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INVITED REVIEW

# Zinc deficiency in low- and middle-income countries: prevalence and approaches for mitigation

S. Gupta, A. K. M. Brazier & N. M. Lowe

Lancashire Research Centre for Global Development, University of Central Lancashire, Preston, UK

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**Correspondence**
N. M. Lowe, Nutritional Sciences, Lancashire Research Centre for Global Development, Faculty of Health and Wellbeing, 230 Darwin Building, University of Central Lancashire, Preston, UK PR1 2HE.
Tel: +44 (0)1772 893599
Fax: +44 (0)1772 892929
E-mail: nmlowe@uclan.ac.uk

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## Abstract

This review addresses the prevalence of zinc deficiency in Low- and Middle-income Countries (LMICs) and assesses the available strategies for its alleviation. The paucity of national-level data on the zinc deficiency in LMICs is partially a result of the lack of a reliable biomarker. Zinc deficiency appears to be a public health problem in almost all the LMICs, irrespective of the recommended indicators (plasma zinc concentration, dietary zinc adequacy and stunting prevalence) used. Based on plasma/serum zinc concentration (PZC), which is the most appropriate indicator at present, the prevalence of zinc deficiency in LMICs is of concern. Among the 25 countries for which national PZC data were available, 23 had a zinc deficiency prevalence of >20% for at least one physiological group. Zinc supplementation is largely restricted as an adjunct therapy for diarrhoea management in children, and the best platform and the most effective way of preventive zinc supplementation delivery remains to be established. Impact assessment for current zinc fortification programmes in LMICs and the effectiveness of zinc supplementation as part of a multi-micronutrient powder is to be determined. Dietary diversification, though promising for LMICs, is in the nascent stages of development at present. Inclusion of meat and animal products can be an important way of improving zinc status. Programmatic experience with the promotion of home processing techniques to increase absorbable zinc in the diet is lacking. Conventional biofortification techniques are gaining recognition in LMICs; however, transgenic biofortification as a strategy remains controversial.

## Introduction

Zinc is ubiquitous to all biological systems and plays an exceptionally versatile role. Participation of zinc in various vital functions at cellular and subcellular levels can be classified under catalytic, structural and regulatory roles[1], which are attributable to its physicochemical properties, including redox-inertness, as well as a flexible and dynamic coordination geometry[2]. Zinc is a component of more than 300 enzymes and numerous other proteins, and plays multiple roles in optimal nucleic acid and protein metabolism, cell growth and differentiation[3,4]. It is also involved in cell-mediated immunity[5,6]. The universal involvement of zinc in all life processes makes it essential for human health and wellbeing. Functional consequences of zinc deficiency are well known and encompass compromised physical growth, immune competence, reproductive function and neurobehavioural development (although the exact mechanisms are not yet fully elucidated)[7]. These functional consequences have the greatest impact in settings with low intakes of absorbable zinc, such as in low- and middle-income countries (LMICs), where they are associated with impaired childhood growth, increased child morbidity and mortality, and adverse maternal health and pregnancy outcomes. Supplementation with zinc in populations at-risk of deficiency have shown a reduction in the incidence of premature delivery, decreased morbidity from diarrhoea and acute lower respiratory tract infection, reduced duration and severity of diarrhoeal episodes, and improved linear growth and weight gain in children less than 5 years of age[8,9,10,11,12,13]. Despite the known detrimental consequences of zinc deficiency and recognised benefits of supplementation in zinc-deficient populations, there have been limited attempts to specifically map the prevalence and severity of deficiency, particularly in LMICs, at a national level to help the development and evaluation of zinc intervention programmes. This could partly be a result of the high financial burden, operational challenges and the lack of a robust biomarker.

Recommended indicators for the estimation of the prevalence of zinc deficiency in a population are: (i) plasma or serum zinc concentration (referred to henceforth as PZC) in a representative sample of all relevant subpopulation groups; or (ii) assessment of intake by employing 24-h dietary recall or other locally validated quantitative dietary assessment methods. Ideally both the above approaches should be used together to derive reliable conclusions [7,14]. However, because of paucity of such data, proxy indicators (such as stunting among children <5 years of age and dietary zinc intake using national food balance sheets) have been suggested for the assessment of at-risk populations and to initiate programme planning for zinc interventions [3,7,14,15,16]. The suggestive evidence indicates that zinc deficiency is widespread in LMICs and it is estimated to cause substantial morbidity and mortality among children. Approximately 4.4% of childhood deaths could be prevented by addressing zinc nutrition alone [17].

This aim of this review is to reflect on the prevalence of zinc deficiency in LMICs using suggestive evidence, as well as reports from the countries that have recently incorporated assessment of zinc status into their periodic nutrition monitoring programmes/surveys, and presenting data from observational studies or trials where zinc assessment was carried out specifically. This review further examines various ongoing as well as possible intervention strategies to address zinc deficiency in LMICs.

## Causes of zinc deficiency

The main causes of zinc deficiency include insufficient intake, increased requirements, malabsorption, increased losses and impaired utilisation [18]. Inadequate intake of zinc is considered to be one of the most significant determinants for the development of zinc deficiency [14]. A daily adequate intake is essential because the body has no specialised storage system for zinc. However, millions of people in LMICs have inadequate levels of zinc in the diet as a result of limited access to foods that are rich in zinc, such as animal products, oysters and shellfish, because of economic, cultural and/or religious reasons [19]. Plant-based sources of zinc include wholegrains, nuts and beans. However, zinc assimilation in such sources depends on the soil zinc content. Beside the intake, the absorption of zinc from the diet is another important factor that needs to be considered. Bioavailability of zinc is known to be greatly influenced by the presence of several inhibitors, including phytic acid, calcium and perhaps polyphenols [20,21,22]. If diets are rich in inhibitors (as is the case with plant-based diets), even at the acceptable intake levels of zinc, the absorption may be insufficient. Phytate is accepted as the most potent inhibitor of zinc absorption and a meta-analysis of 30 studies by Bel-Serrat *et al.* [23] revealed an overall lowering of fractional zinc absorption by 45% of the control values when the phytate: zinc molar ratio of the test meal or diet was greater than 15. Phytic acid forms an insoluble complex with zinc in the small intestine, rendering it unavailable for absorption from cereal-pulse-based phytate rich diets. [3,19,20]. Calculation of zinc bioavailability from diets is a challenge mainly because (i) there are constraints to conducting large-scale dietary assessments in LMICs such as cost, time burden, technical difficulty and restricted investment in dietary research infrastructure, including the necessary tools and databases required to collect individual-level dietary data in large surveys (ii) even when dietary intake data are available, information on zinc content and its bioavailability in local foods is fragmentary.

Zinc requirement is often exacerbated by physiological conditions such as during pregnancy and periods of rapid growth, which may precipitate overt zinc deficiency especially when the zinc intake is marginal [18]. Conditions that impair intestinal integrity not only reduce absorption, but also result in increased endogenous losses of zinc, particularly in the presence of marginal dietary intakes [24].

Faecal excretion of zinc has been shown to increase during acute diarrhoea; however, there is a lack of clarity on the contribution to this loss from unabsorbed dietary zinc and endogenous zinc. Because zinc deficiency increases the susceptibility to childhood diarrhoea and diarrhoeal diseases are common in LMICs, such an infection may further deplete the body zinc and trap the child in a vicious cycle of zinc malnutrition.

## Prevalence of zinc deficiency

Recommended indicators for estimating zinc deficiency at a community or population level are: (i) percentage of population with PZC below an appropriate cut-off; (ii) prevalence of dietary intake of zinc below the estimated average requirement; and (iii) percentage of children <5 years of age with height-for-age *Z* scores below −2 SD of the World Health Organization (WHO) reference as a proxy [14]. Because the data on PZC zinc and 24 h recall for assessment of dietary zinc intake are rarely available for LMICs, investigations using the amount of absorbable zinc from national food supplies have been recommended to evaluate the prevalence of zinc deficiency. Apart from PZC, the analyses/studies using proxy indicators, such as height- for- age (only for under 5-year-olds) and dietary intake of zinc using national food balance sheets (FBS) were also considered for this review. The two proxies (absorbable zinc from national food supplies and stunting), if used synergistically or in combination with PZC, appear to be of value until specific assessments are undertaken.

Walker *et al.* [17] showed that zinc deficiency results in a sizable disease burden among children less than 5 years of age, who are predominantly affected by diarrhoea, malaria and pneumonia. In three regions of the world (Latin America, Africa and Asia), they reported that zinc deficiency was responsible for up to 453 207 deaths (4.4% childhood death) and 1.2% of the burden of disease (3.8% in children 6 months to 5 years). This amounts to over 16 million disability-adjusted life years (DALY). Africa had the highest prevalence of zinc deficiency, followed by Asia and Latin America. In India, Nigeria, Democratic Republic of Congo, Ethiopia and Afghanistan, zinc deficiency accounted for 47% of all deaths. Globally, diarrhoea was responsible for approximately half of deaths related to zinc deficiency, and thus is a leading cause of zinc-deficient deaths in each region/subregion. For the above analysis, prevalence of zinc deficiency among children under 5 years of age was assessed using stunting rates and the risk of inadequate zinc intake based on the estimated absorbable zinc in the diet. The fraction of disease-specific morbidity and mortality attributable to zinc deficiency was then estimated based on reductions in both morbidity and mortality as observed from randomised controlled supplementation trials. Finally, the attributable fraction was applied to the earlier estimates for disease-specific deaths and DALYs among children aged 1–59 months to generate an estimate of the total number of deaths and DALYs that could be prevented if zinc deficiency were eliminated in the age group of 6–59 months.

An analysis by Wessells and Brown [16] aimed to estimate global and regional prevalence of zinc deficiency by exploiting two proxies: zinc availability in national food supplies and the prevalence of stunting among children. This combination of the indicators was assumed to be complementary because the national food balance sheets are expected to represent food intake by adults, whereas stunting can be an indirect indicator for risk of deficiency among children. Based on the zinc intake data, approximately 17–29.6% of the population in South and South-East Asia, Sub-Saharan Africa and Central America were at the risk of inadequate zinc intake. The risk was highest (>25%) for south Asia and Sub-Saharan Africa. Country-wise estimated risk of inadequate zinc intake was found to decrease significantly with increasing energy content ($r = -0.62$; $P < 0.01$), zinc content ($r = -0.60$; $P < 0.01$) and percentage of zinc obtained from animal food ($r = -0.90$; $P < 0.01$) which is also a rich source of zinc with no inhibitory phytate. The total dietary phytate and phytate:zinc molar ratio positively correlated ($r = 0.03$ and 0.92, respectively, $P < 0.01$) with the zinc inadequacy. Stunting in children <5 years significantly correlated with the estimated prevalence of inadequate zinc intake ($r = 0.48$, $P < 0.001$), although there was much variance around the best fit line. Approximately 60% (84 of 114) of LMICs had a stunting prevalence of >20% and 32 of the countries were classed as being at high risk of inadequate zinc intake when the composite index (prevalence of stunting >20% and prevalence of inadequate zinc intake >25%) of both indicators was used. A suggested explaination for this discrepancy was that the high prevalence of zinc deficiency using stunting as an indicator was the result of a high requirement and rate of infection among children living in the LMICs.

The major limitation of two above mentioned studies is the use of stunting rates for estimating zinc deficiency. Because stunting is also caused by factors other than zinc deficiency, it is therefore assumed to overestimate the zinc deficiency prevalence. However, an assessment of zinc deficiency based on PZCs from 19 national-level surveys and its comparison with stunting and FBS methods concluded that the stunting prevalence is a better proxy because the two indicators (i.e. plasma zinc and stunting) resulted in similar categorisation of countries into high versus low risk groups, with a few exceptions, whereas the FBS underestimated the prevalence [25]. Although plasma zinc may not be always reliable for making individual diagnoses, it has been recommended as an indicator of population zinc status and can be used to assess the impact of supplementation programmes at the population level because PZCs normally respond to zinc supplementation, especially in individuals with a low, or moderately low baseline [14,26]. Low plasma zinc prevalence in LMICs for various physiological groups (cut-offs used by each country for defining zinc deficiency based on low plasma zinc prevalence are included in Table 1), updated in the light of recent national surveys, is presented in Table 1. Plasma zinc data were available for only 25 LMICs, with a focus on women of reproductive age and children. Surveys from these countries (other than Fiji) invariably included an assessment of PZC among young children (<5 years of age) and a few countrywide surveys also covered older children in the age range 5–14 years. The prevalence of low plasma zinc was >20% for children from all the countries except Azerbaijan, Afghanistan, China, India, Iran, Maldives and Sri-Lanka. Nigeria was at borderline risk with approximately 20% of young children with serum zinc concentration below the defined cut-offs. However, the cut-offs used by Afghanistan, Pakistan and Maldives for defining low PZC were lower, and, for Nigeria, these cut-offs were higher than the International Zinc Nutrition Consultative Group (IZiNCG) cut-off (65 μg $dL^{-1}$) that has been used by most countries. Therefore, it is possible that the prevalence in Afghanistan, Pakistan and Maldives has been underestimated.

Out of the 25 countries for which PZC data were disaggregated by physiological groups, 18 countries reported PZC for women of reproductive age. Irrespective of the physiological status, these women were at a high risk of zinc deficiency in all the countries (except Fiji). The prevalence of low PZC ranged from 23% in Afghanistan to as high as 82% in Cameroon. A prevalence of 50% or more was common in approximately half of the countries for which the data on PZC were available for women. PZC among adolescents were available for only five countries and varied considerably (11% for Iran; 27–32 % for India, Mexico and Philippines; 68% for Malawi). Surprisingly, the prevalence of low PZC in men (reported by four countries) was approximately 66%, 77%, 42.6% and 31% for Malawi, Kenya, Mexico and Philippines, respectively. This zinc deficiency prevalence rate was comparable with that of women. The high prevalence found in men, along with gender-disaggregated data for adolescent groups, suggests that zinc deficiency is not limited to children and women of reproductive age. However, in contrast to women and children, there is a paucity of evidence relating zinc deficiency to health outcomes in adult men. Studies understanding the consequences of zinc deficiency and assessment of prevalence in males are warranted.

The prevalence of zinc deficiency appears to be further augmented by the economic status. A much higher estimate (43.8%) of low plasma zinc prevalence among children belonging to low socio-economic index was reported in study ($n$ = 1655) from five provinces in India [27] as compared to the findings from national survey (20%). The national survey from India reported a prevalence difference of 4% among the poorest (20%) and richest (16%) households. Similarly, the surveys from Nepal, Sri-Lanka and Cameroon reported zinc deficiency to be associated with low socio-economic status. A recent study using the secondary data from 2010 Colombian National Nutrition Survey for children aged between 12 and 59 months found that zinc deficiency is associated with household income [very poor, odds ratio (OR) = 1.48; poor OR = 1.39] food security (OR = 0.75) and enrolment in nutritional support programmes (OR = 0.76) [28].

The prevalence of low PZC for various countries by rural or urban residence is presented in Fig. 1. Overall, a greater % prevalence of low PZC was observed in rural households across all the population groups, except for a few groups which include- children from Pakistan (5–59 months), Malawi (6–14 years) and Mexico (1–11 years); Indian and Irani adolescents; women from Kenya, Malawi and Iran, as well as Mexican adults. It was interesting to observe a distinct opposite trend for Malawi, non-pregnant females, who had a prevalence of 85% among urban compared to 60% in the rural area. Also, there were regional variations in low PZC prevalence among various countries. These differences were greatest for India, with a low of 1% in Nagaland to a high of 41% in Himachal Pradesh among children aged 1–4 years[29]. Among children aged 5–9 years, zinc deficiency ranged from 2% in Nagaland to 38% in Himachal Pradesh and, among adolescents aged 10–19 years, from 4% in Nagaland to 55% in Gujarat. In Nigeria, the prevalence of zinc deficiency among women and children in Kwara state (highest prevalence) was 54–70% higher with respect to Osun or Edo (lowest prevalence) [30]. Engle-stone *et al.* [31] reported that living in the northern region, and in rural areas are risk factors for low PZC among children and women in Cameroon. It could be worthwhile analysing such data aiming to determine whether the composition of the diet can explain this or whether there are additional factors influencing the prevalence. Understanding these factors may help to inform the development of nutritional programmes to address zinc deficiency in the local regions.

Zinc deficiency is expected to co-exist with iron deficiency in LMICs because of an overlap of food sources and dietary factors inhibiting or facilitating the absorption of the two nutrients. A very recent cross-sectional study among children from Guatemala reported that 56% of infants and toddlers (<24 months) were anaemic, in contrast to 12% of anaemia prevalence in the preschool group (36–60 months) [32]. Iron and zinc deficiencies were high in these anaemic infants and toddlers. The odds of being anaemic were 3.4 times higher among the infants and toddlers who were zinc deficient (PZC) compared to those who were not. Such an association between anaemia and zinc was not observed for the preschoolers. This indicates that multiple micronutrient deficiencies exist among younger children from rural south-west Guatemala who may have higher dietary

**Table 1** Prevalence of zinc deficiency in the Low- and Middle-income Countries based on assessment of plasma/serum zinc concentration in national surveys

| Country | Year of the survey | Children | | Women | | Adolescent | | Men | | Cut-offs used | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | sample | % Prevalence | sample | % Prevalence | sample | % Prevalence | sample | % Prevalence | | |
| Afghanistan | 2013 | 6–59 months (*n* = 950) | 15.1 | 15–49 years (*n* = 950) | 23.4 | – | – | – | – | <60 µg $dL^{-1}$ | (103) |
| Azerbaijan | 2013 | 6–59 months (*n* = 1040) | 10.7 | – | – | – | – | – | – | IZiNCG cut-offs† | (104) |
| Bangladesh | 2011–2012 | 6–59 months (*n* = 662) | 44.6 | 15–49 years, non-pregnant non-lactating (*n* = 1073) | 57.3 | – | – | – | – | IZiNCG cut-offs† | (105) |
| Cameroon | 2009 | 12–59 months (*n* = 845) | 82.6 | 15–49 years, (*n* = 879) | 81.6 | – | – | – | – | IZiNCG cut-offs† | (31) |
| China | 2013 | 36–72 months (*n* = 1483) | 4 | – | – | – | – | – | – | <70 µg $dL^{-1}$ | (25) |
| Colombia | 2008–2010 | 12–59 months (*n* = 4279) | 43 | – | – | – | – | – | – | IZiNCG cut-offs† | (25) |
| Cambodia | 2014 | 6–72 months (*n* = 656) | 67.5 | 15–49 years, non-pregnant (*n* = 720) | 62.8 | – | – | – | – | <65 µg $dL^{-1}$ | (106) |
| Ecuador | 2011–2012 | 12–59 years (*n* = 2045) | 28 | 12–49 years (*n* = 8186) | 56 | – | – | – | – | IZiNCG cut-offs† | (25) |
| Ethiopia | 2015 | 6–59 months (*n* = 1143) | 35 | 15–49 years, Non-pregnant (*n* = 1625) | 33.8 | – | – | – | – | < 70 µg $dL^{-1}$ | (107) |
| | | 5–14 years (*n* = 1569) | 35.8 | – | – | – | – | – | – | | |
| Fiji | 2010 | – | – | 15–45 years, Non-pregnant (*n* = 869) | 0 | – | – | – | – | IZiNCG cut-offs† | (108) |
| Guatemala | 2009–2010 | 12–59 months (*n* = 1196) | 35 | – | – | – | – | – | – | < 70 µg $dL^{-1}$ | (25) |
| India | 2016–2018 | 1–4 years (*n* = 8662) | 18.9 | – | – | Girls 10–19 years (*n* = 5737) | 28.4 | – | – | IZiNCG cut-offs† | (29) |
| | 2016–2018 | 5–9 years (*n* = 11 556) | 16.8 | – | – | Boys 10–19 years (*n* = 5638) | 35.1 | – | – | | |
| Iran | 2011–2015 | 15–23 months (*n* = 4372) | 19.1 | Only pregnant women (*n* = 4395) | 28 | Girls 14–20 years (*n* = 4685) | 13.3 | – | – | Pregnant women < 65 µg $dL^{-1}$; Other age groups < 70 µg $dL^{-1}$ | (109) |

**Table 1** Continued

| Country | Year of the survey | Children sample | Children % Prevalence | Women sample | Women % Prevalence | Adolescent sample | Adolescent % Prevalence | Men sample | Men % Prevalence | Cut-offs used | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2011–2015 | 6 years ($n$ = 4577) | 13.6 | – | – | Boys 14–20 years ($n$ = 4508) | 9.5 | – | – | | |
| Kenya | 2011 | 6–59 months ($n$ = 771) | 81.6 | 15–49 years non-pregnant women, ($n$ = 617) | 79.9 | – | – | – | – | IZiNCG cut-offs† | [110] |
| | 2011 | 5–14 years ($n$ = 901) | 79 | 15–49 years, pregnant women ($n$ = 109) | 67.9 | – | – | 15–54 years ($n$ = 239) | 77.4 | | |
| Malawi | 2015–2016 | 6–59 months ($n$ = 1086) | 60.4 | 15–49 years, non-pregnant women ($n$ = 757) | 62.5 | Girls 11–14 years ($n$ = 183) | 69 | 15–54 years ($n$ = 218) | 65.7 | IZiNCG cut-offs† | [111] |
| | 2015–2016 | 6–14 years ($n$ = 765) | 60.2 | – | – | Boys 11–14 years ($n$ = 162) | 66 | – | – | | |
| Maldives | 2007 | 6–59 months (1255) | 16 | 15–49 years ($n$ = 1282) | 27 | – | – | – | – | <60 μg $dL^{-1}$ | [25] |
| Mexico | 2006 | 1–11 years ($n$ = 1127) | 26.6 | >20 years ($n$ = 1932) | 33.8 | Girls 12–19 years ($n$ = 1 019) | 28.1 | >20 years ($N$ = 924) | 42.6 | For children and adults IZiNCG cut-offs†; Adolescents < 65 μg $dL^{-1}$ | [112,113,114] |
| | 2006 | – | – | – | – | Boys 12–19 years ($n$ = 734) | 24.5 | – | – | | |
| Nepal | 2016 | 6–59 months ($n$ = 1709) | 20.7 | 15–49 years ($n$ = 2144) | 24.3 | – | – | – | – | IZiNCG cut-offs† | [115] |
| Nigeria | 2001 | <60 months ($n$ = 2725) | 20 | Mothers of participating children ($n$ = 3779) | 28.1 | – | – | – | – | <80 μg $dL^{-1}$ | [30] |
| | 2001 | – | – | Pregnant women ($n$ = 795) | 43.8 | – | – | – | – | | |
| Pakistan | 2011 | 6–59 months ($n$ = 6847) | 36.5 | 15–49 years, non-pregnant mothers ($n$ = 5953) | 41.6 | – | – | – | – | <60 μg $dL^{-1}$ | [116] |
| | 2011 | – | – | 15–49 years, pregnant mothers ($n$ = 791) | 48.3 | – | – | – | – | | |

**Table 1** Continued

| Country | Year of the survey | Children | | Women | | Adolescent | | Men | | Cut-offs used | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | sample | % Prevalence | sample | % Prevalence | sample | % Prevalence | sample | % Prevalence | | |
| Philippines | 2008 | 6–59 months (*n* = 2370) | 21.6 | 20 < 60 years (*n* = 2892) | 31.2 | Girls 13–19 years (*n* = 986) | 20.6 | 20 < 60 years men (*n* = 2905) | 30.7 | IZiNCG cut-offs† | (117) |
| | 2008 | 6–12 years (*n* = 3789) | 30.8 | >60 years (*n* = 678) | 24.5 | Boys 13–19 years (*n* = 1208) | 32.2 | >60 years men (*n* = 574) | 33.6 | | |
| | 2008 | – | – | Pregnant women (*n* = 461) | 21.5 | – | – | – | – | | |
| | 2008 | – | – | Lactating women (*n* = 836) | 39.7 | – | – | – | – | | |
| Senegal | 2010 | 12–59 months (*n* = 1151) | 50 | 15–49 years (*n* = 1082) | 59 | – | – | – | – | IZiNCG cut-offs† | (25) |
| South Africa | 2005 | 1–3 years (*n* = 154) | 51 | – | – | – | – | – | – | IZiNCG cut-offs† | (25) |
| Sri-Lanka | 2012 | 6–59 months (*n* = 4463) | 5.1 | – | – | – | – | – | – | IZiNCG cut-offs† | (118) |
| Vietnam | 2010 | 6–75 months (*n* = 563) | 51.9 | 15–49 years, non-pregnant (*n* = 1522) | 67.2 | – | – | – | – | IZiNCG cut-offs† | (119) |

†Cut-offs suggested by International Zinc Nutrition Consultative Group (IZiNCG): <65 μg $dL^{-1}$ in the morning, and <57 μg $dL^{-1}$ in the afternoon for children below 10 years of age; <70 μg $dL^{-1}$ for fasting status in the morning, <66 μg $dL^{-1}$ for non-fasting in the morning, and <59 μg $dL^{-1}$ non-fasting in the afternoon for non-pregnant females aged ≥10 years; <56 μg $dL^{-1}$ in the first trimester, and <50 μg $dL^{-1}$ in second or third trimester for pregnant women aged ≥10 years; <74 μg $dL^{-1}$ for fasting status in the morning, <70 μg $dL^{-1}$ for non-fasting in the morning, and < 61 μg $dL^{-1}$ non-fasting in the afternoon for non-pregnant males aged ≥10 years [7].

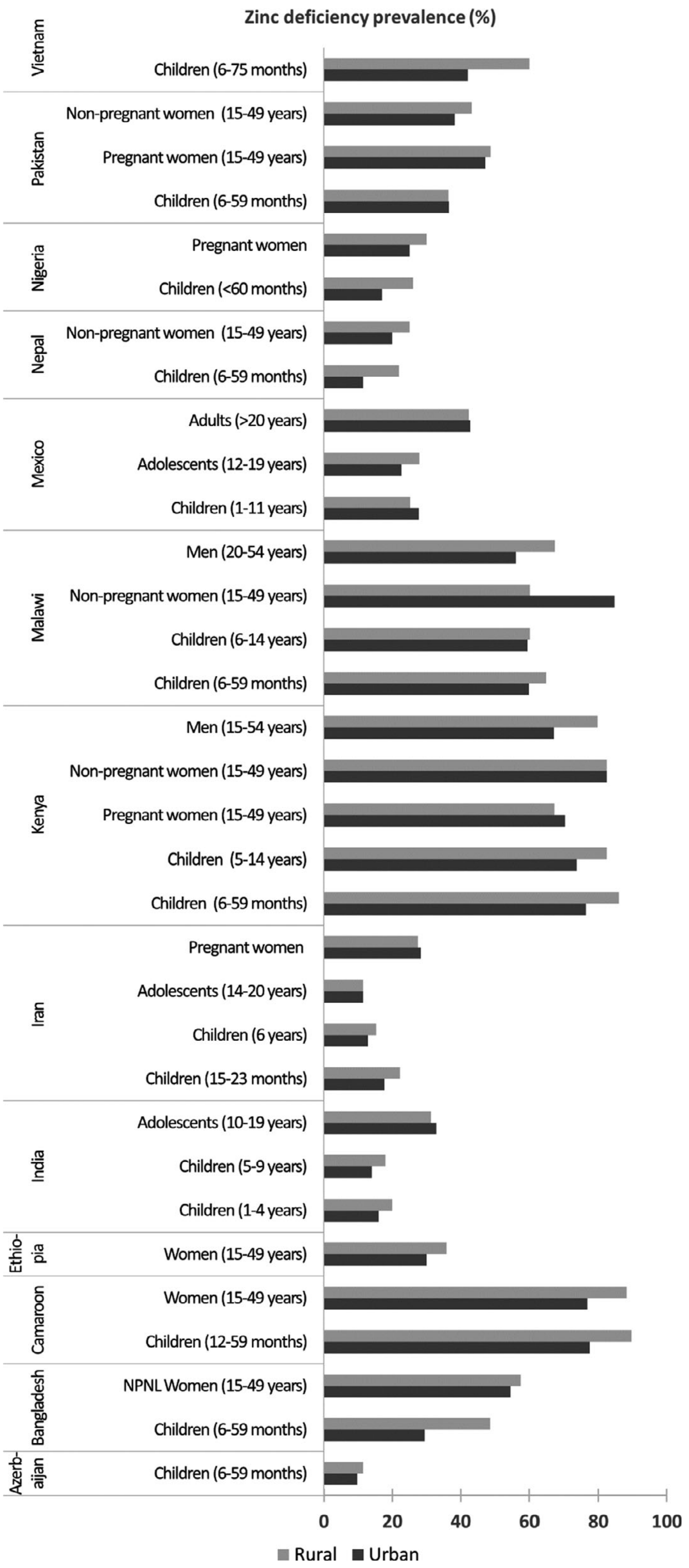


**Figure 1** Prevalence of zinc deficiency by urban or rural residence in low- and middle-income countries. Prevalence of zinc deficiency is based on the assessment of plasma/serum zinc concentration in national surveys. Cut-offs used by the countries are provided in Table 1. NPNL, non-pregnant non-lactating.

requirements to support growth, lower dietary diversity and an increased susceptibility to infection compared to the preschoolers. This may call for examining and improving complementary feeding practices, access to animal sources of food and multiple micronutrient supplements. By contrast, it is interesting to note that a high prevalence of zinc (PZC) but not iron-deficiency among women was reported in rural Malawi in a study by Siyame *et al.* [33] that aimed to understand zinc deficiency in relation to selenium and iron intake. Zinc deficiency (>90 %) was greater than iron deficiency anaemia (6%) or iron deficiency (5%) and this was attributed to diets low in zinc (median 5.7 mg $day^{-1}$) with high phytate:zinc molar ratios (20.0) but high in iron (21.0 mg $day^{-1}$) from soil contamination. However, PZC in the referred study was found to be a determinant of haemoglobin and is in-agreement with previous findings from the other LMICs where zinc deficiency has been found to be associated with anaemia in young children. Although the study did not account for malaria and genetic haemoglobin disorders and was limited by use of a convenience sample, it suggests the importance for micronutrient assessment and understanding the factors relating to the regional context.

The latest Global Nutrition Report has emphasised the estimation of micronutrient deficiencies, highlighted the paucity of information relating to zinc from LMICs [34]. Although there are numerous regional small-scale studies from LMICs for various physiological groups, the national-level data are scant. The available data, irrespective of the indicators employed, suggest that zinc deficiency is a public health problem in LMICs. The prevalence data that are available for 25 countries highlight the gravity of the zinc deficiency issue not only particularly among women and children, but also possibly among other groups such as male adults and adolescents. Therefore, there is an urgent need to assess zinc status among various physiological groups for all LMICs. IZiNCG has committed to conduct key informant interviews with survey representatives from the countries where a recent national nutrition survey included plasma/serum zinc or omitted it. This would help to identify the factors that enable plasma/serum zinc assessment along with the challenges that persist to facilitate availability and utilisation of such data.

## Strategies for addressing zinc deficiencies

The past two decades have witnessed an increasing awareness of zinc nutrition in LMICs. Several zinc intervention (supplementation) trials in settings with inadequate intake have shown beneficial effects on various aspects of human health. However, as mentioned earlier, large-scale intervention programmes have been impeded partially by a lack of reliable biomarkers. Presently, the approaches suggested for tackling zinc deficiency are identical to that in place for iron deficiency and include supplementation, fortification, dietary diversification and the emerging area of biofortification. The choice of intervention will be influenced by the urgency with which the situation needs to be addressed, the resources available to develop and maintain the infrastructure, and/or technology necessary to deliver and sustain the interventions and evidence in the support of the intervention type [7]. Preferably, the above-mentioned approaches should be integrated not only to derive maximum effects, but also to facilitate a smooth transition from short term strategies such as supplementation to the most sustainable strategy of dietary diversification. In addition, complementary approaches should be combined with ongoing national food, nutrition and health programmes, and promoted using nutrition education and social marketing techniques to enhance their effectiveness and sustainability. The success of programmes and policies requires harmonisation and integration of the work of various sectors, such as government, education, public health and industry, as well as international and consumer organisations [35].

### Supplementation

Supplementation programmes are particularly valuable for targeting vulnerable population subgroups whose nutritional status needs to be improved within a relatively short period and are often looked upon as a short-term strategy. A strong argument in support of zinc supplementation in LMICs arises not only because supplementation has been shown to reduce ill effects associated with zinc deficiency, but also it appears to be a viable strategy for reaching specific target groups that do not have access to processed food or whose requirement for zinc (such as young children with frequent episode of diarrheal infections) cannot be met even with a fortification and/or dietary diversification program.

The potential of zinc supplementation programmes in LMICs as a protective approach against diarrhoea, pneumonia, respiratory tract infection, mortality among children and adverse pregnancy outcomes among women is widely documented [9,10,13]. A recent double-blind study has confirmed the beneficial effects of a 6-month zinc supplementation intervention on the length increment among rural young Iranian children (6–24 months) [36]. This study, along with a meta-analysis by Imdad and Bhutta [37] that concluded a significant positive effect of zinc supplementation on stunting reduction in children <5 years of age in LMICs, has brought some clarity to the contrasting findings of the previous meta-analyses by two independent groups. Among these, two meta-analyses by Brown *et al.* [9,38] concluded that zinc supplementation produces a highly significant positive effect on height gain in prepubertal children and is in contrast to a finding by Ramakrishnan *et al.* [39] where no such association was observed among children <5 years.

In LMICs, supplementation programmes are often expensive, rely heavily on donor support and on individual compliance, which may require an alteration in usual behaviour. In such a setting, a health system capable of providing a consistent supply, distribution, and delivery of the supplement to the targeted group is a prerequisite [35], alongside effective compliance monitoring and support. Accordingly, despite the evidence, implementation of preventive zinc supplementation remains a challenge. Zinc supplementation is generally restricted to therapeutic purposes and an increasing number of LMICs have introduced national policies for zinc in the treatment of diarrhoea among children <5 years, based on recommendations by WHO and United Nations Children's Fund [40]. These recommendations were made in response to a growing body of evidence showing a reduction in the duration and severity of diarrhoeal episodes, as well as reduced incidence in the subsequent months. According to the guidelines, 10 mg Zn $day^{-1}$ for 10–14 days for children under 3 years and 20 mg for older children should be administered. However, the coverage for this zinc supplementation as an adjunct therapy for the treatment of diarrhoea remains low in the absence of effective scale-up efforts [41]. Also, this approach appears to be suboptimal for the prevention of zinc deficiency because children only have access to supplemental zinc after they become ill, and if their caregivers actively seek treatment for diarrhoea.

Public health experts, government and donors may be reluctant to scale up a preventive programme that requires daily zinc supplementation, especially when several micronutrient deficiencies often co-exist [42]. The use of the existing supplementation platforms, such as those for iron and folic acid, is suggested with respect to reducing the cost of zinc supplementation. Multiple micronutrient interventions such as multiple micronutrient powders (MNP) that often include zinc have attracted attention [43,44]. However, evidence supporting the beneficial impact of MNP on zinc status and on health and growth outcomes is inconsistent compared to preventative zinc supplementation provided in the form of a single micronutrient [45,46,47,48]. Furthermore, there are some concerns about the potential risks of MNP, which include altered gut microbiota, intestinal inflammation and an increased risk of morbidity in some studies, possibly related to the provision of supplemental iron in MNP and possibly modified by individuals' underlying iron status [47,49,50]. Zinc is absorbed most effectively when taken between meals, and in the absence of other micronutrients. However multiple micronutrient supplementation taken with a meal may dilute the inhibitory effect of other micronutrients on zinc and vice versa. Interactions between zinc and other minerals including copper, calcium and non-haem iron have been reviewed elsewhere[20,23]. The exact mechanisms underlying these interactions are not clearly known. Shared absorptive pathways for iron, copper and zinc through DMT-1 (divalent metal transporter 1), CRT1 (copper tansporter1) and individual pathways in the apical membrane of the intestinal cell are possibly implicated [4,51,52,53,54]. Calcium alone has no inhibitory effect on zinc absorption but, in the presence of phytate, may form insoluble calcium-zinc-phytate complexes that cannot be absorbed [4,20]. Thus, additional research is needed to not only to determine the efficacy of MNP as a preventive zinc supplement, but also to further understand the benefits and risks associated with it [55,56]. A different approach for fostering zinc supplementation (by increasing cost-effectiveness) could be through intermittent/weekly zinc supplementation [57]; however, more robust evidence is required [56,58].

A chemical form that is high in bioavailability, does not evoke a metallic taste, is safe, and yet is cheap, is central to the supplementation programme in any LMIC. Different chemical forms of zinc that can be used as supplements include acetate, chloride, citrate, gluconate lactate, methionine, zinc oxide, zinc stearate and heptahydrate/anhydrous zinc sulphate. Studies conducted to assess the absorption of different chemical forms of supplemental zinc have provided varying results and sometimes conflicting data in terms of their relative absorption. In general, water-soluble compounds, such as zinc acetate, zinc gluconate and zinc sulphate, are considered more readily absorbable than compounds with limited solubility at neutral pH [7]. Based on limited human studies, it appears that zinc gluconate, zinc acetate, zinc citrate and zinc sulphate are absorbed to a similar extent and that zinc oxide is slightly less well absorbed when given without food [7,59,60,61,62]. Zinc methionine/histidine may have enhanced absorption than zinc sulphate because of the facilitation of zinc absorption by the amino acid ligands [63,64]. However, the possible benefit of improved zinc absorption from these compounds may not justify their higher costs. WHO recommends the use of the water-soluble compounds zinc sulphate (23% zinc), zinc acetate (30% zinc) or zinc gluconate (14% zinc) in the form of syrups or dispersible tablets for diarrhoea management in infants based on randomised placebo-controlled trials reporting similar efficacy [40]. However, zinc sulphate and zinc acetate have a strong metallic, bitter and astringent taste that needs to be masked, whereas the low zinc content of zinc gluconate makes this compound more expensive. Wegmüller *et al.* [59] used the double-isotope tracer method to compare zinc absorption in humans from zinc citrate with zinc gluconate and zinc oxide using a randomised, double-masked, three-way crossover design. The group concluded that zinc citrate (which is odourless and has a relatively lower cost), given as a supplement without food, is as well absorbed by healthy adults as zinc gluconate and could serve as a useful alternative. However, further studies using zinc citrate are required to confirm the efficacy.

### Fortification

Food fortification is the addition of one or more nutrients to a food during processing to increase the intake for the correction or prevention of micronutrient deficiencies [65]. Being cost effective and safe, this strategy has gained popularity among developed countries, and is attracting the attention of LMICs. Hess and Brown [66] have set forth a case in favour of zinc fortification, largely based on the clear evidence that zinc fortification enhances dietary zinc intake. However, it was uncertain whether zinc fortification has an impact on PZC or functional indicators of zinc status. Das *et al.* [67] reported that zinc fortification is associated with an increased serum concentration, although overall evidence of the effectiveness of fortification remains inadequate. A relatively recent systematic review attempted to assess the beneficial and adverse effects of fortification of staple foods with zinc on health-related outcomes and biomarkers of zinc status in the general population from middle-income countries where zinc deficiency is expected to be a public health problem [68]. It was found that foods fortified with zinc increased the PZC levels in comparison with foods without added zinc [mean difference (MD) 2.12 $\mu$mol $L^{-1}$], although participants consuming foods fortified with zinc versus participants consuming the same food without zinc had a similar risk of stunting (relative risk = 0.88). Furthermore, the group expressed ambiguity with respect to the effect of zinc fortification, as a result of the very small difference in PZC among the participants consuming foods fortified with zinc plus other micronutrients, compared to participants consuming the same foods with micronutrients but no added zinc (MD 0.03 $\mu$mol $L^{-1}$). Because most of the studies included in the above review had a small number of participants and there were inconsistencies in the results across different studies, a further synthesis of evidence is required in support of the effectiveness of zinc fortification.

The vehicles for zinc fortification include cereal flours and products such as porridge, edible fats, sugar, condiments, seasonings, milk and beverages, bread and infant formulae [67,68]. WHO has given an interim consensus statement on wheat and maize flour fortification with a variety of micronutrients including zinc (for both low and high extraction flour)[69]. Chemical forms of zinc used for fortification purposes are mainly the cheapest ones (i.e. zinc sulphate and zinc-oxide), although several compounds mentioned under the supplementation section may be exploited. MNP also referred to as 'point of use fortificants' (generally added to food at a single point of time in a day) have been suggested for zinc fortification to enhance the cost-effectiveness in settings where several micronutrient deficiencies co-exist. Lipid-based nutrient supplements are semi-solid pastes usually prepared from vegetable oil, groundnut paste, milk and sugar, and may include zinc simultaneously with other micronutrients, serving as yet another form of zinc fortification [70,71]. The concerns with regards to the use of multiple micronutrients/MNP for improving zinc nutrition has been discussed earlier in this review.

Although food fortification appears to be a feasible approach in lower-income countries, there are several underlying determinants that critically impact the successful implementation of fortification programmes in these regions, including government commitment, legislation, education, awareness and cost of fortification. Despite the potential for a positive impact on zinc nutriture, national-level zinc fortification programmes in LMICs are rudimentary. Cereal flours are attractive vehicles for fortification programmes in LMICs and have been shown to have positive impact on zinc nutrition [72]. Mass fortification of cereal flour with zinc was initiated in Mexico and China. At present, there are 24 LMICs that have regulations for mandatory, and another six for voluntary wheat and/or maize flour fortification (Table 2), although evidence on programme effectiveness is scant. Large-scale fortification programmes with robust impact assessment need to be carried out to cover larger populations in all age groups for informed decisions. Cameroon has recently evaluated the impact of mandatory flour fortification with iron, B12, folic acid and zinc (1 year of intervention) through a nationwide survey and reported greater post-fortification mean PZC for both women and children. A significant reduction in the prevalence of low PZC was reported in women by 18% ($P < 0.001$) and children by 19% ($P < 0.001$) [73]. Very few countries have an ongoing voluntary/mandatory rice fortification programme (Table 2). Apart from cereal flour, roots and tubers could be explored as a potential vehicle for zinc fortification. Recently, Vergara Carmona *et al.* [74] demonstrated post-harvest priming of potato tubers with zinc solution could enhance the zinc content. An improved bioavailability of zinc from the uncooked

**Table 2** Regulations on wheat flour, maize flour and rice fortification with zinc in the Low- and Middle-income Countries

| | | Wheat flour fortification | | Maize flour fortification | | Rice fortification | |
|---|---|---|---|---|---|---|---|
| Region | Country | Category | Levels (ppm) | Category | Levels (ppm) | Category | Levels (ppm) |
| Central Africa | Cameroon | Mandatory | 95 | – | – | – | – |
| East Africa | Burundi | Mandatory | 88 | Mandatory | 49 | – | – |
| | Djibouti | Mandatory | 40 | – | – | – | – |
| | Kenya | Mandatory | 40 | Mandatory | 30 | – | – |
| | Uganda | Mandatory | 60 | Mandatory | 30 | – | – |
| | Tanzania | Mandatory | 40 | Mandatory | 22.5 | – | – |
| South Africa | Malawi | Mandatory | 80 | Mandatory | 40 | – | – |
| | Mozambique | Mandatory | 30 | Mandatory | 20 | – | – |
| | South Africa | Mandatory | 15 | Mandatory | 15 | – | – |
| | Zimbabwe | Mandatory | 40 | Mandatory | 40 | – | – |
| | Eswatini | Voluntary | 20 | – | – | – | – |
| West Africa | Ghana | Mandatory | 28.3 | – | – | – | – |
| | Liberia | Mandatory | 95 | – | – | – | – |
| | Nigeria | Mandatory | 50 | Mandatory | 50 | – | – |
| | Togo | Mandatory | 55 | – | – | – | – |
| | Sierra Leone | Voluntary | 28.3 | – | – | – | – |
| East Africa | Rwanda | – | – | Voluntary | 49 | – | – |
| East Asia | Fiji | Mandatory | 30 | – | – | – | – |
| | Indonesia | Mandatory | 30 | – | – | – | – |
| | Kiribati | Mandatory | 30 | – | – | – | – |
| | Mongolia | Mandatory | 18.7 | – | – | – | – |
| | Solomon Islands | Mandatory | 30 | – | – | Mandatory | 45 |
| | Vietnam | Mandatory | 101.3 | – | – | – | – |
| | China | Voluntary | 25 | – | – | – | – |
| Central Asia | Kazakhstan | Mandatory | 25 | – | – | – | – |
| West Asia | Jordan | Mandatory | 20.08 | – | – | – | – |
| South Asia | Afghanistan | Voluntary | 50 | – | – | – | – |
| | Bangladesh | – | – | – | – | Voluntary | 40 |
| | India | Voluntary | 12.5 | – | – | Voluntary | 12.5 |
| Mexico and Central America | Costa Rica | – | – | – | – | Mandatory | 7.5 |
| | Guatemala | – | – | Mandatory | 15 | – | – |
| | Mexico | Mandatory | 40 | Mandatory | 40 | – | – |
| | Nicaragua | – | – | – | – | Mandatory | 25 |
| | Panama | – | – | – | – | Mandatory | 25 |
| South America | Peru | – | – | – | – | Voluntary | 32 |

Data source: Food Fortification Initiative[120]; ppm, parts per million.

potato was suggested, based on a lowered phytate:zinc ratio (<5) in primed compared to non-primed (Zn: phytate ratio 5–15). Further studies are necessary to substantiate the effectiveness of this method on biofortification and bioavailability of zinc *in vivo* and using the cooked/processed form.

An increase in PZC when zinc was taken in the form of a supplement between meals, but not when the same amount was provided in form of fortified food, is intriguing [4]. One of the probable reasons could be the difference in the absorption. Because the diets in LMICs are generally low in animal food and high in phytate, it may be worthwhile to investigate the feasibility of co-fortification with promoters of zinc absorption such as ethylenediaminetetraacetic acid, or the use of phytase to derive maximum benefits from fortification [22]. A recent randomised controlled cross-over trial in young Gambian children (aged 18–23 months) reported that the addition of exogenous phytase to small-quantity lipid-based nutrient (SQ-LNS) supplements enhanced the fractional and total absorption of zinc from a millet-based porridge consumed with SQ-LNS by around two-fold compared to the meal containing SQ-LNS without phytase [75].

## Diet diversification/modification

Dietary diversification/modification (DDM) is a more sustainable, long-term, economically-feasible and culturally-acceptable strategy. It is highly suited for the needs of LMICs because it does not rely on a constant financial support/infrastructure, which is the case with supplementation and fortification, and it can be used to alleviate several micronutrient deficiencies simultaneously without any risk of antagonistic interactions [19]. It entails both enhancing zinc intake as well as its absorbability, in contrast to fortification that addresses only intake.

The potential of DDM strategies to improve zinc intake and absorption has been reviewed in-depth by Gibson and Anderson [76]. These DDM strategies at the community/household level include (i) agricultural interventions; (ii) production and promotion of animal-source foods through animal husbandry or aquaculture; and (iii) processing strategies at the commercial or household level to enhance zinc absorption from plant-based diets that have potential to improve zinc nutrition. Agricultural interventions can increase the production, accessibility and consumption of plant-based foods and hence have the potential to improve intake of several micronutrients including zinc. However, the evidence regarding specifically improving zinc intakes and bioavailable zinc is missing because the agriculture interventions in the past have been conducted largely for the improvement of vitamin A nutrition. An issue with the above approach is that agricultural interventions, focussed on plant-based foods, may only have a small impact on the intake of bioavailable zinc. Because the diets in LMICs are largely plant-based, a combination of dietary strategies involving the increased consumption of animal-source foods and phytate reduction is a preferred method for enhancing both the content and bioavailability of zinc in the household diets. Besides animal foods being rich sources of readily available zinc, there is evidence that the inclusion of even a small amount of animal protein, such as fish, poultry, guinea fowl, rabbit, goat and eggs, increases zinc absorption from a plant-based diet [77]. This effect may be attributable to amino acids, released from animal protein, which keep the zinc soluble and counteract the inhibitory effect of phytate in the meal [20]. Promoting animal foods thus appears the best strategy for enhancing the zinc content of household diets [19]. Fish flour can be used to enrich cereal-based porridges for feeding infants and young children [78]. The cost-effectiveness may be further enhanced by exploring fish powder from cheaper fish and by-products [79]. This source of zinc has the additional advantage of not requiring refrigeration and can be consumed by economically weaker sections and communities in which cultural/religious factors prevent meat and poultry consumption. Nutrition education has been shown to impact the intakes of animal-source foods and thus bioavailable zinc and therefore appears to be a crucial component of DDM [76].

Several household/commercial food preparation and processing methods can be used to reduce the phytate content of foods based on cereals and legumes. Milling is the most commonly used method for removing phytic acid from grains. This technique removes the phytic acid but has a drawback that it also removes minerals including zinc [80]. Other household techniques, including soaking, germination and fermentation, have been reviewed in detail elsewhere [81]. Soaking followed by decanting can also be used to reduce the phytate content of cereal and legume flours by passive diffusion of the water-soluble sodium, potassium and magnesium phytates and may activate endogenous phytase under optimal conditions. Phytic acid degradation during germination and fermentation is based on the enzymic hydrolysis of phytic acid to lower inositol phosphates. Germination may also reduce the content of inhibitory tannins and other polyphenols in some legumes [82]. Organic acids produced during fermentation also have the potential to enhance zinc absorption via the formation of soluble ligands with zinc. However, human studies examining the beneficial effect of fermentation on zinc bioavailability are missing.

The extent of phytate degradation depends on the method and conditions used. Although, with household processes, phytate can be reduced by approximately 50%, almost a complete degradation can be achieved by commercial phytases [76]. WHO has evaluated certain phytases from *Aspergillus niger* for use with food and found it safe for human consumption; however, acceptable daily intake has not been specified [83]. It is of interest that fermentation of germinated pearl millet sprouts with mixed pure cultures of *Saccharomyces diasticus*, *Saccharomyces cerevisiae*, *Lactobacillus brevis* and *Lactobacillus fermentum* at 30 °C for 72 h led to 88.3% reduction in phytate content[84]. Recipes combining germination and fermentation need to be formulated and investigated for the bioavailability of zinc.

Although promising, the promotion of food-based strategies remains in its nascent stages of development in LMICs. Despite evidence for the improvement of zinc absorption from cereal-based foods prepared with a reduced phytate content, programmatic experience with the promotion of home processing techniques to increase absorbable zinc in diet is limited. Information on locally available, low-cost, culturally acceptable zinc-rich foods and identification of best approach to promote their consumption by those who are at risk of zinc deficiency is required for developing such programmes.

## Biofortification

Biofortification involves increasing the nutrient levels in edible plants during the period of growth through (i) Agricultural, (ii) Agronomic and (iii) Transgenic (genetic modification) means, either alone or in combination.

Targeting staple foods for biofortification is appropriate for improving the diet quality in LMICs because it is sustainable and highly cost-effective, and also does not require any changes/modification in the existing practices of food preparation and consumption. Furthermore, it can cover the communities that are hard to reach, who subsist only on staples as a result of the unaffordability of diverse food, where food is grown and consumed locally, and it is applicable to all family members including women and children [85].

The transgenic approach involves inserting genes needed for the accumulation of a micronutrient that would not otherwise exist in that crop. This method provides exciting opportunities not only for making dramatic increases in the contents, but also has the potential to increase bioavailability. Crops including rice, wheat, maize have been genetically engineered to enhance zinc content [86]. Furthermore, bioavailability can also be improved through genetic engineering by decreasing inhibitors or possibly improving the synthesis of enhancers [87]. It has also been possible to accumulate zinc in edible germ through this technique. Despite these benefits and time-effectiveness compared to conventional plant breeding, transgenic crops have limited acceptability among consumers and regulatory bodies [88,89].

Agronomic bio-fortification can be achieved by applying zinc fertilisers to soil, or leaves, or by priming seeds. Although this requires an appropriate infrastructure, it can be successful in regions where mineral fertilisers are used to increase crop yields and zinc is added to these at the point of manufacture or distribution. As reviewed by Cakmak and Kutman [90], agronomic biofortification with zinc has proved to be effective for crop fortification and has additional benefits such as enhanced yields depending on the extent of soil zinc deficiency, improved seed and seedling vigour, as well as reduced root and shoot accumulation of cadmium. A recently published multicentric study across six LMICs revealed that the seeds biofortified with zinc enhanced crop (rice, wheat and common beans) productivity at many locations with different soil and environmental conditions [91]. The use of nanofertilisers offers a new paradigm for biofortification. This method has the potential to significantly improve the efficiency of micronutrient application to crops, reducing nutrient waste and subsequent environmental contamination [92]. It is interesting to note that a very recent study investigating the effect of different agronomical methods for biofortification on human zinc absorption reported no difference in zinc absorption (fractional zinc and total absorbed zinc) between the food prepared from wheat biofortified by foliar application or through the root (hydroponic). At the same time, absorption from the biofortified foods, regardless agronomic-biofortification methodology used, was greater compared to the control [93].

A synergistic usage of application of zinc fertiliser along with breeding/genetic modification is a key to effective biofortification. For enhanced accumulation by conventional breeding or molecular engineering, it is imperative that the soil/vegetative tissues have sufficient zinc for translocation into grain. Although agronomic biofortification has shown a definitive increase in zinc concentration, evidence of the translation of this increase to benefit human health is uncertain [94,95].

Conventional breeding is the most accepted technique for the production of new biofortified crop varieties. Using this strategy, parent lines with high nutrient content are crossed with a recipient line of desirable agronomic traits over several generations to produce plants with the desired nutrient and agronomic traits. As reviewed by Lockyer *et al.* [96], biofortified zinc wheat has been released in China, India, Pakistan and Bolivia; rice in China and Bangladesh; and iron-zinc enriched lentils in India, Nepal and Bangladesh. Among the three small studies conducted to assess the effectiveness of conventionally-bred biofortified cereals, two studies (one with wheat and another maize) found a greater net absorption of zinc from the biofortified crop. The study with rice failed to show any increase in total or in fractional zinc absorption. A study carried out in India aiming to determine the absorption of iron and zinc among children (<2 years) from biofortified pearl millet concluded that the biofortified pearl millet, when consumed as a major food staple, is more than adequate for meeting the physiological requirements for these micronutrients [97]. In addition to cereals and millets, there is some evidence of improved zinc absorption from biofortified beans (high iron and zinc) [98]. Biofortified beans were released in Colombia in 2016. Its acceptability has been tested to understand the feasibility of incorporation of biofortified beans into the national school-feeding programme [99]. Larger studies are needed to draw a more definitive conclusions with regard to the effectiveness of biofortified crops. A large-scale effectiveness study on the potential of biofortified wheat (Zincol-2016) to improve zinc and iron status among adolescent girls and children living in Pakistan is underway (Trial registration No. ISRCTN17107812).

Furthermore, there is some evidence that plant breeding techniques can be applied to improve the bioavailability of zinc. Previously, low phytate content maize, produced through plant breeding techniques, has been shown to improve the fractional absorption of zinc (single day) [100,101]. However, a longer-term study in which low-phytate maize was supplied to school-aged children in Guatemala for 10 weeks failed to demonstrate any improvement in zinc absorption compared to control maize [102]. The reason for such unexpected findings is uncertain. Confirmation of the efficacy of long-term consumption of low-phytate hybrids is warranted because this strategy has the potential to conveniently improve the absorbable zinc intake of populations subsisting on plant-based diets. At present, further exploration of this novel approach to enhance mineral absorption from plant-based diets has been hindered by the association of the low-phytate trait with reduced yields, as well as by technical and cultural constraints such as the need for long-term breeding projects specifically devoted to the low-phytate trait [81].

## Conclusions

The UN Sustainable Development Goal for zero hunger and good health and wellbeing for all cannot be met without alleviating zinc malnutrition. There is paucity of information on zinc deficiency for various physiological groups at a national level in LMICs and the lack of a reliable biomarker is one of the underlying factors that has impeded the assessment of zinc status in national monitoring and surveillance. Zinc deficiency appears to be a public health problem in almost all LMICs, irrespective of the indicators used for assessment (prevalence of low height- or length-for-age >20% among children under 5 years of age; prevalence of low plasma zinc among the population >20%; prevalence of insufficient zinc intake >25%). Using the PZC, which appears to be the most appropriate indicator at present, the prevalence rate of zinc deficiency in LMICs is of concern. Among 25 countries for which the national data was available for PZC, 23 were found to have a prevalence of zinc deficiency greater than 20% for at least one of the physiological groups. Our review suggests that zinc deficiency is common not only among women and children, but also presumably among adolescent and adult males. Because there is a wide intra-regional variation in the prevalence of zinc deficiency, with those belonging to the poorer sections and living in rural areas mostly affected, regional identification of the underlying factors is necessary to devise context-specific strategies and delivery platforms for improving the intake of bioavailable zinc.

Various approaches can be used simultaneously to achieve the improvement in zinc status. Although there is evidence to support zinc supplementation, this approach has been largely restricted as an adjunct therapy for diarrheal management in children. Optimisation of delivery platforms, zinc formulations, and frequency of supplementation are needed to enhance the cost-effectiveness of preventive zinc supplementation. Regulations for mandatory/voluntary zinc fortification are in place for many LMICs, although there is a dearth of impact assessment. Because zinc has been mostly found to be effective when supplemented alone, the effectiveness of MNP and point of use fortificants needs to be ascertained. Dietary diversification, although promising, is still in the nascent stages of its development. Programmes targeting the inclusion of animal products can be an important way of improving zinc status, particularly in children. Programmatic experience with the promotion of home processing techniques to increase absorbable zinc in the diet is lacking.

Supplementation, fortification and dietary diversification are feasible strategies for enhancing zinc status among various population groups; however, conventional breeding and agronomic biofortification techniques are gaining recognition in LMIC settings and point toward a brighter future with respect to a sustainable solution to the global challenge of zinc deficiency.

## Transparency Declaration

The lead author affirms that this narrative review is an honest, accurate and transparent review of some key publications in this field. It does not claim to be a comprehensive Systematic Review of all literature published on this topic.


### Conflict of interests, source of funding and authorship

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NL conceived the structure of the review. SG undertook the literature search and wrote the draft. AB contributed to the initial literature search on zinc deficiency prevalence and the editing of the tables. NL critically reviewed, revised and finalised the manuscript. All the authors read, revised and approved the final manuscript submitted for publication.


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