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Setting priorities for zinc-related health research to reduce children's disease burden worldwide: an application of the Child Health and Nutrition Research Initiative's research priority-setting method

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Abstract

Objective: To make the best use of limited resources for supporting health-related research to reduce child mortality, it is necessary to apply a suitable method to rank competing research options. The Child Health and Nutrition Research Initiative (CHNRI) developed a new methodology for setting health research priorities. To broaden experience with this priority-setting technique, we applied the method to rank possible research priorities concerning the control of Zn deficiency. Although Zn deficiency is not generally recognized as a direct cause of child mortality, recent research indicates that it predisposes children to an increased incidence and severity of several of the major direct causes of morbidity and mortality.

Design: Leading experts in the field of Zn research in child health were identified and invited to participate in a technical working group (TWG) to establish research priorities. The individuals were chosen to represent a wide range of expertise in Zn nutrition. The seven TWG members submitted a total of ninety research options, which were then consolidated into a final list of thirty-one research options categorized by the type of resulting intervention.

Results: The identified priorities were dominated by research investment options targeting Zn supplementation, and were followed by research on Zn fortification, general aspects of Zn nutrition, dietary modification and other new interventions.

Conclusions: In general, research options that aim to improve the efficiency of an already existing intervention strategy received higher priority scores. Challenges identified during the implementation of the methodology and suggestions to modify the priority-setting procedures are discussed.

Keywords
Zinc deficiency
Disease burden
Public health
Intervention

To make the best use of limited resources for supporting health-related research, it is necessary to apply a suitable method to rank competing research options. The Child Health and Nutrition Research Initiative (CHNRI), an affiliated organization of the Global Forum of Health Research, has developed a new methodology for setting global health research priorities on topics that are relevant to the United Nation's fourth Millennium Development Goal: 'to reduce the mortality rate by two-thirds among children under five by 2015'[1]. The CHNRI methodology builds on existing approaches to establish research priorities in child health and nutrition, using a rationale, conceptual framework, application guidelines and strategies to address the needs of various stakeholders, as described in greater detail elsewhere[2]. The major conceptual advance of this methodology is the recognition that health research options should be defined broadly, not just as investigation designed to produce new knowledge, but also as research activities carried out to provide information leading to more efficient

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implementation of existing knowledge, with the ultimate objective being the reduction of the current global disease burden[2].

Briefly, the CHNRI methodology uses a systematic and transparent approach to establish research priorities by considering the opinions of multiple experts and taking into account issues of the feasibility of successfully completing the research, its likely effects on subsequent programme implementation, the maximum potential impact of the resulting programmes on reducing disease burden, and the contribution of the intervention programmes to equity within the target population. CHNRI has now launched a series of projects to apply the priority-setting methodology to a broad range of research topics at both global and national levels. On the global level, the approach has been used to prioritize research options on several diseases that represent the major causes of child mortality and morbidity worldwide, including pneumonia, diarrhoea and birth asphyxia[3].

To broaden experience with this priority-setting technique, we have also applied the method to rank possible research priorities concerning the control of Zn deficiency. Although Zn deficiency is not generally recognized as a direct cause of child mortality, except perhaps in its most severe forms[4], recent research indicates that it predisposes children to an increased incidence and severity of several of the major direct causes of morbidity and mortality, as summarized below. Thus, we applied the CHNRI methodology to develop and assess an expanded list of Zn-related research options.

Recent community-based intervention trials have found that Zn supplementation decreases the incidence of diarrhoea and acute lower respiratory-tract infection[5,6], two of the most important causes of child mortality in lower-income countries, and other studies have found that including Zn supplementation in the therapeutic regimen for treatment of diarrhoea reduces the severity and duration of illness[7]. Notably, several studies have detected dramatically reduced death rates among children who received supplemental Zn[8–11] and a recent large-scale trial found an 18% reduction in mortality among children over 12 months of age, although no impact on mortality among infants under 12 months old[12]. Based on these results, a recent series on child mortality estimated that universal (>90%) coverage with intervention programmes to prevent Zn deficiency would reduce child mortality by ~5% globally, which places such programmes among the top five available approaches for ensuring improved child survival in these settings[13]. In addition to these effects of Zn on the risk of morbidity and mortality from common childhood infections, a number of studies indicate that preventive Zn supplements increase the linear growth and weight gain of stunted or underweight children[14], thereby reducing rates of malnutrition and malnutrition-related morbidity and mortality, as illustrated in Fig. 1.

Methods

A group of seven leading experts in the field of Zn research in child health were identified and invited to participate in this priority-setting exercise. The individuals were chosen to represent a wide range of expertise in Zn nutrition: community nutrition, dietetics, clinical nutrition and paediatrics, maternal nutrition, infectious diseases, public health nutrition programmes, health economics, global nutrition policy and the food industry. These individuals have longstanding experience in their respective field of research and all have worked extensively in lower-income countries in Africa, Asia and/or Latin America.

All seven invited experts agreed to participate and formed a technical working group (TWG). The TWG members were requested to list research options they believed to be important for reducing global Zn deficiency, with a particular focus on lower-income countries and restricting their priorities to those that would be expected to yield some impact on reducing disease burdens within 10 years. The target population was defined as children less than 5 years of age, and the target disease burden as all cases of mortality and morbidity related

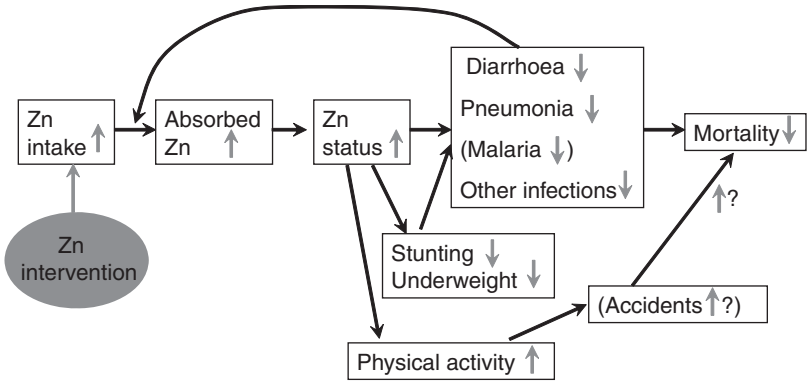

Fig. 1 Conceptual model of interactions between zinc deficiency and morbidity and mortality

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to Zn deficiency. A research option was broadly defined as a research project that proposes to generate new knowledge that would influence one or more health interventions to control Zn deficiency.

The TWG members were asked to categorize each research option into a particular research domain, depending on which aspect of the public health intervention was addressed by the research option. For example, the proposed research options related to the generation of new knowledge for improving the efficiency of already existing interventions were categorized into health policy and system research (domain 1). Research options that could improve existing interventions by increasing their affordability, deliverability or sustainability were listed in research domain 2. Finally, research options aiming to develop new (as yet non-existing) interventions that would be likely to be effective and have the potential to reduce disease burden were assigned to research domain 3[15].

Once the TWG members submitted the full list of research options, we prepared a summary list by combining similar or redundant options, and we then organized the consolidated list by type of intervention strategy: Zn supplementation; Zn fortification; dietary modification; other new intervention strategies; or general issues concerning the control of Zn deficiency, such as novel methods for assessing Zn status or evaluating Zn-related interventions. The TWG members were then asked independently to score each of the research options on the consolidated list, applying the scoring system described by Rudan *et al.*[15]. Specifically, each research option was scored by answering three questions related to each of the following five criteria: (i) answerability and ethics of the research project; (ii) likely efficacy and effectiveness of the resulting intervention; (iii) estimated deliverability, affordability and sustainability of this intervention; (iv) its maximum potential for disease burden reduction; and (v) likely equity in achieved disease burden reduction. The questions were formulated so they could be answered only as yes or no, with one point credited when the answer reflected a positive evaluation with regard to the particular criterion. Intermediate scores were calculated for each criterion as the percentage of positive responses for that criterion, and the final research priority score (RPS) was calculated as mean of the five intermediate scores. In cases where a TWG member could not answer a question, the answer was counted as missing, so the results did not enter the numerator or denominator when calculating the percentage of positive responses. The global RPS estimates the value of each research option when all five criteria are given equal weight, i.e. it assesses the likelihood of the research option to generate new knowledge that would improve or develop an effective and deliverable intervention which would achieve the maximum disease burden reduction per investment in an equitable manner[15]. By using a global RPS, it is also possible to manipulate the weight assigned to each criterion to reflect the values of different stakeholders.

Although the CHNRI methodology recommends including the values and opinions of a broad range of stakeholders[16], we have not yet subjected the current priority scores to review by a larger reference group of stakeholders globally. Nevertheless, the results are of interest with regard to the experience obtained when applying the priority-setting methodology to a risk factor for major childhood diseases, as well as to investigate the impact of assigning more or less importance to the different evaluation criteria. We accomplished the latter objective by modifying the weighting system for developing the final RPS, assigning each specific criterion as much weight as all the others combined and then re-ranking the research option according to this revised weighting system.

Results

The TWG members submitted a total of ninety research options, which we then consolidated into a final list of thirty-one research options categorized by the type of resulting intervention, as shown in shown in Table 1. In the final list of research options, more than a third of the projects (*n* 13) focused on Zn supplementation strategies, either therapeutic Zn supplementation for diarrhoea treatment or supplementation as a general preventive measure to control Zn deficiency. Of the remaining research options, six focused on Zn fortification, one on dietary modification and four on potential new intervention strategies. Seven research options dealt with general aspects of Zn nutrition, which eventually could benefit all of the intervention strategies.

The research options in Table 1 are ranked by the final combined RPS provided by the TWG. This score takes into account the five criteria relevant for priority setting. Among the top five research options, four would create knowledge to improve the efficiency of Zn supplementation and one would provide information relevant for all intervention strategies to control Zn deficiency. Table 2 shows the average RPS and the range of the research options by Zn intervention strategy.

The mean RPS are shown by research domain in Table 3. Most research options in the final list aimed to improve the effectiveness of an existing intervention (health policy and system research, domain 1; *n* 18). In general, research options that fall into research domain 1, i.e. those that address questions on how to make an already existing intervention strategy more efficient, received higher priority scores than those that belong to research domains 2 and 3, which aim to make existing interventions more affordable, deliverable or sustainable or which offer to develop entirely new interventions.

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Table 1 Results from a priority-setting exercise in which technical experts scored thirty-one research options according to their potential to create new knowledge that could be applied to reduce zinc deficiency among children under 5 years of age in lower-income countries. Research options are ranked according to the final research priority score (RPS), as derived from the technical working group

RPS (%)	Rank	Research option	Research domain	Intervention strategy
85·3	1	Effectiveness of scaling up Zn in the treatment for diarrhoea (and pneumonia) in high-risk countries/regions	1	Supplementation
84·4	2	Efficacy and effectiveness of Zn when delivered alone or with other single (e.g. Fe) or multiple micronutrients between meals or with foods (i.e. can Zn be combined with other nutrient delivery systems and remain efficacious?)	1	Supplementation
79·7	3	Optimal dose and duration of Zn supplements provided for treatment of diarrhoea or pneumonia, including longer-term impact on growth and risk of infection	1	Supplementation
79·6	4	Effectiveness of different delivery platforms (growth monitoring, EPI injections, community-based organizations) to provide preventive Zn supplements	1	Supplementation
79·3	5	Cost-effectiveness and cost–benefit analysis of Zn interventions to assist policy decisions	2	General aspect
79·2	6	Optimal efficacious and safe dose of preventive Zn supplements for different age groups (infants, pre-school children): amount, duration and frequency of doses	1	Supplementation
76·1	7	Efficacy of Zn-fortified complementary food intervention	3	Fortification
75·3	8	Impact of Zn interventions on malaria incidence and severity	1	Supplementation
73·6	9	Bioavailability of different chemical forms of Zn from different food vehicles	1	Fortification
73·1	10	Appropriate reference values for serum Zn concentration of infants and pregnant women	1	General aspect
72·8	11	Validation of possible indirect evidence of population risk of Zn deficiency (food balance sheets, stunting, anaemia)	1	General aspect
72·4	12	Efficacy of Zn fortification for high-risk groups (other than complementary foods)	3	Fortification
72·2	13	Socio-cultural, economic and other factors that affect adherence to supplementation regimens in different settings	1	Supplementation
70·6	14	Effects of providing Zn on HIV/AIDS morbidity and response to antiretroviral medication	1	Supplementation
69·8	15	Development of new biomarkers to assess Zn status at low cost to identify target groups most likely to benefit from Zn interventions	1	General aspect
69·4	16	Impact of Zn interventions on tuberculosis incidence and severity and response to antimicrobial treatment	3	Supplementation
69·1	17	Integration of diarrhoea treatment and preventive Zn supplementation programmes to avoid inappropriate dosing (dosing schedule, dose, duration)	2	Supplementation
68·7	18	Impact of Zn interventions immediately before and during pregnancy on pregnancy outcomes and on child health during infancy and later in life	1	Supplementation
67·4	19	Impact of Zn interventions on the incidence and severity of selected parasitic infections	3	Supplementation
64·6	20	Effectiveness of social marketing for sprinkles and fortified foods	1	Fortification
63·3	21	Nutrient interactions in fortified products: optimal Fe:Zn ratio to improve Fe and Zn status and other health outcomes	1	Fortification
63·0	22	Efficacy and effectiveness of agricultural interventions (appropriate fertilizers, selective breeding for high-Zn cultivars) on dietary Zn intake and Zn status	3	New intervention
62·6	23	Effect of parasites on Zn absorption and Zn status	1	General aspect
58·4	24	Development of genetically modified staple crops with both a high Zn content and a low phytate content	3	New intervention
56·0	25	New approaches to increase the availability (improved access, storage) and consumption of Zn-rich foods	2	Dietary modification
55·0	26	Develop an innovative public private–partnership and/or new business model to make fortified complementary foods available to lowest-income groups	2	Fortification
54·4	27	Impact of preventive Zn supplementation of term AGA, term SGA and premature infants during period of exclusive breast feeding (i.e. should supplementation be extended to these high-risk younger age groups?)	1	Supplementation
53·8	28	Development of Zn solutions to include in EPI injections for mother during pregnancy (tetanus) and for infants (tuberculosis, diphtheria), to serve as slow-release depot infections of Zn	3	New intervention
52·6	29	Safe upper limits of Zn intake for different population groups defined by age and physiological status	1	General aspect
50·9	30	Development of innovative Zn intervention strategy to provide slow release of Zn (percutaneous permeation of Zn through use of Zn/Cu bracelets, IM injection of Zn/Cu formulation, Zn salts in water supplies, etc.)	3	New intervention
33·5	31	Relationship between Zn deficiency and risk of obesity (excess body fat)	3	General aspect

EPI, epinephrine (adrenaline); AGA, appropriate for gestational age; SGA, small for gestational age; IM, intramuscular.

Table 2 Mean, minimum and maximum research priority score (RPS) by type of zinc intervention strategy

Research area	Mean RPS (%)	Min. RPS (%)	Max. RPS (%)	*n*
Supplementation	73·5	54·4	85·3	13
Fortification	67·5	55·0	76·1	6
General aspects	63·4	33·5	79·3	7
New interventions	56·5	50·9	63·0	4
Dietary modification	56·0	NA	NA	1

NA, not available.

Table 3 Mean, minimum and maximum research priority score (RPS) by research domain

Research domain	Mean RPS (%)	Min. RPS (%)	Max. RPS (%)	*n*
1. Effectiveness	71·2	52·6	85·3	18
2. Affordability, deliverability, sustainability	64·9	55·0	79·3	4
3. New innovations	60·5	33·5	76·1	9

Table 4 shows the five highest-ranking research options and their RPS when each of the ranking criteria was assigned an equal weight to the weight of all the other criteria combined. These weighted scores provide a method to simulate the impact of different stakeholders who might value one evaluation criterion more than others. For example, if the criterion 'answerability of the research option' were weighted as much as all the other criteria combined, it would indicate that the stakeholders would find it most important that the research option be well-defined and answerable using an ethical research design. In all five scenarios, the research options ranked among the five choices did not vary very much. In most cases, the highest-ranking research options focus on the improvement of the effectiveness of Zn supplementation, regardless of the differential weighting of the evaluation criteria.

Discussion

The CHNRI methodology applied here has been applied by other TWG on other diseases on the global level[3] and on the national level to address the seven main causes of death in South Africa[17]. The comparability of this method proposed by CHNRI with other priority-setting methods has been discussed elsewhere[2]. We therefore limit our discussion to our application of the method for prioritizing Zn-related research.

The present project demonstrates the feasibility of: (i) convening a multidisciplinary group of expert scientists (the TWG) who are knowledgeable about different aspects of human Zn nutrition and public health to participate in a jointly enacted priority-setting exercise; and (ii) eliciting from these individuals a list of Zn-related research priorities, scored according to the newly proposed CHNRI methodology. The TWG was able to complete this task successfully following review of relevant background papers on the methodology and minimal additional instruction from the TWG coordinators, which was provided by electronic correspondence.

Interestingly, the research options that received the highest scores pertain to health and policy system research (domain 1), i.e. research on how to improve the efficiency of delivering already existing Zn intervention strategies. This result is probably attributable to the perception that research on scaling up proven efficacious interventions is likely to have the greatest effect on reducing children's disease burden. The research options that were proposed most frequently focused on therapeutic and preventive Zn supplementation, possibly because these approaches have been tested more extensively to date, so there is more information available on their efficacy.

The TWG encountered several challenges when applying the CHNRI methodology to the problem of Zn deficiency. First, because Zn deficiency is considered a risk factor for other diseases that are primary causes of child mortality, the impact of Zn-related interventions on mortality reduction depends on the link between Zn deficiency and the risk of these other diseases. There is still some inconsistency in research results concerning the relationship between Zn deficiency and the risk of certain diseases, like malaria. Thus, it was not possible to estimate the ultimate impact of Zn interventions on mortality related to these diseases. Second, it was difficult to estimate the true impact of Zn-related interventions for reducing disease burden because of the limited available information on the global prevalence of Zn deficiency. The latter problem is related, in turn, to the difficulty in assessing Zn status. Nevertheless, a working group convened by WHO, UNICEF, the International Atomic Energy Authority and the International Zinc Nutrition Consultative Group has recently published recommendations for assessing population Zn status[18], so these recommendations can now be applied more broadly to determine the true extent of Zn deficiency and the likely impact of Zn interventions.

We encountered several other difficulties regarding the preparation of a consolidated list of research options using the CHNRI method. In retrospect, our attempt to reduce the list to a more easily manageable, relatively small number of research topics probably resulted in excessive aggregation of these options. For example, when attempting to estimate the potential impact of Zn supplementation, it became clear that the results would differ by age group and birth weight category. Thus, by aggregating all these groups of children under one research option, it was more challenging to provide a single estimate of the likely impact on disease burden reduction. Similar difficulties were encountered because

Table 4 Mean research priority score (RPS) of the five highest-ranking research options after weighting one of the five criteria as much as all the remaining four criteria combined (weighed rank) and relationship to original unweighted ranking

RPS (%)	Weighted rank	Original rank	Research option	Intervention strategy
The criterion 'answerability of the research option' is given the same weight as the other four criteria combined				
90·3	1	2	Efficacy and effectiveness of Zn when delivered alone or with other single (e.g. Fe) or multiple micronutrients between meals or with foods (i.e. can Zn be combined with other nutrient delivery systems and remain efficacious?)	Supplementation
89·0	2	1	Effectiveness of scaling up Zn in the treatment for diarrhoea (and pneumonia) in high-risk countries/regions	Supplementation
85·5	3	4	Effectiveness of different delivery platforms (growth monitoring, EPI injections, community-based organizations) to provide preventive Zn supplements	Supplementation
85·3	4	5	Cost-effectiveness and cost-benefit analysis of Zn interventions to assist policy decisions	General aspect
84·6	5	8	Impact of Zn interventions on malaria incidence and severity	Supplementation
The criterion 'effectiveness of the intervention' is given the same weight as the other four criteria combined				
87·2	1	1	Effectiveness of scaling up Zn in the treatment for diarrhoea (and pneumonia) in high-risk countries/regions	Supplementation
86·7	2	2	Efficacy and effectiveness of Zn when delivered alone or with other single (e.g. Fe) or multiple micronutrients between meals or with foods (i.e. can Zn be combined with other nutrient delivery systems and remain efficacious?)	Supplementation
83·4	3	6	Optimal efficacious and safe dose of preventive Zn supplements for different age groups (infants, pre-school children, women of reproductive age, elderly): amount, duration and frequency of doses	Supplementation
82·0	4	3	Optimal dose and duration of Zn supplements provided for treatment of diarrhoea or pneumonia, including longer-term impact on growth and risk of infection	Supplementation
80·8	5	5	Cost-effectiveness and cost–benefit analysis of Zn interventions to assist policy decisions	General aspect
The criterion 'deliverability of the intervention' is given the same weight as the other four criteria combined				
83·5	1	5	Cost-effectiveness and cost–benefit analysis of Zn interventions to assist policy decisions	General aspect
82·9	2	1	Effectiveness of scaling up Zn in the treatment for diarrhoea (and pneumonia) in high-risk countries/regions	Supplementation
81·7	3	9	Bioavailability of different chemical forms of Zn from different food vehicles	Fortification
81·3	4	2	Efficacy and effectiveness of Zn when delivered alone or with other single (e.g. Fe) or multiple micronutrients between meals or with foods (i.e. can Zn be combined with other nutrient delivery systems and remain efficacious?)	Supplementation
81·2	5	11	Validation of possible indirect evidence of population risk of Zn deficiency (food balance sheets, stunting, anaemia)	General aspect
The criterion 'maximum potential for disease burden reduction' is given the same weight as the other four criteria combined				
78·3	1	1	Effectiveness of scaling up Zn in the treatment for diarrhoea (and pneumonia) in high-risk countries/regions	Supplementation
76·3	2	3	Optimal dose and duration of Zn supplements provided for treatment of diarrhoea or pneumonia, including longer-term impact on growth and risk of infection	Supplementation
73·6	3	2	Efficacy and effectiveness of Zn when delivered alone or with other single (e.g. Fe) or multiple micronutrients between meals or with foods (i.e. can Zn be combined with other nutrient delivery systems and remain efficacious?)	Supplementation
70·6	4	4	Effectiveness of different delivery platforms (growth monitoring, EPI injections, community-based organizations) to provide preventive Zn supplements	Supplementation
70·3	5	6	Optimal efficacious and safe dose of preventive Zn supplements for different age groups (infants, pre-school children, women of reproductive age, elderly): amount, duration and frequency of doses	Supplementation
The criterion 'equity' is given the same weight as the other four criteria combined				
90·3	1	2	Efficacy and effectiveness of Zn when delivered alone or with other single (e.g. Fe) or multiple micronutrients between meals or with foods (i.e. can Zn be combined with other nutrient delivery systems and remain efficacious?)	Supplementation
88·9	2	1	Effectiveness of scaling up Zn in the treatment for diarrhoea (and pneumonia) in high-risk countries/regions	Supplementation
85·3	3	4	Effectiveness of different delivery platforms (growth monitoring, EPI injections, community-based organizations) to provide preventive Zn supplements	Supplementation
83·6	4	3	Optimal dose and duration of Zn supplements provided for treatment of diarrhoea or pneumonia, including longer-term impact on growth and risk of infection	Supplementation
83·1	5	6	Optimal efficacious and safe dose of preventive Zn supplements for different age groups (infants, pre-school children, women of reproductive age, elderly): amount, duration and frequency of doses	Supplementation

EPI, epinephrine (adrenaline).

of the need to consolidate these assessments at a global level. For example, the likely impact of a food fortification intervention would depend on the level of development of the food industry in a particular country.

Several other issues, such as the timing of inputs from the larger reference group, the proper interpretation of the rank order of research priorities and more explicit assessment of the cost of research, merit further consideration when applying or adapting the CHNRI priority-setting methodology. Although the current priority-setting methodology suggests consulting a broader reference group of individuals who might be end-users of research results once the list of research options has been developed, it might be preferable to include the perspectives of these stakeholders earlier in this process. This would ensure that the priorities of the broader reference group are represented within the list of research options, not just in the criteria for ranking these already established options.

The final ranking of research options displayed in the present summary should be considered qualitatively rather than quantitatively. The priority-setting method does not currently include statistical considerations, such as confidence limits, of the current rankings; and the relatively small size of the TWG does not lend itself to a more rigorous statistical analysis of the results. Thus, it is not possible to state with any degree of certainty that the first-ranked option is indeed valued more highly than those ranked slightly lower on the list, so it would probably be more appropriate to prioritize groups of research options ranked highly rather than looking at individual scores. The ranking does provide some sense of the general domains of research and research themes that are more appreciated than others according to the group of experts that was convened. We have not tested the reproducibility of this method, and it is not known to what extent the composition of the TWG determines the research priorities and eventually the final scores. To reduce any potential bias, a higher number of TWG members representing a variety of expertise and geographical regions may be required.

The actual cost of implementing the different research options is not explicitly considered in the current priority-setting approach, except perhaps under the criterion of 'feasibility of research'. Thus, it is possible that the cost of implementing some of the more highly valued research options might exceed available donor resources. Nevertheless, these issues can be considered 'down stream' by donor agencies according to the amount of funds available to implement the proposed research priorities.

In summary, we found that it was possible to apply the CHNRI methodology to develop a list of research options concerning the control of Zn deficiency, a known risk factor for excessive child morbidity and mortality, and to assess the relative priority of these research options. The TWG concluded that research options aimed at increasing the efficiency of implementation of interventions known to be efficacious, particularly therapeutic and preventive Zn supplementation, were viewed as most likely to contribute to reducing child morbidity and mortality within the next 10 years in lower-income countries. This exercise should be repeated periodically, possibly with a larger TWG and reference group of stakeholders, as new information becomes available.

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