# GIVING what we can

An update on the effectiveness of the micronutrient fortification programmes by Project Healthy Children (PHC) (Working Paper)

Hauke Hillebrandt, Ph.D., Mark Engelbert, Ph.D.

Email: hauke.hillebrandt@givingwhatwecan.org

Online version:

# **Summary**

Project Healthy Children (PHC) is a charity that we began investigating in recent years, and it has been one of our promising charities for nearly 2 years.

We have <u>reviewed Project Healthy Children</u> in the past and also written an introduction on <u>micronutrient fortification</u>. Our colleagues at Givewell have not officially reviewed PHC, but provide a great overview in form of a <u>conversation note</u> with PHC's Chief operating officer, Laura Rowe. Givewell has also published extensive intervention reviews on Micronutrient fortification as implemented by Project Healthy Children (<u>Salt iodization</u>, <u>Vitamin A fortification</u>, <u>Zinc fortification</u>). Finally, they have also written reports on organisations similar to PHC, such as <u>GAIN</u> and <u>IGN</u>. These programmes are generally considered to be very effective and some of the effectiveness analyses are generalizable to PHC.

In this paper, we give you an update about their efforts that we feel complement Givewell's intervention reports and our previous report. You can find more general information about PHC on our website. In our opinion, PHC continues to be a very promising charity with potentially a very high cost-effectiveness.

# **Contents**

```
Summary
```

Recent Scientific findings that relate to PHC's effectiveness

Differences between micronutrient supplementation and fortification

General considerations of micronutrient fortification

Updates from countries in which PHC is currently active

Rwanda

Liberia

Burundi

**Zimbabwe** 

Sierra Leone

<u>Cost-effectiveness of different micronutrient fortification interventions</u>

**Economic effects** 

Labour productivity lost

Macroeconomic Impact

Effects of micronutrients for mental development

Micronutrient supplementation for children with HIV infection

Recent research on fortification with specific micronutrients

**lodine fortification** 

Benefits and Risks of Iodine

Effect of Iodine on (mental) development in children

<u>lodine loss due to storage and cooking</u>

**Iron fortification** 

<u>Do the effects of supplementation generalize to cheaper population-level fortification of staple foods interventions?</u>

<u>Does iron fortification increase malaria?</u>

Vitamin A

<u>Vitamin A deficiency - disease interactions and risk factors</u>

<u>Zinc</u>

Folic Acid

Is biofortification more effective than industrial fortification?

<u>Updates on Room for additional funding</u>

Long-term view on room for more funding

Other organisations involved in micronutrient fortification

Short-term view on room for more funding

<u>Updates on Fundraising activities</u>

**Updates on PHC's Operations** 

**Fortification programs** 

# Recent Scientific findings that relate to PHC's effectiveness

# Differences between micronutrient supplementation and fortification

To begin, note that there is a difference between micronutrient supplementation and micronutrient fortification. Micronutrient supplementation is here defined as taking capsules or foodstuffs (such as biscuits) that are specifically made to increase micronutrient status of the person eating it, whereas fortification means that commonly eaten staple foods are enriched with micronutrients. Although the aim of this report is to examine the effectiveness of micronutrient fortification, the close relation between supplementation and fortification means that sometimes results from micronutrient supplementation can provide insight into the effectiveness of fortification. Supplementation of all foods is often not as viable or as cost-effective as fortification. Also a recent study suggests that in pregnant adolescents, prenatal supplements cannot fully compensate for preexisting dietary deficiencies <sup>1</sup>; thus, even if supplementation could be cost-effectively distributed to whole populations, it might still be less effective at improving nutritional outcomes than a continuous diet of enriched food by means of micronutrient fortification. Finally, there is also *bio*fortification, which is increasing the micronutrient content of plants directly, which will not be discussed here.

<sup>&</sup>lt;sup>1</sup> Lee, Sunmin et al. "Nutrient Inadequacy Is Prevalent in Pregnant Adolescents, and Prenatal Supplement Use May Not Fully Compensate for Dietary Deficiencies." *ICAN: Infant, Child, & Adolescent Nutrition* (2014): 1941406414525993.

### General considerations of micronutrient fortification

A recent systematic review of 201 studies on the impact of micronutrient fortification of food and on woman and child health<sup>2</sup>, concludes that fortification is promising, but because of high burdens of diarrhea and intestinal inflammation, widespread malabsorption may decrease its effectiveness. Further, even though fortification is potentially an effective strategy, evidence from the developing world is scarce and future programs should measure the direct impact of fortification on morbidity and mortality.

# Epidemiology of malnutrition

While underweight is the number-one contributor to the burden of disease in sub-Saharan Africa<sup>3</sup>,<sup>4</sup>, nutritional deficiencies make up a large part of the overall *direct* disease and disability burden in developing countries (see **Figure 1**). However, nutritional deficiencies are linked to other diseases (see **Figure 2**), and so over 50% of years lived with disability in children can be traced to these deficiencies<sup>5,6</sup>.

<sup>&</sup>lt;sup>2</sup> Das, JK. "Micronutrient fortification of food and its impact on woman ..." 2013.

<sup>&</sup>lt;a href="http://www.systematicreviewsjournal.com/content/pdf/2046-4053-2-67.pdf">http://www.systematicreviewsjournal.com/content/pdf/2046-4053-2-67.pdf</a>

<sup>&</sup>lt;sup>3</sup> "Global Nutrition Report 2014 - The Global Nutrition Report." 2014. 12 May. 2015

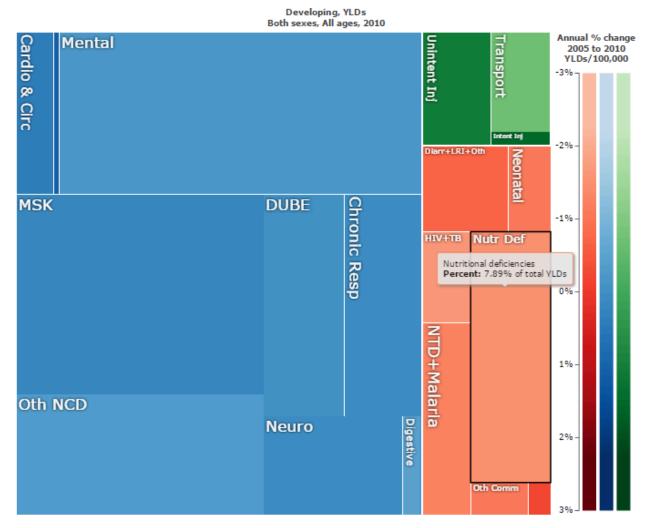
<sup>&</sup>lt;a href="http://globalnutritionreport.org/2014/11/13/global-nutrition-report-2014/">http://globalnutritionreport.org/2014/11/13/global-nutrition-report-2014/</a>>

<sup>&</sup>lt;sup>4</sup> Lim, Stephen S et al. "A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010." *The lancet* 380.9859 (2013): 2224-2260.

<sup>&</sup>lt;sup>5</sup> "Global Nutrition Report 2014 - The Global Nutrition Report." 2014. 12 May. 2015

<sup>&</sup>lt;a href="http://globalnutritionreport.org/2014/11/13/global-nutrition-report-2014/">http://globalnutritionreport.org/2014/11/13/global-nutrition-report-2014/</a>

<sup>&</sup>lt;sup>6</sup> Vos, Theo et al. "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010." *The Lancet* 380.9859 (2013): 2163-2196.



**Figure 1:** Overall "Years Lost due to Disability (YLD)" in developing countries. Nutritional deficiencies are marked in black and make up 7.89% of the total YLDs. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3a5f">http://ihmeuw.org/3a5f</a>. © 2013 <a href="http://ihmeuw.org/3a5f">University of Washington</a> - <a href="http://ihmeuw.org/3a5f">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

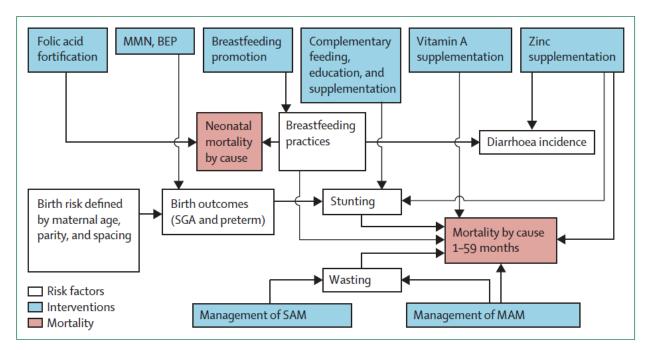


Figure 2: Linkages between risk factors, interventions, and mortality in LiST LiST=Lives Saved Tool. MMN=multiple micronutrients. BEP=balanced energy protein. SGA=small-for-gestational-age. SAM=severe acute malnutrition. MAM=moderate AM.

# Updates from countries in which PHC is currently active

The following updates are quotes from the World Bank's 2013 'Nutrition at a Glance' country reports of those countries in which PHC is active.

### 1. Rwanda<sup>7</sup>

Annually, Rwanda loses nearly US\$50 million in GDP to vitamin and mineral deficiencies. Scaling up core micronutrient interventions would cost US\$6 million per year.

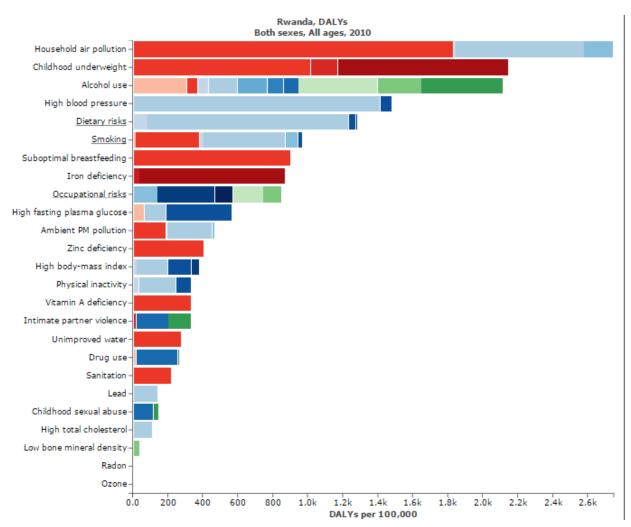
52% of children under the age of five are stunted, 16% are underweight, and 5% are wasted. 6% of infants are born with a low birth weight. Rwanda's progress over the past two decades has not improved to meet MDG 1c (halving 1990 rates of child underweight by 2015) with business as usual.

Rwanda performs worse than countries in its region and income group. Countries with lower per capita incomes, such as Togo and DRC exhibit reduced rates of child stunting.

Rwanda has Higher Rates of Stunting than Lower-Income Peers GNI per capita (US\$2008).

<sup>&</sup>lt;sup>7</sup> "Rwanda - Nutrition at a glance (English) | The World Bank." 2013. 18 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2011/04/17695137/rwanda-nutrition-glance">http://documents.worldbank.org/curated/en/2011/04/17695137/rwanda-nutrition-glance</a>



**Figure 3:** Figure shows risk factors for "Disability adjusted life years" in Rwanda. Micronutritional deficiencies, such as Iron, Zinc, and Vitamin A deficiencies, are substantial risk factors. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3hck">http://ihmeuw.org/3hck</a>. © 2013 <a href="http://ihmeuw.org/3hck">University of Washington</a> - <a href="Institute for Health Metrics and Evaluation">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

### 2. Malawi<sup>8</sup>

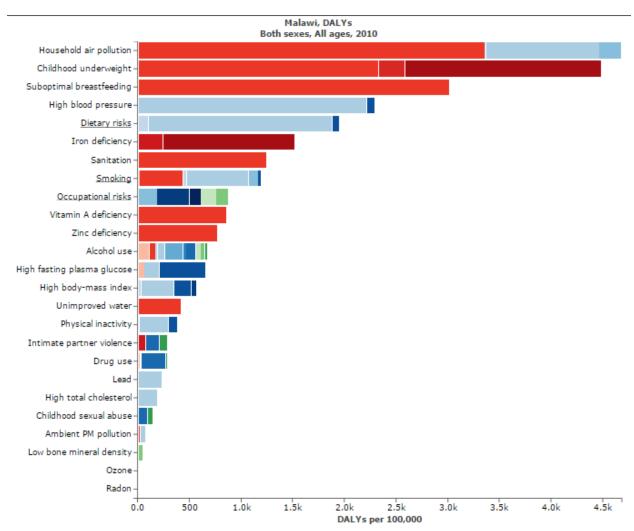
Annually, Malawi loses over US\$600 million in GDP to vitamin and mineral deficiencies. Scaling up core micronutrient interventions would cost less than US\$9 million per year.

Malawi has the 5th-highest stunting rate in the world. 53% of children under the age of five are stunted, 15% are underweight, and 4% are wasted. 13% of infants are born with a low birth weight. Malawi's progress over the past two decades has not improved to meet MDG 1c (halving 1990 rates of child underweight by 2015) with business as usual.

<sup>8 &</sup>quot;Malawi - Nutrition at a glance (English) | The World Bank." 2013. 18 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2011/04/17694769/malawi-nutrition-glance">http://documents.worldbank.org/curated/en/2011/04/17694769/malawi-nutrition-glance</a>

Malawi's stunting rates are higher than many of its income peers in Africa. While per capita income is very low in Malawi, other countries show that it is possible to reduce stunting with the same or lower GNI.



**Figure 4:** Figure shows risk factors for "Disability adjusted life years" in Malawi. Micronutritional deficiencies, such as Iron, Zinc, and Vitamin A deficiencies, are substantial risk factors. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3hck">http://ihmeuw.org/3hck</a>. © 2013 <a href="http://ihmeuw.org/3hck">University of Washington</a> - <a href="Institute for Health Metrics and Evaluation">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

### 3. Liberia<sup>9</sup>

Annually, Liberia loses over US\$11 million in GDP to vitamin and mineral deficiencies. Scaling up core micronutrient nutrition interventions would cost US\$2 million per year

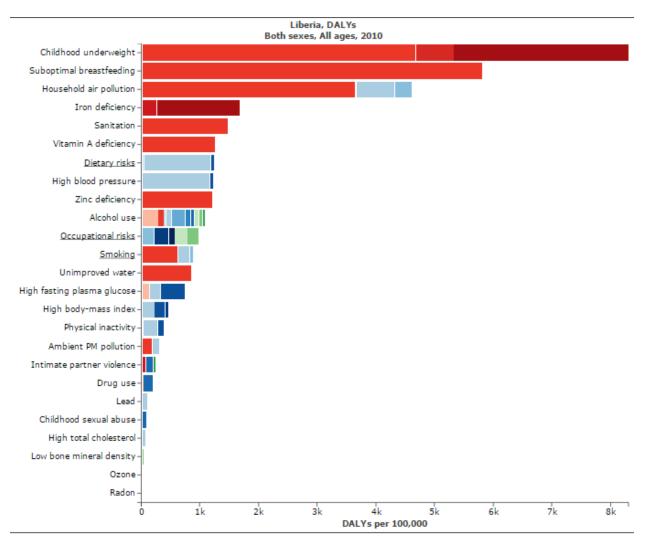
<sup>&</sup>lt;sup>9</sup> "Liberia - Nutrition at a glance (English) | The World Bank." 2013. 18 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2011/04/17694767/liberia-nutrition-glance">http://documents.worldbank.org/curated/en/2011/04/17694767/liberia-nutrition-glance</a>

39% of children under the age of five are stunted, 19% of children under the age of five are underweight, and 8% are wasted.

Liberia will not meet MDG 1c (halving 1990 rates of child underweight by 2015) with business as usual. 14% of infants are born with a low birth weight.

Liberia's stunting rates are higher than many countries in the Africa region with similar per capita income.

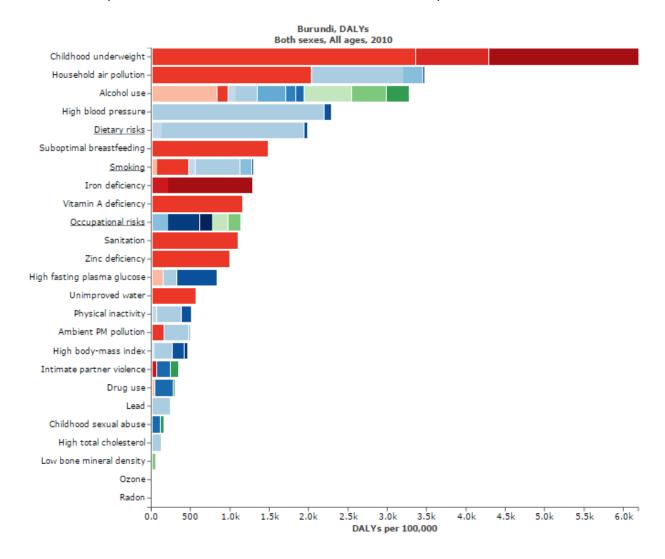


**Figure 5:** Figure shows risk factors for "Disability adjusted life years" in Liberia. Micronutritional deficiencies, such as Iron, Zinc, and Vitamin A deficiencies, are substantial risk factors. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3hck">http://ihmeuw.org/3hck</a>. © 2013 <a href="University of Washington">University of Washington</a> - <a href="Institute for Health Metrics and Evaluation">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

### 4. Burundi<sup>10</sup>

Annually, Burundi loses US\$30 million to vitamin and mineral deficiencies. Scaling up core micronutrient interventions would cost US\$4 million per year.

53% of children under the age of five are stunted, 35% are underweight, and 7% are wasted. 11% of infants are born with a low birth weight...the prevalence of stunting is substantially higher in Burundi compared to other countries in the Africa region with similar per capita incomes. It is possible to achieve better nutrition outcomes despite low income.



**Figure 6:** Figure shows risk factors for "Disability adjusted life years" in Burundi. Micronutritional deficiencies, such as Iron, Zinc, and Vitamin A deficiencies, are substantial risk factors. Figure adapted with 'Global Burden of Disease Compare tool'- see

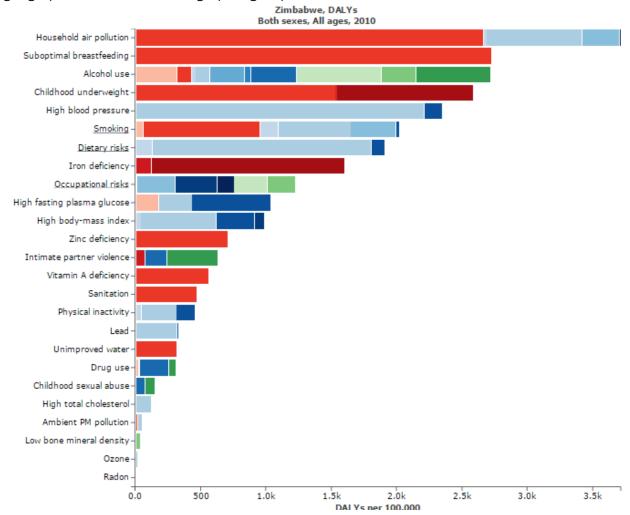
<sup>&</sup>lt;sup>10</sup> "Burundi - Nutrition at a glance (English) | The World Bank." 2013. 18 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2011/04/17688635/burundi-nutrition-glance">http://documents.worldbank.org/curated/en/2011/04/17688635/burundi-nutrition-glance</a>

http://ihmeuw.org/3hck. © 2013 <u>University of Washington</u> - <u>Institute for Health Metrics and Evaluation</u> (Global burden of Disease data 2010, released 3/2013)

### 5. Zimbabwe<sup>11</sup>

Annually, Zimbabwe loses nearly US\$24 million in GDP to vitamin and mineral deficiencies. Scaling up core micronutrient interventions would cost less than US\$8 million per year. 33% of children under the age of five are stunted, 12% are underweight, and 7% are wasted. 11% of infants are born with a low birth weight. Zimbabwe is currently not on track to meet MDG 1c (halving 1990 rates of child underweight by 2015) with business as usual. When overall rates of child stunting are examined, Zimbabwe performs better than countries in its region and income group. However, within the country, there is likely to be variation across geographies and socio-demographic groups.



**Figure 7:** Figure shows risk factors for "Disability adjusted life years" in Zimbabwe. Micronutritional deficiencies, such as Iron, Zinc, and Vitamin A deficiencies, are substantial

<sup>&</sup>lt;sup>11</sup> "Zimbabwe - Nutrition at a glance (English) | The World Bank." 2013. 18 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2013/04/17695179/zimbabwe-nutrition-glance">http://documents.worldbank.org/curated/en/2013/04/17695179/zimbabwe-nutrition-glance</a>

Giving What We Can - An update on the effectiveness of the micronutrient fortification programmes by Project Healthy Children

risk factors. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3hck">http://ihmeuw.org/3hck</a>. © 2013 <a href="University of Washington">University of Washington</a> - <a href="Institute for Health Metrics and Evaluation">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

### 6. Sierra Leone<sup>12</sup>

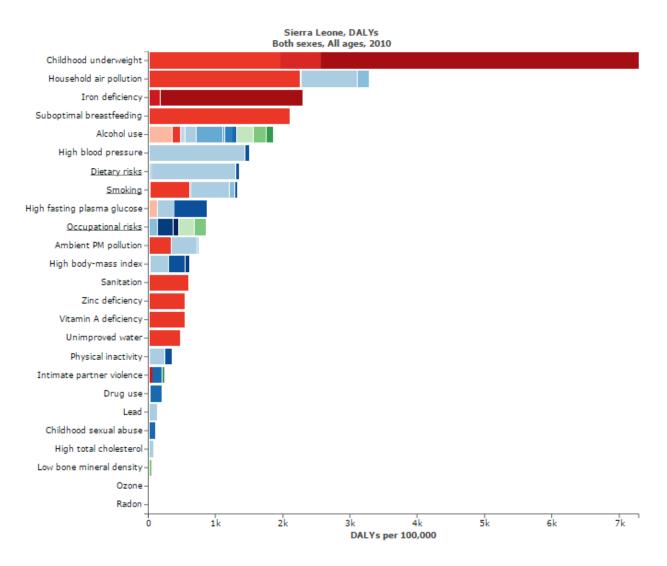
Annually, Sierra Leone loses over US\$28 million in GDP to vitamin and mineral deficiencies. Scaling up core micronutrient interventions would cost less than US\$4 million per year.

36% of children under the age of five are stunted, 21% are underweight, and 10% are wasted. Almost 1 in 4 infants are born with a low birth weight. Sierra Leone will not meet MDG 1c (halving 1990 rates of child underweight by 2015) with business as usual.

Sierra Leone exhibits higher rates of child stunting relative to some other countries with similar per capita income. That Zimbabwe, The Gambia, and Togo have much lower stunting rates demonstrates that it is possible to achieve better nutrition outcomes despite low income.

<sup>&</sup>lt;sup>12</sup> "Sierra Leone - Nutrition at a glance (English) | The World Bank." 2013. 18 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2011/04/17695152/sierra-leone-nutrition-glance">http://documents.worldbank.org/curated/en/2011/04/17695152/sierra-leone-nutrition-glance</a>



**Figure 8:** Figure shows risk factors for "Disability adjusted life years" in Sierra Leone. Micronutritional deficiencies, such as Iron, Zinc, and Vitamin A deficiencies, are substantial risk factors. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3hck">http://ihmeuw.org/3hck</a>. © 2013 <a href="http://ihmeuw.org/3hck">University of Washington</a> - <a href="Institute for Health Metrics and Evaluation">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

### Cost-effectiveness of different micronutrient fortification interventions

Even though there are some uncertainties with regard to estimating the cost-effectiveness of micronutrient fortification programmes and there is variation in cost-effectiveness across programmes<sup>13</sup>, fortification is generally considered to be a very cost-effective intervention. Early estimates suggested that fortification with iron, vitamin A and zinc were well below \$100 per DALY averted (see **Figure 9**).

<sup>&</sup>lt;sup>13</sup> Fiedler, John L, and Chloe Puett. "Micronutrient program costs: Sources of variations and noncomparabilities." *Food & Nutrition Bulletin* 36.1 (2015): 43-56.

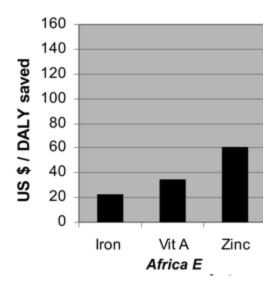


Figure 9: Comparison of cost effectiveness of fortification in East Africa. Figure adapted from<sup>14</sup>

A 2006 report from the Disease Control Priorities Project suggests that overall cost-effectiveness is US\$66 to US\$70 per DALY averted for iron fortification programs and US\$34 to US\$36 per DALY averted for iodine fortification programs<sup>15</sup>.

There is now a vast literature on the cost effectiveness of micronutrient fortification. A recent review article<sup>16</sup> on the economics of nutrition summarizes the evidence of cost-effectiveness for different micronutrient programmes (see Table 2 of this review for a summary of research papers on the topic<sup>17</sup>). Two studies from this paper provide \$ per DALY averted estimates of fortification programmes:

- 1. Folic acid fortification in Chile: costs per neural tube defect case and infant death averted were I\$1,200<sup>18</sup> and I\$11,000, respectively; cost per DALY averted was I\$89; net cost savings of fortification were I\$2.3 million
- 2. Vitamin A fortification of edible oils and sugar in Uganda: Cost per DALY averted is US \$82 for sugar fortification and \$18 for oil fortification

http://nutritionreviews.oxfordjournals.org/highwire/markup/16400/expansion?width=1000&height=500&iframe =true&postprocessors=highwire figures%2Chighwire math%2Chighwire oup table images

<sup>&</sup>lt;sup>14</sup> Horton, Sue. "The economics of food fortification." *The Journal of nutrition* 136.4 (2006): 1068-1071.

<sup>&</sup>lt;sup>15</sup> Jamison, Dean T et al. *Disease control priorities in developing countries*. Dean T Jamison et al. World Bank Publications, 2006.

<sup>&</sup>lt;sup>16</sup> Gyles, CL. "Health economics and nutrition: a review of published ..." 2012.

<sup>&</sup>lt;a href="http://nutritionreviews.oxfordjournals.org/content/70/12/693">http://nutritionreviews.oxfordjournals.org/content/70/12/693</a>>

<sup>&</sup>lt;sup>17</sup> Table may be viewed at:

<sup>18 &</sup>quot;I\$" refers to "international dollars."

A 2009 review by John Fiedler and Barbara MacDonald<sup>19</sup> provides cost-per-DALY-averted estimates for micronutrient fortification programmes in many countries. Although these were not programmes implemented by PHC, they were adopted in many of the same countries where PHC operates. Thus, these data provide some indication of likely cost effectiveness levels that can be expected for similar programmes implemented by PHC in these same countries. **Tables 1** and **2** are adapted from Fiedler and MacDonald's review to show only countries in which Project Healthy Children is currently operating. These estimates suggest high cost-effectiveness at around \$100 per DALY averted, similar to previous high cost-effectiveness estimates of fortification programmes in other countries (see **Table 1**). **Table 2** summarizes key statistics for micronutrient programmes in a number of countries in which PHC operates, along with each programme's ranking among worldwide programmes in terms of cost effectiveness. For instance, wheat fortification in Malawi was the 16th most cost-effective food fortification programme in the world. Taken together, these data indicate that PHC operates in countries where micronutrient fortification programmes have proved to be cost-effective. It should be noted, however, that this table is from 2009, and it is possible that many of the most cost-effective programmes (i.e., the 'low hanging fruit') have in the meantime been executed.

Country	Cost per DALY averted (US\$)							
	Sugar	Vegetable oil	Maize flour		Wheat flour			
			Reduced package	Expanded package	Reduced package	Expanded package		
Burundi	_	106	_	_	_	_		
Malawi	223	105	183	120	24.61	10.81		
Rwanda	225	68	_	_	<u> </u>	_		
Sierra Leone	-	69	<u> </u>	_	<u> </u>	_		
Zimbabwe	33	487	2232	1060	42.54	31.78		

**TABLE 1:** Total incremental 10-year cost and cost per DALY averted arrayed alphabetically by countries in which PHC operates in. Figure adapted from<sup>20</sup>. Full table here<sup>21</sup>

 $\frac{https://docs.google.com/spreadsheets/d/1lMzXga5d3-WPvsUgpFNoTR64CFmYHLfT3fBABA5jN60/edit?usp=sharing$ 

<sup>&</sup>lt;sup>19</sup> Fiedler, John L, and Barbara Macdonald. "A strategic approach to the unfinished fortification agenda: feasibility, costs, and cost-effectiveness analysis of fortification programs in 48 countries." *Food & Nutrition Bulletin* 30.4 (2009): 283-316.

<sup>&</sup>lt;sup>20</sup> Fiedler, John L, and Barbara Macdonald. "A strategic approach to the unfinished fortification agenda: feasibility, costs, and cost-effectiveness analysis of fortification programs in 48 countries." *Food & Nutrition Bulletin* 30.4 (2009): 283-316.

Rank	Country and food	Global Burden of Disease Region	Hotal cost (USS)	Cost per DALY saved (US\$)	Cumulative to cost (US\$)	otal
16	Malawi—wheat	AFR_E	1,344,446	25	24,074,848	
21	Zimbabwe—sugar	AFR E	2,218,527	33	139,567,326	
30	Zimbabwe—wheat	AFR E	1,872,396	43	252,005,760	
46	Rwanda—oil	AFR E	6,623,699	68	482,470,004	
47	Sierra Leone—oil	AFR_D	10,601,950	69	493,071,954	
52	Malawi—oil	AFR E	9,738,123	105	733,345,516	
54	Burundi—oil	AFR E	5,500,917	106	788,260,013	

**TABLE 2.** The ranking of the countries PHC is active in from a table of the 60 countries' micronutrient interventions arrayed by cost per DALY averted. Table adapted from<sup>22</sup>. Full table here<sup>23</sup>

In sum, even though these cost-effectiveness estimates are subject to limitations (i.e., up-to-date cost-effectiveness estimates of the exact fortification programmes that PHC conducts are unavailable, and cost-effectiveness estimates are sometimes uncertain and difficult to compare), overall we believe that that the available evidence suggests PHC's cost-effectiveness is roughly similar to the reported estimates—in other words, that PHC's programmes are highly cost-effective.

### **Economic effects**

Nutritional deficiencies have been shown to have negative economic consequences. Out summary of these effects draws from several recent studies, including the Global Nutrition Report 2014<sup>24</sup>. Note that micronutrient deficiencies only account for *part* of the economic losses from nutritional deficiencies—macronutrient deficiencies (i.e., hunger) also contribute to these losses.

### Labour productivity lost

A study from Guatemala suggests that preventing undernutrition in childhood increases productivity in several ways. Specifically, preventing undernutrition increases hourly earnings by 20% and wage rates by 48%. Moreover, children treated for undernutrition are 33% more likely to escape poverty, while treated girls are 10% more likely to own a business as adults<sup>25,26</sup>. Stunted growth or stunting, is a reduced growth rate in human development due to nutritional deficiencies, is highly prevalent in developing countries (see **Figure 10**) and a

23

 $\underline{https://docs.google.com/spreadsheets/d/1f-SHCw5sWu3fd8bQ0s6r9en5pFmzuflOR8WeiKoUjhw/edit?usp=sharing}\\$ 

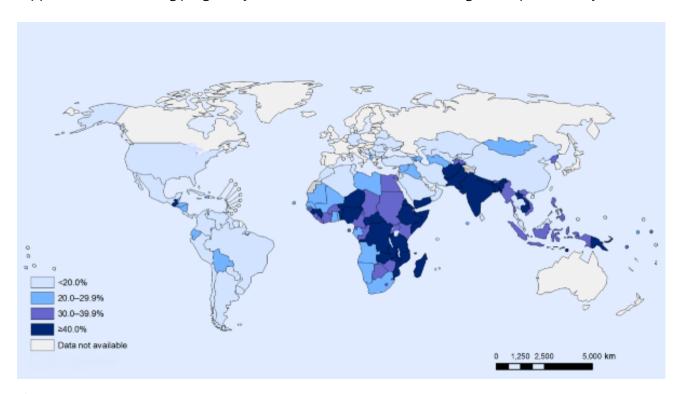
<sup>&</sup>lt;sup>22</sup> Fiedler, John L, and Barbara Macdonald. "A strategic approach to the unfinished fortification agenda: feasibility, costs, and cost-effectiveness analysis of fortification programs in 48 countries." *Food & Nutrition Bulletin* 30.4 (2009): 283-316.

<sup>&</sup>lt;sup>24</sup> "The Global Nutrition Report." 2014. 16 May. 2015 <a href="http://globalnutritionreport.org/">http://globalnutritionreport.org/</a>>

<sup>&</sup>lt;sup>25</sup> "The Global Nutrition Report." 2014. 16 May. 2015 < http://globalnutritionreport.org/>

<sup>&</sup>lt;sup>26</sup> Hoddinott, John et al. "The economic rationale for investing in stunting reduction." *Maternal & Child Nutrition* 9.S2 (2013): 69-82.

significant contributor to lost productivity. Analyses suggest that growth failure in early life has profound adverse consequences over the life course on human, social, and economic capital<sup>27</sup>. One study in particular showed that one extra centimeter of adult height corresponds to a 4.5% increase in wage rates<sup>28,29</sup>. Low birth weight is also associated with increased risk of hypertension and kidney disease in later life; however, micronutrient supplementation during pregnancy reduces the risk of low birth weight and prematurity<sup>30</sup>.



**Figure 10:** Stunting among children under 5: latest national prevalence estimates. Figure taken from<sup>31</sup>

<sup>&</sup>lt;sup>27</sup> Hoddinott, John et al. "Adult consequences of growth failure in early childhood." *The American journal of clinical nutrition* (2013): ajcn. 064584.

<sup>&</sup>lt;sup>28</sup> Haddad, Lawrence. "Ending Undernutrition: Our Legacy to the Post 2015 Generation." *Public Health Nutrition* 1 (2011): 1-7.

<sup>&</sup>lt;sup>29</sup> "The Global Nutrition Report." 2014. 16 May. 2015 < <a href="http://globalnutritionreport.org/">http://globalnutritionreport.org/</a>>

<sup>&</sup>lt;sup>30</sup> Luyckx, Valerie A, and Barry M Brenner. "Birth weight, malnutrition and kidney-associated outcomes [mdash] a global concern." *Nature Reviews Nephrology* (2015).

<sup>&</sup>lt;sup>31</sup> Onis, M. "Full Article (HTML) - Wiley Online Library." 2013.

<sup>&</sup>lt;a href="http://onlinelibrary.wiley.com/doi/10.1111/mcn.12075/full">http://onlinelibrary.wiley.com/doi/10.1111/mcn.12075/full</a>

### Macroeconomic Impact

Economic analyses suggest that undernutrition within a country lowers the overall economic productivity of that country. Specifically, undernutrition has been suggested to lower GDP for Egypt by 1.9%; Ethiopia, 16.5%; Swaziland, 3.1%; and Uganda, 5.6% <sup>32</sup>. Asia and Africa lose 11% of GNP every year owing to poor nutrition<sup>33</sup>. One recent study suggests that, in Cambodia, malnutrition costs more than US \$400 million annually, corresponding to -2.5% of the country's GDP. In Pakistan, protein malnutrition, iodine deficiency and iron deficiency collectively accounted for about 3–4% of gross domestic product (GDP) loss annually<sup>34,35</sup>. A study of 10 developing countries suggest that iron-deficiency anaemia causes an average loss of 4.5% of GDP<sup>36,37</sup>.

A recent World Bank study estimated that investing in nutrition can increase a country's GDP by at least 3 percent annually<sup>38</sup>. The same study concluded that global benefit-to-cost ratio of micronutrient powders for children is 37 to 1; of deworming it is 6 to 1; of iron fortification of staples it is 8 to 1; and of salt iodization is 30 to  $1^{39}$ .

We have calculated the average benefit-to-cost ratio of fortification programmes in the countries where PHC is active. Using the World Bank's estimates of the economic on GDP loss annually to vitamin and mineral deficiencies alone<sup>40</sup>, we have calculated<sup>41</sup> that the average benefit-to-cost ratio in these countries is about 23:1. In other words, the cost of scale-up for fortification programmes is 23 times smaller than the economic benefits. Other researchers have found similarly high estimates of cost-effectiveness: a recent paper<sup>42</sup> looked at the value of stunting-reducing nutrition investments, such as micronutrient fortification, in 17 high-burden countries. The benefit-to-cost ratios ranged from 3.6 (Democratic Republic of

<sup>&</sup>lt;sup>32</sup> ECA, AUC, and WFP NEPAD. "The cost of hunger in Africa Social and Economic Impact of Child Undernutrition in Egypt, Ethiopia, Swaziland and Uganda." *Addis Ababa* (2013).

<sup>&</sup>lt;sup>33</sup> Horton, S, and Richard H Steckel. "Malnutrition: global economic losses attributable to malnutrition 1900–2000 and projections to 2050." *How Much Have Global Problems Cost the Earth? A Scorecard from 1900 to* 2050 (2013): 247-272.

<sup>&</sup>lt;sup>34</sup> "5th Report on the World Nutrition Situation ... - UNSCN." 2009. 16 May. 2015

<sup>&</sup>lt;a href="http://www.unscn.org/lavout/modules/resources/files/rwns5.pdf">http://www.unscn.org/lavout/modules/resources/files/rwns5.pdf</a>

<sup>&</sup>lt;sup>35</sup> Sultan, Saira et al. "Concept of double salt fortification; a tool to curtail micronutrient deficiencies and improve human health status." *Journal of the Science of Food and Agriculture* 94.14 (2014): 2830-2838.

<sup>&</sup>lt;sup>36</sup> Stein, AJ. "The human and economic cost of hidden hunger - Food and ..." 2013.

<sup>&</sup>lt;a href="http://www.fao.org/fsnforum/sites/default/files/resources/Stein%20and%20Oaim.pdf">http://www.fao.org/fsnforum/sites/default/files/resources/Stein%20and%20Oaim.pdf</a>

<sup>&</sup>lt;sup>37</sup> Horton, Susan, and Jay Ross. "The economics of iron deficiency." *Food policy* 28.1 (2003): 51-75.

<sup>&</sup>lt;sup>38</sup> Horton, Susan et al. *Scaling up nutrition: What will it cost?* The World Bank, 2009, xix, http://elibrary.worldbank.org/doi/abs/10.1596/978-0-8213-8077-2

<sup>&</sup>lt;sup>39</sup> Horton, Susan et al. *Scaling up nutrition: What will it cost?* The World Bank, 2009, 38, http://elibrary.worldbank.org/doi/abs/10.1596/978-0-8213-8077-2

<sup>&</sup>lt;sup>40</sup> "Mali - Nutrition at a glance (English) | The World Bank." 2013. 16 May. 2015

<sup>&</sup>lt;a href="http://documents.worldbank.org/curated/en/2011/04/17695766/mali-nutrition-glance">http://documents.worldbank.org/curated/en/2011/04/17695766/mali-nutrition-glance</a>

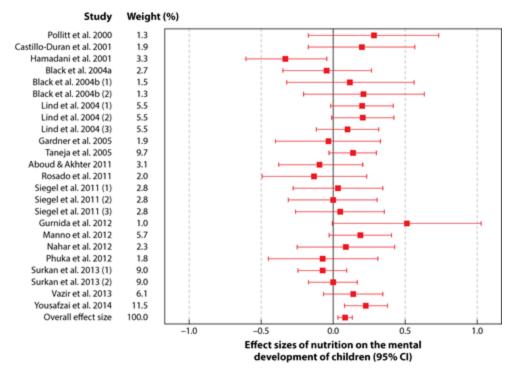
<sup>41</sup> https://docs.google.com/spreadsheets/d/14vMaIa2S098TuzBEEF\_EvoG\_-TYWOibt\_DNPTgdP4SU/edit#gid=0

<sup>&</sup>lt;sup>42</sup> Hoddinott, John et al. "The economic rationale for investing in stunting reduction." *Maternal & Child Nutrition* 9.S2 (2013): 69-82.

Congo) to 48 (Indonesia) with a median value of 18 (Bangladesh). Another recent paper <sup>43</sup>, <sup>44</sup> finds similarly impressive benefit-cost ratios for iodizing salt (80), iron supplements for mothers and small children (24), vitamin A supplementation (13), and zinc supplementation for children (3). Thus, these estimates in the literature are broadly comparable to our calculations.

### Effects of micronutrients for mental development

A review and meta-analysis of 21 interventions examined the effects of multiple micronutrients on mental development, and yielded a very small but significant overall effect size of  $d = 0.09^{45,46}$  (see **Figure 11**). However, even small effect sizes can translate to very high cost-effectiveness, so long as the effects are robust and the interventions are very cheap to implement. However, it is very difficult to estimate the exact cost-effectiveness.



Aboud FE, Yousafzai AK. 2015. Annu. Rev. Psychol. 66:433–57

<sup>&</sup>lt;sup>43</sup> Hoddinott, John, Mark Rosegrant, and Maximo Torero. "Hunger and malnutrition." (2012).

<sup>&</sup>lt;sup>44</sup> Behrman, Jere R et al." Human Capital and Productivity Benefits of Early Childhood Nutritional Interventions."

<sup>&</sup>lt;sup>45</sup> Aboud, FE, and FE Aboud, "Chapter 13, Very Early Childhood Development,"

<sup>&</sup>lt;a href="http://dcp-3.org/sites/default/files/chapters/V2C13%20Earlv%20Childhood%20Development.pdf">http://dcp-3.org/sites/default/files/chapters/V2C13%20Earlv%20Childhood%20Development.pdf</a>

<sup>&</sup>lt;sup>46</sup> Aboud, Frances E, and Aisha K Yousafzai. "Global Health and Development in Early Childhood." *Annual review of psychology* 66 (2015): 433-457.

Giving What We Can - An update on the effectiveness of the micronutrient fortification programmes by Project Healthy Children

**Figure 11**<sup>47</sup> Forest plot for effect sizes (standard mean difference represented as a red square and 95% confidence interval represented as red lines) of nutrition on the mental development of children. Overall effect size was 0.086 (95% CI 0.034, 0.137).

Moreover, another recent study showed that across several countries improving linear growth in children under two years of age by 1 standard deviation adds about half a grade-level to school attainment<sup>48</sup>.

<sup>&</sup>lt;sup>47</sup> Aboud, Frances E, and Aisha K Yousafzai. "Global Health and Development in Early Childhood." *Annual review of psychology* 66 (2015): 433-457.

<sup>&</sup>lt;sup>48</sup> Adair, Linda S et al. "Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies." *The Lancet* 382.9891 (2013): 525-534.

Giving What We Can - An update on the effectiveness of the micronutrient fortification programmes by Project Healthy Children

# Micronutrient supplementation for children with HIV infection

A recent systematic Cochrane review summarized the available evidence on micronutrient supplementation for children with HIV infection<sup>49</sup>. The authors conclude that both Vitamin A and zinc supplementation are safe and carry benefits for children with HIV infection (in particular, zinc appears to have similar benefits in terms of reducing death due to diarrhea in children with HIV as in children without HIV infection. Finally, Cochrane suggests that multiple micronutrient supplements have some clinical benefit in poorly nourished, HIV-infected children.

<sup>49</sup> Irlam, James H et al. "Micronutrient supplementation for children with HIV infection." *The Cochrane Library* (2013).

# Recent research on fortification with specific micronutrients

### lodine fortification

lodine deficiency disorders are prevalent in many African countries (see **Figure 7**), where they make up a substantial part of the overall disease burden (see **Figures 8 and 9**).

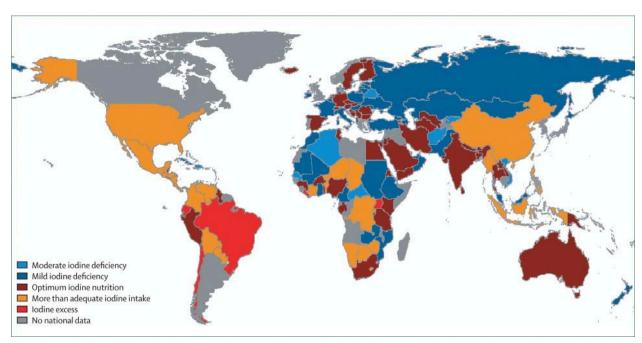
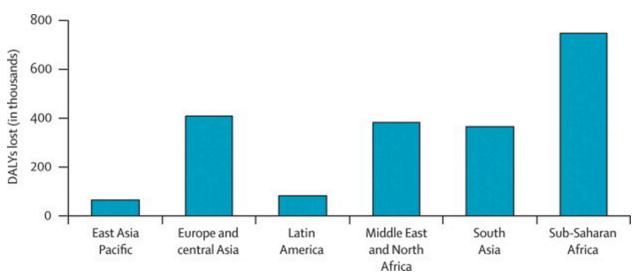


Figure 12: lodine nutrition based on the median urinary iodine concentration, by country<sup>50</sup>

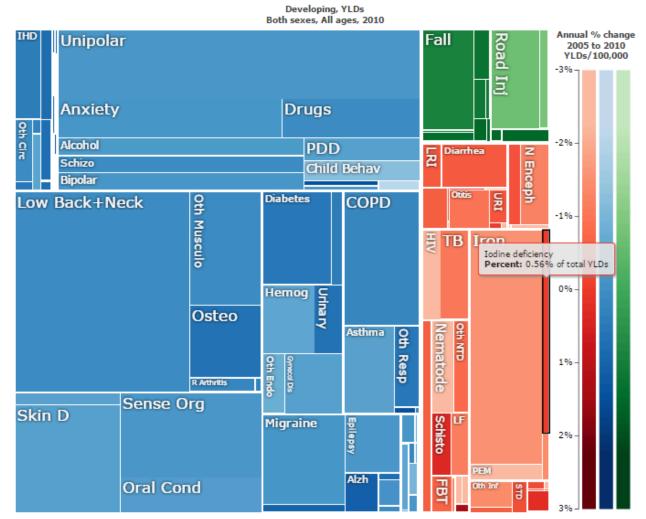
<sup>&</sup>lt;sup>50</sup> Zimmermann, Michael B, Pieter L Jooste, and Chandrakant S Pandav. "Iodine-deficiency disorders." *The Lancet* 372.9645 (2008): 1251-1262.



**Figure 13**. Disability-adjusted life years (DALYs) (thousands) lost due to iodine deficiency in children younger than 5 years of age, by region<sup>51</sup>

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<sup>&</sup>lt;sup>51</sup> Zimmermann, Michael B, Pieter L Jooste, and Chandrakant S Pandav. "Iodine-deficiency disorders." *The Lancet* 372.9645 (2008): 1251-1262.



**Figure 14:** Overall "Years Lost due to Disability (YLD)" in developing countries. Iodine deficiency are marked in black and make up 0.56% of the total YLDs. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3a5v">http://ihmeuw.org/3a5v</a>. © 2013 <a href="http://ihmeuw.org/3a5v">University of Washington</a> - <a href="http://ihmeuw.org/3a5v">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

### Benefits and Risks of Iodine

One risk of iodine supplementation is the possibility of iodine excess. Iodine excess has been suggested to cause hyper- and hypothyroidism, goitre and thyroid autoimmunity, effects which can occur even near the upper recommended daily intake of iodine<sup>52</sup>. In some instances, thyroid autoimmunity and hypothyroidism have been observed after the introduction of salt iodization programmes<sup>53</sup>.

<sup>&</sup>lt;sup>52</sup> Bürgi, Hans. "Iodine excess." Best Practice & Research Clinical Endocrinology & Metabolism 24.1 (2010): 107-115.

<sup>&</sup>lt;sup>53</sup> Fiore, Emilio, Massimo Tonacchera, and Paolo Vitti. "Influence of iodization programmes on the epidemiology of nodular goitre." *Best Practice & Research Clinical Endocrinology & Metabolism* 28.4 (2014): 577-588.

However, most researchers agree <sup>54,55,56</sup> that the available evidence suggests that the benefits of correcting iodine deficiency (chiefly reduction of goitre and hypothyroidism—both too little and too much iodine can be bad for the thyroid), far outweigh the risks of iodine supplementation, although dosing must be handled with care.

One review concludes that most individuals suffer no disturbance from iodine excess, iodine-induced disturbances are mostly transient and easily managed, and that iodine-induced hyperthyroidism, in particular, disappears from the population within a few years of properly dosed iodine supplementation<sup>57</sup>.

Similarly, a recent systematic review and meta-analysis on the effects and safety of salt iodization<sup>58</sup> also concludes that benefits outweigh costs. The review finds that in certain contexts, iodization of salt at the population level may cause a transient increase in the incidence of hyperthyroidism (though not hypothyroidism). However, on the benefits side, evidence suggests that salt fortification causes moderate to low reductions in the incidence of goitre (moderate), cretinism (moderate), low cognitive function (low) and urinary iodine concentration (moderate). Based on this evidence a recent WHO report<sup>59</sup> strongly recommends that all salt be fortified with iodine as a safe and effective strategy to prevent and control iodine deficiency disorders for all populations.

## Effect of Iodine on (mental) development in children

lodine is crucial for normal physiological and cognitive growth and development of children<sup>60</sup>. A recent meta-analysis analyzed randomized controlled trials and found that iodine fortified foods are associated with increased urinary iodine concentration among children<sup>61</sup>. Another recent systematic review and meta-analysis looked at the effects of iodine supplementation on *mental development* of young children under 5<sup>62</sup>. The authors concluded that evidence from recent studies suggests iodine-deficient children suffer a loss of 6.9-10.2 IQ points as compared with children who are not iodine-deficient. However, the authors caution that some study designs were weak and call for more research on the relation between iodized salt and mental development. Another recent cluster randomized trial investigated the

<sup>&</sup>lt;sup>54</sup> Fiore, Emilio, Massimo Tonacchera, and Paolo Vitti. "Influence of iodization programmes on the epidemiology of nodular goitre." *Best Practice & Research Clinical Endocrinology & Metabolism* 28.4 (2014): 577-588.

<sup>&</sup>lt;sup>55</sup> Bürgi, Hans. "Iodine excess." Best Practice & Research Clinical Endocrinology & Metabolism 24.1 (2010): 107-115.

<sup>&</sup>lt;sup>56</sup> "WHO | Fortification of food-grade salt with iodine for the ..." 2014. 4 May. 2015

<sup>&</sup>lt;a href="http://www.who.int/nutrition/publications/guidelines/fortification-foodgrade-saltwithiodine/en/">http://www.who.int/nutrition/publications/guidelines/fortification-foodgrade-saltwithiodine/en/</a>

<sup>&</sup>lt;sup>57</sup> Bürgi, Hans. "Iodine excess." Best Practice & Research Clinical Endocrinology & Metabolism 24.1 (2010): 107-115.

<sup>&</sup>lt;sup>58</sup> "WHO | Effect and safety of salt iodization to prevent iodine ..." 2015. 4 May. 2015

<sup>&</sup>lt;a href="http://www.who.int/nutrition/publications/micronutrients/effect safety saltiodization/en/">http://www.who.int/nutrition/publications/micronutrients/effect safety saltiodization/en/</a>

<sup>&</sup>lt;sup>59</sup> "WHO | Fortification of food-grade salt with iodine for the ..." 2014. 4 May. 2015

<sup>&</sup>lt;a href="http://www.who.int/nutrition/publications/guidelines/fortification-foodgrade-saltwithiodine/en/">http://www.who.int/nutrition/publications/guidelines/fortification-foodgrade-saltwithiodine/en/</a>

<sup>&</sup>lt;sup>60</sup> Lal Shrivastava, SR, PS Shrivastava, and J Ramasamy. "Iodine deficiency disorders: Public health measures to mitigate the global burden." *CHRISMED Journal of Health and Research* 1.2 (2014): 119.

<sup>&</sup>lt;sup>61</sup> Madhavan Nair, K. "A meta-analysis combining parallel and cross-over randomized controlled trials to assess impact of iodine fortified foods on urinary iodine concentration among children."

<sup>&</sup>lt;sup>62</sup> Bougma, Karim et al. "Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis." *Nutrients* 5.4 (2013): 1384-1416.

effectiveness of iodized salt programs to improve mental development and physical growth in young children under 3. The trial found that the treatment group had higher scores on three out of four intelligence and motor tests. Although these results appear to provide support for the benefits of salt iodization programmes, it is worth noting that the study was funded by the Micronutrient Initiative, a non-profit agencies that works to eliminate vitamin and mineral deficiencies in developing countries, which may have biased the results<sup>63</sup>. Another recent natural experiment showed that in iodine-deficient regions of the United States in the 1920s, iodization raised IQ scores by 15 points and the average IQ in the United States by 3.5 points<sup>64</sup>.

A recent double-blind, randomised, placebo-controlled trial compared direct iodine supplementation of infants versus supplementation of their breastfeeding mothers<sup>65</sup>. They found direct supplementation of infants to actually be less effective in improving infant iodine status than giving supplements to the mothers. This suggests that breastfeeding mothers pass on improved iodine status to their children. Will this effect generalize to salt iodization programmes in addition to direct supplementation? A systematic review examined iodine nutrition status among lactating mothers in countries with iodine fortification programmes (the review did not look at iodine status of the mother's infants). The review concluded that although salt iodization is still the most feasible and cost effective approach for iodine deficiency control in pregnant and lactating mothers, iodine status in lactating mothers in most countries with voluntary programmes, but even in areas with mandatory iodine fortification is still within the iodine deficiency range, and so iodine supplementation in daily prenatal vitamin/ mineral supplements in lactating mothers is needed<sup>66</sup>. We assume that in the absence of daily prenatal iodine supplements, iodine fortification, which is also less costly as an intervention, will at least contribute to bettering the iodine status of mothers and their children. Similarly, another recent study from Turkey concluded even after 8 years after introduction of mandatory iodization programmes iodine intake is in pregnant women is still inadequate<sup>67</sup>.

### lodine loss due to storage and cooking

The iodine content of iodised table salt can decline over the course of long-term storage<sup>68</sup>. Givewell has voiced concern that there might be substantial loss of iodine in salt, which could

<sup>&</sup>lt;sup>63</sup> "An Examination of Nutritional Status and Acculturation ..." 2015. 4 May. 2015

<sup>&</sup>lt;a href="http://www.fasebj.org/content/29/1">http://www.fasebj.org/content/29/1</a> Supplement/589.8.short?related-urls=yes&legid=fasebj;29/1</a> Supplement /589.8>

<sup>&</sup>lt;sup>64</sup> Feyrer, James, Dimitra Politi, and David N Weil. "The Cognitive Effects of Micronutrient Deficiency: Evidence from Salt Iodization in the United States." 18 Jul. 2013.

<sup>&</sup>lt;sup>65</sup> Bouhouch, Raschida R et al. "Direct iodine supplementation of infants versus supplementation of their breastfeeding mothers: a double-blind, randomised, placebo-controlled trial." *The Lancet Diabetes & Endocrinology* 2.3 (2014): 197-209.

<sup>&</sup>lt;sup>66</sup> Nazeri, Pantea et al. "Iodine nutrition status in lactating mothers residing in countries with mandatory and voluntary iodine fortification program: An updated systematic review." *Thyroid* ja (2015).

<sup>&</sup>lt;sup>67</sup> Kut, A et al. "Iodine intake is still inadequate among pregnant women eight years after mandatory iodination of salt in Turkey." *Journal of endocrinological investigation* 33.7 (2010): 461-464.

<sup>&</sup>lt;sup>68</sup> Waszkowiak, K. "Effect of storage conditions on potassium iodide stability in ..." 2008.

<sup>&</sup>lt;a href="http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2621.2007.01538.x/abstract">http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2621.2007.01538.x/abstract</a>

potentially render the iodization ineffective<sup>69</sup>. We will now first review the evidence of the relative decrease in iodine content and whether a substantial amount of iodine remains, so that fortification programmes can adjust the absolute iodine content to take into account losses during storage.

One paper investigated this issue and concluded that iodine fortification is at least somewhat robust to storage. After 3.5 years of storage in sealed paper bags at room temperature in high humidity (30%–45%), the salt only lost 58.5% of its iodine content<sup>70</sup>. A more recent study looked at loss under higher humidity settings with unlimited airflow, which is perhaps a more realistic setting for a rural household<sup>71</sup>. The authors found that after 5 months of table salt storage in open jars at high humidity (90%), iodine losses rose to 70%. However, some storage procedures may mitigate these effects.

A study in Ethiopia investigated how this loss of iodine propagates through the supply chain from manufacturer to consumer. The study found that the concentration of iodine in the sampled salts decreased by 57% from the production site to the consumers. They concluded that due to iodine loss, 63% of adults, and 90% of pregnant women, were at risk of insufficient iodine intake.<sup>72</sup>

Food preparation can also affect iodine loss: one study found that, in the lab, after cooking table salt for 24 hours at 200°C, iodine loss was only 58.46%<sup>73</sup>. Another study looked at iodine content in different soups during cooking for 70 min at 100 degrees Celsius and found that bioavailability of iodine still fulfilled daily requirements<sup>74</sup>. Thus, as real-world cooking conditions in households are likely to be much more favourable, iodine loss during cooking should not be a concern.

The WHO advises that iodine losses under local conditions of production, climate, packaging and storage should be taken into account and additional amount of iodine should be added at factory level<sup>75</sup>. PHC has told<sup>76</sup> us that they take local storage and cooking conditions into account when determining fortification levels for iodine, as well as for other nutrients, particularly vitamin A. Specifically, PHC assesses current and local consumption and storage

<sup>69 &</sup>quot;Salt iodization | GiveWell." 2014. 10 Jul. 2015

<sup>&</sup>lt;a href="http://www.givewell.org/international/technical/programs/salt-iodization">http://www.givewell.org/international/technical/programs/salt-iodization">http://www.givewell.org/international/technical/programs/salt-iodization</a>

<sup>&</sup>lt;sup>70</sup> Biber, F Zümrüt, Perihan Ünak, and Fatma Yurt. "Stability of iodine content in iodized salt." *Isotopes in environmental and health studies* 38.2 (2002): 87-93.

<sup>&</sup>lt;sup>71</sup> Waszkowiak, K. "Effect of storage conditions on potassium iodide stability in ..." 2008.

<sup>&</sup>lt;a href="http://onlinelibrary.wilev.com/doi/10.1111/j.1365-2621.2007.01538.x/abstract">http://onlinelibrary.wilev.com/doi/10.1111/j.1365-2621.2007.01538.x/abstract</a>

<sup>&</sup>lt;sup>72</sup> Shawel, Dawit et al. "Post-production losses in iodine concentration of salt hamper the control of iodine deficiency disorders: a case study in northern Ethiopia." *Journal of health, population, and nutrition* 28.3 (2010): 238.

<sup>&</sup>lt;sup>73</sup> Biber, F Zümrüt, Perihan Ünak, and Fatma Yurt. "Stability of iodine content in iodized salt." *Isotopes in environmental and health studies* 38.2 (2002): 87-93.

<sup>&</sup>lt;sup>74</sup> Wisnu, C. "Determination of Iodine Species Content in Iodized Salt and Foodstuff During Cooking." *International Food Research Journal* 15.3 (2008): 325-330.

<sup>&</sup>lt;sup>75</sup> "WHO | Fortification of food-grade salt with iodine for the ..." 2014. 5 May. 2015

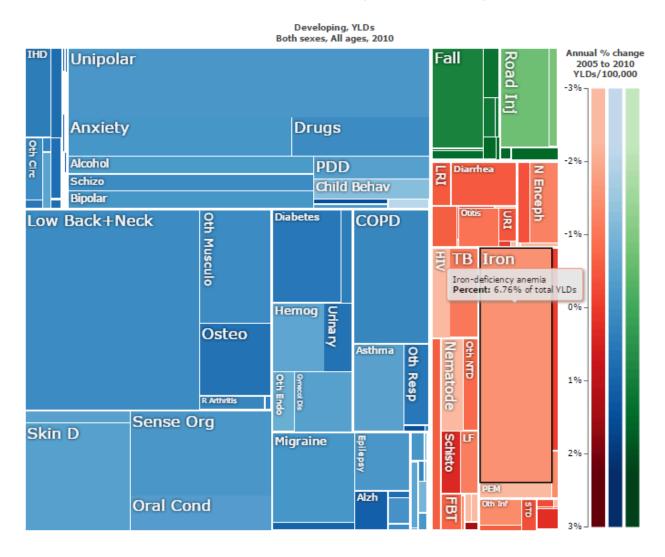
<sup>&</sup>lt;a href="http://www.who.int/nutrition/publications/guidelines/fortification-foodgrade-saltwithiodine/en/">http://www.who.int/nutrition/publications/guidelines/fortification-foodgrade-saltwithiodine/en/</a>

<sup>&</sup>lt;sup>76</sup> E-mail with Laura Rowe, Chief Operating Officer of Project Healthy Children

conditions either by conducting their own assessment, relying on data from the World Food Programme, or adapting ECSA (East, Central, and Southern Africa) fortification standards that are specifically tailored for regional consumption, cooking, and storage patterns.

### Iron fortification

Iron-deficiency anaemia causes around 45 (31–65) million DALYs a year<sup>77</sup>. For comparison, malaria causes 83 million DALYs (63–110)<sup>78</sup>. Iron deficiency anaemia also makes up a major part of years lived with disability (YLD) in developing countries (see Figure 15).



<sup>&</sup>lt;sup>77</sup> Murray, Christopher JL et al. "Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010." *The lancet* 380.9859 (2013): 2197-2223.

<sup>&</sup>lt;sup>78</sup> Murray, Christopher JL et al. "Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010." *The lancet* 380.9859 (2013): 2197-2223.

**Figure 15**: Overall "Years Lost due to Disability (YLD)" in developing countries. Iron deficiency anaemia is marked in black and makes up 6.76% of the total YLDs. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3a5g">http://ihmeuw.org/3a5g</a>. © 2013 <a href="http://ihmeuw.org/3a5g">University of Washington</a> - <a href="http://ihmeuw.org/3a5g">Institute for Health Metrics and Evaluation</a> (Global burden of Disease data 2010, released 3/2013)

Many trials that have looked into iron supplementation and fortification have documented improvements in hemoglobin status (and thus improvement of anaemia). A recent systematic review analysed data from 60 trials and concluded that food iron fortification resulted in a significant increase in hemoglobin (0.42 g/dl; 95% CI: 0.28, 0.56; P<0.001) and serum ferritin but no effect on serum zinc concentrations, infections, physical growth and mental development <sup>79</sup>, <sup>80</sup>.

Because iron is important for development the effects of iron on children have been studied separately. Specifically, there have been four recent reviews and/or meta-analyses of RCTs that have investigated the effects of iron supplementation and fortification in children.

A recent systematic review and meta-analysis of randomized controlled trials on the effects of iron-fortified foods on haemoglobin levels in children under 10 years of age, showed that intake of iron-fortified foods was associated with haemoglobin concentration<sup>81</sup>. The authors concluded that iron-fortified foods could be an effective in reducing iron deficiency anaemia in children.

systematic review examined RCTs supplementation Another 37 on iron primary-school-aged children, and found evidence for improved haemoglobin response<sup>82</sup>. These results were congruent with findings of similar studies in adult populations<sup>83</sup>. Another, more recent systematic review and meta-analysis of RCTs looking at the effects of daily iron supplementation in children in low- and middle-income settings similarly found that iron improved cognition, height, weight, iron deficiency and anaemia and is well-tolerated<sup>84</sup>. However, the evidence for effectiveness in younger children is less robust. A systematic review and meta-analysis examined randomised controlled trials of daily iron supplementation in 4–23 month-old children, and found evidence for reduction of anaemia. The study concluded,

<sup>&</sup>lt;sup>79</sup> Gera, Tarun, Harshpal Singh Sachdev, and Erick Boy. "Effect of iron-fortified foods on hematologic and biological outcomes: systematic review of randomized controlled trials." *The American journal of clinical nutrition* 96.2 (2012): 309-324.

<sup>&</sup>lt;sup>80</sup> "Role of Food Iron Fortification on Hemoglobin Status." 2015. 5 May. 2015 <a href="http://link.springer.com/content/pdf/10.1007%2Fs12098-014-1674-2.pdf">http://link.springer.com/content/pdf/10.1007%2Fs12098-014-1674-2.pdf</a>

<sup>&</sup>lt;sup>81</sup> Athe, Ramesh, M Rao, and K Madhavan Nair. "Impact of iron-fortified foods on Hb concentration in children (< 10 years): a systematic review and meta-analysis of randomized controlled trials." *Public health nutrition* 17.03 (2014): 579-586.

<sup>&</sup>lt;sup>82</sup> Gera, Tarun et al. "Effect of iron supplementation on haemoglobin response in children: systematic review of randomised controlled trials." *Journal of pediatric gastroenterology and nutrition* 44.4 (2007): 468-486.

<sup>83 &</sup>quot;Role of Food Iron Fortification on Hemoglobin Status." 2015. 5 May. 2015 <a href="http://link.springer.com/content/pdf/10.1007%2Fs12098-014-1674-2.pdf">http://link.springer.com/content/pdf/10.1007%2Fs12098-014-1674-2.pdf</a>

<sup>&</sup>lt;sup>84</sup> Low, Michael et al. "Effects of daily iron supplementation in primary-school–aged children: systematic review and meta-analysis of randomized controlled trials." *Canadian Medical Association Journal* (2013): cmaj. 130628.

however, that benefits for development of cognition, motor skills, height, and weight were uncertain<sup>85</sup>.

<u>Do the effects of supplementation generalize to cheaper population-level fortification of staple foods interventions?</u>

One very recent study evaluated the impact of Costa Rica's fortification program on anaemia in women and children <sup>86</sup>. Even though this was not a randomized controlled trial, the particularities of the data<sup>87</sup> strongly hint at a causal relationship between fortification and reduced anaemia . The results suggest that fortification markedly improved iron status and substantially reduced anaemia.

Another very recent study<sup>88</sup> used national-level surveys to conduct a cross country comparison of micronutrient fortification practices and anaemia rates in non-pregnant women. The authors suggest that, after controlling for confounding effects (such as level of development and endemic malaria), anaemia prevalence has decreased significantly in countries that fortify flour with micronutrients, while remaining unchanged in countries that do not, so that for each year of flour fortification anaemia prevalence is reduced by 2.4%, i.e. 2.4% fewer women are anemic<sup>89</sup>.

There are two separate systematic Cochrane reviews underway that summarize the evidence for potential benefits of flour fortification with iron against anaemia, one on maize flour fortification <sup>90</sup> and one on wheat flour fortification <sup>91</sup>. PHC conducts maize flour fortification in countries such as Malawi and wheat flour in countries such as Zimbabwe, so the results of these reviews will be interesting.

Does iron fortification increase malaria?

It has been hypothesized that elevated iron status can increase malaria risk in areas where malaria is endemic. This possibility is concerning for some of PHC's projects, such as the iron

<sup>&</sup>lt;sup>85</sup> Pasricha, Sant-Rayn et al. "Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials." *The lancet global health* 1.2 (2013): e77-e86.

<sup>86 &</sup>quot;Effectiveness evaluation of the food fortification program of ..." 2015. 15 May. 2015 <a href="http://aicn.nutrition.org/content/101/1/210.short?rss=1/share&cited-by=yes&legid=aicn;101/1/210">http://aicn.nutrition.org/content/101/1/210.short?rss=1/share&cited-by=yes&legid=aicn;101/1/210</a>

<sup>&</sup>lt;sup>87</sup> For the sake of brevity, we refer the interested reader to the paper.

<sup>&</sup>lt;sup>88</sup> Pachon, Helena, Jonathan Barkley, and Kathleen Wheeler. "anaemia Prevalence May Be Reduced Among Countries that Fortify Flour." *The FASEB Journal* 29.1 Supplement (2015): 39.6.

<sup>&</sup>lt;sup>89</sup> Pachon, Helena, Jonathan Barkley, and Kathleen Wheeler. "anaemia Prevalence May Be Reduced Among Countries that Fortify Flour." *The FASEB Journal* 29.1 Supplement (2015): 39.6.

<sup>&</sup>lt;sup>90</sup> Pasricha, Sant-Rayn et al. "Fortification of maize flour with iron for preventing anaemia and iron deficiency in populations." *The Cochrane Library* (2012).

<sup>&</sup>lt;sup>91</sup> Peña-Rosas, Juan Pablo et al. "Wheat flour fortification with iron for reducing anaemia and improving iron status in populations." *The Cochrane Library* (2014).

fortification programme in Malawi, where malaria is endemic<sup>92,93.</sup> The hypothesis is biologically plausible, because the malaria parasite needs iron to function (indeed, it has been suggested that anemia might be an evolved response to fight malaria and other parasites)<sup>94</sup>. Studies of increased iron intake (via supplementation or fortification) in malaria-prone areas have yielded conflicting evidence on this question. We review findings from specific studies below, but whether increased iron intake increases malaria risk is a topic of ongoing research, and researchers call for greater study of the mechanisms underlying the negative effects of iron reported in some trials<sup>95</sup>.

One trial from Tanzania showed an increased risk of mortality among children after iron supplementation<sup>96</sup>. As a result, in 2006 the WHO changed its recommendations on iron supplementation for children in areas where malaria is endemic, from universal to targeted supplementation for iron-deficient children only<sup>97</sup>.

However, a recent systematic Cochrane review from 2011 suggested that iron supplementation does not adversely affect children living in malaria-endemic areas<sup>98</sup> and recommended that routine iron supplementation should not be withheld from children living in malaria-endemic countries. Another systematic review and meta-analysis from 2013 summarizing randomised controlled trials on the effect of daily iron supplementation on health in children<sup>99</sup> found no evidence that daily oral iron supplementation increased malaria, diarrhoea, or respiratory infection, but did identify evidence that iron increased fever (the authors note that however, that few studies were done in malaria-endemic areas or specifically reported malaria-related outcomes).

<sup>92 &</sup>quot;WHO | World Malaria Report 2014." 2014. 30 Apr. 2015

<sup>&</sup>lt;a href="http://www.who.int/malaria/publications/world\_malaria\_report\_2014/en/">http://www.who.int/malaria/publications/world\_malaria\_report\_2014/en/</a>

<sup>93 &</sup>quot;Malawi: Fortified Sugar on the Market - Project Healthy ..." 2013. 30 Apr. 2015

<sup>&</sup>lt;a href="http://projecthealthychildren.org/malawi-fortified-sugar-on-the-market/">http://projecthealthychildren.org/malawi-fortified-sugar-on-the-market/</a>

<sup>&</sup>lt;sup>94</sup> Schümann, Klaus, and Noel W Solomons. "Can iron supplementation be reconciled with benefits and risks in areas hyperendemic for malaria?." Food & Nutrition Bulletin 34.3 (2013): 349-356.

<sup>&</sup>lt;sup>95</sup> Baumgartner, Jeannine, and Tanja Barth-Jaeggi. "Iron interventions in children from low-income and middle-income populations: benefits and risks." Current Opinion in Clinical Nutrition & Metabolic Care 18.3 (2015): 289-294.

<sup>&</sup>lt;sup>96</sup> Harding, Kimberly B, and Lynnette M Neufeld. "Iron deficiency and anaemiaanemia control for infants and young children in malaria-endemic areas: a call to action and consensus among the research community." Advances in Nutrition: An International Review Journal 3.4 (2012): 551-554.

<sup>&</sup>lt;sup>97</sup> Harding, Kimberly B, and Lynnette M Neufeld. "Iron deficiency and anaemia control for infants and young children in malaria-endemic areas: a call to action and consensus among the research community." *Advances in Nutrition: An International Review Journal* 3.4 (2012): 551-554.

<sup>&</sup>lt;sup>98</sup> Okebe, Joseph U et al. "Oral iron supplements for children in malaria-endemic areas." *The Cochrane Library* (2011).

<sup>&</sup>lt;sup>99</sup> Pasricha, Sant-Rayn et al. "Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials." *The lancet global health* 1.2 (2013): e77-e86.

However, a more recent study from 2012 found that iron status predicts malaria risk in children<sup>100</sup> and another suggests that iron deficiency might protect against severe malaria and death in children<sup>101</sup>.

Another recent trial from 2013 did not find iron to increase the incidence of malaria among children in a malaria-endemic setting in which insecticide-treated bed nets were provided and appropriate malaria treatment was available 102.

The most recent systematic review that we could find<sup>103</sup> suggests that overall, weighting positive and negative effects of iron, improving iron status reduces mortality risk similarly in children with malaria and in those without malaria<sup>104</sup>.

Given the conflicting evidence in the research literature, we have asked experts in this field for their opinion on whether iron fortification of wheat and maize flour in Malawi (as conducted by PHC) is on the whole harmful or beneficial. One such expert said that the question is currently unanswerable, but that most experts in the field would tend to assume that *fortification* will be safer than *supplementation*. The same expert noted, however, that this hypothesis is unproven and that research on the relative benefits and risks of fortification versus supplementation is ongoing. He concluded that, despite these uncertainties, he thinks it is fairly safe to assume that iron *fortification* is likely to be benign<sup>105</sup>. Another international expert suggested that the effects of iron fortification on malaria risk are not as well studied as those of iron supplementation, though an upcoming randomized controlled trial in Malawi should provide further evidence on the topic. The expert noted that that the risks associated with iron probably depends not only on the iron status of the host, but also on the manner/dose of giving the micronutrients<sup>106</sup>.

The WHO also suggests that conclusions from trials of iron supplementations risks should not be extrapolated to fortification or food-based approaches for delivering iron, where the patterns of iron absorption and metabolism may be substantially different<sup>107</sup>.

We have also asked PHC about this issue and they have reported that they are aware of the potential risks in malaria-prone areas, and are regularly consulting with national and

<sup>&</sup>lt;sup>100</sup> Jonker, Femkje AM et al. "Iron status predicts malaria risk in Malawian preschool children." *PLoS One* 7.8 (2012): e42670.

<sup>&</sup>lt;sup>101</sup> Awah, NW. "Iron Deficiency and Severe Plasmodium falciparum Malaria." 2012.

<sup>&</sup>lt;a href="http://cid.oxfordiournals.org/cgi/content/short/cis020v2?rss=1">http://cid.oxfordiournals.org/cgi/content/short/cis020v2?rss=1</a>

<sup>&</sup>lt;sup>102</sup> Zlotkin, S. "Effect of Iron Fortification on Malaria Incidence in Infants and ..." 2013.

<sup>&</sup>lt;a href="http://iama.iamanetwork.com/article.aspx?articleid=1734705">http://iama.iamanetwork.com/article.aspx?articleid=1734705</a>>

<sup>&</sup>lt;sup>103</sup> Scott, Samuel P et al. "The Impact of anaemia on Child Mortality: An Updated Review." *Nutrients* 6.12 (2014): 5915-5932.

<sup>&</sup>lt;sup>104</sup> Scott, Samuel P et al. "The Impact of anaemia on Child Mortality: An Updated Review." *Nutrients* 6.12 (2014): 5915-5932.

<sup>&</sup>lt;sup>105</sup> Email conversation with scientist 1 who is an expert on this topic

<sup>&</sup>lt;sup>106</sup> Email conversation with scientist 2 who is an expert on this topic

<sup>&</sup>lt;sup>107</sup> "Iron supplementation of young children in regions where ..." 2006. 19 May. 2015

<sup>&</sup>lt;a href="http://www.who.int/nutrition/publications/WHOStatement">http://www.who.int/nutrition/publications/WHOStatement</a> %20iron%20suppl.pdf>

international consultants (e.g. from the WHO) as well closely monitoring the current research on this topic and working with malaria prevention programmes on the ground.

In sum, we think that, placing more weight on expert opinion and the most systematic review that we could find, iron fortification is very likely to be beneficial as overall mortality and morbidity is reduced, even though there is some probability that it might increase malaria incidence or severity, however, this is effect is probably small.

### Vitamin A

Vitamin A deficiency is the leading cause of preventable blindness in children and increases the risk of disease and death from severe infections<sup>108</sup>. In the recent Lancet series on maternal and child undernutrition, deficiencies of vitamin A were estimated to be responsible for 600,000 deaths per year, and together with zinc deficiency, a combined 9.8% of global childhood Disability-Adjusted Life Years (DALYs) (most deaths were due to diarrhea and measles: see **Figure 16**)<sup>109,110</sup>. Given that PHC's work in Burundi has led to the start of vegetable oil fortification with vitamin A<sup>111</sup>, below we review the evidence for the cost-effectiveness of vitamin A fortification programmes.

Vitamin A fortification has been shown to be very cost-effective. A recent study from Uganda showed that the cost-per-DALY-averted for vitamin A fortification is only US \$82 for sugar fortification and \$18 for oil fortification<sup>112</sup>. A recent study suggested that even during prolonged deep frying with cooking oil, 45% of the fortified vitamin A remains intact, which is sufficient to meet daily requirements<sup>113</sup>. In line with this, a recent correlational study finds that it is strongly plausible that oil fortified with vitamin A increases vitamin A status in Indonesian women and children<sup>114</sup>.

<sup>&</sup>lt;sup>108</sup> World Health Organization. "Global prevalence of vitamin A deficiency in populations at risk 1995-2005: WHO global database on vitamin A deficiency." (2009).

<sup>&</sup>lt;sup>109</sup> Hess, Sonja Y. "The impact of common micronutrient deficiencies on iodine and thyroid metabolism: the evidence from human studies." *Best Practice & Research Clinical Endocrinology & Metabolism* 24.1 (2010): 117-132.

<sup>&</sup>lt;sup>110</sup> Black, Robert E et al. "Maternal and child undernutrition: global and regional exposures and health consequences." *The lancet* 371.9608 (2008): 243-260.

<sup>111</sup> http://projecthealthychildren.org/burundis-largest-cooking-oil-factory-to-begin-fortification/

<sup>&</sup>lt;sup>112</sup> Fiedler, John L, and Ronald Afidra. "Vitamin A fortification in Uganda: comparing the feasibility, coverage, costs, and cost-effectiveness of fortifying vegetable oil and sugar." *Food & Nutrition Bulletin* 31.2 (2010): 193-205. <sup>113</sup> Akhtar, H. "Loss of vitamin A in fortified edible oils and ghee during ..." 2012.

<sup>&</sup>lt;a href="http://www.banglaiol.info/index.php/BJSIR/article/view/11461">http://www.banglaiol.info/index.php/BJSIR/article/view/11461</a>>

Jus'at, Idrus et al. "Vitamin A-fortified cooking oil reduces vitamin A deficiency in infants, young children and women: results from a programme evaluation in Indonesia." *Public health nutrition* (2015): 1-12.

Givewell has extensively reviewed Vitamin supplementation interventions<sup>115</sup> among them a large-scale trial<sup>116</sup> that found no reduction of mortality. This trial has led some researchers to suggest that Vitamin A policies should be revised, and that there should be more of an emphasis on vitamin A *fortification* as opposed to (biannual) vitamin A *supplementation*<sup>117</sup>. Other researchers have pointed to some severe limitations of the large trial and suggest that abandonment of vitamin A supplementation programmes is not prudent<sup>118</sup>. Moreover, an accompanying meta-analysis<sup>119</sup> suggested that taking into account all available evidence—including the large trial—simply yields a smaller estimate of 11% mortality reduction (rather than 25% as previously assumed). Benefits of vitamin A fortification are well established in western countries<sup>120</sup> and a Cochrane review to examine the effects of staple food fortification with vitamin A for preventing vitamin A deficiency is currently being conducted<sup>121</sup>.

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<sup>&</sup>lt;sup>115</sup> "Vitamin A Supplementation | GiveWell." 2015. 19 May. 2015

<sup>&</sup>lt;a href="http://www.givewell.org/international/technical/programs/vitamin-A">http://www.givewell.org/international/technical/programs/vitamin-A</a>

<sup>&</sup>lt;sup>116</sup> Awasthi, Shally et al. "Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial." *The Lancet* 381.9876 (2013): 1469-1477.

<sup>&</sup>lt;sup>117</sup> Mason, John et al. "Vitamin A policies need rethinking." *International journal of epidemiology* (2014): dyu194.

<sup>&</sup>lt;sup>118</sup> Bhutta, Zulfiqar A, and Shawn K Baker. "Premature abandonment of global vitamin A supplementation programmes is not prudent!." *International journal of epidemiology* 44.1 (2015): 297-299.

<sup>&</sup>lt;sup>119</sup> Awasthi, Shally et al. "Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial." *The Lancet* 381.9876 (2013): 1469-1477.

<sup>&</sup>lt;sup>120</sup> Mason, John et al. "Vitamin A policies need rethinking." *International journal of epidemiology* (2014): dyu194.

<sup>&</sup>lt;sup>121</sup> Saeterdal, Ingvil, Jose O Mora, and Luz Maria De-Regil. "Fortification of staple foods with vitamin A for preventing vitamin A deficiency." *The Cochrane Library* (2012).

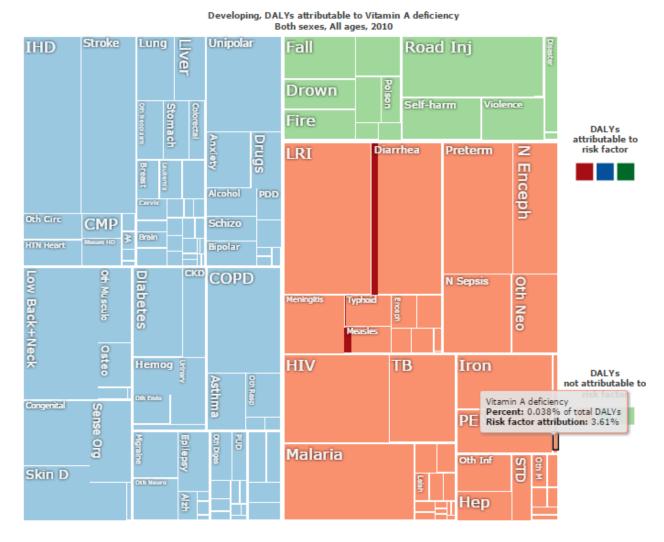


Figure 16: Overall "Disability Adjusted Life Years (DALYs)" lost in developing countries. Vitamin A deficiency direct impact is marked in black and make up 0.038% of the total DALYs. Risk factor attributions of Vitamin A deficiency for other diseases are in red. For instance, Vitamin A deficiency accounts for 10% of the risk factor of DALYs lost to do Diarrhea and 15% of DALYs lost due to Measles. Figure adapted with 'Global Burden of Disease Compare tool'- see <a href="http://ihmeuw.org/3ba4">http://ihmeuw.org/3ba4</a> © 2013 University of Washington - Institute for Health Metrics and Evaluation (Global burden of Disease data 2010, released 3/2013)

### Vitamin A deficiency - disease interactions and risk factors

Vitamin A deficiency interacts with other conditions, increasing the risk of contracting other diseases. For instance, DNA damage from micronutrient deficiencies is likely to be a major cause of cancer<sup>122</sup> and a recent meta analysis clearly demonstrated that low doses of vitamins

<sup>&</sup>lt;sup>122</sup> Ames, Bruce N. "Micronutrient deficiencies: A major cause of DNA damage." *Annals of the New York Academy of Sciences* 889.1 (1999): 87-106.

can significantly reduce the risk of gastric cancer, especially vitamin A among other vitamins 123

Vitamin A deficiency is also associated with hepatitis C infection and not being responsive to antiviral therapy<sup>124</sup>.

Research also suggests that vitamin A supplementation is beneficial for thyroid function and size—and potentially more so in combination with iodized salt<sup>125</sup>.

Studies have also linked vitamin A deficiency to infection with certain types of worm infections (i.e., soil-transmitted helminth *Ascaris lumbricoides*), with robust evidence for a relationship between high-intensity *ascaris* infection and lower levels of vitamin A<sup>126</sup>.

#### **Zinc**

Zinc deficiency is a significant public health problem in developing countries<sup>127</sup>. In the recent Lancet series on maternal and child undernutrition, deficiencies of vitamin A and zinc were estimated to be responsible for 500,000 deaths per year, respectively, and together with zinc deficiency, a combined 9.8% of global childhood Disability-Adjusted Life Years (DALYs)<sup>128</sup>.

Zinc supplementation to children is cost-effective with one recent study estimating the cost per DALY averted at US\$ 606 for pill supplementation, US\$ 1,211 for micronutrient biscuits, and US\$ 879 per DALY saved for water filtration systems <sup>129</sup>.

A recent trial from China<sup>130</sup> showed that zinc-fortified flour increases zinc levels in rural Chinese women. A Cochrane Review summarizing the evidence on fortification of staple foods with zinc for improving zinc status and other health outcomes in the general population is currently underway<sup>131</sup>. Finally, a recent trial showed that zinc supplementation might lead to a

<sup>&</sup>lt;sup>123</sup> Kong, Pengfei et al. "Vitamin Intake Reduce the Risk of Gastric Cancer: Meta-Analysis and Systematic Review of Randomized and Observational Studies." *PloS one* 9.12 (2014): e116060.

<sup>&</sup>lt;sup>124</sup> Bitetto, Davide et al. "Vitamin A deficiency is associated with hepatitis C virus chronic infection and with unresponsiveness to interferon-based antiviral therapy." *Hepatology* 57.3 (2013): 925-933.

<sup>&</sup>lt;sup>125</sup> Hess, Sonja Y. "The impact of common micronutrient deficiencies on iodine and thyroid metabolism: the evidence from human studies." *Best Practice & Research Clinical Endocrinology & Metabolism* 24.1 (2010): 117-132.

<sup>&</sup>lt;sup>126</sup> Rajagopal, Selvi, Peter J Hotez, and Donald AP Bundy. "Micronutrient Supplementation and Deworming in Children with Geohelminth Infections." *PLoS neglected tropical diseases* 8.8 (2014): e2920.

<sup>&</sup>lt;sup>127</sup> Shah, Dheeraj et al. "Fortification of staple foods with zinc for improving zinc status and other health outcomes in the general population." *The Cochrane Library* (2013).

Hess, Sonja Y. "The impact of common micronutrient deficiencies on iodine and thyroid metabolism: the evidence from human studies." *Best Practice & Research Clinical Endocrinology & Metabolism* 24.1 (2010): 117-132.

<sup>&</sup>lt;sup>129</sup> Fink, Günther, and Jesse Heitner. "Evaluating the cost-effectiveness of preventive zinc supplementation." *BMC* public health 14.1 (2014): 852.

<sup>&</sup>lt;sup>130</sup> Huo, Junsheng et al. "Effectiveness of fortified flour for enhancement of vitamin and mineral intakes and nutrition status in northwest Chinese villages." *Food & Nutrition Bulletin* 33.2 (2012): 161-168.

<sup>&</sup>lt;sup>131</sup> Shah, Dheeraj et al. "Fortification of staple foods with zinc for improving zinc status and other health outcomes in the general population." *The Cochrane Library* (2013).

significant reduction in respiratory morbidity among children with acute lower respiratory infections in zinc-poor population<sup>132</sup>.

#### Folic Acid

Neural tube defects affect an estimated 320 000 newborns worldwide annually<sup>133</sup>

A systematic review Cochrane review concludes that folic acid supplementation, alone or in combination with vitamins and minerals, prevents neural tube defects<sup>134</sup>.

A recent trial from China<sup>135</sup> showed that folic acid fortified flour increases folic acid levels in rural chinese women.

A recent systematic review<sup>136</sup> on the on the impact of folic acid fortification of flour on neural tube defects concludes that this intervention had a major impact on neural tube defects in all countries where this has been reported. For instance, the authors report that folic acid fortification in Chile showed a 55 % reduction in neural tube defect prevalence between 1999 and 2009 (this is a fairly typical effect: countries that mandate folic acid fortification of wheat flour report an average reduction of 46% in NTD birth prevalence<sup>137</sup>). We found several studies that were not included in this review that show similar effects: after food fortification with folic acid is introduced, or folic acid intake is increased, folate levels increase and neural tube defects often decrease<sup>138, 139, 140, 141</sup>.

<sup>&</sup>lt;sup>132</sup> Shah, Ubaid H et al. "The efficacy of zinc supplementation in young children with acute lower respiratory infections: A randomized double-blind controlled trial." *Clinical Nutrition* 32.2 (2013): 193-199.

<sup>&</sup>lt;sup>133</sup> Pachón, H et al. "Folic acid fortification of wheat flour: A cost-effective public health intervention to prevent birth defects in Europe." *Nutrition Bulletin* 38.2 (2013): 201-209.

<sup>&</sup>lt;sup>134</sup> Liu, Jufen et al. "Plasma folate levels in early to mid pregnancy after a nation-wide folic acid supplementation program in areas with high and low prevalence of neural tube defects in china." *Birth Defects Research Part A: Clinical and Molecular Teratology* (2015).

<sup>&</sup>lt;sup>135</sup> Huo, Junsheng et al. "Effectiveness of fortified flour for enhancement of vitamin and mineral intakes and nutrition status in northwest Chinese villages." *Food & Nutrition Bulletin* 33.2 (2012): 161-168.

<sup>&</sup>lt;sup>136</sup> Castillo-Lancellotti, Cecilia, Josep A Tur, and Ricardo Uauy. "Impact of folic acid fortification of flour on neural tube defects: a systematic review." *Public health nutrition* 16.05 (2013): 901-911.

<sup>&</sup>lt;sup>137</sup> Pachón, H et al. "Folic acid fortification of wheat flour: A cost-effective public health intervention to prevent birth defects in Europe." *Nutrition Bulletin* 38.2 (2013): 201-209.

<sup>&</sup>lt;sup>138</sup> Britto, Jéssica Carrilho, Rodolfo Cançado, and Elvira Maria Guerra-Shinohara. "Concentrations of blood folate in Brazilian studies prior to and after fortification of wheat and cornmeal (maize flour) with folic acid: a review." *Revista brasileira de hematologia e hemoterapia* 36.4 (2014): 275-286.

<sup>&</sup>lt;sup>139</sup> Liu, Shiliang et al. "A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects." *BMC pregnancy and childbirth* 4.1 (2004): 20.

<sup>&</sup>lt;sup>140</sup> Bailey, Regan L et al. "Total folate and folic acid intake from foods and dietary supplements in the United States: 2003–2006." *The American journal of clinical nutrition* 91.1 (2010): 231-237.

<sup>&</sup>lt;sup>141</sup> Colapinto, Cynthia K et al. "Folic acid supplement use is the most significant predictor of folate concentrations in Canadian women of childbearing age." *Applied Physiology, Nutrition, and Metabolism* 37.2 (2012): 284-292.

Neural tube defects place a significant economic burden on the healthcare system and the wider society<sup>142</sup> and for this reason folic acid fortification also has a very good benefit cost ratio of 12–48:1, depending on the country<sup>143</sup>.

A recent meta-analysis and systematic review found no evidence that folic acid increase causes increase in bowel cancer <sup>144</sup> and another study found no increase in breast cancer or other cancers<sup>145</sup>.

#### Is biofortification more effective than industrial fortification?

Biofortification refers to the process of selectively breeding or genetically engineering crops to have higher micronutrient content. Even though this approach has not been practised so far, it has been suggested that it could potentially be more cost-effective and might reach a wider population than traditional industrial fortification of staple foods as conducted by PHC <sup>146,147</sup>. However, according to a recent paper by the Copenhagen Consensus Center <sup>148</sup>, in order to establish the cost-effectiveness of large scale biofortification, nutritional effectiveness must first be verified. In addition, acceptance of new plant varieties among farmers and consumers must be secured in order for biofortification to be a viable health intervention.

<sup>&</sup>lt;sup>142</sup> Yi, Yunni et al. "Economic burden of neural tube defects and impact of prevention with folic acid: a literature review." *European journal of pediatrics* 170.11 (2011): 1391-1400.

<sup>&</sup>lt;sup>143</sup> Pachón, H et al. "Folic acid fortification of wheat flour: A cost-effective public health intervention to prevent birth defects in Europe." *Nutrition Bulletin* 38.2 (2013): 201-209.

<sup>&</sup>lt;sup>144</sup> Vollset, Stein Emil et al. "Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 individuals." *The Lancet* 381.9871 (2013): 1029-1036.

<sup>&</sup>lt;sup>145</sup> Taylor, Caroline M et al. "Folic acid in pregnancy and mortality from cancer and cardiovascular disease: further follow-up of the Aberdeen folic acid supplementation trial." *Journal of epidemiology and community health* (2015): jech-2014-205324.

<sup>&</sup>lt;sup>146</sup> Chow, Jeffrey, Eili Y Klein, and Ramanan Laxminarayan. "Cost-effectiveness of "golden mustard" for treating vitamin A deficiency in India." *PloS one* 5.8 (2010): e12046.

<sup>&</sup>lt;sup>147</sup> "Biofortification of Food with Microelements - Science ..." 2014. 19 May. 2015

<sup>&</sup>lt;a href="http://thescipub.com/PDF/aiabssp.2011.544.548.pdf">http://thescipub.com/PDF/aiabssp.2011.544.548.pdf</a>

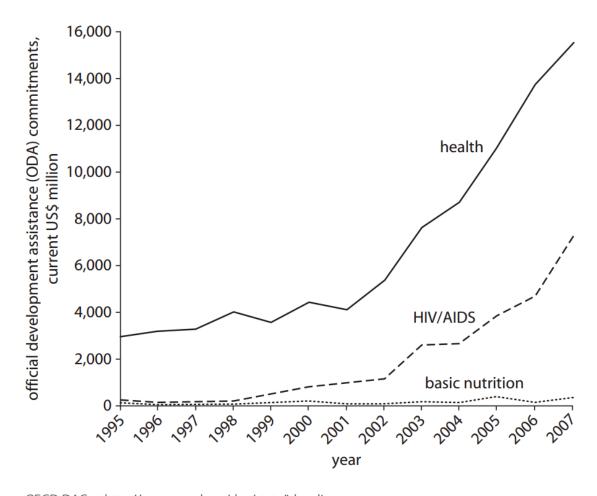
<sup>&</sup>lt;sup>148</sup> "Biofortification | Copenhagen Consensus Center." 2014. 19 May. 2015

<sup>&</sup>lt;a href="http://www.copenhagenconsensus.com/publication/biofortification">http://www.copenhagenconsensus.com/publication/biofortification</a>

# Updates on Room for additional funding

## Long-term view on room for more funding

The data in **Figure 17** suggest that, despite the potential for huge benefits, nutrition is grossly underfunded through aid <sup>149</sup>.



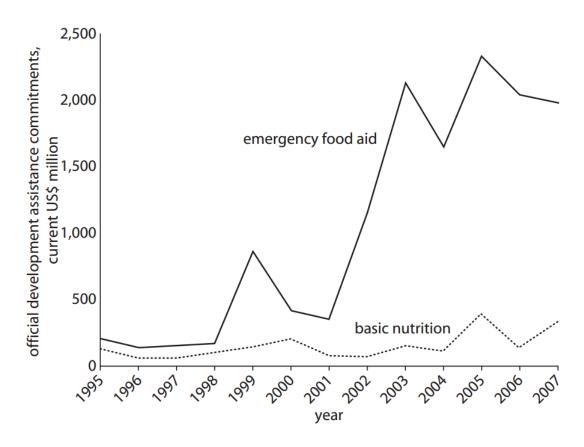
Source: OECD DAC at http://www.oecd.org/dac/stats/idsonline.

**Figure 17** Official Development Assistance Commitments for Health, HIV/AIDS, and Nutrition, 1995–2007<sup>150</sup>

<sup>&</sup>lt;sup>149</sup> Shekar, Meera. *Scaling up nutrition: what will it cost?*. World Bank Publications, 2010.

<sup>&</sup>lt;sup>150</sup> Shekar, Meera. Scaling up nutrition: what will it cost?. World Bank Publications, 2010.

Moreover, while aid for emergency food aid has increased dramatically (Figure 18), nutrition has remained chronically underfunded. <sup>151</sup>



Source: OECD DAC at http://www.oecd.org/dac/stats/idsonline.

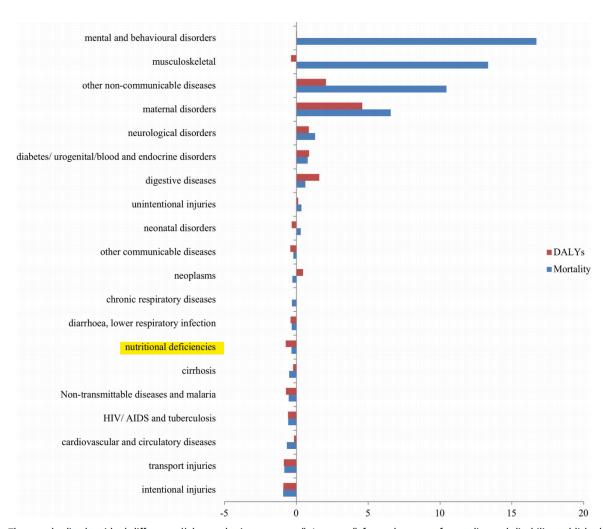
**Figure 18** Official Development Assistance Commitments for Nutrition and Emergency Food Aid, 1995–2007<sup>152</sup>

Finally, as can be seen in **Figure 19**, nutritional deficiencies might be under researched, insofar as the number of studies published in the Cochrane database is fewer than would be expected given the global DALY and mortality burden of nutritional deficiencies.

<sup>&</sup>lt;sup>151</sup> Shekar, Meera. Scaling up nutrition: what will it cost?. World Bank Publications, 2010.

<sup>&</sup>lt;sup>152</sup> Shekar, Meera. *Scaling up nutrition: what will it cost?*. World Bank Publications, 2010.

Giving What We Can - An update on the effectiveness of the micronutrient fortification programmes by Project Healthy Children



The standardised residual difference ((observed minus expected) /expected) for each cause of mortality and disability published in the Cochrane Database of Systematic Reviews in 2012/2013.

**Figure 19:** Nutritional Deficiencies are under researched in relation to their DALY and Mortality burden<sup>153</sup>.

<sup>&</sup>lt;sup>153</sup> "Alignment of systematic reviews published in the Cochrane ..." 2015. 21 Apr. 2015 <a href="http://jech.bmj.com/content/early/2015/04/17/jech-2014-205389.full">http://jech.bmj.com/content/early/2015/04/17/jech-2014-205389.full</a>

How much more could be spend on nutrition? A recent review<sup>154</sup> suggests that the total annual cost of achieving 90% coverage in the the 34 countries most affected by nutritional deficiencies would be around \$9.6 Billion (see **Table 3**).

	Cost	
Salt iodisation	\$68	
Multiple micronutrient supplementation in pregnancy (includes iron-folate)	\$472	
Calcium supplementation in pregnancy	\$1914	
Energy-protein supplementation in pregnancy	\$972	
Vitamin A supplementation in childhood	\$106	
Zinc supplementation in childhood	\$1182	
Breastfeeding promotion	<b>\$</b> 653	
Complementary feeding education	\$269	
Complementary food supplementation	<b>\$1</b> 359	
SAM management	\$2563	
Total	\$9559	

**Table 3**: Total additional annual cost of achieving 90% coverage with nutrition interventions, excluding management of moderate acute malnutrition, in 34 countries with more than 90% of the burden.

This estimate is in line with a World Bank study<sup>155</sup> which estimated a funding gap of \$10.3 billion per annum globally for scale-up of nutrition interventions. Closing this gap would provide preventive nutrition services to about 356 million children, save at least 1.1 million lives and 30 million DALYs, and reduce the number of stunted children by about 30 million worldwide. Another study by Bhutta et al. (2013) produced similar estimates.

Of course, not all of this money could be spent by PHC. However, we believe that PHC has substantial room for more funding, based on estimates of the cost required to implement micronutrient fortification in the countries where PHC is active. A recent World Bank report estimates that iron fortification of all staples in Sub-Saharan Africa would cost \$130.5 million

<sup>&</sup>lt;sup>154</sup> Bhutta, Zulfiqar A et al. "Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost?." *The Lancet* 382.9890 (2013): 452-477.

<sup>155</sup> Shekar, Meera. Scaling up nutrition: what will it cost?. World Bank Publications, 2010.

and salt iodization of all staples would cost \$12.2 million per country. Although these costs would largely be paid for by the consumers of the fortified foods, there are substantial additional costs associated with full-scale implementation of fortification programs. Specifically, an additional US\$50 million per year would be required for technical assistance, initial subsidy for fortificant, and social marketing for iron fortification and salt iodization; US\$1.0 billion would be needed for capacity development for program delivery; and US\$200 million for monitoring, evaluation, and operations research<sup>156</sup>. While these are projected worldwide costs, much of this investment would necessarily target Sub-Saharan Africa. Based on data from the World Bank, we estimate that the overall costs for scaling up micronutrient fortification programmes in countries where PHC is currently active (mostly small African countries), is around \$33 million<sup>157</sup>.

A conversation in late 2012 between Givewell and a senior micronutrient adviser at UNICEF<sup>158</sup>, suggests that UNICEF does not have sufficient funding to meet every country's need for Vitamin A supplementation. For instance, Uganda has solicited UNICEF and other donors for funding several times, indicating a strong need in Uganda for additional micronutrient funding, at least as of 2012. Other countries noted by the advisor as potentially having strong need for Vitamin A supplementation funding are Burundi, Comoros, Malawi and Rwanda. Project Healthy Children is currently active in all of these countries except for Comoros.

Other organisations involved in micronutrient fortification

We do not believe other organisations that are similar to PHC currently have as much room for additional funding as PHC. For instance, the Iodine Global Network (IGN) will receive approximately US \$500,000 in funding from USAID in 2015<sup>159</sup> and Global Alliance for Improved Nutrition (GAIN) has funding from the Bill and Melinda Gates Foundation through mid-2015, which may also be renewed<sup>160</sup>. Moreover, PHC is only active in small African countries with small populations (<17 million), whereas GAIN is not currently active in these countries<sup>161</sup>.

Gates Foundation's recent investment in malnutrition

The Gates Foundation recently announced a \$776 million investment in nutrition, which will also unlock matching funds from the United Kingdom. At least some of this money will fund

https://docs.google.com/spreadsheets/d/14yMala2S098TuzBEEF\_EvoG\_-TYWQjbt\_DNPTgdP4 SU/edit?usp=sharing

159

http://files.givewell.org/files/conversations/Michael%20Zimmermann%202-11-15%20(public ).pdf

<sup>&</sup>lt;sup>156</sup> Shekar, Meera. *Scaling up nutrition: what will it cost?*. World Bank Publications, 2010.

<sup>158</sup> http://files.givewell.org/files/conversations/UNICEF%20Vitamin%20A%20notes.pdf

<sup>160 &</sup>quot;Global Alliance for Improved Nutrition (GAIN ... - GiveWell." 2014. 20 May. 2015

<sup>&</sup>lt;a href="http://www.givewell.org/international/top-charities/GAIN">http://www.givewell.org/international/top-charities/GAIN</a>

<sup>161</sup> http://www.gainhealth.org/programs/

food fortification<sup>162</sup>. However, the focus will be on India, Ethiopia, Nigeria, Bangladesh, and Burkina Faso<sup>163</sup>, and so it does not include any of the priority countries in which PHC currently works. This increases our confidence that the marginal dollar donated to PHC will not go to an already crowded funding landscape. At the same time, the fact that the Gates Foundation (which is very much concerned about cost-effectiveness and has vast research capacity and expertise) is investing in food fortification increases our confidence that food fortification should be a priority intervention.

## Short-term view on room for more funding

PHC currently holds about \$200,000 in reserves<sup>164</sup>, which translates to about 3-4 months of operational costs, which we think is not excessive. Thus, in the short-term there is room for more funding. PHC has told us that with additional funding they would intensify their monitoring efforts, which is one of the most critical components to any national fortification program.

<sup>&</sup>lt;sup>162</sup> "The Bill & Melinda Gates Foundation announces new \$776 ..." 2015. 10 Jul. 2015

<sup>&</sup>lt;a href="http://www.gatesfoundation.org/Media-Center/Press-Releases/2015/06/Nutrition-Strategy-Launch">http://www.gatesfoundation.org/Media-Center/Press-Releases/2015/06/Nutrition-Strategy-Launch</a>

<sup>&</sup>lt;sup>163</sup> "The Bill & Melinda Gates Foundation announces new \$776 ..." 2015. 10 Jul. 2015

<sup>&</sup>lt;a href="http://www.gatesfoundation.org/Media-Center/Press-Releases/2015/06/Nutrition-Strategy-Launch">http://www.gatesfoundation.org/Media-Center/Press-Releases/2015/06/Nutrition-Strategy-Launch</a>

<sup>&</sup>lt;sup>164</sup> Personal communication and financial statements of PHC

# Updates on Fundraising activities

PHC has told us that their current fundraising activities involve 'news blasts' and quarterly letters to current and previous donors. Yet it would seem that PHC has received less funding from private foundations and private donors than one might expect given the organization's effectiveness, reputation, and room for additional funding. Therefore it may be a good idea for PHC to use additional resources to attract more funding (additional resources directed to non-program activities would not necessarily make Giving What We Can less likely to recommend donating to PHC; we assess charities based on overall effectiveness rather than exclusively on overhead costs). PHC is also now in the process of being evaluated by Givewell, which is a very good opportunity for them to receive increased exposure and funding.

## **Updates on PHC's Operations**

### Fortification programs

Our colleagues at Givewell provide a great general overview of PHC's operations in form of a <u>conversation note</u> with PHC's Chief operating officer, Laura Rowe.

PHC reports its fortification program in Rwanda is almost completed and operations are being handed over to the local government. PHC's efforts are now focused on industry engagement, consumer and policymaker awareness, and establishing an institutionalized monitoring and evaluation system<sup>165</sup>. They report that in 2015, priorities in Rwanda will be to (1) continue to support appropriate sourcing of equipment and premix; (2) secure gap funding where needed; (3) guide appropriate testing, monitoring, and reporting structures within industry and at the government level to track compliance; and (4) ensure the design of a surveillance system to track coverage and ultimately measure the impact of fortification on micronutrient status. Finally, PHC is working closely with the Rwandan Ministry of Health to secure funds for the hiring of a short-term Fortification Monitoring Specialist to be placed within the government to guide the program through this critical, post-implementation phase.

Similarly, in Sierra Leone, where PHC has been active since 2014, PHC reports that they are supporting the Ministry of Health in (1) drafting relevant fortification policies; (2) designing training protocols for inspectors of fortified foods; (3) creating advocacy structures; and (4) developing appropriate monitoring and reporting systems<sup>166</sup>.

<sup>&</sup>lt;sup>165</sup> "Rwanda - Project Healthy Children." 2012. 20 May. 2015

<sup>&</sup>lt;a href="http://projecthealthychildren.org/where-we-work/rwanda/">http://projecthealthychildren.org/where-we-work/rwanda/</a>

<sup>&</sup>lt;sup>166</sup> "Sierra Leone - Project Healthy Children." 2014. 20 May. 2015

<sup>&</sup>lt;a href="http://projecthealthychildren.org/where-we-work/sierra-leone/">http://projecthealthychildren.org/where-we-work/sierra-leone/</a>

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