**Justification for the exclusion of biomarkers and functional outcomes in GFDx’s health impact indicator**

In 2019, GFDx expanded its suite of indicators to include an indicator documenting differences in health status pre- and post- fortification. The indicator will include biomarker assessments of micronutrients included in mandatory fortification standards and will include a limited number of relevant functional outcomes. The purpose of this document is to provide justification for excluding specific functional outcomes in its documentation of the health status of populations before and after fortification initiation.

**Iodine functional outcomes:**

Salt is the only vehicle with iodine added through fortification. GFDx has elected not to include any functional outcomes for the health impact assessment of iodine added to salt, for the following reasons by functional outcome:

*Excluded: Goiter*

Goiter assessment by palpation or by ultrasound may be useful in assessing thyroid function but is difficult to interpret once salt iodization has started. [[1]](#footnote-1) Changes in goiter prevalence lag behind changes in iodine status, and therefore cannot be relied upon to accurately reflect current iodine intake. [[2]](#footnote-2) There is also significant subjectivity in the measurement of small goiters, even when ultrasound is used.[[3]](#footnote-3)

**Vitamin A biomarker and functional outcomes:**

Oil is the primary food with vitamin A added through fortification, although several countries also fortify cereal grains with vitamin A. Below are vitamin A indicators GFDx excludes in the health impact assessment:

*Excluded: Liver stores*

Liver reserves of vitamin A are considered the gold standard to measure vitamin A status, but this measure is not feasible for population evaluation[[4]](#footnote-4).The process is invasive, and costly due to the biopsy procedure required to take a liver sample.

**Multi-nutrient functional outcomes**

Deficiencies in one or more nutrients are predisposing and aggravating factors for comorbidities such as diarrhea (vitamin A, vitamin B3), respiratory infections (vitamin A), measles (vitamin A), whooping cough (vitamin A), neuropathy (vitamin B1), neurological conditions (vitamin B1, vitamin B3), moderate and severe forms of malnutrition (vitamin A, vitamin B1), low infant birth weight (vitamin B9), preterm delivery (vitamin B9), fetal growth retardation (vitamin B9) and different skin conditions (vitamin A, vitamin B2, vitamin B3)[[5]](#footnote-5),[[6]](#footnote-6),[[7]](#footnote-7).,[[8]](#footnote-8),[[9]](#footnote-9)

Additionally, several nutrients, including iron, copper, vitamins A, B2, B9, B6, B12, C, D, E[[10]](#footnote-10) , may have similar functional outcomes associated with a deficiency in their intake (such as anemia), making it difficult to attribute any pre-/post- evaluation outcomes to the addition of that nutrient.

These outcomes can also be influenced by non-nutrition related interventions and/or causes (such as infectious disease control and genetics in the case of anemia). Given the breadth of potential outcomes, limited ability to attribute these outcomes to nutrients added through fortification, and that non-nutrition interventions can contribute to the improvement of these conditions, the following functional outcomes will not be included.

*Excluded: Diseases or conditions related to infectious diseases and the immune system, such as but not limited to: diarrhea, respiratory infections, measles, whooping cough, moderate and severe forms of malnutrition in children.*

*Excluded: Anemia (except nutritional anemias). This exclusion does not apply to anemias due to nutrient deficiencies (such as folate-deficiency anemia), which will be included.*

**Birth outcomes**

Maternal vitamin and mineral deficiencies are linked to poor birth outcomes, such as miscarriage, stillbirth, preterm birth, higher risk of birth defects, low birth weight, and neurological outcomes. However many of these outcomes also have non-nutritive causes and differences in the prevalence of these conditions pre-post fortification are difficult to attribute to fortification alone. With the exception of neural tube defects, for which baseline rates not due to folate insufficiency are known are estimated, all other birth outcomes are excluded from GFDx’s health indicator.

*Excluded: any birth outcomes, except neural tube defects*

**Anemia (except nutritional anemias)**

Because anemia can be due to non-nutritional causes such as parasitic infections and inherited blood disorders, anemia is excluded as a functional outcome in the GFDx. However, anemias due to nutrient deficiencies (such as folate-deficiency anemia) will be included.

*Excluded: non-nutritional anemias*

**Iron functional outcomes**

Iron deficiency is associated with several adverse functional outcomes such as reduced work performance and child development, and increased mortality[[11]](#footnote-11). None of these are included because of other non-nutritional causes of these adverse outcomes.

*Excluded: any functional indicator attributed to iron*

**B vitamin functional outcomes**

Deficiencies in B vitamins (thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamin B6, folate (B9) and vitamin B12) are known to have adverse effects in health and brain function[[12]](#footnote-12). For some of these deficiencies such as thiamine, clinical manifestations are variable[[13]](#footnote-13) and for most, improvements in these outcomes cannot be attributed solely to the effects of a fortification program among a population. In most cases, clinical outcomes are also not available from a national population and cannot be reported as pre-post fortification differences.

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