarine and/or oils, eight are described as "industry-led" (or voluntary), one in which it is permitted, and seven where it was not specified [216]. Importantly, around half of those with mandatory fortification are LMIC. A recent new example was reported in 2015 when Savoror, Burundi's only cooking oil facility holding a 60% market share, began fortification, despite continued political turmoil [219]. Developed as a public-private sector partnership, Savoror's fortified oil is described as being available on the market throughout the country and with the Burundi Bureau of Standards (BBN) working closely with Savoror staff to ensure internal monitoring systems are in place and to ensure compliance with the national cooking oil standard. In the countries of South West Africa, fortified oils (cottonseed, peanut and refined palm) have shown considerable success, often combined with other fortified foods such as soup bouillon cubes, wheat flour and sugar [220, 221]. From only one country in South West Africa

with mandatory fortification in 2002 (Nigeria), by 2014, all countries but Gambia, had mandatory fortification of some combination or another, including fortification of vegetable oil (Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Guinea-Bissau, Liberia, Ghana, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Togo) while Mali had a voluntary oil fortification program [221].

**Figure 8: Countries having fortification of oil and fats programmes both mandatory and voluntary**



Used with permission by GAIN [Garrett personal correspondence 2017]. Available at:

<http://www.gainhealth.org/wp-content/uploads/2016/10/Oil-Map-October-2016-new.png>

Today, 45 countries fortify oils and fats with vitamin A. In Senegal, a recent survey reported 73% of WRAs were consuming fortified oil at least once a week getting on average at least 10% of the vitamin A RNI, and similar surveys in the state of Rajasthan in India and Abidjan in Côte d'Ivoire reported that fortified vegetable oil was contributing between 20% to 35% of the daily requirement of WRAs (Garrett and Manus personal communication 2016). While some technical issues remain with respect to storage, awareness and effective regulatory monitoring, this vitamin A fortification route is likely to grow.

#### *4.3.2 Other vehicles such as milk*

Iodine in milk has been important in the control of iodine deficiency in countries such as Australia [222] and Denmark [180]. In addition, in many countries of northern Europe, in the UK and in the USA, milk iodine is now a major adventitious source of iodine, as an inadvertent side-effect of iodophors used to clean the teats of cows before milking [11]. The virtual elimination of childhood rickets in much of Europe and North America has been attributed mainly to the addition of vitamin D to milk that began in the USA and Canada in the 1930s. Rickets may be reappearing in African American women [223]. Vitamin D fortification of milk also reduces the risk of osteoporosis in the elderly, especially in winter in northern Europe (when incident ultraviolet light levels are lower). A randomised controlled trial showed a reduction in the decrease in serum 25-hydroxyvitamin D concentrations during winter, and ensured adequate concentrations in both adults and children [224]. Although many countries continue to fortify both margarine and milk, it may not be ideal for some of these countries because of a skewness of milk intake across some population groups now [224]. Nevertheless, the fortification of milk and margarine was a critical source of vitamins A and D during both World Wars, and continues to be important, particularly for vitamin D, during the winter in countries such as Canada [223-225]. Part of the successful fortification programme in Costa Rica added ferrous bisglycinate to liquid and powdered milk in 2001 (along with fortifying maize and wheat flour) [91].

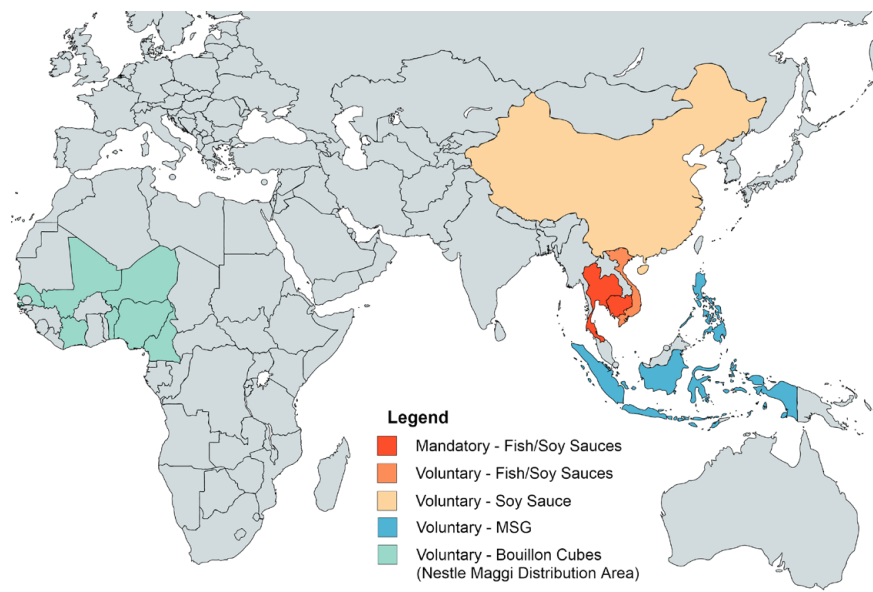
#### *4.3.3 Other condiments such as soy sauce, fish sauce and bouillon cubes*

Condiments, spices and seasonings are increasingly being used as vehicles to increase the intake of vitamins and minerals [226]. Fortification of condiments or seasonings has the potential to improve micronutrient intakes in many populations, especially as they tend to be consumed consistently by most of the targeted population, as is the case in many Asian and African countries [105]. Market-driven food fortification with iron has been used with various vehicles: soy sauce, fish sauce, salt, beverages, and bouillon cubes [11]. A systematic review has demonstrated that iron fortification of condiments is associated with increased haemoglobin, improved iron status, and reduced anaemia across targeted populations [105]. Other proposed benefits include feasibility, cost-effectiveness, sensory acceptability, targeting of sub-populations, and frequent and consistent use. Since herbs, spices, seasonings and condiments (e.g. seasoning for instant noodles) are intended to enhance the aroma and taste of food, this intervention is thought to be important as a way of reaching populations in resource-poor settings who use condiments to improve the palatability of monotonous diets that often consist of the main staple [70].

Herbs, spices, seasonings and condiments that are predominantly intended to enhance the organoleptic properties of foods are clearly defined by the Codex Alimentarius Commission, which is currently considering a revision of the nomenclature. A proposed Cochrane systematic review of iron fortification of condiments plans to include interventions in the review in which condiments or seasonings have been fortified with any combination of iron and other vitamins and minerals, regardless of the fortification technology used [227]. The review will also cover the whole range of possibilities and so “will include fortification of herbs, spices, seasonings and condiments” (e.g. seasoning for instant noodles and bouillon cubes), sauces (soy sauce, fish sauce, Thai sauce), salt and its substitutes and any other substance intended to enhance the

aroma and taste of food, including blends in powder or paste form (e.g. chilli seasoning, chilli paste, curry paste, curry roux and dry cures or rubs), onion salt, garlic salt, oriental seasoning mix (dashi), topping to sprinkle on rice (furikake, containing, e.g. dried seaweed flakes, sesame seeds and seasoning)” [227]. Until now, most of the research on fortification of condiments and seasonings has been on NaFeEDTA added to soy and fish sauces in Southeast Asian countries and various micronutrients to salt in other countries. Cambodia, with high levels of micronutrient malnutrition, has government-issued standards for the fortification of fish sauce but faced the problem that all the major brands found in markets and village and provincial levels are imported and rarely fortified [228]. Other condiments, such as bouillon cubes in Africa or curry powder in Asia are now being fortified with iron and other vitamins and minerals [229]. More than two-thirds of dietary iodine ingested by children in Ghana comes from bouillon cubes containing iodised salt [230]. The suitability of these condiments and seasonings as safe and efficacious vehicles for additional vitamins and minerals, and how such programmes would work in real-world settings require a clear understanding of several aspects from production, consumption and trade as well as acceptability in the population [227].

**Figure 9: Countries in Africa and Asia with significant fortification of condiments programmes (GAIN 2015)**



References: Murphy, P. 1995. History of Technology Development for Vitamin A Fortification of Foods in Developing Countries. Rome, Italy. Food and Agriculture Organization. Solon, F. S., Sanchez-Fermin, L. E. & Wambangco, L. S. 2000. Strengths and weaknesses of the food fortification programme for the elimination of vitamin A deficiency in the Philippines. Food and Nutrition Bulletin. 21: 239-246. Report on Regulatory Status of Micronutrient Fortification in Southeast Asia. 2011. Washington, DC. International Life Sciences Institute - Southeast Asia. Preedy, V. R., Srirajaskanthan, R. & Patel, V. B. 2013. Handbook of Food Fortification and Health: From Concepts to Public Health Applications, Volume 2. New York, NY: Humana Press.

The review will help inform a WHO guideline on the fortification of condiments and seasonings. While the review was in progress, WHO, in collaboration with the Micronutrient Initiative (MI) and the Sackler Institute for Nutrition Science, brought together technical experts, researchers, producers, policy-makers and programme implementers for a consultation on the fortification of condiments and seasonings with vitamins and minerals in public health: from proof of concept to scaling up, in New York City, NY, USA, which was held on August 26 – 28, 2014. Among the objectives were questions on the amount of fortificants used, their stability and bioavailability, as well as the acceptability of the final product, economic aspects of condiment and seasoning fortification, and the need for equitable marketing to ensure access by vulnerable populations, legal and regulatory issues and research priorities to better support evidence of improved nutrition and unintended adverse effects.

Legal frameworks become important here. In an example quoted by Mejia and Bower [231], Vietnam is able to have a soy sauce fortification programme but Indonesia does not have regulations that allow fortification of condiments (while allowing fortification of wheat flour, margarine, and rice). Many other factors can affect fortification of condiments and seasonings. For instance, a recent analysis of population data from Vietnam suggests that consumption of flavouring powders and sauces tends to slightly increase with socio-economic status, particularly in urban areas and so there might be a risk of lesser benefit for those with greater nutritional need. A national plan to launch iron-fortified fish sauce to prevent iron deficiency was planned and developed in Vietnam (with the support of GAIN), and which planned to take advantage of the fact that the fish sauce industry was state-run. A subsequent privatisation of the state-run industry greatly affected the project implementation and participating manufacturers declined from 30 to 10 [232]. Factors contributing to successful programmes, including their sustainability, are discussed in the following chapter.

**CALL OUT BOX 4: GUIDELINES AND TECHNICAL RESOURCES FOR ENSURING APPROPRIATE SELECTION AND QUALITY OF FORTIFIED FOODS**

## Websites:

- FAO (Food and Agricultural Organization of the UN) [www.fao.org](http://www.fao.org)
- FFI (Food Fortification Initiative) <http://ffinetwork.org>
- GAIN (Global Alliance for Improved Nutrition) [www.gainhealth.org](http://www.gainhealth.org)
- HKI (Helen Keller International) [www.hki.org](http://www.hki.org)
- IGN (Iodine Global Network) [www.ign.org/index.cfm](http://www.ign.org/index.cfm)  
*previously ICCIDD (International Council for Control of Iodine Deficiency Disorders)*
- ILSI (International Life Sciences Institute) [www.ilsa.org](http://www.ilsa.org)
- Industry websites such as BASF (<https://www.basf.com/en.html>); DSM, Nutritional Products (<https://www.dsm.com/corporate/about/business-entities/dsm-nutritional-products.html>) etc.
- Nutrition International <https://www.nutritionintl.org>
- Project Healthy Children [www.projecthealthychildren.org](http://www.projecthealthychildren.org)
- Sight and Life [www.sightandlife.org](http://www.sightandlife.org)
- UNICEF [www.unicef.org](http://www.unicef.org)
- WFP (World Food Programme) [www.wfp.org](http://www.wfp.org)
- WHO (World Health Organization) [www.who.int](http://www.who.int)  
*(see especially the "Guidelines on food fortification with micronutrients" (2006) and eLENA facility [www.who.int/elena/en/](http://www.who.int/elena/en/))*

**CALL OUT BOX 4: GUIDELINES AND TECHNICAL RESOURCES FOR ENSURING APPROPRIATE SELECTION AND QUALITY OF FORTIFIED FOODS**

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- HKI (Helen Keller International) [www.hki.org](http://www.hki.org)
- IGN (Iodine Global Network) [www.ign.org/index.cfm](http://www.ign.org/index.cfm)  
*previously ICCIDD (International Council for Control of Iodine Deficiency Disorders)*
- ILSI (International Life Sciences Institute) [www.ilsa.org](http://www.ilsa.org)
- Industry websites such as BASF (<https://www.basf.com/en.html>); DSM, Nutritional Products (<https://www.dsm.com/corporate/about/business-entities/dsm-nutritional-products.html>) etc.
- Nutrition International <https://www.nutritionintl.org>
- Project Healthy Children [www.projecthealthychildren.org](http://www.projecthealthychildren.org)
- Sight and Life [www.sightandlife.org](http://www.sightandlife.org)
- UNICEF [www.unicef.org](http://www.unicef.org)
- WFP (World Food Programme) [www.wfp.org](http://www.wfp.org)
- WHO (World Health Organization) [www.who.int](http://www.who.int)  
*(see especially the "Guidelines on food fortification with micronutrients" (2006) and eLENA facility [www.who.int/elena/en/](http://www.who.int/elena/en/))*

# 5

## Components of Successful Food Fortification Programmes

### 5.1 TECHNICAL ISSUES

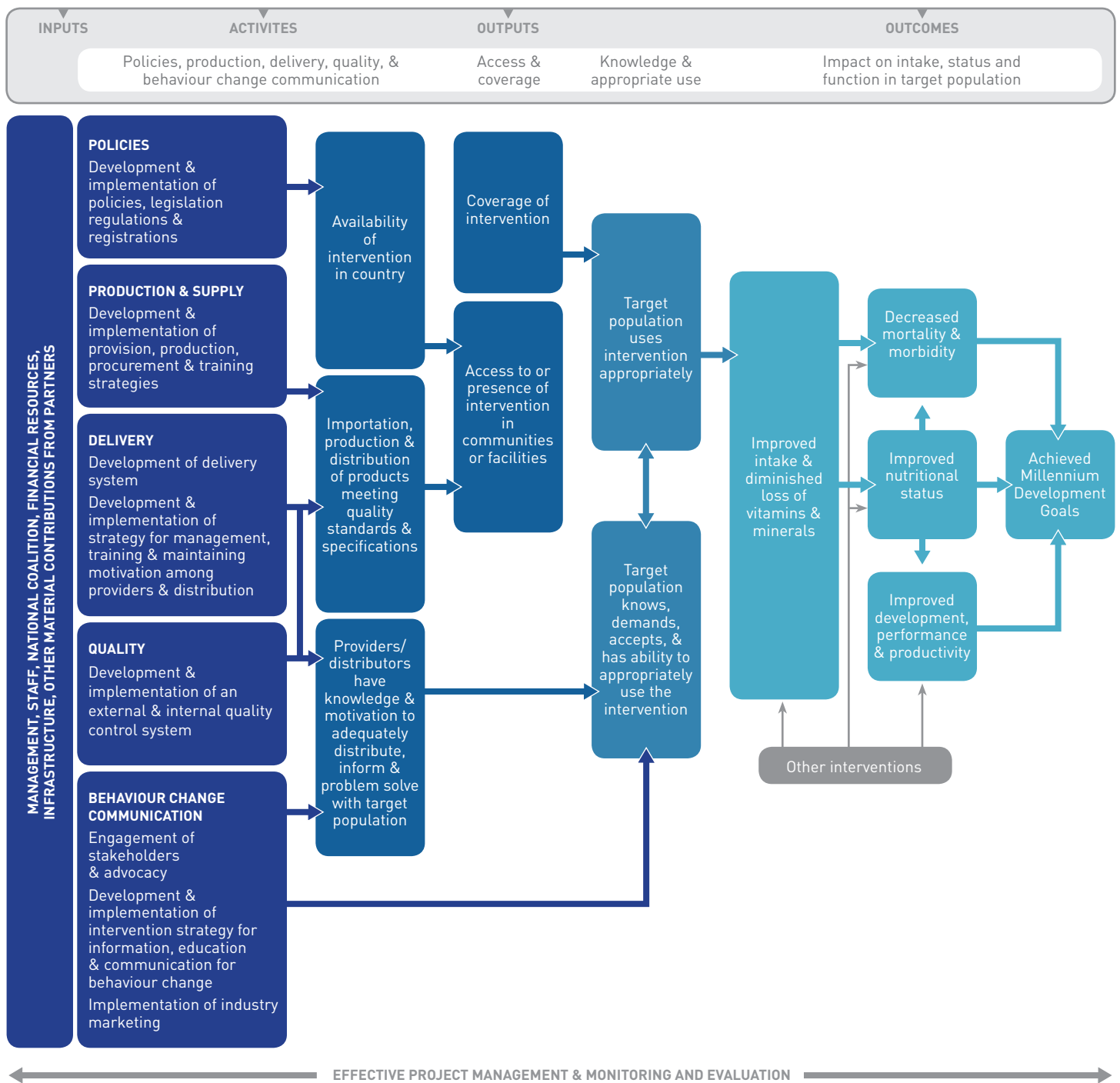
The fundamentals of a successful micronutrient fortification programme have been well described by WHO/FAO in the 2006 guidelines on food fortification with micronutrients [11] and are outlined in the WHO/CDC logic model for micronutrient interventions in public health (*Figure 10*) and the GAIN impact model (*Figure 12*). Planning goes from inputs such as identification of the problem, to activities including establishing policy, outputs identifying access and coverage, and finally outcomes including impact [233, 234]. Although there have been earlier reviews of successes and failures in LMIC and advocacy, on the basis of a successful programme [20, 235], the most commonly used guidance is now the WHO/FAO 2006 guidelines, along with intermittent technical updates [234, 236, 237] and with industry and factories having their own user manuals.

The WHO/FAO 2006 guidelines [11] note that the “fundamental requirement in the adoption of food fortification as a public health intervention is the selection of the most appropriate and suitable foods to serve as the vehicle for the extra nutrients.” The appropriate food vehicles for the fortificant need to be consumed in constant quantities by the target population, to be affordable and to be available all year round (*Call out box 5*) [11]. This will clearly depend, both for staples and condiments, on the cultural preferences and traditions of different countries and their dietary patterns. Other components are more technical, requiring that the fortificant is compatible with the food, including during its preparation and cooking, and cost, among other requirements [11].

As noted earlier, fortification of foods is but one intervention for the prevention and control of micronutrient malnutrition, and is complementary with other food-based approaches and supplementation, as well as disease prevention and control. It is now recognised that there are a range of nutrition-sensitive interventions by other sectors [44] that are necessary to cover the whole population and complement fortification interventions. Fortification does however, have the advantage of requiring relatively fewer changes in consumer behaviours than many of the other interventions - although this does not mean that nutrition education and social marketing can be ignored [20]. Without convincing consumers, policy-makers and producers of the need and benefits of food fortification, its sustainability will always be at risk, as has been seen for example, with the experience of fortification of sugar in Guatemala [211, 238] and iodine in Vietnam [239].



Figure 10: WHO/CDC logic model for micronutrients interventions in public health



Taken with permission from the WHO [140]

**CALL OUT BOX 5: REQUIREMENTS FOR A FOOD VEHICLE FOR FORTIFICATION [10]**

- Commonly consumed by the target population
- Constant consumption pattern with low risk of excess consumption
- Good stability during storage
- Relatively low cost
- Centrally processed with minimal stratification of the fortificant
- No interactions between the fortificant and the carrier food
- Contained in most meals with the availability unrelated to socio-economic status
- Linked to energy intake

The FDA of the USA established its Food Fortification Policy in 1980 with six basic principles: (i) the nutrient intake without fortification is below the desirable content for a significant portion of the population; (ii) the food being fortified is consumed in quantities that would make a significant contribution to the population's intake of the nutrient; (iii) the additional nutrient intake resulting from fortification is unlikely to create an imbalance of essential nutrients; (iv) the nutrient added is stable under proper conditions of storage and use; (v) the nutrient is physiologically available from the food to which it is being added; and, (vi) there is reasonable assurance that it will not result in potentially toxic intakes [240]. The FDA has stated that decisions relative to food fortification should be based primarily on clinical and biochemical data rather than on dietary data alone, as had been the basis of earlier guidance on fortification [241]. Although it has not always happened, the choice of the food vehicle should nevertheless be based on consumption data to ensure that the vehicle is consumed throughout the population and in sufficient quantity to have a physiological impact, but distributed so that no one group might consume too much, and the fortificant to be added is appropriate with respect to bioavailability, sensorial stability, mixing properties, and cost constraints [11]. Selecting a food vehicle for fortification and identifying which populations might be at risk of micronutrient inadequacies or excess are difficult in populations with increasingly diverse dietary patterns [24] and infrequently are the data available to address all the requirements as in Call out box 5. Consequently, programmes are often started with incomplete information, based on the experience in other countries, and so require even more monitoring and evaluating and modification and adaptations over time.

## 5.2 ENABLING ENVIRONMENTS, INCLUDING PARTNERSHIPS

One of the distinguishing features of mass fortification of staples is the degree to which it is a multisectoral undertaking, especially between the private industry milling/food sector and governments in terms of legislation, regulations and quality control. Academia is frequently instrumental in helping to identify the problem, often funded by donor countries' bilateral aid, and by single micronutrient consultative bodies such as IGN (previously ICCIDD) for iodine and USAID, Johns Hopkins University and other partners such as Helen Keller International for vitamin A. A good recent example is that of the Solomon Islands where three government ministries (the Ministries of Health and Medical Services, of Agriculture and Livestock, and of Finance and Treasury) were all signatories, along with Australian Government's Department of Foreign Affairs and Trade, the business sector such as Delite Flour Mill and Solomon Rice Company Ltd. (Solrice) and Non-Government Organisations (NGOs) such as FFI and the UN Agencies UNICEF and WHO. It is not uncommon for such a constellation of stakeholders to be necessary to get the initiative off the ground; sometimes later joined by consumer NGOs that keep an eye on the implementation and quality of the ongoing process on behalf of consumers. The early fortification of Star Margarine<sup>®</sup> in the Philippines has been praised as exemplifying a successful close collaboration of government and non-governmental organisations, industry, academics, and other sectors in confronting a public health problem [218]. More recently multi-stakeholder fortification alliances have been critical in success in many African programmes [220]. Harmonisation of fortification standards and regulations across sub-regions [220] and even across countries in the same regions [42], have encouraged programmes by encouraging trade, reducing barriers and expanding the size of markets [220]. Facilitating components of partnerships can include practical measures such as identification of a pre-mix supplier, a revolving fund, a distributor and fortified produces along with other regulating and monitoring stakeholders [242] and models for estimating nutrient addition [243, 244].

### 5.2.1 Government

Particularly with mandatory fortification of national staples, the role of the government is paramount in terms of authority and endorsement, although even with voluntary fortification government-derived regulations and quality control are necessary. Again, various templates and UN and NGO assistance are available to countries embarking on large-scale fortification, including templates for legislation [245]. Fortification is likely to have the greatest potential to improve the nutritional status of a population when implemented within a comprehensive nutrition strategy [6, 246]. In a discussion of the role of governments and academics, Harvey and Dary [62] describe key issues that governments need to include to ensure for a sustainable programme:

- Identification of the right food and fortificant (accounting for bioavailability, interaction with other foods, availability, acceptability, and cost)
- Identification of the target population (which is often the total population)
- Ensuring quality of product
- Consumption of sufficient quantity of the fortified foods

To accomplish these aims, and to ensure sustainability, there needs to be demand that is sustained through behaviour change communication at the consumer level, and ready access to a sufficient supply of products that maintain standards set through legislative process from production to point-of-consumption [20, 62].

To ensure a competitive (or at least consistent) market, which both the private sector wants and the consumers need, government monitoring of compliance to standards and public-private partnerships is essential [246]. In a slightly different model, the success of the Chinese salt iodisation programme has been attributed to a partnership between the national salt industry and the government because “the industry is uniquely organized as a monopoly with a strong centralized Governmental control” [247]. There have also been examples where a strong central government can simply proclaim that “the country will be fortified”, again with somewhat different models of governance such as the Kingdom of Jordan and Republic of Turkmenistan, an often very effective and rapid first step. Another model described in Oman and Saudi Arabia, is one where millers obtained guidelines and expertise from their contacts in the milling industry and started fortification with minimal contribution from the government [38].

### 5.2.2 Private sector

No one sector alone is sufficient for either the launching or sustaining of mandated mass-fortification programmes. In a commentary on the relationships between different sectors, Mannar and van Ameringen [246] noted that effective and sustainable fortification is only achieved when “the public sector (which has the mandate and responsibility to improve the health of the population), the private sector (which has experience and expertise in food production and marketing), and the social sector (which has grass-roots contact with the consumer) collaborate to develop, produce, and promote micronutrient-fortified foods”. As noted also by Harvey & Dary [62], a “fundamental rationale for the cost efficiency of fortification programmes is that they use products manufactured and distributed by the food industry that increase target populations’ accessibility to foodstuffs that will increase their intake of micronutrients.” There has been a long history in the private sector of doing this – in fact it would be fair to say that there cannot be mass fortification of staples without the private sector. Often, the private sector has taken the lead and continues to do so in commercial, voluntarily fortified foods. Where the private sector is not involved, sustainability is unlikely, as was the case in Vietnam where salt iodisation was a government-funded activity that largely collapsed when national legislation was revoked in 2005 [239].

The cost of monitoring and quality control is firmly in the court of the government sector in LMIC and is one of the weak links due to often inadequate funds being available for these activities [56]. Public-private partnerships are credited in raising the countries in West Africa with mandatory fortification (from Nigeria in 2002) to interest in 14 West African countries by 2014 following country assessments by industry, establishment of legal frameworks by governments and partners and the conclusions by partners that as one single fortified food could not be expected to reach all deficient populations, fortifying two to three foods would be an effective approach [221].

An important contributing factor from the private sector has been the industry bodies, such as those for salt, millers and so on – at all levels, global, regional (especially) and national. In the Middle East, the International Association for Operative Millers is given credit for “open lines of communication between the regional and international millers in acquiring ‘know-how’” [38]. The Salt Institute, as an industry body, has been critical in the development of sustainable iodisation programmes (<http://www.saltinstitute.org/news-articles/iodizedsalt/>) along with the European Salt Association, the Indian Salt Manufacturers Association and the China National Salt Industry Association, amongst other such national industry bodies (Venkatesh Mannar personal communication, 2014). A case study has been developed demonstrating building a strategic alliance for the fortification of oil and other staple foods (SAFO), showing the need for the private sector to embed itself into existing structures and processes to establish effective alliances for fortification [248]. Such bodies also contribute expertise and support to Civil Society Organisations (CSOs) such as GAIN and FFI, both of which see involvement of the private sector as a large part of their modus operandi.

### 5.2.3 International organisations

The role of the international agencies has been critical but varied. In the early days of fortification, it was mainly provincial or state governments in industrialised nations that often had their own federal or sub-national standards and legislation. When mandatory fortification moved to LMIC (then called “developing countries”), such institutions were often not there. The two technical organisations of the UN responsible for setting standards, FAO and WHO, assisted in these areas, not least through Codex Alimentarius which, as was seen in *Section 2*, has defined most of the terms used around safe and effective fortification. FAO took an early role in fortification [249] but then became less active, working mainly through Codex [54]. WHO then became more involved; for example, WHO was the vehicle through which ICCIDD became a global force [113], a role which subsequently extended to the control of micronutrient deficiencies and fortification. The UN agencies have often provided the endorsement of civil society’s early efforts, and added standardisation and legitimacy to such efforts.

Examples abound, and even when reaching relatively small communities, as in emergency situations, international agencies have provided national government endorsement for useful models of demonstrated partnerships between local communities, governments, UN agencies and NGOs, both local and international. For example, in Angola, when maize was fortified to combat the persistent occurrence of pellagra, the World Food Programme of the UN system (WFP) provided fortification equipment to a commercial mill at the port of Lobito and, using a vitamin and mineral pre-mix provided by UNICEF, this project was able to address many of the difficulties common in countries emerging from conflict to provide monthly fortified maize rations to some 115,000 beneficiaries. Similarly, in Zambia, iron deficiency anaemia was a serious problem among camp-restricted refugees. WFP and its partners imported, installed and trained workers in the use of two containerised milling and fortification units, and so helped to decrease cases of iron-deficiency anaemia by half, and reduced VAD among camp residents [250]. In Afghanistan, attempts to mill and fortify wheat flour using small-scale

chakki mills were successful, but it was concluded that much larger-scale efforts would be needed to promote demand and reach the level of consumption required to address serious iron deficiencies across the country [250], and to which the World Bank has since convened technical advice, along with GAIN and MI. Ghana has successfully adopted a system for procuring and distributing potassium iodate locally, and a salt bank cooperative was specifically designed to meet local needs and ensure competitive and stable prices [251]. Recently WHO involvement with academia and CSO, including the Sackler Institute for Nutrition Science of the New York Academy of Sciences (and government in terms of the USA CDC and NIH) has resulted in important updating of standards such as those for wheat and maize flour cereal fortification [68]. In addition, a WHO regional meeting in the South East Asia Region (SEARO) was organised in Bangkok in 2014 to discuss challenges in food fortification with different stakeholders [232].

#### *5.2.4 Civil Society Organisations*

CSOs, NGOs and PVOs (Private Voluntary Organisations of the USA) offer real variety in their composition and even in their roles. Few act without other sectors and partners. Earlier CSOs such as the micronutrient Consultative Groups were often based in academic institutions, mainly funded by USAID at the time, and worked closely with WHO in particular, as governments often needed that seal of approval for the initial adoption of programmes. More recently, CSOs have taken on a role of ensuring that fortification is done properly, quality is maintained (especially where governments may not have the resources for this), and there is equity in access. It is fair to say that the iodisation of salt would not have happened globally without the advocacy and effort of ICCIDD (now IGN), with other national partners and the WHO Western Pacific Regional Office [113]. ICCIDD always had both a large academic component (especially of endocrinologists) but always worked with national governments and UN agencies.

Even though described as CSOs, NGOs and PVOs, sometimes their funding has been almost entirely from one or two governments working through an academic institution or a PVO (which can be for-profit). Vitamin A was put on the international agenda by International Vitamin A Consultative Group (IVACG) - a partnership managed by a PVO (ILSI), largely driven by Johns Hopkins School of Public Health and funded by USAID. The Canadian government has been equally influential but in a different way by funding MI and providing vitamin A supplements globally. Similar models to IVACG, and largely funded by USAID, have been the International Nutritional Anemia Consultative Group (INACG) (for iron deficiency and “nutritional anaemia”) but which was perhaps less effective, and then IZiNCG (the last with broader funding). What might be considered their successor, the Micronutrient Forum, has a wide array of global stakeholders involved in micronutrient deficiencies with funding from the Bill & Melinda Gates Foundation amongst others. FFI, GAIN and MI have been tremendously effective in the field of fortification. Information on FFI, GAIN and MI is available on their websites – suffice to say, it would be a different fortification world today, especially in LMIC, without their being so active.

### 5.2.5 Academia

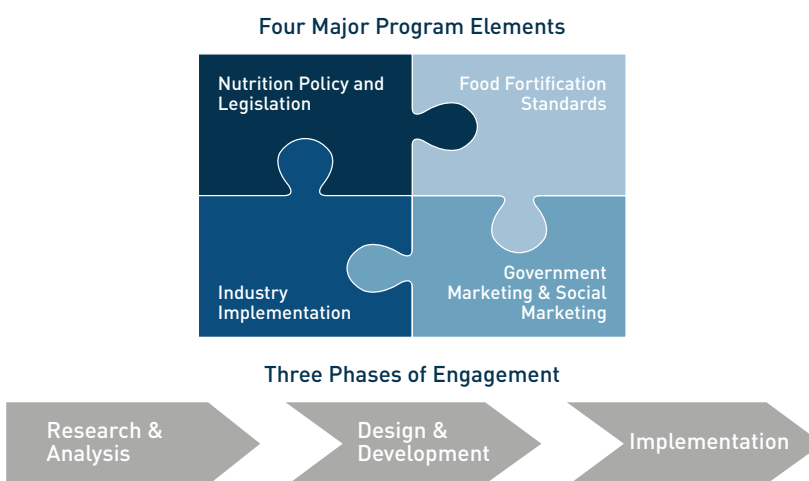
None of the above could have been done without the influence of academics and universities – often by providing the necessary “champion”. However, the evidence base for fortification effectiveness and impact is surprisingly sparse and the recent review of effective nutrition interventions notes that whereas “fortification seems to be a potentially effective strategy... evidence of benefits on morbidity and functional outcomes from large-scale programmes in developing countries is scarce” [6]. This appears to be changing, for example, the recent evidence that iron fortification programmes do appear to make a difference, at least compared to countries without these programmes [104]. Again, it is almost impossible to define the role of simply “academia” because of government and other funding, the links with civil society, and of course the populations who are the “subjects” of research, and the links with the private sector and with the UN system. Especially the last is true as WHO continues developing their evidence base for nutritional guidelines (eLENA) [71], they almost invariably use the expertise of academics, but frequently now in partnership with other groups like the recent partnership of the Sackler Institute of the New York Academy of Science, WHO and MI, GAIN and FFI. They have been working together to hold workshops on different aspects of fortification such as the recent consultation on “The global regulatory landscape regarding micronutrient fortification of condiments and seasoning” [231].

Research is critical for at least four reasons: (i) to establish the magnitude and distribution of micronutrient deficiencies; (ii) basic research that establishes bioavailability, fortificant effectiveness and nutrient and dietary component interactions; (iii) programmatic research; and finally, (iv) an adequate surveillance system designed to evaluate the long-term impact of the programme on the population’s micronutrient status [73].

### 5.2.6 Cooperation and collaboration

Categorisation of partners in fortification is probably somewhat irrelevant, as all are increasingly part of a mixture of sectors and partnerships. Nevertheless, in a presentation at the Arusha Summit in 2015, it was noted that governments are currently contributing an average of about 5% of the funds needed for large-scale food fortification in LMIC, and donors another 5%, while the rest comes from the private sector, millers and consumers [1]. The challenge, largely being met, will be to continue playing to their respective comparative advantages. A simplified but helpful framework developed by a civil society group PHC working largely in Africa on fortification programmes is used to work closely with the government and private sector partners [73] (*Figure 11*).

**Figure 11: Major programme elements in the development of large-scale food fortification programmes**



Taken with permission from Rowe & Dodson [73]

CSOs and academia have often provided the important champions – both globally and nationally, and locally such as in Guatemala’s experience with the sugar fortification programme and where “changing economic or even just political context such as a new Government can often raise barriers to the sustainability of fortification programmes.” Champions are therefore also needed to continue advocating for programmes once they have been established [211]. They are also quite essential in getting programmes off the ground in many instances – folic acid, iodine, iron, and zinc all being examples where champions have been prominent.

The different partnerships have often been responsible for the initial high financial investment in fortificant and/or factory infrastructure, and setting up standards and quality assurance and quality control programmes. There are many examples – a recent published one was in the mandatory fortification of wheat flour in Morocco and Uzbekistan [168], which now have wheat flour enriched with iron and folic acid, which had initial support provided by GAIN through a grant administered by the World Bank. In Uzbekistan almost all (33 out of 34) state mills and 4 private mills were fortifying flour, while in Morocco 8 industrial mills were fortifying flour, surpassing the target for 2008 [168]. All the CSOs quoted above have many similar stories of success in getting programmes off the ground, although clearly challenges remain, and program require ample time and on-going management to respond to these challenges[168].



### 5.3 LEGISLATION AND REGULATIONS

As micronutrient fortification of staple foods and condiments plays an ever larger role, the legal frameworks are adapting to various national [252], regional [253] and international legal systems [11]. It is nearly one and half century since the first general pure food law, at least in the English-speaking world, was passed in the UK in 1860: *An Act for Preventing the Adulteration of Articles of Food or Drink*. Subsequently the *Codex Alimentarius Commission of the Food and Agricultural Organization of the United Nations and the World Health Organization* (to give it its full, rather grand, title) was established in 1958 and remains the source of much of the fortification framework and definitions. The legal framework should ensure the commitment of government policy-makers and industrial producers to fortification in principle, regulate the costing (if necessary), ensure accurate information and communication (including product labelling), encourage the integration of social marketing, and provide the means to monitor and then enforce fortification practices [252].

A major challenge is the critical gap between fortification legislation and compliance, which is still limiting the potential positive impact [254]. National food laws and their application are described in the WHO/FAO manual [11], and the influence of international law and trade agreements can be helpful, for example congruence of legislation in countries of a global region, or a barrier such as when the fortification of a foodstuff is used as barrier to its export to another country which may be trying to protect its own products – for example, regionally as in ASEAN countries [253] or Central American countries [11, 255]. The legal framework has been described as being instrumental in ensuring the quality, safety, availability, cost-effectiveness and sustainability [252].

#### 5.3.1 Mandatory legislation/voluntary regulation

The WHO/FAO 2006 guidelines [11] note that one of the roles of government is to protect the public health of its citizens. One aspect of this for food fortification is to have appropriate legislation and/or be clearly regulated and transparent so that the safety of consumers is ensured, and monitored, and the maximum benefit for populations of targeted groups is achieved. Within the legal context, fortification is categorised as either mandatory or voluntary with mandatory fortification generally considered more likely to deliver a sustained source of fortified foods for consumption and a public health benefit [11].

*Mandatory fortification* is when governments legally obligate food producers to fortify particular foods or categories of foods with specified micronutrients [11]. When governments chose the mandatory approach, they need to be able to ensure efficacy and effectiveness in terms of addressing the micronutrient deficiencies being addressed, while at the same time, the mandatorily fortified food remains safe for both targeted and non-targeted consumers. If properly supported by adequately resourced enforcement and information dissemination systems, there is a reasonably high level of certainty that the foods will be appropriately fortified and in constant supply [11], although such compliance is far from certain [56] and is discussed more below. Access to fortified foods, because of issues of equity and socio-economic determinants, is more likely when the programme is one of mandatory fortification. However,

unless there is appropriate enforcement and quality assurance mechanisms in place (regulatory monitoring), having national legislation will not necessarily lead to increased coverage of fortified foods [253].

*Voluntary fortification* is when a food manufacturer chooses to fortify a particular product, such as a breakfast cereal, because there is a likely commercial advantage in doing so, or occasionally, when actively encouraged by the government to do so. The commercial advantage comes because consumers see a probable health advantage, although scientifically the resulting public health benefit may range from nil to perhaps substantial depending on the consumer's profile [11]. However in the case of voluntary fortification, governments do, and need to, exercise an appropriate degree of control (the definition of "appropriate" often differing) through food laws or other cooperative arrangements, such as industry codes of practice [11]. Potential benefits should be at least plausible or in some cases demonstrable; but either way, governments have a duty to ensure that the voluntary fortification is consistent with their national nutrition policies, and that consumers are not misled or deceived by either the fortification practices or the claims made about the product [11].

Some voluntary programmes, especially if supported by public education activities, are capable of achieving similar outcomes to mandatory fortification and avoid the need for complex mandatory legal requirements, such as salt iodisation in Switzerland [11]. By the 1990s, voluntarily fortified breakfast cereals had become the principal source of iron for young children in the UK [256]. Nevertheless, this is only likely in smaller, wealthier countries and the emphasis in this review is on mandatory fortification, as it is more likely to be effective in the sometimes challenging conditions in terms of resources and enforcement capacity to be found in many LMICs. A recent national workshop in China noted that worldwide, voluntary salt iodisation models have generally not achieved USI goals [247]. Sometimes, voluntary fortification has been introduced by producers before governments have seen the need (or lack of political risk) to mandate fortification. In most LMIC, mandatory fortification is thought likely to be more effective, as will be seen below in some of the challenges of compliance, and most countries are choosing this option.

### 5.3.2 Efficacy

Efficacy of food fortification with a specific micronutrient is generally accepted [6, 11] and so much of the variability in effectiveness is due to programmatic and compliance factors. Efficacy trials evaluate the impact of a test intervention under the most ideal conditions possible, usually by having all test subjects consuming a known amount of fortified foods under the same conditions to the extent that can be achieved. In a review of earlier efficacy trials in the WHO/FAO 2006 guidance, it was concluded that in "the majority of efficacy trials conducted to date, fortified foods have been shown to improve micronutrient status" [11]. The efficacy trials described in the guidance included one in Vietnam with iron-fortified fish sauce [257] and a trial with curry powder with NaFeEDTA which produced significant improvements in an Indian population in South Africa [258]. At time of publication of the guidelines in 2006, the authors felt there were no well-designed trials of the impact of iron fortification of flour [11]. Vitamin A

fortification efficacy has been established in the Philippines with monosodium glutamate [259], margarine [218], and wheat buns [182] trials [11]. And finally, several studies evaluated the efficacy of multiple fortification in Botswana, South Africa and Tanzania (cited in [11]).

Sadighi et al. [260] found efficacy in a study of food fortification in women of reproductive age in Iran by demonstrating a lower resulting prevalence of low ferritin levels. Hotz et al. [195] found an improvement in serum iron concentration after a randomised controlled trial following rice being fortified with micronized and encapsulated ferric pyrophosphate rice. Conversely, a lack of improvement in iron status following fortification with electrolytic iron has been found in efficacy studies [67], which reflects a lack of efficacy of iron fortification, when using an inappropriate fortificant [261]. Most recently, a systematic Cochrane review of randomised and pseudo-randomised controlled trials found 60 acceptable trials (including biofortification) and found that iron fortification of foods resulted in a significant increase in haemoglobin (0.42g/dL 95% CI 0.28-0.56  $P < 0.0001$ ) and serum ferritin, a reduced risk of anaemia and iron deficiency, improvement of other indicators of iron nutriture, and no effect on zinc concentrations, infections, physical growth and mental and motor development [105]. The findings also found a higher response with the use of iron-fortified condiments. Always limited funds should now be spent on improving effectiveness and improved monitoring of programmes, and especially on large-scale impact evaluations.

### 5.3.3 Effectiveness

Fortification was highly effective in contributing to the virtual elimination of the risk of deficiency diseases such as beriberi, goitre, pellagra and rickets and the evidence for this is extremely convincing [11, 19, 20, 24]. However, as the situation has changed, fortification has become more preventative, including of disease states not normally seen as conventional deficiency syndromes, such as NTDs. Although effectiveness trials and the evaluation of coverage have previously been infrequently done [11], the effectiveness and impact of fortification of flour with folic acid is an exception, no doubt partly due to the intense scrutiny it received when first advocated for [4, 241]. All the national evaluations since have found a reduction of NTDs over time [262]. For example, post-fortification assessment in Canada found that between 1995 and 1999, folic acid fortification reduced the prevalence of NTDs by almost one-half, from 16.2 to 8.6 per 10,000 in Canada [263], with similar results in the USA [264]. However, NTDs still occur, suggesting that insufficient folate is only one contributing factor, as might be expected. Most authorities now accept the effectiveness of the national programme, which does not necessarily mean that all countries have, or intend, to adopt fortification with folic acid.

The effectiveness of flour fortification in reducing anaemia prevalence has been considered equivocal [104]. To further address this question, Barkley et al. [104] used existing national-level data to assess whether anaemia in non-pregnant women was reduced after countries began fortifying wheat flour, alone or in combination with maize flour, with at least Fe, folic acid, vitamin A or vitamin B<sub>12</sub>. Countries with at least two anaemia surveys were considered for inclusion and nationally representative data from Demographic and Health Surveys (DHS), the WHO Vitamin and Mineral Nutrition Information System (VMNIS) database and other available national-level surveys. Anaemia prevalence was modelled for countries that had pre- and post-fortification data

(n=12) and for countries that never fortified flour (n=20) using logistic regression models that controlled for time effects, human development index (HDI) and endemic malaria. After adjusting for time effects, HDI and malaria, each year of fortification was associated in the 12 countries with a 2.4% reduction in the odds of anaemia prevalence (PR 0.976, 95 % CI 0.975, 0.978) compared with no reduction in 20 countries that had never fortified [104].

Disentangling confounding factors caused by inadequate implementation, failure to monitor and correct problems and using appropriate biomarkers are found in any large public health intervention. In the second Lancet Nutrition series, Bhutta et al. [6] report on a meta-analysis of multiple micronutrient fortification in children which showed an increase in haemoglobin concentrations, a reduced risk of anaemia by 57% and a mean significant ferritin increase with fortification. A meta-analysis of 60 trials showed that iron fortification of foods resulted in a 41% reduction in the risks of anaemia (Relative Risk 0.59, 95% CI 0.48–0.71,  $p < 0.001$ ) and a 52% reduction in iron deficiency (0.48, 0.38–0.62,  $p < 0.001$ ) [105]. Similarly, vitamin A fortification has been found to increase mean retinol levels in a systematic review of four studies [265] and in the Lancet review by Bhutta and colleagues [6]. The publication of forthcoming systematic analyses should provide even more evidence. However, effectiveness of mass fortification to reduce at least some biomarkers of micronutrient deficiency is now quite convincing.

#### 5.3.4 Ensuring safety

Understandably, there remains concern about safety, even given the long natural experiments that have taken place in many countries [24]. It has been observed that despite the documented success of fortification staple foods eliminating several deficiency diseases, "... 'tampering' with people's food always provokes opposition, much of it from health professionals" and that it is rarely based on research [30]. Political factors also play a role in the discussion of safety. In Chile (and elsewhere) there has been concern that population sub-groups are at risk of consuming usual intakes above the UL for folate as the consumption of wheat flour is approximately

200 g/day and fortification with folic acid was targeted at 200 µg folate/100 g flour to deliver 400 µg folic acid [174]. Despite the actually higher additional intake of folic acid for the overall population, the fortification of wheat flour has been so effective in reducing the prevalence of NTDs in Chile, that there is reportedly little support for reducing the level of folic acid fortification [174]. While safety issues have been largely set to rest in the USA [241] and elsewhere, concerns of high folic acid intakes remain. An early concern was the masking of vitamin B<sub>12</sub> deficiency, particularly in countries with often low levels due to vegetarian sub-populations. However, the prevalence of low serum vitamin B<sub>12</sub> status in the absence of anaemia or macrocytosis did not increase among older USA adults after mandatory folic acid fortification [147].

Ensuring safety requires all partners to properly do their part in the system, but is ultimately the responsibility of governments and requires enforcement of legislation and regulations and that there is active and rigorous compliance to established standards. Besides establishing efficacy and effectiveness, and cost implications, assurance of safety is essential if governments and policy-makers are to invest in food fortification. Monitoring additional intakes and nutritional

status associated with the consumption of fortified foods should be actively and consistently monitored as an integral part of any fortification programme [24, 266].

In China and nine other countries, careful monitoring has identified counties within the country where much of the population is likely to be getting too much iodine as judged by urinary iodine levels, and in some areas, iodine levels in salt are being reduced [247]. Using modelling techniques for fortificants, one study concluded that the adoption of fortification content for staple foods near the safe limit also brings into consideration the need for restricting the voluntary addition of the specific nutrient to other foods in the diet and to dietary supplements [267]. A consultative research agenda setting meeting in Vienna found that while parts of Cameroon, Guatemala and Zambia have adequate national intakes due to vitamin A fortification programmes, dietary patterns in several countries suggested that some people may be consuming excessive pre-formed vitamin from fortified foods and that further studies are needed to confirm if this is so [268]. A recent article using folic acid-based and other fortification scenarios illustrated different shifts for tails of the distribution curve of serum 25-hydroxyvitamin D concentrations [269]. The authors concluded that fortification affects those at the low end of the status distribution curve differently from those at the high end and noted that where the risk of deficiency is not universal, fortification “is at best a blunt instrument...” [269]. Nevertheless, there is “little evidence of over-consumption of micronutrients in European countries” [4] and so seems even less likely with consumption patterns in LMIC. The importance of proper monitoring is again emphasised.

### *5.3.5 Cost-effectiveness*

While governments need to be assured of effectiveness, impact and safety before introducing a mandated national fortification programme, they equally need assurance on cost-effectiveness and overall benefits to the country’s economy. The considerable short- and long-term costs of undernutrition [270, 271] and the available relatively inexpensive technologies to deliver micronutrients [5] led an update of the 2004 Copenhagen Consensus to designate micronutrient supplementation/fortification as highly cost-effective. Harvey and Dary [62] have cited its “identified potential as one of the most cost-effective approaches ... to improve nutrition globally.” Nevertheless, they note also that undernutrition, including micronutrient malnutrition, has multiple causes and therefore multiple interventions are likely to be needed to address different aspects most effectively.

Many structural factors affect the cost-effectiveness of fortification, and their relative importance will be different according to the country’s development and resources, including health care and other costs. As one systematic review noted, the more the industrial sector of wheat flour is centralised, formalised and has an established and efficient distribution system, the lower the costs associated with mass fortification will be [103]. In terms of delivering micronutrients to populations, fortification tends to have a lower unit cost than supplementation [5]. Local conditions, deficiencies and resources will all affect cost-effectiveness. For example, while fortification with folic acid in the USA is highly cost-effective, this is unlikely to be so in LMIC where health care costs are far lower, and benefits of improved folate levels are better expressed in terms of reduced mortality and morbidity [62].

Fiedler & Macdonald [272] have suggested that which foods to fortify, with which micronutrients, and in which countries, remain essential questions that to date have not been adequately addressed in a systematic way at the global level. In 2009, they proposed a tool to organise the next phase of the unfinished global fortification agenda by prioritizing roughly 250 potential interventions in 48 priority countries. By explicitly defining the structure and operations of the fortification interventions in a detailed and transparent manner, and incorporating a substantial amount of country-specific data, their study also provided a potentially useful starting point for policy discussions in each of the 48 countries, to help catalyse the development of public-private partnerships and accelerate the introduction of fortification and reduction of micronutrient deficiencies [272]. The likelihood of cost-effectiveness of the different models was then able to be estimated. The feasibility of fortifying vegetable oil and sugar with vitamin A and fortifying wheat flour and maize flour with two alternative multiple micronutrient formulations was assessed, resulting in 122 feasible country-, food-, and fortification formulation-specific interventions, and the costs of each intervention were estimated. Making assumptions of a 30% reduction in the micronutrient deficiencies of the persons consuming the food, and the number of DALYs saved by each of the programmes, Fiedler & Macdonald estimated that the 60 most cost-effective interventions would carry a 10-year price tag of US\$1 billion and have costs per DALY saved ranging from US\$1 to US\$134. The single “best bet” intervention – i.e. the most cost-effective intervention – in each of the 48 countries was identified but it is unclear how much this mechanism has subsequently been used in the countries’ decision-making.

#### *5.3.6 Cost-benefits*

For an annual cost of US\$286 million, the Copenhagen Consensus in 2004 estimated the corresponding benefits would be US\$2.7 billion (a benefit:cost ratio of 9.5:1) [5]. More recently, a presentation by Horton at the Arusha #FoodFortification Summit in 2015 clearly demonstrated the important economic return on investment that food fortification represents in LMIC. In the case of iron, for instance, the median benefit:cost ratio (in 10 countries with high levels of anaemia) was calculated to be 8.7:1. For iodisation of salt, benefit:cost is around 30:1; and for folic acid, the range extends from 11.8:1 for Chile to 30:1 in South Africa [1]. For fortification with vitamin A, cost is currently estimated at a very cost-effective US\$81/DALY. The cost estimate for 25 LMIC placed the donor investment necessary for building, improving, and sustaining programming over 15 years at US\$120–150 million, a figure considered very achievable [1].

There are also other benefits that are not always costed in, such as iron fortification reducing blood lead levels in children in Bangalore, India and presumably elsewhere [273] – this being a significant problem especially among poor children in the megalopolises of LMIC such as Kolkata and Manila. Much of the food delivered by WFP is fortified with iron, vitamin A and other micronutrients before being shipped. But there are several reasons to mill and fortify food as close to the beneficiaries as possible, not least being that milling and fortifying food locally helps to overcome the problems of the short shelf-life of whole fortified maize meal while enhancing the nutritional value of locally procured cereals. There are other potentially significant benefits for the health of entire communities by such side effects as fostering demand for fortified foods among local consumers beyond WFP beneficiaries [250]. Many

of these side benefits can improve the apparent cost-benefits, especially in hard-to-reach populations who currently, while most affected by micronutrient malnutrition, remain a challenge in terms of the delivery of fortified staples. Nevertheless, where mandated and available and accessible, the fortification of commonly consumed staples is more cost-effective than most other interventions, and achieves an impressive cost benefit.

### *5.3.7 Sustainability*

A non-systematic review of selected fortification initiatives in LMIC identified different factors that contributed to their successful implementation, as well as challenges that continually threaten the future of these programmes [20]. Nevertheless, the Food Fortification Summit in Arusha reflected the enormous increase in fortification programmes over the last couple of decades in LMIC. Sustainability of some of these programmes remains under some threat. Ultimately, the long-term sustainability of fortification programmes is ensured when consumers are willing and able to bear any additional cost of fortified foods. However, poor compliance, political shifts in support, and even complacency, can all threaten the sustainability of national programmes. Dary [238] has described the Guatemalan experience, whereas governments changed, the industry became less committed, which meant that even for a successful, ground-breaking enterprise that stretched across Central America, sustainability has at times not been assured. This was also the case for salt iodisation in Vietnam [236]. Many factors may change over time, for example similar to salt, sugar has also become less favoured as a food vehicle for health concerns. Consumers must therefore be convinced and, perhaps through an NGO or CSO, express their determination to keep the fortification programme alive [274]. Nevertheless, the sustainability of programmes over three-quarters of a century in some affluent countries, admittedly with different factors in play, demonstrate the potential sustainability of such programmes.

The introduction of iodised salt has considerably improved the iodine-deficiency situation globally. In 2003 there were 54 iodine deficient countries and now there are only 25, but there are parts of South Asia and some Sub-Saharan African countries where many households do not have access to iodised salt [108]. In many affluent countries, mild iodine deficiency has returned to young women of reproductive age [16, 75]. Salt, the main vehicle for fortification, is being actively advocated for reduced intakes due to concerns of high levels of hypertension globally (although not necessarily intakes incompatible with iodisation [210]). Dietary fads come and go, and various non-iodised salts are regularly recommended by chefs. Well-documented incidences of iodine excess could undermine a government's commitment to salt iodisation programmes. Vitamin A deficiency is still a problem for between 17%-25% of children under five in LMIC, and new delivery modes are being increasingly called for [33]. A predicted lack of present donor levels of support for vitamin A supplementation is partly driving the current expansion of fortified oils and this may encourage increased sustainability. Iron, the third of the original big three public health micronutrients, despite having the longest history in the mass fortification of cereals has been harder to address and there has been relatively modest change in prevalence levels of iron-deficiency anaemia in LMIC [40]. More effective fortificants and coverage will improve outcomes and sustainability of programmes.

Integral to the success of fortification programmes, as has been noted above, is close collaboration and coordination between, and across, different sectors, multiple ministries and agencies. However, as constant experience shows, obtaining such coordination and cooperation between ministries is a real challenge. Besides initially complicating the introduction of national fortification programmes, continued attention and strong support from a champion or a minister is required, and one who must be willing to look beyond his or her own ministry needs, and especially so, if there are no funding benefits [73]. However, when a fortification programme is established, sustainability is more likely to be ensured when it “benefits from private industry strengths, has a strategy that is institutionalized within and owned by the country, and avoids long-term dependency on outside assistance” [73]. But even here the government’s mandate is to ensure that the private industry which is implementing the fortification complies with producing a quality product and that such enforcement continues to be maintained. The passive role of consumers, while important in acceptance and coverage, has sometimes been over-emphasised as a factor suggesting that consumers need not to be aware that they are part of a large-scale fortification programme [275]. This may not always be true for sustainability, where actively engaged, or at least knowledgeable, target populations can influence policy, as consumer education and awareness are important for both compliance and sustainability.

#### **CALL OUT BOX 6: COMPONENTS OF SUCCESSFUL FOOD FORTIFICATION PROGRAMMES**

- Foundation building using evidence and advocacy
- Establishing standards, enabling legislation and regulations, achievable goals and building multisectoral partnerships
- Launching the programme by setting up a compliance and enforcement framework, procuring equipment and pre-mix, training, developing a marketing and communication strategy and crucially, developing a monitoring system
- Initiating production and distribution
- Scaling-up production and delivery
- Demonstration of health impact to ensure programme effectiveness and sustainability



# 6

## Assessing Programme Effectiveness and Evaluating Impact

The often underestimated complexity of fortification and the many links in the chain to successful impact, any of which could be the weak link, makes establishing effectiveness, causality, and ultimate impact something of a challenge. It has also been noted that impact evaluations of most health and nutrition programmes, including food fortification interventions, are rarely performed, in part because they are seen as “being complex, costly and sometimes threatening” [11]. A systematic evaluation of 76 studies and 41 contextual reports presented by Professor Zulfiqar Bhutta and co-authors at the #FutureFortification Global Summit on Food Fortification in Arusha, Tanzania in 2015 concluded that fortification of staples with vitamin A, iron and iodine can confidently be expected to be effective in LMIC [1]. It was concluded that there is now “strong evidence of important and measurable improvements in micronutrient status and health outcomes in women and children in wide geographic settings in LMIC.” Fortifying with vitamin A was estimated to reduce the prevalence of deficiency in children less than five years of age from 33.3% to 25.7% globally; effectively fortifying with iron would be expected to reduce anaemia by 14%; salt iodisation has reduced goitre by 40% in countries such as Pakistan; and fortifying flour with folic acid has reduced NTDs by 40%–50% [1].

Evaluation has been defined as the assessment of the effectiveness and the impact of the programme on the target population [11]. Evaluations are therefore undertaken to provide evidence that the programme is reaching its nutritional goals which might be: (i) an increased intake of the fortified food or of specific micronutrients; or (ii) an improvement in the nutritional status, health or functional outcomes of the target population. As a poorly implemented programme (as detected by monitoring), is unlikely to achieve its planned outcomes, resources should not be wasted in undertaking evaluations until programme operational problems and inefficiencies have been corrected [11]. Clearly, for a fortification programme to be effective, the fortified product must be available for purchase from locally accessible outlets and retail stores, and has to be actually purchased and consumed with sufficient frequency and in appropriate amounts by the targeted population [11]. Issues of equity and socio-economic determinants of those who may or may not have access to fortified foods will affect the impact of large-scale fortification [63], but must obviously be part of a successful fortification programme. Besides technical implementation, to achieve the desired impact, the tools described here need to be used to identify problems; but once identified, there needs to be active compliance in addressing them.

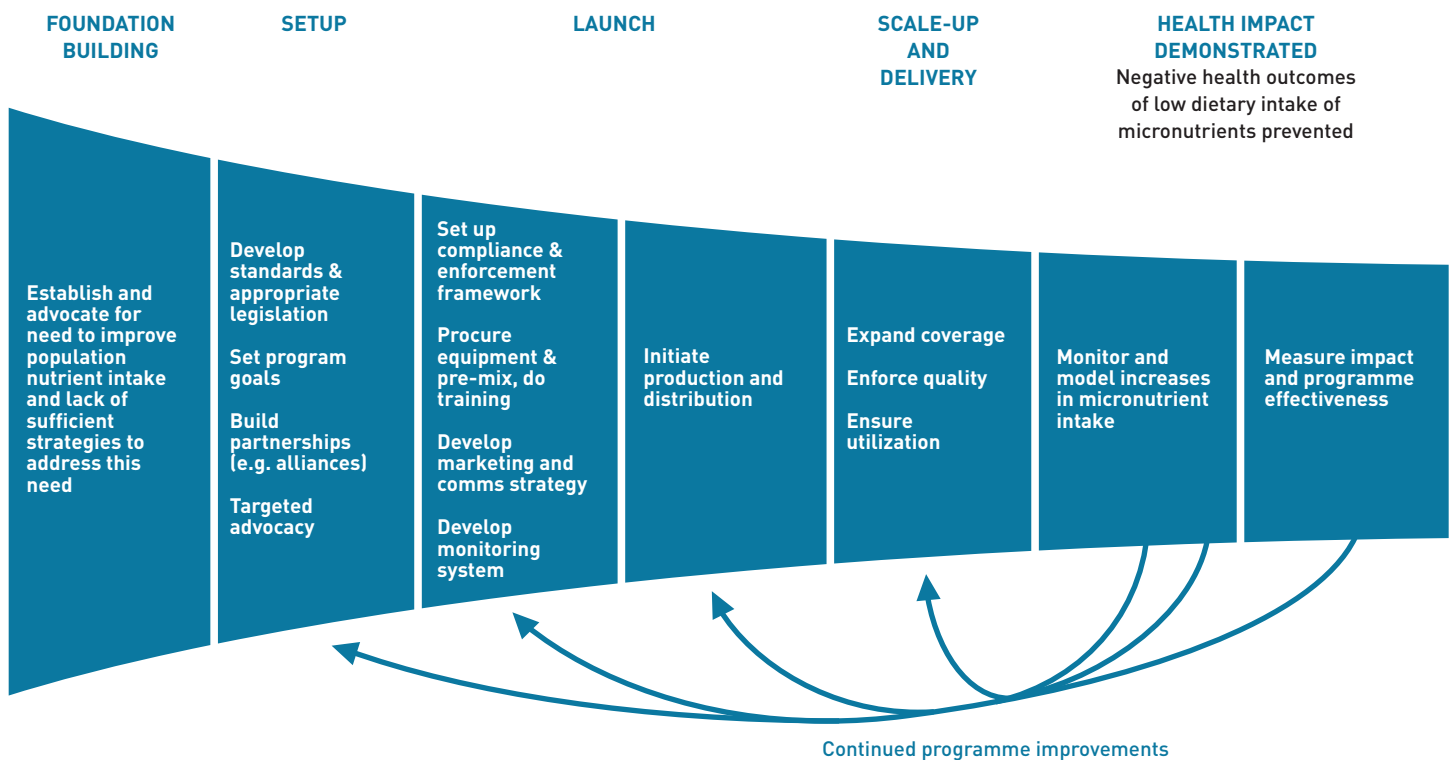
There have been at least three other systematic reviews done or have protocols published to establish effectiveness of fortification, specifically on the fortification of maize flour [184], wheat flour fortification [103], and rice [202] on micronutrient status and functional outcomes in women and children [276]. Evidence that food fortification programmes do indeed improve nutritional status has been reported from either efficacy trials and/or reports of programme effectiveness rather than specific intentions to measure effectiveness or impact [11]. Of the three broader systematic reviews, one is apparently at title registration phase [277], one was published in Nutrition Reviews on multi-micronutrient fortification of foods [278], and one in Systematic Reviews [276]. The overall conclusions of these reviews showed that “multi-micronutrient food fortification consistently improved micronutrient status and reduced anaemia prevalence” but that overall effects on morbidity, growth, and cognitive outcomes were equivocal [278]; and that “fortification is potentially an effective strategy but evidence from the developing world is scarce” [276]. Further identification of challenges and improved approaches resulted from the Regulatory Monitoring Working Group at the Arusha #FutureFortified Summit [69] (as in Annex 1). There is a continued need for more programme evaluations to be conducted in order to assess the direct impact of fortification on morbidity and mortality [276].

Building upon the WHO/CDC logic framework described earlier (p54) [234], GAIN has developed an impact model as in *Figure 12*. It demonstrates the major steps that need to be taken up to the scale-up and delivery and finally the demonstration of impact. Each of these steps need to be effectively done to achieve positive outcomes, and the impact being aimed for. To do this, effective coverage, utilisation and product quality all need to be known. Providing the steps needed to evaluate impact is the “Fortification Assessment Coverage Tool (FACT)” which has been used in several countries including Ethiopia, Senegal and Uganda [221, 279].

Important program planning steps need to address four main issues [69]:

- (i) Evidence of key factors that will facilitate scaling-up and sustainability.
- (ii) Identification of appropriate stakeholders who will need to be engaged, how to ensure accountability, and how can any National Fortification Alliance/Council be strengthened.
- (iii) Supply issues such as solid pre-mix procurement mechanisms, and quality systems.
- (iv) Demand issues including the cost-effectiveness of social marketing and behaviour change communication, especially to low-income consumers.

Figure 12: Impact model for staple food fortification programmes



Taken with permission from GAIN

### 6.1 MONITORING, QUALITY ASSURANCE AND QUALITY CONTROL

For mandatory fortification to work, consistent and effective monitoring and evaluation to ensure quality assurance and quality control are entirely necessary [11] and therefore need to be in place at the very inception of any fortification programme. Done properly, monitoring, and then appropriate actions being taken based on the results of the monitoring, will both assess the quality of the implementation and delivery, but also the degree to which the fortified food is actually reaching households and individuals, and thus presumably achieving its nutritional goals. It also is critical for providing programme planners and policy-makers with the necessary information to make decisions about how the programme is going and thereby deciding whether to continue, expand, modify, replicate or end a programme [11], although political and economic factors can all distort these decisions.

Monitoring the operational performance (or implementation efficiency) is detailed in the WHO/FAO 2006 guidelines [11] but basically the whole operation must be monitored through a system of continuous data collection at key delivery points that identify bottlenecks or operational inefficiencies. These must then be brought to the attention of the programme person

responsible and remedial action taken – this whole set of actions constitutes programme monitoring [11] of which the two main categories are of regulatory monitoring and household/individual monitoring. Programme monitoring needs to pay more attention to programme coverage as assessing the availability, access and utilisation of public health nutrition programmes [242].

Regulatory monitoring includes all monitoring activities conducted at the production levels (e.g. factories, packers etc.), as well as monitoring at customs warehouses and at retail stores, by regulatory authorities, as well as by producers themselves as part of self-regulation of programmes [11]. Production level regulatory monitoring comprises both: (i) internal monitoring where quality control (QC) and quality assurance (QA) practices are carried out by producers, importers and packers; (ii) external monitoring which is basically the inspection and auditing of activities at production centres and importation and customs sites and where government authorities are responsible for assuring compliance with standards and regulations; and, (iii) commercial monitoring, also usually the responsibility of government, but is conducted at the level of retail outlets. The latter can also be done by civil society, such as the testing of nominally fortified salt for acceptable iodine levels by schoolchildren through UNICEF and NGOs. At this point, indicators of the use of fortified foods to verify compliance have only been incorporated in a few countries' national surveillance systems, such as in Nicaragua [242].

There is also household and/or individual monitoring, such as the testing of household salt to see if adequately iodised, or testing sugar samples brought into school by pupils to see if there is adequate vitamin A [11]. Just because a food is monitored as being adequately fortified at factory, or even retail level, by the time it reaches the household to be consumed, several factors might be affecting the levels. It may have been stored too long or in an inappropriate way, it may not be consumed by some members of the family, or the household may be buying (perhaps cheaper) non-fortified versions of the food [11]. Finally, are individual family members consuming sufficient amounts of fortified products that will increase their intake of specific micronutrients (and/or to meet programme nutritional goals for specific age/physiological groups) [11]?

Appropriate indicators are needed for each of the above activities, for example the percentage of samples that must comply with minimum levels and maximum tolerable levels [11].

Quantitative analysis methods for the accurate control of added fortificant is often a challenge but affordable methods are emerging. For example, Ghana is implementing a rapid test device for vegetable fortification which has confirmed that 95% of vegetable oil is adequately fortified in the country [251]. Even if all other aspects of programming have been successful, if fortified foods are not routinely monitored to ensure levels fall within the designated appropriate ranges, the programme may have too little, or even no impact, and so will risk losing support for the programme as a whole [73].

### 6.1.1 Quality assurance/Quality control

Quality assurance and control (QA/QC) should be complementary and both need to be used for the best end product, in this case the fortified food. The International Organization for Standardization (ISO9000 - the independent, non-governmental membership organisation that develops voluntary international standards to ensure “that products and services consistently meet customer’s requirements, and that quality is consistently improved”) defines QA as “part of quality management focused on providing confidence that quality requirements will be fulfilled.” It is the implementation of planned and systematic activities necessary to ensure that products (or services) meet quality standards [11]. QA, when applied to fortified products (both in pre-production meeting of specifications and requirements, and during manufacturing production making sure the system runs to meet specified quality controls) has both administrative and procedural activities that need to be implemented.

In the context of food fortification, the following procedures for QA are listed in the WHO/FAO 2006 guidelines [11] and are repeated here to give some idea of the complexity that often under-resourced programmes need to address:

- Obtain from the providers a certificate of quality for any micronutrient mixes used
- Request, receive and store in a systematic, programmed and timely manner the ingredients and supplies for the preparation of a pre-blend
- Produce the pre-blend according to a schedule that is adjusted to the rate of food manufacturing and fortification
- Control the adequate performance of the pre-blend equipment
- Appropriately label and deliver the pre-blend
- Use the pre-blend in the same order of production (i.e. first in, first out)
- Verify appropriate functioning of the feeder machines and the mixers in a continuous and systematic manner
- Ensure that the product is adequately packaged, labelled, stored and shipped
- Consider other process variables, such as pH and temperature/time exposure

Quality control (QC) is defined as the techniques and assessments used to document compliance with established technical standards through the use of objective and measurable indicators that are applicable to products (fortified foods) [11]. It is usually conducted by government, or at least for the government by an appropriate agency. QC focuses on quality earlier in the process than quality assurance. Many publications on good manufacturing practice are available including through ISO and the public health aspects are covered more fully in the WHO/FAO guidelines of 2006 [11].

The QC procedures will typically consist of taking samples of the fortified food, either by batch or in a continuous manner depending on the system of production, and determining their micronutrient content – the variations in sampling timing and other factors are again available in technical manuals and outlined in the WHO/FAO manual [11]. The whole process can be a considerable challenge to under-resourced national programmes [56]. While it has been observed that local, as well as central, governments have a key role in regulatory enforcement, good manufacturing practices, and distribution and control of the fortificant pre-mix [238], the resource and capacity constraints are likely to be even greater at local and sub-national, often under-resourced, levels.

Awareness that a fortified product might be checked by government food control authorities is presumed to be a strong motivational factor in compliance [11] but not always so in practice [56]. Ideally, inspection and verification of legal compliance is based on the analytical assessment of the micronutrient content of a food product by means of a quantitative assay [11]. This should allow the monitoring reports to say that at least 80% of samples from factories, importation sites and warehouses have the legal minimum amount, and less than 20% of samples had a micronutrient content that is above but always near the Maximum Tolerable Level [11]. Not all government laboratories can consistently do this, and some of the partnerships discussed above have been instrumental in strengthening capacity by either training in methods, providing reagents and instruments, or both.

## 6.2 COMPLIANCE

Compliance to legislation and regulation as assessed by both QA and QC is necessary to achieve a suitably fortified product. Compliance appears to be worryingly low in many LMIC programmes, suggesting a systematic problem [56]. A review of external quality assurance and quality control activities in GAIN-supported staple food fortification programmes in 25 countries found that the external pass rate ranged from 18% to 97%, and averaged under half of all programmes (45%-50%). When the survey factored in available national data, market surveys as well as anecdotal observations from other programmes, the average pass rate was even lower – around 40% [56]. Many of these non-compliant fortified foods were found to be labelled as compliant, further misleading consumers on vitamin and mineral content, and contributing to a reduced health impact of fortification programmes when foods are not adequately fortified [253].

There are five underlying issues reported that are leading to poor compliance in the 25 countries supported by GAIN [56]:

- (i) Food laws and regulations related to monitoring, inspection, and enforcement are too often fragmented and not appropriately set within legal frameworks, leading to a lack of, or weak, enforcement.
- (ii) Food safety and quality control practice and culture do not prioritise fortification, especially where resources are limited. Preventing food contamination that might present high safety risks typically has a clear budget line, while under-fortification or checking quality parameters of foods are often under-budgeted. Over 80% of government respondents noted that their current funding was not sustainable over the next five years.

- (iii) There is political risk in enforcing compliance with regulations. Even where resources and capacity exist, over 60% of respondents thought that regulatory agencies are often unwilling to enforce regulations due to perceived or real resistance from interest groups.
- (iv) There is the cost to industry to fortify and some industries lack appropriate internal budget and expertise to fortify appropriately while others purposely under-fortify.
- (v) Fortified food is a type of credence good – consumers must trust what is stated on packages in relation to vitamin and mineral content but often enough regulatory monitoring agencies and consumer protection groups are not actively protecting consumers from under-fortified or non-fortified foods, or fraudulent labelling.

How can compliance be improved? The review of Association of Southeast Asian Nations (ASEAN) countries' regulatory monitoring concluded that unless there are appropriate enforcement and quality assurance mechanisms in place to motivate compliance by food producers, having national legislation will not necessarily lead to increased coverage of fortified products and associated outcomes [253]. However, this may not in itself be sufficient. The strength of the review on 25 GAIN-supported country programs on compliance [56] is that it aimed to find the actual compliance rates and attitudes to different aspects of compliance by conducting a questionnaire survey that included regulatory monitoring agencies. Thirty-nine respondents (71% participation rate) in 17 LMIC countries (out of 28) demonstrated clearly that the attitudes of the different sectors involved in compliance have both different perceptions and priorities. The study questions addressed the five major components necessary for adequate fortification [11]:

- (i) food law and regulations; (ii) food management; (iii) inspection services; (iv) laboratory services; and, (v) information, education, communications and training [56].

The information and communications aspect in particular were seen as important while over two-thirds (65%) of respondents cited the need for clearer regulations as their top priority for factors that would lead to better compliance. Various studies of industry behaviour towards complying with legal requirements have found that an important component for compliance is the perception that both detection and prosecution is probable, and that similar treatment will be transparently applied to all – the oft-cited “levelling of the playing field” [280]. Apart from consensus on the importance of having clear regulations, there was little agreement on other factors. The industry respondents then rated incentives and penalties for enforcement, communication between sectors, and industry engagement as the next highest priorities. These factors however were among the lowest priorities for regulatory agencies, suggesting a somewhat different world view of priorities among stakeholders, and probably ways of dealing with them [56].

Suggested actions included: (i) ensuring that improved legislation, regulations and clear and consistent enforcement mechanisms are in place; (ii) more robust national budget allocations for effective regulatory monitoring and enforcement than is currently being provided for the necessary inspectors, training, and improved laboratory micronutrient testing capacities required; and, (iii) the potential of civil society or “third parties” to be strengthened, as it is still

a largely untapped resource for monitoring fortification programmes and can be a powerful watchdog, exposing the names of those industries passing off their non- or under-fortified products as good consumer choices [56]. It has been noted elsewhere that resources must be applied strategically and focus on essential proven elements of monitoring fortification programmes to be effective [281]. While an impressive number of LMIC governments have supported the establishment of national fortification programmes, stronger leadership of all sectors is necessary, including revisiting their fortification programmes and strengthening the effectiveness, sustainability, budgets, and especially improving compliance, with consistent national standards. All the partners discussed above have a role to play in strengthening compliance. A recent article identifying the barriers and good practices to adequate regulatory monitoring of fortified foods expanded the means by which process can be reinforced by ensuring: clear legislation, government leadership, strong enforcement of regulations, improved financial and human capacity at the regulatory agency and industry levels, civil society engagement, simplified monitoring processes, and relationship building between industry and government [56].

### 6.3 ASSESSMENT OF FORTIFICATION COVERAGE

Effective coverage is defined as proportion of the population who utilize an intervention as per intended to achieve a biological/health impact [282]. For food fortification this could be interpreted as the proportion of the population consuming adequately fortified food [283]. The FACT tool has the objectives (depending on local conditions and aims [279]) to:

- (i) Assess the coverage and consumption of fortified vegetable oil and fats, wheat flour, maize flour, and salt among households.
- (ii) Measure the levels of select nutrients in samples of the above fortified foods as gathered at the household level.
- (iii) Estimate the contribution of fortified vegetable oil, wheat flour maize flour and salt to the intake of the population group of interest (in this case women of reproductive age).
- (iv) Evaluate other health and nutrition indicators and their association with coverage and consumption of fortified foods.

There are frequently no recent data in country on the performance of large-scale programmes, including addressing questions on who is benefitting. Are vulnerable populations being reached? What is the actual household coverage and intake of the fortified foods? One model that has been adapted is that of Tanahashi [284] used for health services coverage. Using this process, the dietary contribution (%RNI) of selected nutrients (vitamin A, iron and iodine) from consumption of fortified foods among a population of interest (such as WRA) can be estimated [279].



## 6.4 IMPACT EVALUATION

Impact evaluation has been a big gap in fortification programmes but is receiving more attention now. The decisions on the most appropriate biochemical indicators or biomarkers to be used in measuring impact can be a challenge, as may the capacity, both human and equipment to apply them. For example, haemoglobin levels, which are relatively easy to obtain are well known to be an insensitive indicator of iron deficiency [62, 285]. The measurements used for impact assessment of the fortified food should also be linked to changes in the intakes of nutrients measured in the overall diet [11]. Both public health considerations and political consequences of impact evaluation are important.

Evidence of impact, even from programmes with apparently adequate coverage may be seen as disappointing, if not done properly. Although the programme reach may be adequate, an inappropriate fortificant may have been used, or the measurements of outcomes are inadequate. For example, in Costa Rica, after the ineffective fortificant, reduced iron was replaced by ferrous fumarate in wheat flour, and ferrous bisglycinate added to maize flour and milk, anaemia and iron deficiency significantly reduced in women and children [91]. It has been recommended that evaluations are more likely to be useful when based upon a sound programme theory – “a causal pathway developed explicitly to identify the critical points through which a programme is predicted to provide the desired impacts” [62], such as the WHO/CDC logic framework or its streamlined version in the GAIN Impact model above. If there is high coverage of fortified foods but only limited impact, it is likely due to regulatory monitoring that insufficiently “identifies and holds producers accountable for under-fortified products” [56].

Studies need to be conducted to determine the efficacy and effectiveness and the impact of the nutritional deficiencies being targeted. This has infrequently taken place, such as for example establishing the effectiveness of wheat flour fortification with iron to reduce iron deficiency and iron-deficiency anaemia [32, 245, 286-288]. A systematic review in 2015 concluded that the effectiveness of flour fortification for reducing the prevalence of anaemia is “limited” but evidence for reducing the prevalence of low ferritin in women was “more consistent” [261]. A further systematic review of results from both experimental and observational studies is underway [103] using the WHO/Centers for Disease Control and Prevention (CDC) logic model (*Figure 10*) that incorporates the many factors involved: those of appropriate policies, legislation and regulations, external and internal food quality assurance and control systems, and the development and implementation of strategies for information, education and communication for behaviour change among consumers [103, 233]. A recent study published in 2015 to determine whether anaemia prevalence has been reduced among countries that fortify flour concluded that anaemia prevalence had in fact decreased significantly in countries that fortify flour with micronutrients, compared with countries that do not [104]. Although, the authors warned for caution because the type of evidence used precluded direct causal attribution, they also found that countries that had been fortifying for a longer time were more likely to see reductions in anaemia [104]. Further research is needed for large-scale fortification in general, both as evidence of impact and to identify constraining factors.

# 7

## Challenges and Evidence Gaps

While numerous studies and reports attest to fortification's effectiveness and feasibility [11, 287, 289, 290], challenges and evidence gaps do remain. Although many of these issues have been identified for decades, some complex questions and issues continue to need addressing. The remaining technical challenges include: the need for better biomarkers, especially in the face of high levels of infectious diseases; the magnitude of any negative side effects over time and whether these side effects are significant issues; upper limits being exceeded in the face of concomitant voluntary commercial fortification and supplementation; interactions with other micronutrients or diseases such as iron and malaria; and the most appropriate forms and use of effective fortificants. In addition, programmatic challenges remain: ensuring effective coverage of large-scale programs; ensuring and endorsing quality control and monitoring; and ensuring accessibility and equity of mass fortification programmes.

### 7.1 TECHNICAL CHALLENGES AND EVIDENCE GAPS

Despite this long history of fortification, technical issues remain – sometimes genuinely not completely known, and at other times, known but not adequately implemented. As the technical recommendations report emerging from the #FutureFortified process noted: “While there has been significant progress in terms of the number of countries mandating the fortification of staple foods and condiments, there is much work required to ensure the impact and sustainability of these programs” [69].

Besides the identification of key questions from the #FutureFortified Summit process [69], there has been a series of technical meetings addressing the different issues and questions. Following one relatively recent consultation, for example, research gaps were identified for rice fortification [291]. Further evidence was noted as being needed to: (i) determine the stability of different micronutrients in various context-specific environments; (ii) study the nutrient-nutrient interaction to better understand relative bioavailability and phytate effect on iron absorption; (iii) evaluate the optimal delivery platforms for reaching the target populations; and (iv) study the effectiveness of different fortification methods in different contexts. Other related challenges identified for fortification with multiple micronutrients include dietary interactions with fortificants and interactions between micronutrients used in fortification, although novel forms and encapsulations have largely overcome the latter. Increased experience and technical knowledge of the most appropriate fortificants [67] have largely resolved [67] many of technical issues. Appropriate and better biomarkers, building on the BOND Initiative of the NICHD, continue to need more work [285]. It seems likely though that many of the issues holding up

implementation are more about resources, compliance and capacity than about technical constraints – a positive reflection on the various technical meetings, country experience and the knowledge pool of the private sector millers.

However, different fortificants behave differently depending on the vehicle. For example, although these observations are now quite well-known, ferrous fumarate and ferrous sulphate are relatively bio-available, but ferrous sulphate can affect product flavour, especially after long-term storage [67, 292]. Although NaFeEDTA is protected from chelation by phytates in high extraction rate wheat flour and has other advantages, it is also considerably more costly than the other iron forms that have been used for fortification [67]. However, a recent article has suggested that phytates are less of a problem than usually thought, at least in women with sub-optimal iron stores [164]. Recently published recommendations suggest suitable iron fortificants and levels, which also take into account wheat flour extraction rates and consumption levels [67, 68, 293] – there is no longer any justification for not using the recommendations of the Interim Consensus Statement report. Consequently, the problems then become those of QA/QC and, for iron, public health considerations around associated high disease populations, especially malaria. Other challenges include multiple fortified vehicles such as double – or even triple – fortified salt, and the best form of zinc. These are all problems that can be addressed over time, but as in the iron fortificant history, the gap between technical knowledge and widespread adoption of science-based recommendations (often for reasons of cost) can be extensive, wasting both resources and credibility.

Not all micronutrients that fall short of recommended contents (e.g. magnesium and potassium) are suitable for fortification [24]. The recent review of Dwyer et al. [24] citing an international symposium organised by the Federal Agency for the Safety of the Food Chain in the framework of the Belgian EU Presidency, suggested new technical opportunities that should be investigated: (i) overcoming organoleptic problems posed by some fortificants such as iron, fibre, and potassium; (ii) establishing a better understanding of bioavailability; (iii) overcoming the degradation of certain fortificants such as vitamins B<sub>12</sub> and C; and interestingly, (iv) the efficacy of nanotechnology for fortification [24]. The last item is an area for the future and somewhat beyond the scope of this review but such innovative approaches are potentially exciting and useful.

In addition to remaining technical challenges, there are still evidence gaps with respect to the potential for impact on public health, as well as on effective impact.

### *7.1.1 Evidence gaps on effective impact*

If a programme is not designed or implemented properly, it cannot be expected to be effective or to have the expected impact [11]. Description and analysis of the population nutritional problem may be incorrect, the fortified food may not be effectively reaching the intended population audience, or if reaching them, it may not be consumed in a big enough amount or too infrequently to have the expected impact, or the fortificant being used may not be adequately bio-available and so on.

Translating evidence into policy and programmes requires establishing the extent of the micronutrient problem in a country and then advocating for how this might be addressed. Identifying the costs and benefits in countries not yet using fortification to its maximum requires an often complex overview of different assessments of the existing problems and diets and then developing scenarios and resource needs that would be most cost-effective in addressing the problem, country by country [34]. Before committing to the legislation needed and resources for ensuring compliance, governments need to know the extent of the problem and the costs and benefits of addressing them. The conclusions of at least two systematic reviews show there are still gaps in fairly fundamental knowledge of effectiveness and impact, including on growth, cognitive development, morbidity and mortality, especially in LMIC [276, 278].

Changes in diets and environments can occur with increasing prosperity, changing dietary fads and fashions (e.g. artisanal salts), fluctuations in food prices, emergency situations, crises and civil strife, and increased consumption of supplements and commercially-fortified foods, especially breakfast cereals. Such changes can be both a challenge (the need to continually understand which dietary gap is being addressed) and an opportunity (as the changing environment leads to consolidation of industry that would facilitate fortification and oversight). The increased use of commercially produced foods is a global trend, and now contributes greatly to the micronutrient intakes of children [24]. Iodine, iron and folic acid levels in diets seem particularly susceptible to these trends, at least partly due to folic acid in breakfast cereals, iron in supplements and iodine in changing dietary habits. Iodine status has somewhat declined in countries such as Australia, Italy and other affluent countries, especially in women of reproductive age [75, 115, 178], possibly requiring complementary measures such as iodine fortification of bread [222] or supplementation for women likely to become pregnant [16, 177]. The intake of table salt is decreasing as more processed foods are consumed (in most societies), and which may or may not use iodised salt and those wishing to heed warnings around salt consumption and hypertension [294]. A recent study in north-east Italy found that, while consuming iodised salt improved iodine status in young girls, females at puberty and fertile women, dietary iodine status declined from childhood to adulthood due to changes in eating habits, and particularly milk consumption [295]. In a recent study in China, the risk of intakes beyond optimal and safe upper limits of iodine intake for early pregnancy in iodine-replete regions in China (of which there is an increasing number) has led to suggestions for reducing iodised salt intakes in some counties. China, which introduced mandatory salt iodisation in 1994 has had great success and the target of sustained elimination of IDD has already been met at the national level [247]. While in school-aged children the iodine status is adequate or more than adequate in almost all provinces, pregnant women in six of China's 31 provinces are classified as borderline deficient [247], somewhat complicating public health interventions and messages.

There is an identified gap existing between research and the dissemination and implementation of scientific findings, including in food fortification [73], despite many decades of experience [20]. An earlier review concluded that what is needed are "clear channels of communication, well-defined in-country leadership, and a stream-lined and focused approach that can be adapted to country-specific contexts" using a model based on past success and failures [20].

More recently, a model based on African experience noted programme elements critical to design and implementation [73]. Using examples from Malawi and Rwanda, the authors suggest four core principles, often overlooked: (i) government commitment to, and prioritisation of, a national mandatory programme; (ii) focused guidance through an identified catalyst, in support of a national, mandatory programme; (iii) a data-driven approach that includes a focus on robust monitoring; and, (iv) systemic, national leadership within a national guiding body [73]. Part of the communication gap is that different sectors have differing perceptions of both constraints (e.g. to compliance) and so, not surprisingly, differing priorities and ways of addressing them [56, 275].

### *7.1.2 Evidence gaps on impact on public health*

While the effectiveness of food fortification on nutrient intakes and nutrient status is well established, there is still insufficient evidence of effectiveness on functional outcomes, including growth, cognitive development, morbidity and mortality, especially in LMIC. This is an issue since much emphasis is currently being placed on the prevention of stunting, especially since the 2008 and 2013 Lancet Maternal and Child Nutrition series [296] identified its predictive power for quality, health and productivity throughout life [7, 270]. At present, the relevance of micronutrients in the prevention of stunting lacks a clear connection [297] but it seems clear that stunting cannot be adequately addressed without taking into account adequate diets as well as other socio-economic factors such as concomitant diseases and poverty. Nevertheless, the known relationships between anaemia and birth weights, and antenatal multiple micronutrient supplementation on increasing birthweights, suggest there is a potentially important relationship. As stunting is such a prominent feature of chronic undernutrition in the same populations as those most at risk of micronutrient deficiencies, further work needs to be done urgently on the timing of interventions, the use of multiple micronutrient supplementation experience [297] and any impact of fortification. Clearly, expectations need to be realistic and the impact of large-scale fortification on a population's nutritional status needs to be clearly defined.

As noted earlier, the first fortification programmes were used to treat and prevent readily diagnosed nutrient deficiencies such as beriberi, goitre, rickets, and pellagra that were either epidemic or occurred in specific population groups. Fortification programmes, at least in more affluent countries, now increasingly tend to be based on dietary intakes below recommendations on the basis of age and sex, as demonstrated by dietary surveys, rather than attempting to correct a recognised health issue or disease [24]. A recent article on changing aspects and challenges of fortification emphasises the health impact that the more recent focus of fortification will have on the population, so that both the total additional intake and the quality of the nutrient or nutrients supplied must be taken into account – not just the intake of the food vehicle alone [24]. Particularly in diverse populations, effectiveness may be best achieved by the use of more than one fortification vehicle to reach the largest number of people and present the lowest risk of excessive intakes, as has been done in Mexico [24, 244] and West Africa [221]. Several countries, especially those with a limited number of fortified foods allowed (as in much of northern Europe), have determined the maximum allowable nutrient intake from fortification so as to avoid exceeding the safe upper limits that have been established. These countries include Denmark, Finland and the Netherlands, [298] amongst others.

Individual differences that go beyond cultural and socio-economic conditions can affect the public health outcome of fortification. Numerous gene polymorphisms can alter the digestion, absorption, and metabolic responses of individuals to certain nutrients [299]. Diet can cause epigenetic changes that can turn certain genes on or off, ultimately affecting cellular function and metabolism [300]. Fortification with folic acid was initiated in part because of the identification of a high prevalence of polymorphisms in several folate-dependent genes involved with single-carbon metabolism [124]. It is recognised that some of these polymorphisms can significantly alter folate requirements among pregnant women, and vary between geographic populations (e.g. MTHFR C677T with increased risk of NTD in Asian and American populations) [124]. Extensive national experience over many years of fortification with folic acid has not identified this as being a problem of public health significance, but the whole area of epigenetic changes and gene polymorphisms will be a future area of research attention in many public health approaches. Such variations – such as susceptibility to iron overload and haemochromatosis – show marked regional and ethnic variation [184], although again, this does not appear to have been a public health problem in fortified populations. Another emerging area of interest identified by the review of Dwyer et al. [24] that could influence the outcome of fortification is the composition of the gut microbiome. The size and diversity of the gut microbiome within specific populations can be influenced by an individual's diet, which could, in turn, affect absorption of certain nutrients [24]. The research questions will need to be addressed and monitored in future, to assess their potential impact on public health programmes, including fortification programmes.

## 7.2 ENSURING EFFECTIVE COVERAGE

Effective coverage is a precondition for impactful programmes, as are other factors described in this report. Part of scaling-up is expanding effective coverage in a way that maintains quality and ensures utilisation. Issues of reach and equity need to be addressed and there are questions of the best approach for all these factors.

Coverage needs to be broadly defined beyond the numbers of households or individuals receiving fortified foods and ingesting them in biologically useful quantities, to include geographic and social issues [56, 242, 262]. These include: populations or sub-populations not being identified or accurately profiled; sub-populations not having access; households not being reached for any number of reasons; and, amongst others, insufficient quantity of micronutrient fortificant in the overall diet that the targeted group is actually consuming. It should also be well established, both initially in the design of the programme, but also by regular monitoring, that those at risk, are actually “reachable” by food fortification.

Right from the early days of mandatory enrichment in Mississippi, it has been recognised (if not always remembered) that there is a lag period between enactment of mandatory law and impact [19]. Even when the legislation/regulations actually take effect, it takes a few years for unfortified products to be cleared from the marketplace, and then more time for compliance by all mills to be enforced, especially mills serving small communities [19], and acceptance of the product by health authorities, millers and sometimes the targeted group. Such challenges including choosing appropriate fortification vehicles, not reaching target populations, avoiding

overconsumption in non-targeted groups, and adequate monitoring of nutritional status, are relevant to all countries [24], many of which will have differing social and political environments and resources.

One of the stated advantages of fortification is the relative ease of fortification and the relative ease of coverage (e.g. compared with supplementation), especially where there are large centralised mills. However, technical issues arise with achieving micronutrient fortification in small local production mills. This is an issue because small-scale mills are the predominant source for both wheat and maize flours with iron fortification (and other micronutrients) in rural subsistence farming areas, while small-holding salt production units require small batch iodisation. Small hammer and chukka mills have helped address this for flour and more recently innovations such as the “Sanku” device (recently designated a “top solution... offered by private sector companies and NGOs to support humanitarian aid and disaster relief efforts” by the Aid and International Development Forum) [219]. Nevertheless, the more the mills are small-scale and dispersed, the greater the costs are likely to be, as well as increasing challenges in monitoring and quality control.

Untargeted fortified foods generally contain micronutrients in quantities too low to meet the high micronutrient requirements of children aged 6 to 23 months of age, women and lactating women [301], particularly in LMIC where status before pregnancy is often equivocal and physiological needs are higher [2, 16, 43, 87]. Nevertheless, large-scale fortification will ensure that the baseline diet is much improved and impact on NTDs and some measures of iron-deficiency anaemia have been demonstrated. Modelling will help to get a more realistic picture of the likely benefits of a large-scale food fortification programme in a given setting. The levels of fortificant, while raising baseline micronutrients in the diet, are also often too low for the complementary food needs of infants and children (6 to 23 months) and consequently, improved diets and targeted fortified complementary foods are often also necessary [301]. In Jordan, fortified wheat flour delivers sufficient iron to improve iron status in children, but the amount of iron delivered to women is thought to be inadequate. As a result of iron fortification, IDA decreased significantly in children from 26% to 13.7%, but no improvement was observed in women [24]. Conversely, the vitamin A provided via wheat flour fortification in Jordan is thought to be inadequate for children but sufficient for women [62]. These situation-specific examples demonstrate the need for both adequate baseline information and appropriate expectations and advocacy. There is increasing interest in using several food vehicles to increase coverage [221].

In addition, there are still some concerns about potential over-exposure in certain population groups due to total levels of a particular micronutrient, which must be addressed when designing the programme. The intake may be greater than expected from the theoretical calculations (based on consumption of the proposed vehicle when added onto existing levels in the diet), and which may differ in sub-sections of the population [24]. This may happen because of increasing numbers of commercially-fortified voluntary foods which may be consumed at varying amounts by different population sectors, such as children in affluent countries.

One of the global trends is for greater availability of such foods. Sacco et al. [302] have examined the possibility that individuals in the USA with greater frequency of exposure to micronutrients

from voluntarily fortified foods are more likely to have usual intakes approaching or exceeding the respective tolerable upper intake levels (UL). They found an increased probability of consuming intakes above the UL for zinc, retinol, folic acid, selenium and copper in children, and for calcium and iron among adults [302]. It is known that the consumption of fortified foods and supplements is correlated; people with high intakes of fortified food tend to also use supplements [302]. It seems unlikely this is problem in most LMIC populations.

### 7.3 ENSURING QUALITY CONTROL AND MONITORING

Poor compliance is frequently identified as one of the biggest challenges to effective mass fortification [56]. Especially in countries with constrained resources, personnel capacity and poor histories of governance (including enforcement of regulations, and problems with budgeting, in particular) have been identified as inhibiting adequate quality control and compliance [56]. Another identified constraint is the differing perceptions around achieving good compliance; whereas both producers and regulators put high importance on having clear regulations (i.e. ones that provide a good regulatory environment and clearly delineate roles and responsibilities), other issues around incentives and penalties for enforcement and communications between sectors and industry engagement show a startling disconnect [56]. These issues (incentives and penalties, and communication) were found to be the next highest priorities (after clear regulations) for industry, but were amongst the lowest priorities for regulatory agencies [56].

#### 7.3.1 *Measuring programme performance*

Compliance and enforcement frameworks must be established as part of the setting up process. The programme planning phase needs to include the development of standards and appropriate legislation, setting programme goals and building partnerships and more targeted advocacy. There is considerable experience globally in doing this, by international and industry organisations; it is rarely a barrier to developing a national model. An important part of this phase is the development of partnerships, not least because different partners (such as health and industry) may be involved in a programme, with different expectations and concerns on legislation, regulations and enforcement [56]. There have been good examples of national fortification groups or councils comprised of government, industry, health and nutrition, perhaps consumer groups, and others, which have continued during the scaling-up and maintenance periods, and have helped to address different needs and perspectives.

Procuring equipment will depend on whether the programme is purely commercially driven or stimulated by health and nutrition organisations. Often in LMICs it is a mixture of both, such that industry is supported in the capital costs of new machinery by a donor, or start-up pre-mixes of fortificants. Developing a marketing and communications strategy, as well as monitoring systems, are both part of this step in the process.

Ensuring effective programme functioning, gaining evidence of effective coverage, tracking trajectories of national programmes, and finally, evidence of impact, require ongoing, serious and properly financed monitoring. Two particular challenges to doing this are a lack of allocated resources and a dearth of current information available. One of the reasons for this is the lack



of simple tracking tools that can readily be used to get the information and data needed for increasing accountability to those who need to take action. As noted, the FACT tool is proving useful [279]. Monitoring effectively is an area of concern but how it is done, and how rigorously, differ according to a country's resources and legal environment factors [56, 242]. As part of the outcomes of the #FutureFortified Global Summit on Food Fortification, a Technical Advisory Group identified key barriers and obstacles to regulatory monitoring [69]. The report concluded that the barriers could be broadly categorised as:

- Difficulty in collecting the data needed for regulatory monitoring due to unclear and fragmented systems and responsibilities.
- Inadequate testing of samples and compiling of data due to poor laboratory capacity and inadequate personnel training.
- Not acting upon the data due to perceived political risks, limited personnel, unclear legislation and regulations, and unrealistic non-compliance measures.
- Non-compliance due to ineffective measures, costs and lack of know-how and documentation, ineffectiveness due to incentives and/or penalties being insufficient, and even corruption.

Further detail is available from Annex 1. The #FutureFortified Summit identified four main barriers:

- (i) In collecting the data due to unclear roles and responsibilities and lack of funds;
- (ii) When testing and compiling the data, again noting inadequate resources and poor overall capacity;
- (iii) Failing to act upon the data collected due to limited personnel, corruption, perceived political risk in doing so and unclear roles and responsibilities; and,
- (iv) Non-compliance due to competition, resources and lack of consumer demand/advocacy and ineffective non-compliance measures.

For example, in China, it is argued that high household coverage of private sector iodised salt is only possible with government-led monitoring to ensure industry compliance with national salt standards [247]. Different countries have different comfort zones around mandatory programmes and voluntary systems, even where the fortification is addressing an identified national problem, such as in the voluntary iodisation of salt in the USA. It has been observed that the private sector/industry's perception of what is important in terms of monitoring is not necessarily the same as the national regulatory bodies, which sets up an inevitable degree of tension [56].

Many national programmes are currently not achieving national targets, especially in iodine "because of weak regulatory/monitoring systems" (Yusafali, personal communication cited in [247]). A recent report on the global regulatory landscape regarding micronutrient fortification of condiments and seasonings [231] recommends that countries with existing fortification programmes covering condiments and seasonings revise their voluntary fortification regulations

to change them to mandatory regulations. For example, in 2005, over 90% of Vietnamese households were using adequately iodised salt; by 2011, it was down to 45%. This was attributed to the unsustainable design as a government-funded activity rather than becoming the industry norm. When national legislation for mandatory salt iodisation was revoked in 2005 and political importance downgraded with consequential effects on budget, staff and authority [236], the programme essentially collapsed.

### *7.3.2 Measuring programme impact*

An important part of setting up a potential programme is to decide on realistic programme goals. To do this, it has been suggested that the objectives must be consistent with the impact pathway for large-scale fortification based on the most recent evidence on efficacy and effectiveness [69]. The technical team recommending that common sense approach also suggested that the primary focus of food fortification initiatives should be on increasing intake of micronutrients (as opposed to improving micronutrient status or reducing anaemia, which are also affected by multiple other factors). Not all countries formulate objectives and targets for programmes but demonstrating effective coverage and even health impact of the programme is more easily done against agreed-to objectives. Clearly they need to be realistic, appropriate and achievable within the impact pathway [69].

Impact evaluations are needed in order to determine whether programmes have achieved their goals, as well as to make any needed changes to programme or policy based on those results, and ultimately to see if there has been a health impact. The measurement of impact remains one of the major gaps and challenges in mass fortification [69].

Government monitoring and evaluation should be integrated into policy guidelines to ensure adherence and compliance “and to enable the assessment of the systematic impact of fortification on the target populations” [231]. Monitoring and modelling can both assist in measuring programme effectiveness and impact. The main barriers to doing this are a lack of commitment, inertia, and especially a lack of funds. Back at the stage of setting up, budgets should include a provision for programme evaluation and measurement of impact.

There are examples of fortification programme evaluation that have been done and published in the last five years (e.g. a special issue of *Public Health Nutrition* [160]) but usually with a view to lessons learned rather than demonstrating health impact, including those in Ghana [251] and Vietnam [236]. To adequately evaluate the impact, baseline data and a control group are necessary and not always available [91]. Effective fortification coverage is being facilitated by the FACT tool (as described above) and has already been used in Ethiopia, Senegal and Uganda [279].

Impact evaluations should ideally be conceived and designed before programmes begin, in order to maximise the potential to measure changes in status and function and attribute them to the programme. When such designs are not feasible, then impact evaluations should be accompanied by strong process evaluations that measures key indicators along the pathway to impact and so build evidence as to whether any changes could feasibly be due to the programme [69]. The recommendations for Food Fortification Programmes that came out of the Arusha #FutureFortified Summit suggests that whatever the design, attempting to measure

the impact of programmes should only be done when programmes are “evaluation ready,” meaning that they are applying WHO-recommended standards, are well-monitored, compliance is adequate, and a high proportion of the population has been consuming fortified foods on a regular basis so that biochemical or functional outcomes could feasibly reflect the ongoing fortification. They further note that if “any of these components are not fulfilled, then the lack of impact of a program may be due to its ineffective implementation and not to its lack of potential” [69].

#### 7.4 ENSURING ACCESSIBILITY AND EQUITY

One of the criticisms of mass fortification is that it may not be accessible to all [63, 231, 303] although there is the counter-argument that it may also reach populations that are not getting adequate health care and that are not being reached by supplementation. Zamora and De-Regil [63] took an impressive look at maize fortification from a Social Determinants Approach suggesting that this could contribute to increasing and guaranteeing access to fortified maize flour and corn meal, and presumably other fortified foods. This approach is not yet common in the development of fortification programmes and would need to be made very “user-friendly” to be adopted, despite its importance.

The Copenhagen Consensus has observed that the cost of iron fortification varies according to the fortificant used and the food vehicle, and is likely cheaper to the degree that processing is concentrated in a few mills and manufacturers [5]. In terms of equity and reaching populations that are often highly disadvantaged and at risk, alternatives to a strictly economic rationale may sometimes be necessary. Trial programmes with appropriate technology using hammer mills and other methods at village and community levels usually increase costs, but fortification at village level remains one of the main strategies to address equity challenges and ensure accessibility for all the micronutrients, including iodine in local salt. While the Copenhagen Consensus noted that subsidies are often expensive and generally not cost-effective, the marginal cost of adding fortificants is small, and has often achieved significant benefits including Mexico’s subsidised milk and India’s public distribution system [5] despite the inefficiencies of the latter.

Inequity in access to fortified foods needs to be locally researched and contextually understood, as reasons for lack of accessibility and even availability will differ according to country-specific contexts. It has been observed that being female, and especially a child, in many cultures is likely to increase the risk of micronutrient (and other) deficiencies [17, 304], among others because of intra-household distribution that can have a negative impact on the micronutrient intakes of women and children [304]. In this sense, fortification of staples that women consume (unlike the more restricted intakes of some of the more expensive animal source, micronutrient dense, foods) might be seen as a way of reducing the dietary disadvantage. In many countries, even those with an expected problem of deficiencies, basic information on existing dietary intakes is lacking and makes inclusive planning a challenge. Accurately assessing intakes of fortification vehicles is needed to assess the dietary impact of any fortification programme. In addition, calculation of intakes are problematic for nutrients which do not have clear requirements for some sex and age groups [24]. Differential health outcomes are affected by the health system’s capacity to generate data because appropriate interventions to reduce

health inequities require reliable information on the population. Studies have found that while food consumption surveys do target low-income households, they often fail to collect data from these households [231]. Data may sometimes be in the hands of the industry but not in the health systems. This should be considered when interventions are designed so baselines are as accurate as possible [232].

Because food fortification is a complex public health intervention, albeit perhaps less so in the technical sense, strategies for fortification need to be aligned between sectors, especially with poverty reduction programmes and other social intervention schemes [63]. Although it has been suggested that the long-term sustainability of fortification programmes can be ensured when consumers are willing and able to bear the additional cost of fortified foods, this can be exceptionally difficult in contexts of extreme and extended poverty and lack of opportunities. Other challenges are those of communication, such as the integration between salt reduction for the prevention and reduction of hypertension, and the same populations receiving iodised salt [210].

## 7.5 SUMMARY OF IDENTIFIED GAPS AND NEW EVIDENCE NEEDS

As noted, several recent regional meetings and at least four recent systematic review articles have identified challenges remaining in food fortification. Challenges of course are not necessarily gaps – some issues that constrain achieving a successful fortification outcome are well-known and attempts are made regularly to address them. Maybe the gap in these instances is the “how-to?” component. The technical issues ranged widely from better dietary data, better biomarkers to nanotechnology but were also notably still quite basic in terms of information on bioavailability, stability of fortificants and so on. Annex 1 provides a comprehensive overview of evidence gaps and needs that have been identified in this review (and are referenced there) and from the findings of the Technical Advisory Groups in section B of the #FutureFortified Summit proceedings and their listings of barriers and research questions [69]. The categorisation of the gaps and questions is based on the GAIN adaptation of the WHO/CDC logic frame.

Further detail can be seen in Annexes 2 and 3 from the #FutureFortified Summit proceedings. Many of the above observations were encapsulated in the work of the Guideline and Evidence group who identified five strategic areas:

- Strategic area 1: Measuring the magnitude and distribution of micronutrient malnutrition
- Strategic area 2: Understanding the diverse causes of micronutrient malnutrition
- Strategic area 3: Developing large-scale fortification programmes to reduce micronutrient malnutrition
- Strategic area 4: Implementing, monitoring, and process evaluation of large-scale fortification programmes
- Strategic area 5: Evaluation of large-scale fortification programmes

The 32 research priorities identified in the WHO guidelines, and the many other questions and research priorities identified in that process, are seen in Annex 3 (and the complete report at [www.sightandlife.org](http://www.sightandlife.org)).

**CALL OUT BOX 7: KEY BARRIERS/OBSTACLES TO REGULATORY MONITORING AND KEY QUESTIONS IDENTIFIED BY THE #FUTUREFORTIFIED GUIDELINE AND EVIDENCE WORKING GROUP [69] (SEE ANNEX 2 FOR MORE DETAIL)**

Key barriers and obstacles to regulatory monitoring:

- Collecting the data due to unclear and fragmented systems and responsibilities
- Testing of samples and compiling the data due to poor laboratory capacity and inadequate personnel training
- Acting upon the data not happening due to perceived political risks, limited personnel, unclear legislation and regulations, and unrealistic non-compliance measures
- Non-compliance due ineffective measures, costs, and lack of know-how and documentation

Key questions identified and research priorities:

- Strategic area 1: Measuring the magnitude and distribution of micronutrient malnutrition
- Strategic area 2: Understanding the diverse causes of micronutrient malnutrition
- Strategic area 3: Developing large-scale fortification programmes to reduce micronutrient malnutrition
- Strategic area 4: Implementing, monitoring, and process evaluation of large-scale fortification programmes
- Strategic area 5: Evaluation of large-scale fortification programmes

# 8

## Conclusions, Implications and Some Next Steps

Fortification has a relatively long history as a public health intervention of over three quarters of a century and has proven effectiveness, especially in essential nutrient deficiencies. In more affluent countries, food fortification has played a major role in the substantial reduction and elimination of a number of micronutrient deficiency diseases and has now expanded into preventing NTDs and addressing health more generally. Safety remains a consideration, especially in the light of inadequate or insufficient baseline dietary, health and consumption and monitoring data, but is currently outweighed by the advantages and cost-benefits. The level of fortification should take into account variations in food consumption to ensure safety for those at the higher end of the scale and impact for those at the lower end. Fortification of staples adds to the nutrient intakes of nearly everyone in a population and remains a critical and necessarily ongoing public health nutrition intervention in all countries. The current increased attention to the more critical need in LMIC – where rates of deficiency through poor diets tend to be higher, and alternatives such as supplementation, are not necessarily available, and both availability and accessibility may be problematic to less economically affluent sectors – is well overdue. For all these reasons, large-scale fortification needs appropriate policies and resources and needs to be supported by adequate food regulations and labelling, quality assurance and monitoring to ensure compliance and desired impact. As has been identified above, successful impact requires the different partners and sectors involved to fulfil their contribution – and adequate support, resources and enforcement where this is not happening.

The Arusha Statement on Food Fortification coming out of the Summit in 2015, defined five critical areas of action [1].

1. Modest but new investment is essential;
2. There is need for a major effort to improve oversight and enforcement of food fortification standards and regulations - poor compliance with laws and regulations limits potential for impact and undermines effectiveness;
3. There is a need to generate more evidence to guide fortification policy and programme design, to continually improve programmes and demonstrate impact;
4. Progress requires more transparent accountability and global reporting. We support the call for a global observatory or annual report of the state of fortification; and,
5. Continuing advocacy is a high priority for all stakeholders such as the SUN movement and African Union to advocate for greater attention by governments.

Achievement of these recommendations will need to be underpinned by better leadership and accountability within the sector. Increased attention to policy support, quality control, monitoring compliance and assessing impact are needed to extend and maximise potential for health impact via food fortification. Further detail of key questions to be addressed in the near future, as identified by the guideline and evidence working group to help address these five strategic areas, includes research priorities identified in WHO guidelines and others and are itemised in the Annex.

Given the attention to nutrition-sensitive factors and the integration demonstrated in the proposed SDGs, there are other complementary interventions that need to be addressed at the same time as the expansion of mass, mandated fortification. Food systems as a whole impact all nutrition outcomes, as was vividly seen in the global financial crisis when food prices rocketed, particularly affecting the urban poor, and often promoting civil unrest. Although rates of stunting have been halved since 1990, still over 800 million people remain undernourished, and even more suffer from micronutrient malnutrition. New challenges such as climate change, along with increasing population growth, rapid urbanisation, changing lifestyles and globalisation will all have the possibility to increase the prevalence of micronutrient malnutrition. Evidence-based and cost-effective interventions must be scaled up across countries. One such intervention, as this overview makes clear, is the large-scale fortification of staples and condiments.

In summary, fortification is an important public health intervention with the potential to effectively reach millions but must be applied prudently, its effects monitored diligently, and the public informed about its benefits through consumer education efforts [24]. There has been an acceleration of knowledge about large-scale fortification over the last two decades or so, and there have been a series of systematic reviews and policy meetings of different aspects of fortification, both technical and programmatic over this time that have resulted in valuable insights. Nevertheless, a surprising number of gaps in knowledge remain to be filled despite the long and successful history of fortification.

The number of people reached by mass fortification of staple foods has also expanded enormously, and importantly a lot of this has happened in low- and middle-income countries. It is likely to continue, not least as the technology for fortifying rice becomes stronger and simpler. There is also emerging evidence that fortification is finally having an impact on anaemia levels. The iodisation of salt is a public health triumph and the reduction of NTDs largely because of fortification with folic acid has been a blessing for those involved. Of course, the consumption of fortified foods does not take place in a vacuum and multisectoral approaches, both nutrition-specific and nutrition sensitive, will need to play a role. Inequities in access and availability are the prime reason for differences in health and development outcomes and these must be addressed at the same time. However, the mass fortification of staples that people are already eating has a greater chance of reaching people in need than many other interventions. Technologies allowing pockets of local milling to be covered will also expand the reach of fortified foods to those most in need.

CONCLUSIONS, IMPLICATIONS AND SOME NEXT STEPS

The successes need to be better disseminated, not least to governments but also partner agencies and donors, and especially to those consumers who then have the information to demand that their foods be fortified. Social marketing will continue to be important, as are the publication and sharing of technical findings and manuals and related information and academic advances. All of these need a greatly strengthened monitoring and evaluation of programmes. The importance of this needs evidence of results and impacts – hopefully followed by resources. The various recommendations of technical meetings need to be followed up and explored in more detail and practical recommendations implemented.



# 9

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# Annexes

## Annex 1: Evidence Gaps and New Evidence Needs in Food Fortification Programmes

### *Foundation building*

Public health nutrition gaps, and gaps in baseline data necessary to identify the extent of the need and preliminary planning for addressing a national micronutrient gap.

### **PUBLIC HEALTH ISSUES - MORE INFORMATION IS THEREFORE NEEDED ON:**

- Basic and baseline dietary data and intake distribution and how these change over time in rapidly changing food environment
- How to encourage/ensure well-defined country leadership, government commitment and prioritisation to national mandatory programmes through an effective national body towards effecting policy change that supports mandatory fortification
- How to engage stakeholders/agencies/donors to understand the importance of more comprehensive and up-to-date databases on food and nutrient intakes, and act to establish databases that are disaggregated to national level at least
- Policy-makers' actions on providing and prioritizing resources to establish baselines by facilitating the collection of data and creating structures to allow the next stage of setting up a programme
- Better biomarkers associated with nutritional status, especially micronutrient status
- How to maintain sustainability and guard against policy changes with new governments, circumstances, and changes in donor priorities
- "Scaling up" by mobilizing sustainable support for fortification programmes in the form of multi-stakeholder partnerships and moving towards a sustainable business models
- The development of terms of engagement and governance for multi-stakeholder partnerships and effective public-private relationships
- How to better identify the barriers that prevent access to fortified foods
- Identifying, quantifying and achieving buy-in on the "unfinished agenda" of mass fortification through modelling, calculating and obtaining the resources needed
- Optimal delivery programmes that ensure sub-populations within the mass population are being reached, such as different ages, gender (especially adolescent girls), different cultural and socio-economic settings; if not, targeted programmes may be needed to complement the mass fortification
- The aetiology and causation of anaemia beyond the health sector as an indication of how effective large-scale fortification with iron-containing fortificants is likely to be

*Setting up and technical issues for which evidence is still needed***TECHNICAL ISSUES - MORE INFORMATION, DATA AND RESEARCH ON:**

- Evidence of key factors that will facilitate scaling-up sustainability
- Identification of appropriate stakeholders who will need to be engaged, how to ensure accountability, and how can a proposed National Fortification/Council be strengthened?
- Supply issues such as functioning pre-mix procurement mechanisms and quality systems
- Individual variation – biological, physiological, genetic (polymorphisms), influence of diets and the gut microbiome, cultural, gender and socio-economic and whether such variation affects national programmes
- Measurement of impact on other outcomes such as growth (including stunting), cognitive development, and reductions in morbidity and mortality, especially in LMIC
- Fortificants - especially for maize and corn flours - and their bioavailability, stability with different processing methods (e.g. nixtamalisation) and for rice; iron fortificants appeared to have been studied more with a greater degree of consensus on which are most appropriate and when to be used
- Small home or rural mills and processing, multiple origins of salt, unfortified cornmeal and so on for adequate fortification and monitoring
- Relative bioavailability of different chemical forms of different micronutrients, including nutrient-nutrient interactions
- A greater understanding of how food intake influences biomarker concentrations so that more appropriate vehicles for food fortification can be identified and a better use made of appropriate biomarkers to better identify who is more at risk
- Safety (beyond better monitoring and evaluation), which apparently remains a surprisingly frequent concern, especially any long-term risks of too high intakes of folic acid and iron, and perhaps vitamin A, as fortificants
- Better information on total intakes of specific micronutrients when added to voluntary fortification levels, changing diets and so on, including a concern about a lack of solid data on ULs (depending on demographics) for folic acid, retinol, copper, selenium, zinc and maybe calcium and iron
- Other specific issues including bioavailability, organoleptic issues, degradation over time, especially in storage under less than ideal conditions, fortification effectiveness with double, triple and multiple micronutrients
- Vitamin B<sub>12</sub> – why is it not used as a fortificant? And should it be?
- Future innovations such as using nanotechnology for fortifying foods

*Launching including communications, quality assurance and control and compliance - implementation needs for which evidence is still needed*

**QUALITY CONTROL AND COMPLIANCE - ISSUES IDENTIFIED INCLUDE:**

- Tracking tools that can be readily used to give the ongoing data needed to increase accountability and compliance and that can be used in resource-constrained settings
- Weak or sometimes non-existent enforcement by authorities
- The gulf between different sectors and their perceptions of both constraints and priorities
- Frequently inadequate capacity and resources of governments and quality control authorities when testing for compliance of regulations and legislation
- More effective use of consumer organisations to strengthen compliance
- Unclear regulation and legal instruments
- A better understanding of effective and realistic enforcement mechanisms (incentives, penalties, or a combination of the two) to encourage industry to improve compliance
- Enabling environments that allow for effective enforcement by inspectors
- Improving financial and human capacity at regulatory agency and industry levels to create well-trained inspectors and improve the detection and enforcement of non-compliant and under-fortified products
- Having governments creating national budgets that specifically ensure a sustainable means and line items for monitoring compliance
- A need for simplified monitoring processes and streamlined data collection mechanisms
- Improved mechanisms for relationship building between industry and government
- Ensuring quality control during emergencies or during civil strife?

**COMMUNICATION, AND HOW TO IMPROVE:**

- More information and knowledge on demand issues including the cost-effectiveness of social marketing and behaviour change communication, especially to low-income consumers
- Communicating change, and its benefits and risks
- Continued use of Copenhagen Consensus conclusion that micronutrient interventions are among most highly cost-effective nutrition interventions tackle (while noting the next most cost-effective intervention is nutrition education, particularly when focused on the needs of pregnancy, breastfeeding and preschool children, especially those under two years of age)
- Communication channels so they are clear and understood by different sectors and partners, including the consumer

- Communication channels between research and those responsible for dissemination and application of relevant findings
- Communication channels between implementing mills and industry and regulators around compliance and communication priorities
- The better use of focused guidance/encouragement by “champions” acting as catalysts and influencers
- The use of civil society engagement to increase demand
- Knowledge to effect policy change, including especially information based on results of evaluations and impact studies
- Increased awareness and uptake of fortified products through social marketing campaigns
- Manage concerns with public health efforts to reduce salt intakes (for hypertension) and sugar intakes (for obesity prevention) and appropriate messaging

*Scaling-up and delivery for effective coverage, including accessibility and equity*

**COVERAGE - BETTER INFORMATION ON:**

- Effective coverage - how to better achieve it and how best to measure it
- All aspects of coverage and accurate profiling – who, when, how, consistency of intake
- Coverage, especially women of reproductive age, including adolescents specifically, and young children
- Reconciling apparent contradictory intakes, and hence potential effectiveness, when the level of fortificant is not high enough for one demographic but cannot go higher because limits have been reached in another sub-population
- Other sources in the diet of the fortifying micronutrient including supplementation programmes, and commercially, voluntarily fortified food sources such as breakfast cereals
- Missing data for many countries (e.g. IDD Global Score Card has no data for 41 countries)
- Coverage of target population if donors or international organisations cease to support logistics, supplies etc. (e.g. salt compliant samples dropped in Cambodia after external procurement support for iodine was stopped)
- The availability of micronutrient fortificants of appropriate combinations and dosages of micronutrients is apparently continuing constraint in parts of South Asia at least
- Expanding coverage data reporting to include beneficial effects such as increased work capacity or intellectual development, and so re-enforcing advocacy

**HOW TO ENSURE THAT ACCESS AND EQUITY ISSUES ARE CONSIDERED:**

- Estimate and set appropriate expectations for food fortification programmes in each specific context
- Groups that are at high risk of inadequacy and/or excess get the special focus in all countries, recognizing that the need for, and the effectiveness of, fortification varies by age, sex, life stage, and biological and cultural profiles
- Disadvantaged (socio-economically, minorities, geographically etc.) groups are addressed when fortified foods do not reach them, given they are often those most in need
- Intra-household distribution if negative (as it often is to women and sometimes children) to receiving micronutrients and perhaps fortified foods (although mandatory fortification of staples may actually mitigate negative intra-household distribution)
- Other pro-poor programmes are linked and help reinforce fortification programmes and vice versa
- Any negative effects of international and regional obligations and trade treaties are guarded against

*Monitoring including the use of modelling***THE BARRIERS IDENTIFIED WERE:**

- Difficulty in collecting the data needed for regulatory monitoring due to unclear and fragmented systems and responsibilities
- Inadequate testing of samples and compiling the data due to poor laboratory capacity and personnel training
- Not acting upon the data due to perceived political risks, limited personnel, unclear legislation and regulations and unrealistic non-compliance measures
- Non-compliance due to ineffective measures, costs and lack of know-how and documentation, ineffectiveness due to incentives and/or penalties being insufficient, and even corruption

**MONITORING AND EVALUATION - HOW TO:**

- Strengthen monitoring and enforcement of monitoring
- Develop and adopt tracking tools to increase accountability, and that can be used in resource-constrained settings to establish baselines and ongoing progress, or lack of it
- Use more data-driven approaches to reinforce action when negative or insufficient results from monitoring



- Improve monitoring and evaluation in virtually all countries to allow a better understanding of the distribution and magnitude of micronutrient deficiencies, how they change over time, (including after fortification programmes), and whether sub-populations are covered or not
- More accurately assess intakes of fortification vehicles to assess the dietary impact of fortification programmes
- Use databases for research purposes by constantly updating in order to reflect the rapidly evolving marketplace, so that the contribution of both added and intrinsic micronutrients accurately estimates population intakes
- Ensure adequate resources are available to those monitoring (and those responsible for quality control)
- Know when changes to diets over time require modifying dosages of fortificant by following “impact trajectories” of national programmes
- Make monitoring more likely by making fortification mandatory (e.g. of condiments)
- Long-term monitoring of the programme’s compliance and efficacy in light of limited resources
- Improve use of monitoring and evaluation of different interventions for the control and prevention of micronutrient deficiencies to generate efficacy and effectiveness data required for informed policy-making and planning
- Strengthening methods for impact evaluation: criteria, how to establish the best methodology under different situations, and the key outcomes to be measured
- How to provide evidence for effectiveness, particularly for new fortification vehicle/nutrient combinations, specifically addressing the impact on nutrient intake, nutrient status, and functional outcomes, and whether there are any potential negative impacts of fortification

#### *Questions around health impact demonstration*

- How better to measure real impact in different target groups and overall health impact?
- What design characteristics in fortification programmes are most likely to influence the success of a programme (e.g. selection of target groups, selection of foods, selection of nutrients, selection of fortification compounds, planning for training, planning of monitoring activities, planning for impact evaluation)?
- How can expected impacts in fortification be set up, going from efficacy to effectiveness?
- What, if any, are the long-term impacts of folic acid fortification on the population other than that of reducing the incidence of neural tube defects?
- What are the best practices for implementing programme evaluations (since logistics often limit these to pre-post, or just post, surveys, which are limited in terms of causality claims)?

- Can impact be monitored by measuring intake?
- When is there a need to demonstrate improved nutritional status and improved functional outcomes?
- How can the contribution of fortified staples and condiments used as ingredients in processed foods be captured?
- What is the public health impact (effectiveness) of the programme on nutrient intake, nutrient status and functional outcomes?
- Does effectiveness match that predicted by dietary simulations?
- What are the cost:benefits of the impact of the fortification programme?
- What are the potential long-term negative impacts of fortification with any micronutrients (e.g. contribution to obesity, cancer, less dietary diversity)?
- If programmes are not achieving the expected/desired effectiveness, what steps along the impact pathway need to be strengthened? Are these consistent across settings?

## Annex 2: Key Barriers/Obstacles to Regulatory Monitoring

### KEY BARRIERS/OBSTACLES TO REGULATORY MONITORING

Members of the Regulatory Monitoring working group (Rowe LA, Garrett GS, Luthringer CL, Pachón H, Verster A) compiled this information for Summit Recommendation 2 from peer-reviewed and grey literature and individual field experiences [#FutureFortified Report Part B Annex 1. 2016].

#### Collecting the data

- Fragmented system for collecting the data, agency/inspector overlap
- Unclear roles and responsibilities
- Lack of mandates to collect/unclear mandates
- Lack of technical capacity and lack of budget to sample and/or audit:
  - Lack of technically trained staff (72%)
  - Lack of knowledge on how to sample and how to store the samples, resulting in poor quality collection
  - Limited knowledge on how to harmonise fortification with existing collection forms in order to streamline collection
  - No funds for additional inspectors, need for more inspectors and more trained inspectors at government level, need for greater monitoring frequency (88%)
  - No funds for transport for sample collection
  - Limited knowledge and/or trust and trust in auditing processes, relying only on product sampling/testing
- Low priority for enforcement:
  - No line item in the inspectorate budget for fortification
  - Fortification not included with regular food safety inspections

### Testing and compiling the data

- Poor lab capacity/budget constraints:
  - Lack of equipment, reagents, staff
  - No sustained government funding for inspectorates, some have just enough to keep the lights on, not to mention food safety or fortification
  - Public-private partnerships needed
- Limited training within the lab on how to test
- Limited understanding of how testing methodology and equipment can affect results, leading to false positives and false negatives
- No central database to house the data once collected and tested
- Fragmented system for receiving the data
- Unclear roles and responsibilities

### Acting upon the data

- Limited personnel for legal action/time lag between testing and communicating test results:
  - Infrequent monitoring capacity
- Corruption among inspection personnel/collusion between inspectors and industry
- Results never reported out/results lost
- Perceived political risk of enforcement by government inspectors:
  - 60% perceived a political risk around strong and consistent enforcement, resulting in inconsistent follow-through and underwhelming usage of enforcement strategies
  - Fear of strike threats or resistance from interest groups
- Unclear legislation and regulations, especially unclear or lack of objective enforcement mechanisms stated in regulations
- Unclear roles and responsibilities (i.e. who has authority to enforce)
- Non-compliance measures that are unrealistic and therefore are not used by inspectors (e.g. Canada has recently completed a study regarding their compliance standards and ability to actually test for these. Even they came to the conclusion that their lab methods are just not precise enough for the very small ranges allowed in the standards)

### Non-compliance

- Competition with non-fortifying producers (which reinforces the issue of acting upon non-compliance)
- Corruption among inspectors
- Compliance/non-compliance measures which are ineffective (i.e. incentives/penalties not effective):
  - Over 60% did not consider incentives/penalties to be effective
- Lack of duty-free equipment and/or pre-mix
- Lack of consumer demand/advocacy
- Cost of pre-mix, equipment, internal monitoring
- Lack of know-how
- Poor quality or unsafe inputs
- Poor processing procedures and expertise
- Improper packing and handling
- Lack of awareness of standards
- Purposeful under-fortification
- Lack of SOPs and documentation

### REFERENCE

1. Luthringer CL, Rowe LA, Vossenaar M et al. Regulatory monitoring of fortified foods: Identifying barriers and good practices. *Glob Health Sci Pract* 2015;3(3):446–461

## Annex 3: List of key questions identified by the guideline and evidence working group

### LIST OF KEY QUESTIONS IDENTIFIED BY THE GUIDELINE AND EVIDENCE WORKING GROUP

Members of the Guideline and Evidence Working Group (Peña-Rosas JP, Solon JA, Centeno Tablante E, Neufeld L, Gorstein J, Hurrell R, de Pee S) compiled this information for Summit Recommendation 3 from peer-reviewed literature (including from WHO priorities), grey literature and individual field experiences [#FutureFortified Report Part B Annex 3. 2016].

#### Strategic area 1: Measuring the magnitude and distribution of micronutrient malnutrition

##### Research priorities identified in WHO guidelines:

1. Relationship between iodine excretion and urinary iodine in different ages, pregnancy and lactation, and under different climactic conditions and physical activity level to allow adjustments of population criteria.
2. Identification of optimal indicators for iodine nutrition during pregnancy, lactation and infancy.
3. Validation of neonatal serum TSH concentration as an indicator of iodine status in pregnancy.
4. Investigation of the usefulness of thyroglobulin as a functional indicator of iodine status, to complement the use of UIC as an indicator of iodine intake.
5. Prevalence of iodine deficiency among pregnant and lactating women and the potential negative impact in their health and the development of their offspring.
6. Prevalence of iodine deficiency status of infants.
7. Prevalence of iodine-induced thyroiditis and iodine-induced hyperthyroidism.
8. Relative contribution of iodine from table salt and salt-containing processed foods (including bouillon cubes, condiments, powder soup).
9. Alignment of salt reduction and salt iodisation.
10. Identification of different vehicles for iodine fortification.
11. Field-friendly, affordable, automated microbiological assays for the assessment of red blood cell folate.
12. Less invasive methods for the assessment of folate status.
13. Interaction between red blood cell folate and TB, HIV and antimalarial drugs.
14. Effect of living at high altitude on red blood cell folate concentrations.
15. Surveillance systems for the prevalence of NTDs.
16. Assessment of the distribution of red blood cell folate status in women of reproductive age.

17. The distribution of red blood cell folate concentrations in women of reproductive age, and their association with NTDs, in different settings.
18. The lowest concentrations of red blood cell folate at which potential negative health outcomes appear, if any.
19. Optimal blood folate thresholds for reduced risk of NTD-affected pregnancy among women with overweight and obesity.
20. Population thresholds for serum folate for the prevention of NTDs.
21. The lowest total folate intake level (dietary and/or synthetic form of this vitamin) required to reach the target optimal red blood cell or serum folate concentration at the population level that is considered to be protective against NTDs.
22. What is the prevalence and distribution of micronutrients deficiencies and/or excess at national level across age groups, socio-economic groups and ethnic groups?
23. Which are the most high-risk groups at sub-national level?
24. What methodology can be put in place to improve the identification of high risk groups at sub-national level?
25. How can national surveillance systems be improved to provide information at sub-national level?
26. Are current cut-off points valid for different populations (age, pregnancy & lactation, ethnic groups)?
27. What is the relationship between currently used biomarkers, cut-off points and functional outcomes?
28. What are the cut-off points for biomarkers of vitamin D deficiency and excess? What are the prevalence and cut-off points of vitamin D deficiency? How can we obtain greater resources for analysing the micronutrient level problems and impact – both nationally and globally?
29. Which proxy indicators can be used to indicate the need for food fortification and to make fortification policy decisions?
30. How far have methodology and tools been developed to provide adequate instruments to improve information provision in food fortified surveillance system?
31. How can existing data sets and data collection systems (e.g. DHS, MICS, national nutrition surveys) be used to answer questions that will inform the nutritional situation of the population?
32. What effort has been taken to link the gap between evidence and policy in overcoming micronutrient deficiencies at national and global levels and across age groups?

## Strategic area 2: Understanding the diverse causes of micronutrient malnutrition

### Research priorities

1. What is the effect of vitamin B<sub>12</sub> on NTD recurrence?
2. For multi-factorial health problems, such as anaemia and child mortality, what proportion is attributable to poor nutrition and to what extent are other types of interventions needed?
3. What is the nutrient content of the existing diet? Is this consistent with the prevalence of deficiency (or excess) indicated by biomarkers? Or might deficiency be due to something other than total dietary nutrient content (absorption, infections, etc.)?
4. Have methodology and tools been developed to provide adequate instruments to improve fortified food surveillance?
5. Are the women responding to folic acid genetically predisposed to folate deficiency and can they be detected and targeted in another way?
6. How do host factors such as other nutrient deficiencies, infection, inflammation, gut health and microflora influence the efficacy of fortified foods and how are these accounted for in efficacy studies?
7. Should we automatically combine fortification programmes with infection control, improved sanitation and clean water provision programmes?
8. How do we best target anaemia control in areas of widespread infection, especially malaria?

## Strategic area 3: Developing large-scale fortification programmes to reduce micronutrient malnutrition

1. Knowledge and awareness of the general population about the use of iodised salt is important to address barriers such as religious concerns and existing demand for non-iodised salt.
2. What is the capacity in terms of trained staff, equipment, and budgetary resources to monitor compliance of food fortification?
3. What are the best institutional practices related to the implementation of food fortification programmes at national level?
4. What are the population's values and preferences regarding fortified foods?
5. What are the food consumption patterns of staple foods suitable for fortification at national level across geographical location, age groups, socio-economic and ethnic groups?
6. What tools are available to estimate national or sub-national food consumption patterns?
7. What is the linkage between investing in communications and social marketing, and increased coverage of fortified foods?



8. How should NFAs function and what is the role of the NFA in implementing a food fortification programme?
9. What cost:benefit tools can be standardised and used to advocate at the national policy-maker level for the need to implement a national, mandatory programme?
10. How do we harmonise the needs of compliance and regulations with industry perceptions?
11. How can the private and public sectors and NGOs collectively address public health issues on micronutrient deficiencies among the marginalised groups of society?
12. What is the best way to engage the food companies that produce staple foods such as oils, flours, and salt to implement effective fortification practices?
13. What are the attitudes of governments and communities in LMIC to fortification?
14. What new, more streamlined indicators may need to be standardised and disseminated to move from an ideal regulatory compliance system to a realistic system?
15. How to establish in any given country where private sector communications and social marketing are sufficient and where government investment is needed (e.g. best use of foods, non-market forces for information and safety issues)?
16. What are the decision-makers' values and perception of fortified foods, especially staples being used strategically/politically, such as rice?
17. Does the industry have capacity to fortify in terms of capital investments in fortification equipment, existing ability to monitor production (i.e. labs)?
18. Is the industry fragmented (e.g. tens of thousands of small mills) or modern and consolidated?
19. How can food fortification be better mainstreamed and linked with ongoing initiatives aimed at improving production quality and quantity?
20. Have all food science questions (organoleptics, acceptability, etc.) about fortification of the selected food vehicle been answered?
21. What is the industry structure of that specific food vehicle?
22. Are other foods already fortified?
23. Are we convinced that fortification compounds recommended by WHO (2006 and 2009) are still the best available or is there some new evidence from human studies to warrant revision?
24. What are the best and most effective forms of micronutrients that can be used without changing the inherent characteristics of the fortified foods?
25. What is the most effective vehicle for vitamin A fortification in terms of stability, cost and subsequent health impact?

26. How to set nutrient levels when two or more foods are fortified and there are other programmes that provide micronutrients (e.g. supplementation, micronutrient powders)?
27. How do we best overcome the inhibitory effect of phytic acid in cereals fortified with zinc or iron to ensure adequate absorption?
28. Can we find an iron fortification compound to add to bouillon cubes and show impact of bouillon cube fortification?
29. Are we sure that rice fortification technology is good enough to ensure efficacy given there is little evidence yet for extruded and coated rice?
30. What are the predicted effects of different combinations of fortification vehicles and levels of fortification on dietary adequacy and excess? How do these vary by sub-national region and by target group?
31. Does effectiveness of food fortification programmes at the country level need to be determined at sub-national levels with different characteristic socio-cultural groups?
32. Can we improve the efficacy testing of zinc-fortified foods to get more consistent results?
33. What are the accepted ways of measuring the efficacy of foods fortified with Fe, Zn, vitamin A, vitamin D, folic acid, and iodine?
34. Can the efficacy studies be improved, simplified and made less expensive?
35. Can we agree on the time frame for feeding studies?
36. Do we need to test in each population group?
37. What interventions will effectively address persistently high levels of anaemia among women of reproductive age and children under the age of five in rural areas?
38. What type of evidence is required at national level and what can be used from elsewhere (e.g. do findings on bioavailability of specific iron compounds from one country likely apply in another; is WHO interim guidance on which type of fortificant to select for our fortification universally applicable, or should it be confirmed in-country?)
39. What impact do mycotoxins have on the effectiveness of fortification in maize?
40. Can we better link nutritional status to functional outcomes?
41. Which function outcomes should we focus on?
42. How can we best analyse the food system to identify fortifiable vehicles and opportunities to reach specific groups who have the highest need for an increased intake of micronutrients (e.g. do the poorest consume processed foods, and if limited, how could they be provided better access)?

43. How can existing data sets and data collection systems (e.g. living standard measurement studies, HIES, food basket surveys, food frequency questionnaires) and available market data be used to answer questions that will inform the selection of food vehicle(s) and nutrient(s)?
44. How are local producers from resource-scarce countries able to compete with imported duty-free fortified products in the region?
45. How can we ensure that the primary focus of food fortification initiatives is on increasing intake of micronutrients (as opposed to improving micronutrient status or reducing anaemia, which are also affected by multiple other factors), and focus the efforts on ensuring access to adequately fortified foods (including selection of appropriate fortificants and vehicles, good QA & QC, good shelf-life, good distribution and/or market penetration, ensure that people receive or purchase it etc.)?
46. What is the best methodology for developing standards in a setting with multiple fortified foods with the same micronutrients?
47. How can we better use all possible delivery channels for food fortification (e.g. school feeding, food distribution for the poor, etc.)?
48. How far can implementing a food fortification programme in countries contribute significantly in terms of Scaling Up Nutrition Movement to reduce stunting?
49. When is the best time to engage the private sector companies that produce fortifiable foods?
50. We need to develop easily measured metrics that distinguish the effects (beneficial/harmful) of fortification from those due to other concurrent nutritional interventions and test such metrics for accuracy, reliability and ease of use.
51. There is a need to estimate the potential for delivery of inadequate and excessive amounts of the micronutrient for different scenarios of fortification and combinations of fortified foods consumed.
52. How can the information generated in the initial steps of the programme cycle (steps 1–3) best be introduced into the programme planning process?
53. How should decision-makers prioritise among nutrients and population groups, recognizing that there may be trade-offs in terms of which food fortification level combinations are likely to be more effective than others for different regions or age groups (and may have different costs)?
54. How can expected impacts in fortification be set up, going from efficacy to effectiveness?
55. What is the willingness of the private institutions (food manufacturers) to invest in communications and social marketing of fortified food products?

56. What design characteristics in fortification programmes are most likely to influence the success of a programme (e.g. selection of target groups, selection of foods, selection of nutrients, selection of fortification compounds, planning for training, planning of monitoring activities, planning for impact evaluation)?
57. What does a government have to do to ensure sustainability of programmes?
58. How much time and length of investment is needed for an effective programme to be self-sustaining?
59. How can NGO efforts be sustained after successfully influencing the government to mandate iron fortification?
60. What are the minimum requirements in the planning for scale-up of fortification programmes?
61. What design characteristics in fortification programmes are most likely to influence the success of a programme (e.g. selection of target groups, selection of foods, selection of nutrients, selection of fortification compounds, planning for training, planning of monitoring activities, planning for impact evaluation)?
62. How much do models differ according to culture, resources and traditions, and existing inequities?
63. Should monitoring plans be taken into consideration when planning the implementation, and if so how?
64. How do you strengthen National Fortification Alliances (NFAs)?
65. How should NFAs function and what is the role of the NFA in implementing a food fortification programme?
66. Who are the main parties and participants that need to be engaged in the planning processes?
67. Do all parties in the fortification implementation have equal representation and weight?
68. How is responsibility for actions determined, and correspondingly how is accountability ensured given that fortification programmes require multisectoral participation and coordination?

69. What is the best pre-mix procurement mechanism for a very stratified industry such as maize flour?
70. How should programmes work with suppliers to improve the quality of raw vehicle provided to millers for fortifying?
71. Does social marketing and behaviour change communication among low-income consumers increase the demand for fortified foods or are resources better spent on engaging consumer protection groups so as to ensure consumers have access to fortified foods?

#### Strategic area 4: Implementing, monitoring, and process evaluation of large-scale fortification programmes

1. What incentive measures can be put in place at government level to increase manufacturer's compliance with national fortification regulations?
2. How can accurate and field-friendly methods be improved and rolled out to monitor the level of fortification in food vehicles, at different stages of production and distribution?
3. How do you get sufficient government and industry investment in lab networks and in training and employing inspectors?
4. What incentives can be put in place to increase government's willingness/efforts to obtain compliance information on a regular basis?
5. How can the quality of fortified products be regulated within the framework of free trade agreements in Asia?
6. How can monitoring efforts for fortification be integrated with existing monitoring efforts (e.g. food safety monitoring) to improve efficiency and sustainability?
5. What sustainable tools and instruments are needed to monitor compliance level of producers of the food vehicle?
6. What is the most effective way of monitoring food manufacturing to ensure compliance with all regulations governing foods?
7. What are best practices for establishing a monitoring system and ensuring that the information is acted on in a timely manner?
8. What are the minimum compliance and impact indicators to determine progress and impact of fortification programmes?
9. When to use individual food samples vs composite samples to assess fortification levels?
10. What fortified foods are contributing to intake, and how much do supplements contribute?
11. What are consumption patterns of foods in the population after implementation of fortification?

12. How should a fortification programme be modified as consumption patterns change in the country considering both under- and over-consumption?
13. What national, regional, or international health report cards can include fortification and be used as a mechanism to increase government push for effective coverage and compliance?
14. What is the coverage of the fortified food?
15. Will a new staple food specifically target sub-group populations that are still at risk?

#### Strategic area 5: Evaluation of large-scale fortification programmes

1. What are the long-term impacts of folic acid fortification on the population other than that of reducing the incidence of neural tube defects?
2. What are the best practices for implementing programme evaluations (since logistics often limit these to pre-post, or just post, surveys, which are limited in terms of causality claims)?
3. Are we sure we can monitor impact by measuring intake?
4. When do we need to demonstrate improved nutritional status and improved functional outcomes?
5. How do we capture the contribution of fortified staples and condiments used as ingredients in processed foods?
6. What is the public health impact (effectiveness) of the programme on nutrient intake, nutrient status, and functional outcomes?
7. To what extent does effectiveness vary by region, age, or other target groups?
8. Does effectiveness match that predicted by dietary simulations conducted in Step 3 of the programme cycle?
9. What are the cost:benefits of the impact of the fortification programme?
10. What are the potential long-term negative impacts of fortification with any micronutrients (e.g. contribution to obesity, cancer, less dietary diversity)?
11. If programmes are not achieving the expected/desired effectiveness, what steps along the impact pathway need to be strengthened? Are these consistent across settings?







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