Zinc-enriched fertilisers as a potential public health intervention in Africa

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Abstract

Background
In this review, we examine the potential of Zn-enriched fertilisers to alleviate human dietary Zn deficiency. The focus is on 10 African countries where dietary Zn supply is low and where fertiliser subsidies are routinely deployed on cereal crops.

Scope
Dietary Zn supply and deficiency prevalence were quantified from food supply and composition data. Typical effects of soil (granular) and foliar Zn applications on Zn concentrations in maize (*Zea mays* L.), rice (*Oryza sativa* L.) and wheat (*Triticum aestivum* L.) grains were based on a systematic literature review. Reductions in disease burdens attributable to Zn deficiency and cost-effectiveness were estimated using a disability-adjusted life years (DALYs) approach.

Conclusions
Baseline Zn supply in 2009 ranged from 7.1 (Zambia) to 11.9 (Mali) mg *capita*$^{-1}$ d^{-1}; prevalence of Zn deficiency ranged from 24 (Nigeria) to 66 % (Zambia). In reviewed studies, soil Zn application led to an increase in median Zn concentration in maize, rice and wheat grains of 23, 7 and 19 %; foliar application led to increases of 30, 25 and 63 %. Enriching granular fertilisers within current subsidy schemes would be most effective in Malawi, reducing DALYs lost due to Zn deficiency by 10 %. The cost per DALY saved ranged from US$ 624 to 5,893 via granular fertilisers and from US$ 46 to 347 via foliar fertilisers. Foliar applications are likely to be more cost effective than soil applications due to fixation of Zn in the soil but may be more difficult to deploy. Zinc fertilisation is likely to be less cost-effective than breeding in the longer term although other micronutrients such as selenium could be incorporated.

Keywords

Agronomic biofortification; Fertiliser; HarvestPlus; Micronutrient deficiency; Phytic Acid; Zinc

Introduction

Zinc (Zn) is an integral component of thousands of proteins for all organisms. Adult human bodies contain 1.5-2.5 g of Zn with a daily intake requirement of 10-14 mg (WHO and FAO 2004). The estimated prevalence of inadequate dietary Zn intake is >25 % in sub-Saharan Africa (Wessells and Brown 2012; Wessells et al. 2012; Joy et al. 2014). Dietary Zn deficiency can have a range of health impacts including increased risk of child mortality due to diarrhoeal disease and stunting (Salgueiro et al. 2002) and imposes considerable individual suffering as well as social and economic costs (Stein 2010, 2014). An estimated 0.7 % of the global disease burden is attributable to Zn deficiency, rising to 1.5 % in low income countries (WHO 2009). Factors contributing to Zn deficiency in humans include low consumption of animal products, high phytate intakes that inhibit Zn absorption and low concentrations of Zn in crops grown on Zn deficient soils (Cakmak et al. 1999; Sandstead 2000; Gibson 2012). Phytate refers to mixed salts of phytic acid (PA), the principal form of phosphorus (P) in cereal grains, and is a potent inhibitor of Zn absorption in the human gut. A PA:Zn molar ratio of >15 is commonly used to classify diets having low levels of bioavailable Zn.

In crop plants, a leaf Zn concentration of 15-20 mg Zn kg^{-1} dry weight (DW) is typically required for adequate growth (Broadley et al. 2007). However, Zn deficiency in crops is widespread globally, in particular, due to low phytoavailability of Zn in soils. Such soils are commonly defined as having a Zn concentration extractable by ethylene diamine tetra-acetic acid (EDTA) or diethyl triamine penta-acetic acid (DTPA) less than 1.5 and 1.0 mg kg^{-1} DW of soil, respectively (Trierweiler and Lindsay 1969; Lindsay and Norvell 1978). Low phytoavailability of Zn can result from low soil Zn concentrations or the influence of soil characteristics that limit Zn solubility such as high pH values or large concentrations of available phosphate or $CaCO_3$ (Brümmer et al. 1983; Graham et al. 1992; White and Zasoski 1999; Cakmak 2002, 2004; Alloway 2008; Lu et al. 2011). Deficiency of Zn on cultivated soils is widespread, affecting >50 % of soils in India, Pakistan and Turkey, >30 % of soils in China and most soils in Western Australia and Africa (Alloway 2008).

Zinc fertilisers are widely used to improve crop yields where soil Zn phytoavailability is low (Ahmad et al. 2012). The first reports of using Zn fertilisers to ameliorate crop Zn deficiency were in peach, pecan and pineapple orchards (Hoagland 1948). However, major increases in arable crop production due to Zn fertiliser use are now well-established. For example, wheat grain yield increases of >600 % were reported in Central Anatolia in Turkey from the mid-1990s which returned economic benefits of *ca*. US$ 100 million annually in the following decade (Cakmak 2004). More recently, there has been research exploring the use of Zn fertilisers to increase Zn concentrations beyond that which is needed for maximum yield, to enrich the edible portions of crops for human health benefits (Rengel et al. 1999; Genc et al. 2005; Ortiz-Monasterio et al. 2007; Broadley et al. 2007; Cakmak 2008; White and Broadley 2009, 2011). However, the cost-effectiveness of this approach has not previously been determined.

Several Zn forms have been used in fertilisers, including Zn-sulphate ($ZnSO_4$) and Zn-oxide. Such forms can be delivered either in combination with granular nitrogen (N) fertilisers or as a foliar spray. An advantage of enriching granular fertilisers is that farmers already using fertilisers can be reached with no extra labour or machinery required at the farm level, nor additional distribution infrastructure. However, plant uptake of soil-applied Zn is limited by a low availability or diffusion of Zn in certain soils, particularly those with high pH, organic matter or $CaCO_3$ contents (Tye et al. 2003; Zhao et al. 2014). For example, recovery of soil-applied Zn may be <1 % in calcareous soils (Lu et al. 2012). Thus, a more effective strategy for increasing grain Zn concentrations might be *via* foliar sprays. With foliar application, Zn is absorbed by the leaf epidermis, remobilized and transferred to the grain through the phloem (Fernández and Eichert 2009; White and Broadley 2011).

Common soil fertility management practices can also affect soil Zn status and concentrations of Zn in the grain. For example, N application can increase Zn uptake, xylem transport and remobilization *via* the phloem, and hence the concentration of Zn in the grain (Erenoglu et al. 2002, 2011; Kutman et al. 2010, 2011; Xue et al. 2012), while excessive P fertilisation can reduce availability of Zn in the soil

(Marschner 1993; Lu et al. 2011). Manzeke et al. (2012) reported that farmer fields in Zimbabwe receiving cattle manure or leaf litter in combination with NPK had greater concentrations of EDTA-extractable Zn in soils and greater concentrations of Zn in maize grain compared to unfertilised fields or those receiving only NPK, while rotation with legumes was also reported to increase concentration of Zn in maize grain.

The use of Zn-containing fertilisers to increase dietary Zn supply is one of several strategies to address dietary Zn deficiency. These include dietary diversification, provision of supplements and addition of Zn during food processing (Gibson et al. 2000; Shrimpton et al. 2005). Other agricultural strategies to increase the concentration of Zn in harvested grain include crop breeding for high-Zn varieties (Cakmak 2008; White and Broadley 2009, 2011; Bouis and Welch 2010), while soaking or 'priming' of seeds in $ZnSO_4$ solution might be more efficient than soil applications and confer yield benefits (Slaton et al. 2001; Harris et al. 2007; Harris et al. 2008) although increased Zn concentration in progeny grain is not consistently reported (Johnson et al. 2005). It may also be possible to breed lower PA concentrations into the grains of staple crops and the benefits of even marginal reductions in grain PA concentration on Zn bioavailability could be large at population scales (Joy et al. 2014). Interestingly, it has been reported that Zn-enriched fertilisers can decrease concentrations of PA in cereal grains while Zn deficiency may lead to increased P uptake and accumulation in plants (Loneragan et al. 1982; Erdal et al. 2002).

The impact of public health interventions can be measured using a disability-adjusted life-years (DALYs) approach. A DALY is equivalent to a lost year of 'healthy life' and is the sum of years of life lost due to premature mortality and years of life lost due to a disability (YLD; Murray 1994). The YLD is the product of the number of incident cases, average duration of the disease and a disability weight to reflect the severity of the disease, which ranges between 0 (i.e. full health) and 1 (i.e. death). As there are limited resources available to invest in public health, a DALY approach allows direct comparison between different public health interventions to guide policy making and to increase the efficient use of scarce funds. Previously, Stein et al. (2006) estimated that biofortification *via* breeding for high-Zn rice and wheat varieties could save up to 55 % of the 2.8 million DALYs lost annually due to Zn deficiency in India at a cost of US$ 0.68 and 8.80 *per* DALY saved, for optimistic and pessimistic scenarios respectively. Fielder et al. (2013) estimated that fortifying maize meal with a premix containing vitamin A, iron and Zn at large-scale mills in Zambia could save 5,657 DALYs annually of which 1,757 were due to Zn deficiency, at a cost of US$ 401 *per* DALY saved. Similar studies have not yet been conducted for fertilisers and so the aim of this review is to assess the cost-effectiveness of Zn fertilisers in reducing disease burdens due to dietary Zn deficiency.

The focus of the review is sub-Saharan Africa because of the high incidence of Zn deficiency relative to other regions of the World (Lim et al. 2012; Wessells and Brown 2012). Specifically, we have focussed on 10 countries which routinely deploy fertiliser subsidy schemes (Burkina Faso, Kenya, Ghana, Mali, Malawi, Nigeria, Senegal, Tanzania and Zambia) or which have government control of imports (Ethiopia) as this offers a mechanism for mandating Zn-enrichment of fertilisers (Jayne and Rashid 2013; Wanzala-Mlobela et al. 2013).

The first aspect of this review quantifies dietary Zn supply and deficiency prevalence for the 10 focus countries using food supply and food composition data, the latter adjusted according to cereal processing methods. The second aspect is a meta-analysis of published field experiments that investigate the effect of soil- and foliar-applied Zn fertilisers on Zn and PA concentrations in the grain of three staple crops: maize (*Zea mays* L.), rice (*Oryza sativa* L.) and wheat (*Triticum aestivum* L.). The third aspect of this study models the effect of enriching fertilisers with Zn on dietary Zn supplies, deficiency and associated disease burdens using a DALY framework. We model the effect of enriching subsidised fertiliser with Zn and compare it to a scenario in which subsidised and non-subsidised fertilisers are enriched.

Materials and methods

Baseline dietary Zn supplies and deficiency prevalence

Baseline national dietary Zn supplies and deficiencies were estimated for 10 countries on the basis of food supply and composition data: Burkina Faso, Ethiopia, Ghana, Kenya, Malawi, Mali, Nigeria, Senegal, Tanzania and Zambia. Food supply and population data were downloaded from United Nations datasets (UNDSEA 2013; FAO 2014a). Food Balance Sheets (FBSs) compiled by the FAO record estimates of food supply for up to 92 edible items at a national level, representing net *per capita* food supply calculated from national production, trade, transport loses, storage, non-food uses, livestock feed *etc.*, but with no adjustment for household waste or inter- and intra-household variation in access to food (FAO 2001). Data are now available for 2011, but 2009 was chosen as the reference year to match with available fertiliser usage statistics (Supplementary Table 1). The Institute for Health Metrics and Evaluation's (IHME) estimates of DALYs lost due to Zn deficiency are based on the study of Wessells and Brown (2012) (Lim et al. 2012). Thus food composition data compiled by Wessells and Brown (2012) are used in the present study, including adjustments made due to processing of staple foods, such as milling and fermentation of cereals and cassava (*Manihot esculenta* Crantz; Supplementary Table 2). Food supply and composition data were combined in order to generate estimates of dietary Zn and PA supplies by food item (Wessells and Brown 2012; Supplementary Tables 2 and 3). National mean supplies of Zn and PA were estimated and the amount of absorbable Zn in the diet was calculated using the Miller equation (Miller et al. 2007; Supplementary Table 4). As assumed previously (Wessells and Brown 2012; Wessells et al. 2012), variation in individual intakes was captured through a coefficient of variation in absorbable Zn intake of 25 %. We adopted the approach employed in the Estimated Average Requirement (EAR) cut-point method, in that the proportion of the population below the mean national physiological requirement for Zn was assumed to be deficient.

Effect of Zn-enriched fertilisers on concentrations of Zn and PA in the grains of maize, rice and wheat

A systematic literature review was conducted in order to assess the impact of Zn fertilisers on Zn concentrations in major grains. The terms 'zinc OR Zn AND biofortification', 'zinc OR Zn AND fertili*', 'zinc OR Zn AND application', 'zinc OR Zn AND concentration', 'zinc OR Zn AND response', 'zinc OR Zn AND uptake', 'zinc OR Zn AND soil' and 'zinc OR Zn AND foliar' were queried in the search engines Web of Science (Thomson Reuters, New York, U.S.A.), Science Direct (Elsevier, Philadelphia, U.S.A.) and Google Scholar (Google Inc., California, U.S.A.). Further studies were identified by searching reference sections of review and research papers found using the search terms stated. Criteria for inclusion were that studies were published in a peer-reviewed journal, that Zn was added *via* either soil or foliar applications under field conditions, and that concentrations of Zn in the grain were reported for treatments and controls. Both rainfed and irrigated plots were included. A number of studies assessed Zn applications in combination with varying N or P application rates. In such instances, the treatment closest to 100 kg ha^{-1} yr^{-1} of N and 25 kg ha^{-1} yr^{-1} of P was included for consistency. The effect of Zn fertiliser was determined for maize, wheat and rice; insufficient studies were identified to allow a similar systematic analysis of data on other crops. The most commonly used form of Zn in both granular and foliar fertilisers is $ZnSO_4.7H_2O$. Other forms of Zn including Zn-bonded amino acids may be more effective at increasing grain Zn concentrations (Ghasemi et al. 2013), however insufficient studies were identified to include alternatives to $ZnSO_4$ in this review.

The effect of Zn fertiliser was quantified as concentration of Zn in the grain at harvest as a percent of control and the median effect was used across studies by taking study site, crop type, cultivar, application method (soil or foliar) and application rate (kg Zn ha^{-1}) as factors. Mean effect over seasons was taken for multi-season trials. Some studies examined the residual effect of Zn fertilisers but these data were not included; this is revisited in the Discussion. Studies examining the effect of different application timings of foliar sprays with later applications (i.e. post-flowering) appeared to have a greater impact on grain Zn concentration but possibly a lower impact on grain yield (Cakmak et al. 2010; Mabesa et al. 2013); in such instances, the treatment when Zn was applied at flowering or heading stages was taken for consistency.

Results from 26 journal articles were included in the literature review: four studies of maize, six of rice, 15 of wheat and one of maize and wheat (Table 1). Fourteen and four studies, respectively, reported effects of soil and foliar applications while eight reported effects of both soil and foliar applications. No studies were identified that reported the effect of Zn application *via* soil on PA concentration in the grain of rice, nor *via* foliar spray in maize. Preliminary analysis of results from all studies revealed that Zn application *via* soil and foliar routes tended to increase concentrations of Zn in the grain. However, larger application rates did not appear to increase concentrations more than smaller rates when comparing trials. This is likely to be due to the variety of soil characteristics encountered. The majority of studies did not report variance of Zn or PA concentration in the grain so it was not possible to perform a standard meta-analysis in which variance is used to weight the contribution of effect size (Field and Gillett 2010). For these reasons, results were pooled by crop and application method (soil or foliar) with the median effect on crop Zn and PA concentrations taken.

Milling of maize, rice and wheat grains is common practice. It was assumed that the relative increase in Zn concentration in the whole grain and the endosperm fraction were equivalent (the assumption is revisited in the Discussion). Thus, studies that reported whole grain data were assumed to give a good prediction of the effect of Zn fertilisation on the Zn concentration of edible portions. Rice is most commonly eaten in its polished form; data for polished rice were used where available, otherwise, brown rice data were used.

Effect of Zn fertilisers on Zn deficiency prevalence

Four scenarios were modelled to quantify the impacts of agronomic biofortification with Zn on dietary Zn and PA supplies at national levels in the 10 focus countries:

- the first scenario modelled a policy to enrich *subsidised* fertiliser, which would be easiest to implement given the pre-existing government involvement;
- the second scenario modelled a policy to enrich *subsidised and non-subsidised* fertiliser;
- the third scenario modelled a policy to introduce foliar fertilisation of cereals with a target of 50 % coverage; and
- the fourth scenario modelled a policy to introduce foliar fertilisation of cereals with a target of 75 % coverage.

All scenarios assumed that maize, rice and wheat crops were targeted. In Ethiopia, teff (*Eragrostis tef* (Zucc.) Trotter) was also included as this grain accounts for almost one-fifth of national energy consumption from cereals and *ca.* 40 % of national inorganic fertiliser consumption (CSA 2011; FAO 2014a). Demand for fertiliser was also assumed to arise from millet (*Eleusine coracana* L. and *Pennisetum glaucum* L.), sorghum (various spp.), cocoa (*Theobroma cacao* L.), coffee (*Coffea* spp.), cotton (*Gossypium* spp.), palm oil (*Elaeis guineensis* Jacq.), sugarcane (*Saccharum officinarum* L.) and tobacco (*Nicotiana* spp.). Scenarios one and two assumed that fertiliser used as basal dressing was enriched using $ZnSO_4.7H_2O$ to give a N:Zn mass ratio of 2:1. Assuming recommended application rates of N (see below) this would provide 23, 12, 20 and 12 kg ha^{-1} yr^{-1} of Zn for hybrid maize, local maize, rice and wheat, respectively. A compliance of 90 % was used to account for enforcement problems. Scenarios three and four assumed that 600 L ha^{-1} of 0.5 % (w/v) aqueous $ZnSO_4.7H_2O$ solution was sprayed twice annually on maize, rice and wheat crops, supplying 1.36 kg ha^{-1} of Zn.

The efficacy and costs of scenarios one and two are partly determined by the quantity of fertiliser enriched and the proportion of maize, rice, wheat and teff covered by this fertiliser. Fertiliser usage data were derived from the International Fertilizer Development Center (IFDC) for subsidised fertiliser consumption (IFDC 2013a) and total national fertiliser consumption (IFDC 2011, 2012a-f, 2013 b,c; Supplementary Table 5) from which the supply of N was calculated. Fertiliser was assumed to contain 23 % N by mass where product information was not available. ‘Demand’ for N was calculated as the product of crop-specific fertiliser requirements and cropping areas of maize, rice, wheat and cash crops (Supplementary Table 5). Cropping areas were derived from FAO production data (FAO 2014b; Supplementary Table 5)[1]. Half of maize production area was assumed to be hybrid varieties and half local varieties in all countries. Crop-specific recommended fertiliser application rates were identified only for Malawi, (Malawi Government Ministry of Agriculture and Food Security, date unknown, accessed 2014; Supplementary Table 5) and were applied to all countries for most crops. Teff was assumed to require the same N rate as wheat. Requirements for tea, coffee, palm oil and cocoa were identified through a literature search (FAO 1984; Grice 1990; Makono and Chanika 2008).

Thus, the proportion of crops receiving Zn-enriched fertiliser in scenarios one and two was calculated as supply of N divided by demand for N (equation 1).

$$P_{Zn} = F_{s,w} \times q / \sum (C_{a-l} \times A_{a-l}) \qquad (1)$$

Where:
P_{Zn} = proportion of crop receiving Zn-enriched fertiliser;
$F_{s,w}$ = national N usage (metric tonnes, t) *via* subsidised fertiliser (s) or subsidised and non-subsidised fertiliser (w);
$C_{a\text{-}j}$ = Cropping area of maize (a), rice (b), wheat (c), teff (d), millet (e), sorghum (f), cocoa (g), coffee (h), cotton (i), palm oil (j), sugarcane (k) and tobacco (l);
$A_{a\text{-}j}$ = Recommended N application rate (t ha^{-1} yr^{-1}) for maize (a), rice (b), wheat (c), teff (d), millet (e), sorghum (f), cocoa (g), coffee (h), cotton (i), palm oil (j), sugarcane (k) and tobacco (l); and
q = compliance factor (0 to 1).

The effect of Zn fertilisers was modelled through changes to the concentrations of Zn and PA in the grains of maize, rice and wheat. The proportion of each crop receiving fertiliser was multiplied by the median effects of applied Zn on grain Zn and PA concentrations to generate new composition data for maize, rice, wheat and teff. Teff grain was assumed to have the same response to Zn-enriched fertiliser as wheat grain. National dietary Zn and PA supplies, quantity of absorbable Zn in the diet and estimated prevalence of Zn deficiency were re-calculated using the new composition data, assuming that composition of all other food items and quantity of food supply had not changed. The proportion of DALYs saved was assumed to equal the reduction in proportion of deficiency prevalence.

Estimating the cost-effectiveness of an agronomic biofortification approach to addressing Zn deficiency in sub-Saharan Africa

Baseline disease burdens attributable to Zn deficiency for the 10 focus countries were derived from the Global Burden of Disease Study in which a proportion of ‘diarrheal diseases’, ‘typhoid and paratyphoid fevers’ and ‘lower respiratory infections’ are attributed to Zn deficiency and assigned a ‘disability weight’ (Lim et al. 2012; IHME 2014).

The cost of enriching fertilisers with Zn was estimated assuming a wholesale retail price of $ZnSO_4.7H_2O$ of US$ 500 t^{-1}. Only the fertiliser used by maize, rice, wheat and teff was assumed to be enriched and, for soil applications, only the proportion applied as a basal dressing (Supplementary Table 6). The proportion of crops receiving basal fertiliser was assumed to equal the proportion of crops receiving fertiliser (equation 1). The cost of supplying knapsack sprayers was estimated for the foliar scenarios by assuming that knapsack sprayer sets cost US$ 150 *per* unit and that each would last 10 years and cover 20 ha of cropland annually through sharing among farmers (Supplementary Table

[1] Total cereal production area in Ethiopia in 2009 was 9.2 * 10^6 ha and teff appears to be included in the production sub-category ‘Cereals, nes’ (production area 2.6 * 10^6 ha) rather than the sub-category ‘Millet’ (production area 0.4 * 10^6 ha), contrary to the FAO’s own production definitions (FAO 2014c). ‘Cereals, nes’ production area was assumed to be solely teff.

6). Other implementation costs including agricultural extension services and the distribution of equipment and fertiliser were not considered.

Results

Baseline dietary Zn supplies and deficiency prevalence

Dietary Zn deficiency is likely to be widespread in sub-Saharan Africa. Using national-level food supply and food composition data adjusted by common processing methods, we estimate a high prevalence of Zn deficiency in the 10 focus countries, ranging from 24 % in Nigeria to 66 % in Zambia (Table 2; Supplementary Table 4). The estimated large disease burden attributable to Zn deficiency is consistent with previous work. For example, IHME (2014) estimated that the burden of Zn deficiency in the 10 focus countries ranged from 161 to 1,219 DALYs lost 100 k population^{-1} in Ghana and Burkina Faso, respectively. This is two orders of magnitude greater than in the UK where it is estimated that <4 DALYs 100 k population^{-1} are lost due to Zn deficiency (IHME 2014).

Effect of Zn-enriched fertilisers on concentrations of Zn and PA in the grains of maize, rice and wheat

A summary of the studies included in the literature review is presented in Table 1. The trials combined a range of soil types and cultivars (Table 3; Supplementary Tables 7 and 8). In control plots (i.e. without application of Zn), concentration of Zn in maize grain ranged from 14.9 mg kg^{-1} DW on calcareous, Zn-deficient silty-clay-loam soils in Pakistan (Harris et al. 2007) to 22.5 mg kg^{-1} DW on Zn-deficient sandy-loam in Pakistan (Kanwal et al. 2010); concentration of Zn in brown rice (i.e. husk removed but grain unpolished) ranged from 9.9 mg kg^{-1} DW in Thailand (Phattarakul et al. 2012) to 41.6 mg kg^{-1} DW in ‘high-Zn’, upland soil in the Philippines (Wissuwa et al. 2008); concentration of Zn in polished rice grain ranged from 12.3 mg kg^{-1} DW in pH 7.7 soils in Turkey (Phattarakul et al. 2012) to 28.0 mg kg^{-1} DW in Zn-adequate soils in China (Wei et al. 2012); and concentration of Zn in wheat grain ranged from 6.6 mg kg^{-1} DW in borderline Zn-deficient soils with pH 7.8 in Iran (Khoshgoftarmanesh et al. 2012) to 40.2 mg kg^{-1} DW in Zn-adequate soils in India (Zou et al. 2012).

The median increases in Zn concentration in the grains of maize, rice and wheat were, respectively, 28, 11 and 18 % for soil application and 30, 24 and 63 % for foliar application (Table 4; Figure 1; Supplementary Tables 7 and 8). The result for maize with foliar-applied Zn is based on only one data point (Wang et al. 2012). Application of Zn-enriched fertilisers *via* the soil decreased PA concentration in the grain of wheat by 11 % while foliar application decreased concentration in the grain of rice and wheat by 1 and 13 %, respectively. No studies were identified that reported the effect of Zn application *via* soil on PA concentration in the grain of rice, nor *via* foliar spray in maize.

Yield data are important to rule out the ‘concentration effect’ whereby lower yields may lead to greater Zn concentrations in the grain as the Zn taken up by the plant is distributed to fewer or smaller grains. This is particularly so for foliar applications as high concentrations of Zn in the spray solution could damage leaf cuticles (Eichert and Fernández 2012). Yield was reported for only 122 out of 273 plots included in the systematic review so a consistent approach to excluding plots with low yield relative to control was not possible, although this is re-visited in the Discussion. Of the studies that reported yield data, soil application led to a median 10-11 % increase in grain yield for maize, rice and wheat, whereas foliar application had no obvious effect (Table 4; Supplementary Table 7). In addition, of the studies that did not report yield data by plot, Mabesa et al. (2013) found no significant difference in yield of rice due to foliar application of Zn, but also reported a significant negative correlation among different varieties between grain yield and grain Zn concentration, a relationship also reported by Wissuwa et al. (2008). Very high yield responses of >150 % of control were found in 10 and four wheat data points for soil and foliar-applied Zn, respectively (Supplementary Table 7). All of these data points also exhibited high Zn concentrations in grains relative to controls, with Q1, median and Q3 of 170, 189 and 257 % for the soil-applied treatments and 252, 295 and 316 % for the foliar-applied treatments.

Effect of Zn fertilisers on Zn deficiency prevalence

The effectiveness of the biofortification approach is greatly dependent on the coverage of fertilisers, i.e. the proportion of crops that would receive fertilisers enriched with Zn. Scenario one modelled the potential impact of Zn-enrichment of granular fertiliser currently distributed under national subsidy schemes. The Ethiopian Government control fertiliser imports so all fertiliser usage was considered under the 'subsidised' bracket. The percentage of cereal production receiving subsidised fertiliser was: Burkina Faso (2), Ethiopia (18), Ghana (6), Kenya (8), Malawi (24), Nigeria (10), Senegal (9), Tanzania (6) and Zambia (20) (Supplementary Table 5). Data for Mali were not available. The estimated reduction in DALYs lost due to Zn deficiency was lowest in Burkina Faso (<1 %) and greatest in Malawi (10 %) where there would be a 3 % increase in the mean amount of absorbable Zn in the diet (Table 5; Supplementary Tables 9 and 10).

Scenario two modelled the potential impact of Zn-enrichment of all fertiliser currently used. The percentage of cereal production receiving both subsidised and non-subsidised fertiliser was: Ghana (24), Kenya (39), Malawi (39), Mali (14), Nigeria (22), Senegal (21), Tanzania (13) and Zambia (33) (Supplementary Table 5). Data for Burkina Faso were not available. The estimated reduction in DALYs lost due to Zn deficiency was lowest in Mali (3 %) and greatest in Malawi (15 %) where there would be a 5 % increase in the national mean amount of absorbable Zn in the diet (Table 5; Supplementary Tables 9 and 10).

Scenarios three and four modelled the potential impact of foliar Zn application, covering 50 and 75 %, respectively, of maize, rice and wheat production. The response of grain Zn concentration to foliar Zn application was greater in wheat than in maize or rice and it was assumed that Zn concentration in teff grain responded as in wheat. Wheat and teff consumption combined was greatest in Ethiopia, (161 g *capita*$^{-1}$ d^{-1}; Supplementary Table 1), where the increase in mean amount of absorbable Zn in the diet for scenarios three and four, respectively, was 13 and 19 % and the estimate of DALYs lost due to Zn deficiency decreased by 41 and 54 %, respectively (Table 5; Supplementary Tables 9 and 10). Response of grain PA concentration to foliar Zn application was greatest for rice, and dietary PA supply in scenario four decreased by 2.8, 1.5 and 1.4 % in Senegal, Ghana and Mali where rice consumption was 188, 157 and 72 g *capita*$^{-1}$ d^{-1}, respectively (Table 5; Supplementary Tables 1 and 9).

Estimating the cost-effectiveness of an agronomic biofortification approach to addressing Zn deficiency in sub-Saharan Africa

The cost effectiveness of agronomic biofortification of crops using soil or foliar-applied $ZnSO_4.7H_2O$ was estimated. Where the outcomes of public health interventions are not measured in monetary terms, decision-makers cannot rely on conventional tools of economic evaluation, such as internal rates of return or benefit-cost ratios, to determine whether the 'investment' in an intervention represents a good use of scarce resources. Instead, their relative cost-effectiveness can be assessed by comparing the average cost of saving one DALY across interventions, or against benchmarks.

Scenario one modelled a policy to enrich granular fertilisers currently distributed under government subsidy schemes with Zn. The cost *per* DALY saved ranged from US$ 624 to 5,747 in Burkina Faso and Ghana, respectively (Table 5; Figure 2; Supplementary Table 11). Scenario two modelled a policy to enrich subsidised and non-subsidised granular fertilisers used as basal dressings and cost *per* DALY saved ranged from US$ 977 to 5,893 in Senegal and Ghana, respectively (Table 5; Figure 2; Supplementary Table 11). Variation in cost effectiveness between countries was partly a function of the baseline disease burden attributable to Zn deficiency with higher burdens leading to lower costs *per* DALY saved. Foliar application is likely to be a more efficient use of Zn by avoiding fixation of Zn in the soil. Costs *per* DALY saved in scenario three, in which 50 % of cereal production received foliar Zn fertiliser, ranged from US$ 46 to 332 in Senegal and Ghana, respectively, while in scenario four, in which 75 % of cereal production received foliar Zn fertiliser, the cost ranged from US$ 49 to 347, also in Senegal and Ghana, respectively (Table 5; Figure 2; Supplementary Table 11).

The World Health Organization (WHO 2001) and the World Bank (World Bank 1993) have provided benchmarks to assess the cost-effectiveness of health interventions; if the cost of saving a DALY is below the benchmark then it is considered a good investment. The WHO benchmark is calculated in relative terms as 300 % of a country's *per-capita* Gross Domestic Product (GDP), hence in 2009, from US$ 678 to 5,550 *capita*$^{-1}$ in Malawi and Ghana, respectively (World Bank 2014; Supplementary Table 11). The World Bank benchmark is in absolute terms, taking a value of US$ 150 *per* DALY in 1990 as a base year which is equivalent to US$ 246 in 2009 after adjusting for inflation. Thus, even in the poorest country, the World Bank benchmark is lower and harder to meet than that of WHO. According to the WHO benchmark, pursuing Zn enrichment of soil-applied granular fertilisers appears to be cost-effective in Burkina Faso, Ethiopia, Kenya, Senegal and Zambia, but not other countries, while foliar application of Zn appears to be cost-effective in all countries. According to the World Bank benchmark, the only cost-effective scenarios are foliar application of Zn in Burkina Faso, Ethiopia, Kenya, Malawi, Mali, Nigeria, Senegal and Zambia (Table 5; Figure 2; Supplementary Table 11).

Discussion

Baseline dietary Zn supplies and deficiency prevalence

Robust estimates of dietary Zn supplies and risk of deficiency underpin the evaluation of approaches to address Zn deficiency. There are potential weaknesses in using FBS food supply data including underestimating food supply as some subsistence production is not captured, or overestimating supply by failing to account for household-level food waste (FAO 2001). These weaknesses have been discussed extensively elsewhere (de Haen et al. 2011; Wessells et al. 2012; Joy et al. 2014). A further source of error may arise from composition data derived from sources that will not capture local variation in elemental composition of crops and there is a lack of spatially-resolved food composition data in sub-Saharan Africa (Joy et al. 2014; Joy et al. 2015). However, in the absence of wide-scale analysis of biomarkers of nutrient status, e.g. blood serum, estimating national dietary supplies of bioavailable Zn remains a valuable method of estimating the prevalence of Zn deficiency at a national level (Gibson et al. 2008).

An alternative to FBSs is to use food consumption data captured in nationally-representative household surveys (Fielder et al. 2008). These data are available for eight of the 10 focus countries in this study (Ethiopia, Ghana, Kenya, Malawi, Mali, Nigeria, Tanzania and Zambia). For example, Fielder et al. (2013) estimate mean and median intakes of Zn in Zambia of 5.8 and 4.4 mg *capita*$^{-1}$ d^{-1} and a 73.1 % prevalence of inadequate Zn intakes, compared to US Institute of Medicine dietary requirements of Zn. An advantage of household surveys is that they allow sub-national resolution of dietary estimates and shed light on distributional issues. One drawback is that they rely on household member recall, which is subject to misreporting, both intentional and unintentional (Archer et al. 2013; Moltedo et al. 2014). Zinc intakes and status can also be measured directly through analysis of dietary composites or concentration of Zn in blood plasma or serum samples. Through such methods, high prevalence of Zn deficiency have been reported previously in sub-populations in Burkina Faso (e.g. Müller et al. 2003), Ethiopia (e.g. Abebe et al. 2007; Kassu et al. 2008; Stoecker et al. 2009), Kenya (e.g. Siekmann et al. 2003), Malawi (e.g. Siyame et al. 2013), Nigeria (e.g. Gegios et al. 2010), Tanzania (e.g. Veenemans et al. 2011) and Zambia (e.g. Duggan et al. 2005).

New baseline Zn deficiency estimates correlated well with the IHME estimates of DALYs lost due to Zn deficiency (Spearman’s Rank, $r = 0.588$, $p = 0.018$, d.f. = 9). This is expected as both the present study and the IHME DALY estimates were derived from the underlying data and methodology developed by Wessells et al. (2012) (Wessells and Brown 2012; Lim et al. 2012). However, there is no correlation between the results of Joy et al. (2014) and Wessells and Brown (2012) which is surprising given the similar underlying methodologies. This may have arisen because the studies used different reference years and food composition tables and prevalence of deficiency in the Wessells and Brown (2012) study are based on estimated dietary supplies of ‘bioavailable’ Zn. Also, Wessells and Brown (2012) assumed certain milling and fermentation practices of cereals and other crops and adjusted the concentrations of Zn and PA accordingly. For example, estimated dietary PA supplies in Ethiopia are 2,802 mg *capita*$^{-1}$ d^{-1} in the Joy et al. (2014) study, but 1,724 mg *capita*$^{-1}$ d^{-1} in the Wessells and Brown (2012) study in which 59 % of wheat, 90 % of maize, millet and sorghum and 100 % of other cereals (i.e. teff) are assumed to be fermented (Supplementary Table 2).

Zinc deficiency confers increased risk of diarrhoea and is a potential underlying cause of stunting which is defined as having a height-for-age more than two standard deviations below the median of the WHO growth reference (WHO 1995). Although deficiency estimates in the current study, which are based on dietary intakes of Zn and PA, show a general positive relationship with the WHO estimates of childhood stunting prevalence, the relationship is not statistically significant (P >0.1) for both the absolute and log-transformed values. Other potential underlying causes of stunting include caloric deficiency (Stein et al. 2003), mother's body mass index (Mamiro et al. 2005) access to clean drinking water (Esrey et al. 1988) and sanitation and hygiene practices (Fink et al. 2011; Spears et al. 2013).

Effect of Zn-enriched fertilisers on concentrations of Zn and PA in the grains of maize, rice and wheat

The efficacy of applied Zn in increasing grain Zn concentration depends in part on the crop species and cultivar. Across studies, the effect of soil-applied Zn on grain Zn concentrations was greater in maize and wheat than in rice (Table 4; Figure 1). This may be due to abiotic factors such as the reducing conditions and high organic matter content typically found in anaerobic flooded paddy soil (Alloway 2008), or biotic factors such as root morphology or root exudates (Widodo et al. 2010). Cereal crops can respond to Zn deficiency stress by releasing compounds capable of chelating soil-bound Zn including low-molecular-weight organic acids and a class of non-protein amino acids known as phytosiderophores (Kochian 1993; Hoffland et al. 2006; Suzuki et al. 2006, 2008; Widodo et al. 2010). Alternatively, the lower efficacy in rice may have been due to the higher soil pH values and lower baseline DTPA-extractable Zn concentrations in maize and wheat trials than rice trials, possibly leading to lower concentrations of Zn in grains from control plots and a greater response to Zn application (Table 3). In addition, average Zn application rates were greater in maize and wheat trials than rice (Table 3).

The effect of foliar-applied Zn was greater in wheat than in rice (Table 4; Figure 1). Biotic factors including the ability to remobilize Zn from ageing leaves to the grain may be responsible, while the rate at which remobilization occurs may be dependent on the Zn nutritional status of the plant which will, in turn, be affected by soil properties. Also, a portion of the foliar-applied Zn may run down the stem and reach the rhizosphere where availability to the plant root will depend on soil properties.

Several studies reported significant differences in the Zn concentration of grains and the efficacy of soil or foliar Zn application between cultivars of rice and wheat (Yilmaz et al. 1997; Ekiz et al. 1998; Erdal et al. 2002; Wissuwa et al. 2008; Yang et al. 2011a; Khoshgoftarmanesh et al. 2012; Phattarakul et al. 2012; Wei et al. 2012; Ghasemi et al. 2013; Mabesa et al. 2013), suggesting that agronomic and crop breeding biofortification efforts should be aligned. Only one study investigated different cultivars of maize, finding no significant difference between two cultivars (Kanwal et al. 2010).

The majority of trials reviewed here were conducted in Western, Central and Eastern Asia where Zn-deficiency in crops commonly arises in calcareous soils with pH >7.5 (Table 1; Alloway 2008). In highly-weathered tropical soils, Zn deficiency may be a product of leaching and low total Zn content (Alloway 2008). Only two of the studies reviewed here included trials located in Africa, both of soil-applied Zn, reporting an 18 % increase in the concentration of Zn in the grain of maize on borderline Zn-deficient soils in Zimbabwe (Manzeke et al. 2014) and a 4 % increase in the concentration of Zn in the grain of wheat grown on Zn-deficient soils in Zambia (Zou et al. 2012). Clearly, more studies are required across the varied environmental conditions found in sub-Saharan Africa to verify the estimates of the effects of applied Zn on grain Zn concentration.

Although soil-application of Zn is likely to improve yields of crops grown on Zn-deficient soils, it could inhibit the absorption of other nutrients such as copper, while foliar sprays with high Zn concentration could damage leaf cuticles. Reduced yields could lead to a 'concentration effect', where Zn in the leaves or shoot is distributed to fewer or smaller grains. Although this may increase concentrations of Zn in the edible portion, it would clearly be undesirable. Yield data were reported for 122 treatment plots in total with soil applications appearing to generally improve yields while foliar applications had no obvious effect (Table 4). The yields of just six of the treatment plots were <90 % of the relevant control plot and all of these plots also exhibited increased concentration of Zn in the grain relative to the control plot (Supplementary Table 7). However, removing these data points from the study had minimal impact on the estimated efficacy and cost-effectiveness of the four Zn-fertilisation scenarios: median effects across studies of soil applied Zn would remain unchanged for maize, rice and wheat and median effect of foliar-applied Zn would be unchanged for maize and would be 124 and 160 % for rice and wheat, compared to 125 and 163 %.

Zinc is distributed unevenly across cereal grain fractions, with higher concentrations in the bran and embryo than the endosperm. Thus, milling and processing generally reduce the concentration of Zn in the edible product (Bityutskii et al. 2002; Ozturk et al. 2006; Liang et al. 2008; Cakmak et al. 2010; Joy et al. 2015). Many of the studies included in the meta-analysis only reported Zn concentrations in whole grain, with and without application of Zn. It is possible that greater concentration of Zn in the whole grain with Zn fertilisation is a result of increased concentrations in the bran and embryo and not the endosperm. However, Cakmak et al. (2010) examined Zn concentrations across the different fractions of wheat grain and reported that the greatest relative increase in Zn concentrations with Zn fertilisation is likely to be in the endosperm. In addition, those studies that reported milled or polished grain Zn concentrations generally found positive effects of Zn fertilisation. For example, Wei et al. (2012) found that foliar application increased Zn concentration in the polished grains of three rice cultivars by 18-28 % and Zhang et al. (2012) found significantly greater Zn concentrations in 60-65 % extraction wheat flour (i.e. bran and germ removed) with soil (P <0.05) and foliar (P <0.001) applications of Zn. Despite these findings, when looking across the studies reviewed here, application of Zn *via* the soil increased concentrations of Zn in brown rice (median = 110, Q1 = 102, Q3 = 120 % of control, n = 27) but not white rice (median = 99, Q1 = 98, Q3 = 104 % of control, n = 3) and foliar application increased concentrations more in brown (median = 130, Q1 = 114, Q3 = 147 % of control, n = 28) than white (median = 117, Q1 = 112, Q3 = 122 % of control, n = 6) rice. Thus, agronomic biofortification of rice may be less effective at increasing Zn in the diet than assumed and future studies could confirm or allay this concern by reporting data for both whole grain and polished rice.

No studies were identified that reported the effect of Zn application *via* soil on PA concentration in the grain of rice, nor *via* foliar spray in maize. Were such data available, it is likely that estimates of efficacy and cost-effectiveness of the agronomic biofortification strategies would improve. In addition, this review excluded data reporting the effects of residual soil-applied Zn in subsequent crops. Thus, applied Zn that is not taken up by the crop or permanently 'fixed' within mineral phases is potentially available for subsequent crop uptake and some studies show a cumulative increase in grain Zn concentrations in successive seasons following Zn application (Srivastava et al. 2009; Wang et al. 2012; Abid et al. 2013; Manzeke et al. 2014), although positive residual effects are not always found (Lu et al. 2012; Yang et al. 2011a). Therefore, the efficacy of Zn fertilisation might be under-estimated here by excluding residual effects, especially in lower-pH soils. Conversely, meta-analyses are subject to systematic bias due to preferential reporting and publishing of 'positive' findings (Dickersin et al. 1992). This may lead to an over-estimate of the efficacy of Zn-enrichment on concentrations of Zn in grains.

Cereals contribute *ca.* 50 % or more of energy intake across 46 countries in Africa, but root and tuber crops contribute >30 % of energy supplies in 10 countries (Joy et al. 2014). Concentration of Zn in the tuber of potato (*Solanum tuberosum* L.) is generally low (i.e. 10-20 mg kg^{-1}) due to limited translocation of Zn from shoots to tubers *via* the phloem, although there is significant variation between genotypes and concentrations up to *ca.* 30 mg kg^{-1} are achievable with foliar Zn application (White and Broadley 2011; White et al. 2012). Hence, Zn biofortification of potatoes appears to be feasible, in principle. The prospect for supplying Zn *via* granular fertilisers to cassava and sweet potato (*Ipomoea batatas* L.) is likely to be more limited as these crops are generally grown with few external inputs (Kelly 2006), while a foliar fertilisation programme must consider that the leaves of these crops are consumed in some cultures in sub-Saharan Africa. Leafy vegetables contribute little to dietary energy, but substantially to dietary Zn, intakes due to greater concentrations of Zn in leaves than grains, tubers or fruits (Broadley et al. 2007). For example, Joy et al. (2015) report concentrations of Zn in edible leaves from Malawi of *ca.* 40-70 mg kg^{-1} DW. The concentration of Zn in edible leaves is dependent on both environmental factors, such as the concentration of extractable Zn in the soil, and genetic factors which show high heritability in some, but not all, species (Wu et al. 2007, 2008; Broadley et al. 2010); thus there is scope for biofortification of edible leaves through agronomic or breeding approaches.

Effect of Zn fertilisers on Zn deficiency prevalence

Assumptions were made regarding the coverage of fertilisers and hence the proportion of crops that could receive fertiliser enriched with Zn. The proportion of maize, rice, wheat and teff receiving fertiliser was derived from the ratio of national N demand and usage. Demand may be underestimated (thus coverage overestimated) as some crops were not included (e.g. horticultural and oil crops), or may be over-estimated (thus coverage underestimated) as some non-target crops such as millet and sorghum are grown extensively in sub-Saharan Africa with little fertiliser applied (Ahmed et al. 2000). In addition, fertiliser usage data were generally derived from national government statistics (IFDC 2011, 2012a-f, 2013 b,c) and are likely to vary in accuracy. Fertiliser usage data for 2009 were used due to the availability of IFDC reports. However, usage, and thus the potential reach of a programme to enrich granular fertilisers with Zn, is likely to vary annually depending on prices, farmer purchasing power and government subsidy programmes. For example, estimated N consumption in Zambia in 2009 was 39,400 t based on total fertiliser consumption of 171,000 t in 2007/08 (IFDC 2013c). By 2012/13, estimated fertiliser consumption had increased to 250,000-300,000 t (IFDC 2013c).

A further limitation of the study is that average changes in the composition of maize, rice and wheat (a product of the average effect of Zn-enriched fertilisers on crop composition and coverage of fertiliser usage) were applied to all of the national supply of these food items provided in the Food Balance Sheets. However, a national programme to introduce Zn enrichment *via* soil or foliar applied fertilisers will only alter the composition of crops produced in-country. Thus, the effect on average Zn concentration may be over-estimated as imported crops are not enriched while some of the benefits of the fortification may not be captured as exported crops are enriched.

Estimating the cost-effectiveness of an agronomic biofortification approach to address Zn deficiency in sub-Saharan Africa

In the current study, costs of Zn and knapsack sprayers were considered whereas other costs, including for agricultural extension, intra-national distribution of consumables and quality control, were not. This is likely to underestimate the cost of the modelled strategies. Estimating full costs would require detailed study of national agricultural extension services, laboratory capacities *etc.*

The EAR cut-point approach might underestimate the cost-effectiveness of a population-level fortification programme to alleviate Zn deficiency as only the reduction in deficiency prevalence is considered. In this study, 'deficient' status was defined as dietary Zn supply below the mean national EAR. Increasing Zn concentration in staple foods and in the national diet moves a proportion of the population from below to above the EAR cut point. However, those who remain below the EAR may still have derived health benefits from increased Zn intake, (e.g. individuals who move from 'severe' to 'mild' Zn deficiency), and this benefit is not captured. Moreover, a non-linear relationship between the level of dietary micronutrient deficiencies and the severity of related health outcomes is normally assumed (Stein et al. 2005). Hence, even if an intervention does not completely eliminate a deficiency, it will have a relatively larger impact when alleviating the more severe levels of the deficiency.

Several studies have demonstrated that Zn-enrichment of granular fertilisers can be a cost-effective strategy due to improvements in crop yield (e.g. van Asten et al. 2004; Harris et al. 2007; Cakmak 2009). From the limited yield data available in the studies reviewed here, it appears that soil-applied Zn has a small (*ca.* 10 %) positive impact on yield of maize, rice and wheat while foliar application has minimal effect. The lack of yield response with foliar sprays may be because post-flowering applications were preferred as these late applications have a greater impact on grain Zn concentration with a smaller impact on grain yield (Cakmak et al. 2010; Mabesa et al. 2013). The very high yield responses (i.e. >150 % greater than control) found in a few cases are likely to be due to severe crop deficiency of Zn and these plots also exhibited great response in grain Zn concentration. Thus, an economic argument for the use of Zn fertilisers due to yield improvements will be highly dependent on the soil characteristics.

The feasibilities of the different scenarios require consideration. Previously, it has been suggested that the yield of crop varieties bred for high-Zn concentration must be maintained or improved if farmer acceptance is to be encouraged (Welch and Graham 2004) and yield improvements have been an important driver of the uptake of Zn-enriched fertilisers in Turkey in areas of Zn-deficient soils (Cakmak 2009). Further studies are required to test whether potential yield improvements due to granular or foliar Zn application are sufficient to drive their uptake among resource-poor smallholder farmers in sub-Saharan Africa. Governments or international donors might be persuaded to subsidise or mandate Zn-enrichment of fertilisers due to the potential public health benefits, possibly implemented through existing fertiliser subsidy schemes. To the authors' knowledge, acceptance of micronutrient sprays by smallholder farmers in sub-Saharan Africa has not been studied and is likely to depend on observable benefits such as yield improvements. In addition, it is questionable whether knapsack sprayers are suitable for foliar application of Zn to maize, which might be *ca*. 2 m in height at tasselling, compared to *ca.* 1 m for mature stands of rice, wheat and teff.

Comparison of agronomic biofortification with other strategies to alleviate Zn deficiency

A fertiliser approach can be compared directly against other Zn interventions. Crop breeding is another strategy to potentially decrease the prevalence and disease burden of Zn deficiency. The HarvestPlus (H+) programme is developing nutrient-rich staple crops through exploitation of existing genotypic variation including in wild relatives, setting target Zn concentrations of 38, 28 and 38 mg kg^{-1} DW in whole maize grain, polished rice grain and whole wheat grain, respectively (Bouis and Welch 2010; Velu et al. 2014). Stein et al. (2006) estimated that biofortification of crops by breeding for high Zn concentration would be one-to-three orders of magnitude more cost effective than the fertiliser approaches modelled here. However, the potential of new varieties to deliver greater concentrations of Zn in the grain depends on there being plant-accessible Zn stores in the soil, thus breeding and agronomic biofortification strategies are likely to be complementary.

Fielder et al. (2013) estimated that fortifying maize meal with a premix containing Zn at large-scale mills in Zambia could save 5,657 DALYs annually of which 1,757 were due to Zn deficiency, at a cost of US$ 401 *per* DALY saved. The cost *per* DALY saved is favourable compared to application of Zn *via* the soil and equivalent or slightly more expensive than *via* foliar spray, although it should be noted that this is not a direct comparison as the premix also contained iron and vitamin A. Flour fortification during milling currently has limited reach in Zambia as few households purchase maize flour from large, centralised milling factories and those that do are generally wealthier with greater baseline Zn intakes (Fielder et al. 2013). Thus, while application of Zn to crops *via* the soil is approximately 10-fold more expensive than *via* foliar sprays or fortification of flour at centralised mills, it has the potential to reach more households and consequently be more equitable in outcome.

In the studies reviewed here, median Zn concentrations in grain from control plots were 19.0 (Q1 = 15.4, Q3 = 22.0, n = 7) and 15.8 (Q1 = 9.8, Q3 = 25.2, n = 141) mg kg^{-1} for whole maize and wheat grains, respectively, and 18.8 (Q1 = 15.2, Q3 = 23.9, n = 6) and 18.8 (Q1 = 13.4, Q3 = 27.6, n = 44) mg kg^{-1} for polished and brown rice, respectively. That there was no difference in median Zn concentration between polished and brown rice samples across studies is surprising and cannot be explained with the available data. If brown and polished rice are considered together and median increases found in reviewed studies are applied, Zn concentrations of 23.4, 16.9 and 22.4 mg kg^{-1} in maize, rice and wheat appear achievable using soil-applied Zn, and 24.7, 19.8 and 30.6 mg kg^{-1} using foliar-applied Zn. Even with 100 % coverage of soil or foliar-applied Zn, these concentrations are well below the H+ breeding targets (Figure 1; White and Broadley 2009; Bouis and Welch 2010). Thus, while agronomic biofortification of staple grains with Zn may be a useful strategy to mitigate inadequate dietary Zn supplies, the elimination of Zn deficiency will require complementary approaches including crop breeding, dietary diversification and possibly fortification during processing. If synergies can be exploited when pursuing such a combined approach, the cost-effectiveness of these interventions might also improve.

Zinc is just one of a number of micronutrients with widespread risk of deficiency in sub-Saharan Africa. For example, in Malawi, approximately 80 % of the population is at risk of selenium (Se) deficiency due to low concentrations of Se in edible portions of crops grown on low-pH soils (Chilimba et al. 2011; Hurst et al. 2013; Joy et al. 2015). Adding Se to the staple crop maize *via* subsidised fertiliser could supply adequate amounts of Se in the diets of the *ca.* 1.5 million households who benefit from the Malawi government Fertiliser Input Subsidy Scheme, at a total cost of 250-550 US$ k yr^{-1} (Chilimba et al. 2012). This is approximately 50-fold cheaper than scenario one in the present study, at US$ 0.016-0.035 $capita^{-1}$ yr^{-1} compared to US$ 1.08 $capita^{-1}$ yr^{-1}, assuming that costs are spread equally across the national population. However, unlike for Zn, the disease burden of Se deficiency has not yet been quantified so cost *per* DALY saved cannot be estimated using the same frameworks. Agronomic fortification *via* soil-applied fertiliser requires only 5 g ha^{-1} yr^{-1} of Se compared to *ca.* 10-25 and 1-4 kg ha^{-1} yr^{-1} of Zn *via* soil and foliar application methods, respectively. Thus, although the unit cost of Se is greater than that of Zn, fortification with Zn is more expensive. However, combining multiple elements such as Zn and Se in granular or foliar fertilisers could deliver wider health benefits and improve the cost-effectiveness of agronomic biofortification strategies.

Conclusions

Agronomic biofortification of crops with elements important for human health has been advocated as a public health strategy to address mineral element deficiencies in humans that can have severe consequences for the well-being of individuals and the welfare of affected societies. We systematically reviewed the literature for studies of the impact of Zn fertiliser on Zn and PA concentrations in the grains of maize, rice and wheat. In a simplified meta-analysis, the median effects of soil-applied Zn on the concentration of Zn in the grains of maize, rice and wheat were 23, 7 and 19 % increases above the control, respectively, while the corresponding figures for foliar applied Zn were 30, 25 and 63 %.

We focused on 10 countries in sub-Saharan Africa that currently implement fertiliser subsidy schemes or have strong governmental control over fertiliser imports and therefore have the necessary leverage to implement and enforce Zn enrichment of granular fertiliser. For the nine countries with the necessary data available, enriching subsidised fertiliser with Zn could save a total of 63 k DALYs yr^{-1} lost due to Zn deficiency with cost effectiveness ranging from US$ 624 to 5,747 $DALY^{-1}$ saved. Enriching subsidised and non-subsidised fertilisers in the eight countries with necessary data could save a total of 83 k DALYs yr^{-1} with cost effectiveness ranging from US$ 977 to 5,893 $DALY^{-1}$. Foliar sprays may be a more cost-effective approach, saving 375 k and 523 k DALYs yr^{-1} for 50 and 75 % coverage of cereals, respectively, at a cost of US$ 46 to 347 $DALY^{-1}$ although it is likely that there would be significant administrative costs in implementing such a programme and these costs were not considered here.

Cost-effectiveness of the fertiliser approach varies and, if compared against international cost-effectiveness benchmarks, these results indicate that adoption of a fertiliser approach needs to be assessed on a case-by-case basis to allow decision-makers to optimise the allocation of scarce resources to alternative and complementary public health interventions. Generally, the cost-effectiveness of foliar-applied Zn appears to be equivalent to fortification of staple flours at centralised milling facilities. Soil-applied Zn appears to be more expensive but has the potential advantage of reaching more households. Moreover, synergies might be realised if agronomic (fertilisation) and genetic (breeding) biofortification efforts are combined, potentially improving both impact and cost-effectiveness of these interventions.

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table

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Table 1 Summary of studies included in the meta-analysis. Application methods of zinc (Zn) are soil (S) or foliar (F). ‘n’ is the number of data points contributing to the meta-analysis in which individual studies were stratified by crop, cultivar, location and Zn application rate and pooled by application method

Crop	Varieties	Application *via* (n)	Country	Reference
Wheat		S (4)	Pakistan	Abid et al. 2013
Wheat	Bread and durum	S (1), F (3)	Turkey	Cakmak et al. 2010
Wheat		S (12)	Turkey	Ekiz et al. 1998
Wheat	20 cultivars	S (20)	Turkey	Erdal et al. 2002
Wheat	2 Zn-deficiency tolerant cultivars	F (2)	Iran	Ghasemi et al. 2013
Maize		S (2)	Pakistan	Harris et al. 2007
Maize	2 cultivars	S (6)	Pakistan	Kanwal et al. 2010
Wheat	30 cultivars	S (60)	Iran	Khoshgoftarmanesh et al. 2012
Wheat		S (1)	China	Lu et al. 2011
Wheat	2 winter wheat cultivars	S (8)	China	Lu et al. 2012
Rice	10 biofortification breeding line genotypes	F (19)	Philippines	Mabesa et al. 2013
Maize		S (1)	Zambia	Manzeke et al. 2014
Maize		S (2)	Spain	Martín-Ortiz et al. 2009
Rice	Cultivars commonly used	S (10), F (10)	China, India, Lao PDR, Thailand, Turkey	Phattarakul et al. 2012
Rice		S (4)	India	Shivay et al. 2008
Rice		S (1)	India	Srivastava et al. 2009
Maize, wheat		S (1,1), F (1,1)	China	Wang et al. 2012
Rice	3 cultivars	F (3)	China	Wei et al. 2012
Rice	5 ‘high-’;5 ‘low-’ Zn genotypes	S (15)	Philippines	Wissuwa et al. 2008
Wheat	10 cultivars	S (15), F (6)	China	Yang et al. 2011a
Wheat		F (1)	China	Yang et al. 2011b
Wheat	3 bread, 1 durum	S (4), F (4)	Turkey	Yilmaz et al. 1997
Wheat	Common cultivars	S (1), F (7)	China	Zhang et al. 2012
Wheat		S (4)	China	Zhao et al. 2011
Wheat	5 cultivars. (Results not presented by cultivar)	S (1), F (1)	China	Zhao et al. 2014
Wheat	11 cultivars	S (14), F (13)	China, India, Kazakhstan, Mexico, Pakistan, Turkey, Zambia	Zou et al. 2012

Table 2 Baseline national-level estimates of zinc (Zn) deficiency and associated disease burden in comparison to published studies for the 10 focus countries of this review

Country	**Estimated risk of inadequate Zn supply**			**Stunting**	**DALYs lost due to Zn deficiency**
	% total population			% children 0-59 months	100 k population^{-1}
	Rank of country for each study in (brackets)				
	Present study	Wessells & Brown (2012)	Joy et al. (2014)	UNICEF (2013)	IHME (2014)
Reference year	2009	2003-7	2009	2007-11	2012
Burkina Faso	49.6 (3)	39.4 (3)	5.5 (9)	35 (7)	1,219 (1)
Ethiopia	31.6 (6)	11.0 (10)	81.5 (1)	44 (3)	344 (7)
Ghana	27.1 (7)	21.6 (8)	36.4 (5)	28 (9)	161 (10)
Kenya	27.0 (8)	25.3 (5)	60.6 (4)	35 (7)	281 (9)
Malawi	54.8 (2)	40.6 (2)	32.8 (6)	47 (1)	769 (2)
Mali	25.5 (9)	22.3 (7)	5.2 (10)	38 (6)	448 (5)
Nigeria	24.1 (10)	20.6 (9)	8.7 (8)	41 (5)	408 (6)
Senegal	36.0 (5)	24.6 (6)	11.7 (7)	27 (10)	489 (4)
Tanzania	41.1 (4)	34.1 (4)	64.4 (3)	42 (4)	341 (8)
Zambia	65.7 (1)	44.9 (1)	72.4 (2)	45 (2)	665 (3)

Table 3 Summary of baseline soil properties and zinc (Zn) application rates in maize, rice and wheat crops . 'n' is the number of data points contributing to the meta-analysis in which individual studies were stratified by crop, cultivar, location and Zn application rate and pooled by application method. Q1 and Q3 are first and third quartiles, respectively

Crop	**Method**	**Baseline soil properties**												**Zn application rate**					
		DTPA-extractable Zn						pH (H_2O)											
		n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
			mg kg^{-1}												kg ha^{-1}				
Maize[†]	Soil	11	0.69	0.12	0.68	0.72	0.72	11	8.05	0.11	7.98	7.98	8.20	12	15.72	18.75	3.44	8.50	18.00
Rice		29	1.75	1.52	0.79	0.97	2.70	30	6.89	1.13	5.70	6.85	7.80	30	11.77	4.18	11.00	13.00	15.00
Wheat		158	0.82	0.79	0.10	0.67	1.00	137	7.73	0.32	7.55	7.80	7.98	158	25.36	13.55	11.00	23.00	50.00
Maize	Foliar	1	0.56	*	*	0.56	*	1	8.24	*	*	8.24	*	1	0.91	*	*	0.91	*
Rice		33	1.30	1.74	0.28	0.36	2.10	34	6.59	0.76	6.35	6.40	6.95	34	3.18	1.51	1.25	4.00	4.00
Wheat		38	0.80	1.13	0.32	0.52	0.71	37	7.69	0.50	7.53	7.80	7.98	38	1.62	0.73	1.29	1.59	1.63

[†] Manzeke et al. (2014) measured pH in $CaCl_2$ and extractable Zn using EDTA so these data were excluded

Table 4 Summary of the effects of zinc (Zn)-enriched fertiliser on Zn and PA concentration in the grain of maize, rice and wheat. 'n' is the number of data points contributing to the meta-analysis in which individual studies were stratified by crop, cultivar, location and Zn application rate and pooled by application method. Q1 and Q3 = first and third quartiles, respectively

Crop	**Application *via***	**n**	**Mean**	**SD**	**Min**	**Q1**	**Median**	**Q3**	**Max**
			Zn concentration in the grain, % of control						
Maize	Soil	12	128	18	106	114	123	139	173
Rice		30	111	15	84	102	107	119	157
Wheat		158	143	57	51	105	119	174	373
Maize	Foliar	1	130	*	130	-	130	-	130
Rice		34	127	19	107	114	125	140	172
Wheat		38	178	55	112	143	163	203	333
			PA concentration in the grain, % of control						
Maize	Soil	3	96	7	7	92	93	104	104
Wheat		26	91	15	65	83	89	98	121
Rice	Foliar	3	86	1	85	85	87	87	87
Wheat		15	97	10	82	89	99	102	121
			Yield, % of control						
Maize	Soil	12	110	10	95	100	111	120	125
Rice		15	111	8	102	103	111	117	129
Wheat		47	188	246	90	99	110	129	1,607
Maize	Foliar	1	98	*	98	*	98	*	98
Rice		15	100	7	84	98	102	104	109
Wheat		32	142	173	77	99	102	111	1,071

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Table 5 Effect of different zinc (Zn) fertilisation scenarios on dietary Zn and phytate supplies and estimated risk of Zn deficiency in 10 example countries in sub-Saharan Africa. Scenario '0' is baseline; 1 and 2 model enrichment of granular fertilisers, either subsidised or subsidised and non-subsidised; 3 and 4 model application of foliar Zn sprays to 50 and 75 % of target crops. Scenarios that are cost-effective in comparison to WHO (*) or World Bank and WHO (**) benchmarks are highlighted

Country	Scenario	Dietary Zn supply	Dietary phytate supply	Zn deficiency risk	DALYs lost due to Zn deficiency	Programme cost	Cost *per* DALY saved
		mg *capita*$^{-1}$ d^{-1}		%	100 k population^{-1}	US$ '000s yr^{-1}	US$ yr^{-1}
Burkina Faso	0	11.2	3,617	49.6	1288		
	1	11.2	3,615	49.4	1282	584	624*
	2	-	-	-	-	-	-
	3	11.7	3,606	43.3	1123	1,267	49**
	4	12.0	3,601	40.4	1048	1,900	51**
Ethiopia	0	8.2	1,830	31.6	329		
	1	8.4	1,818	28.9	300	31,983	1,302*
	2	-	-	-	-	-	-
	3	9.5	1,821	18.7	195	11,392	98**
	4	10.2	1,816	14.6	152	17,089	111**
Ghana	0	8.0	1,371	27.1	162		
	1	8.0	1,370	26.7	160	2,791	5,747
	2	8.1	1,366	25.8	155	10,640	5,893
	3	8.4	1,358	22.7	136	2,088	332*
	4	8.6	1,351	20.9	125	3,133	347*
Kenya	0	8.9	1,858	27.0	280		
	1	8.9	1,851	26.2	272	6,021	1,830*
	2	9.2	1,822	23.4	242	29,583	1,932*
	3	9.5	1,851	21.4	222	3,811	162**
	4	9.8	1,847	19.2	199	5,716	172**
Malawi	0	8.9	2,700	54.8	768		
	1	9.2	2,663	49.6	695	15,675	1,431
	2	9.3	2,641	46.6	653	25,115	1,456
	3	9.7	2,696	43.5	610	3,132	132**
	4	10.1	2,694	38.7	542	4,698	138**
Mali	0	11.9	2,795	25.5	495		
	1	-	-	-	-	-	-
	2	12.0	2,787	24.8	482	6,324	3,428
	3	12.4	2,769	21.5	419	2,072	194**
	4	12.7	2,756	19.8	385	3,108	203**

Nigeria	0	8.6	1,751	24.1	406		
	1	8.7	1,749	23.6	397	20,791	1,593
	2	8.7	1,745	23.0	388	45,002	1,613
	3	9.1	1,737	20.0	337	9,790	89**
	4	9.3	1,729	18.2	307	14,685	94**
Senegal	0	8.4	1,820	36.0	471		
	1	8.4	1,816	35.2	461	1,261	964*
	2	8.5	1,810	34.2	447	3,027	977*
	3	9.0	1,786	27.6	362	656	46**
	4	9.3	1,769	24.2	317	984	49**
Tanzania	0	8.0	2,037	41.1	341		
	1	8.4	2,033	40.4	335	9,630	3,547
	2	8.5	2,028	39.6	328	19,813	3,573
	3	9.0	2,026	33.8	280	7,323	267*
	4	8.8	2,021	30.6	253	10,985	279*
Zambia	0	7.1	2,100	65.7	664		
	1	7.3	2,076	61.3	620	7,222	1,237*
	2	7.4	2,059	58.2	589	12,358	1,244*
	3	7.8	2,097	53.1	537	1,817	108**
	4	8.1	2,095	47.4	480	2,726	112**

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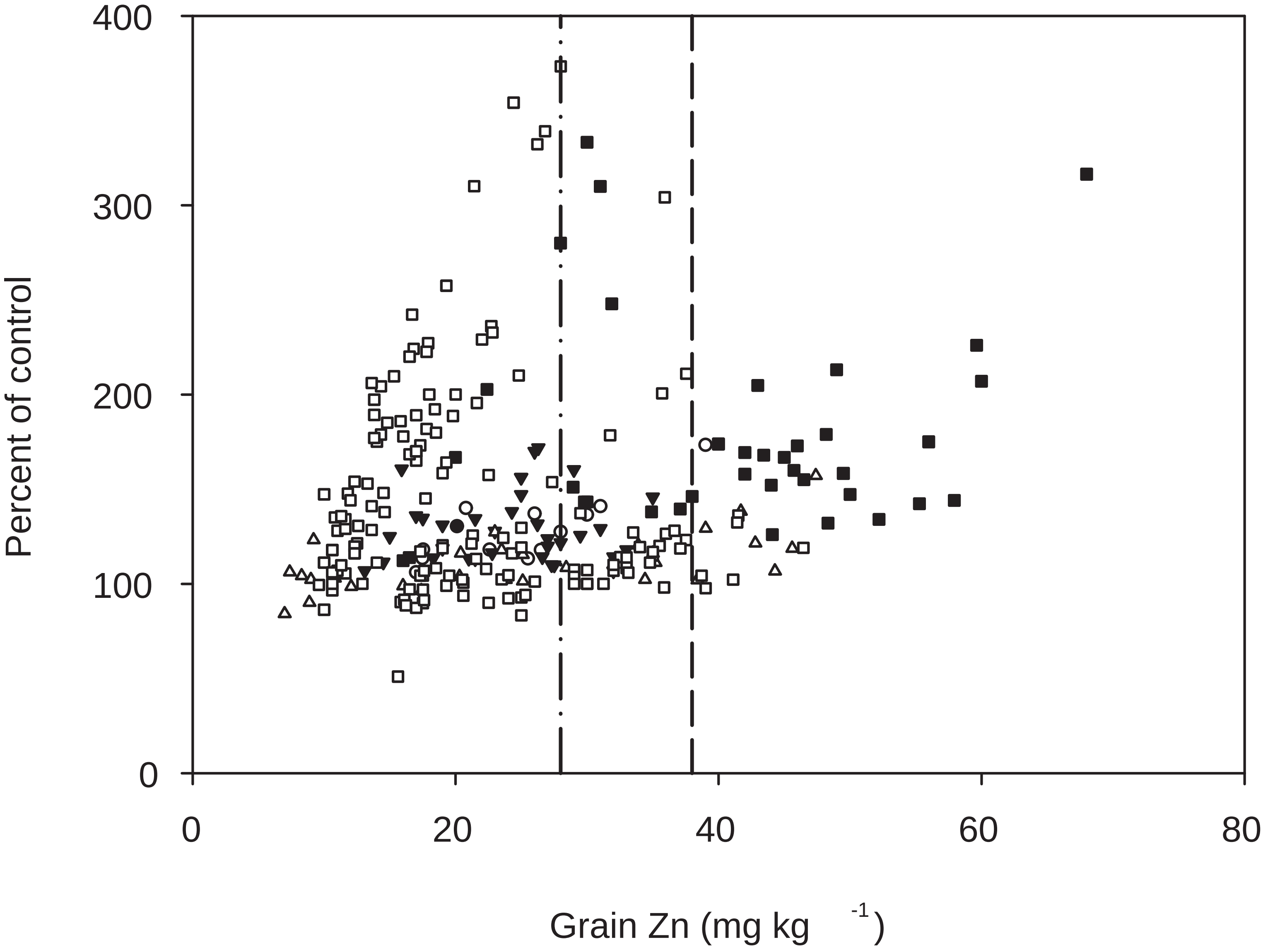

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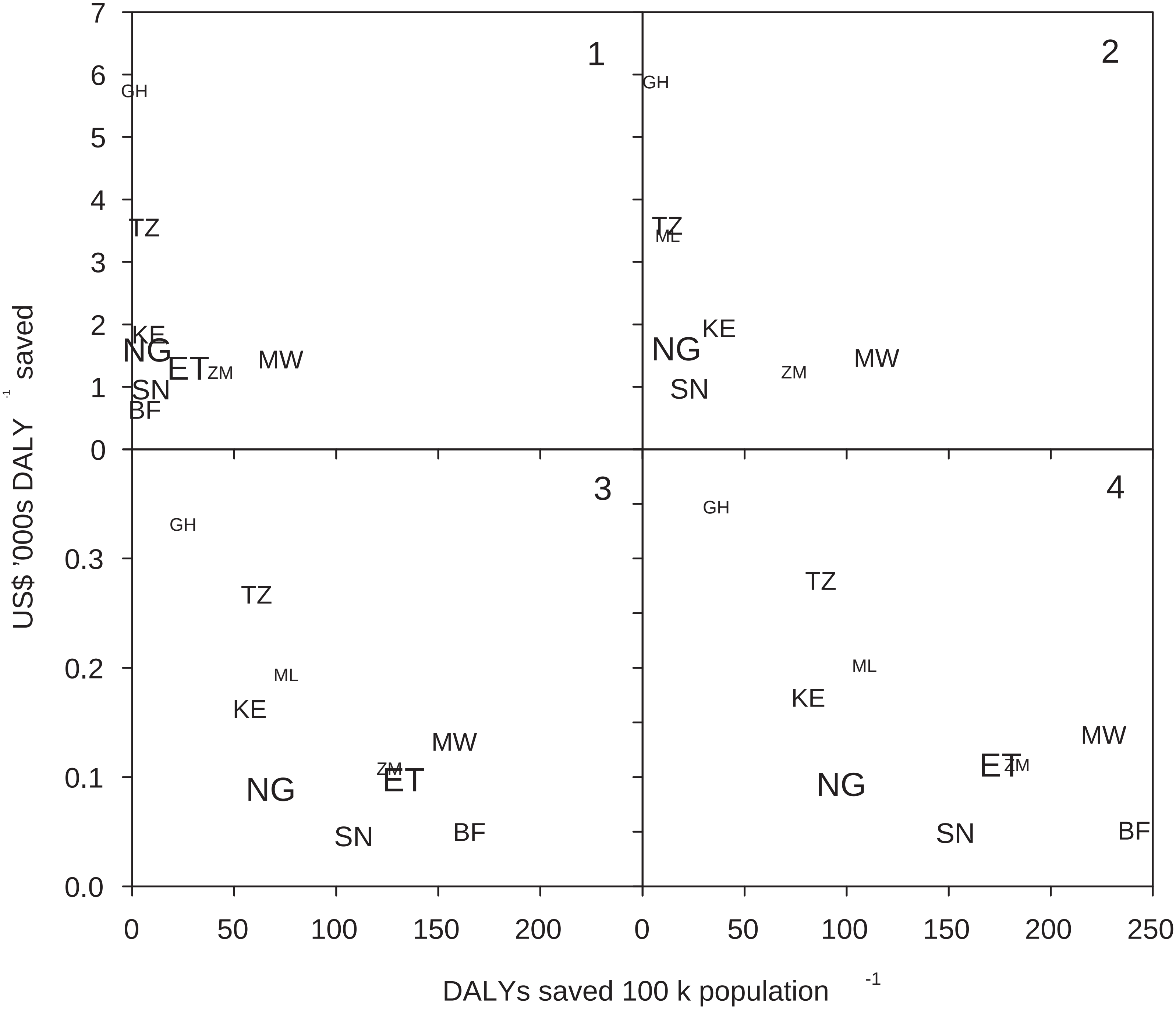

Fig 1 Concentration of zinc (Zn) in the grains of maize (circles), rice (triangles) and wheat (squares) following Zn application *via* soil (open) or foliage (filled). Y-axis represents the concentration as a percentage of control. Vertical lines mark Harvest Plus breeding targets for maize and wheat (dashed) and rice (dash-dot)

Fig 2 Impact and cost-effectiveness of four zinc (Zn) fertilisation scenarios in 10 countries in sub-Saharan Africa: Burkina Faso (BF), Ethiopia (ET), Ghana (GH), Kenya (KE), Malawi (MW), Mali (ML), Nigeria (NG), Senegal (SN), Tanzania (TZ) and Zambia (ZM). Impact is defined as the reduction in disease burden attributable to Zn deficiency and is quantified in disability-adjusted life-years (DALYs; Supplementary Table 10). Cost-effectiveness is quantified in US$ *per* DALY saved (Supplementary Table 11). Scenario 1 models enrichment of subsidised granular fertilisers; Scenario 2 models enrichment of subsidised and non-subsidised granular fertilisers; Scenarios 3 and 4 model foliar application of Zn to 50 and 75 % of cereals, respectively. Not all countries are represented in Scenarios 1 and 2 due to lack of data. The text size represents the absolute number of DALYs saved annually (highly dependent on the country’s population size): from smallest to largest, <25,000, 25-50,000, 50-75,000 and 75,000+